



Mnemonic discrimination relates to perforant path integrity: An ultra-high resolution diffusion tensor imaging study



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ABSTRACT

Pattern separation describes the orthogonalization of similar inputs into unique, non-overlapping representations. This computational process is thought to serve memory by reducing interference and to be mediated by the dentate gyrus of the hippocampus. Using ultra-high in-plane resolution diffusion tensor imaging (hrDTI) in older adults, we previously demonstrated that integrity of the perforant path, which provides input to the dentate gyrus from entorhinal cortex, was associated with mnemonic discrimination, a behavioral outcome designed to load on pattern separation. The current hrDTI study assessed the specificity of this perforant path integrity–mnemonic discrimination relationship relative to other cognitive constructs (identified using a factor analysis) and white matter tracts (hippocampal cingulum, fornix, corpus callosum) in 112 healthy adults (20–87 years). Results revealed age-related declines in integrity of the perforant path and other medial temporal lobe (MTL) tracts (hippocampal cingulum, fornix). Controlling for global effects of brain aging, perforant path integrity related only to the factor that captured mnemonic discrimination performance. Comparable integrity–mnemonic discrimination relationships were also observed for the hippocampal cingulum and fornix. Thus, whereas perforant path integrity specifically relates to mnemonic discrimination, mnemonic discrimination may be mediated by a broader MTL network.

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1. Introduction

A fundamental component of memory is the ability to encode a given event as distinct from even highly similar events (e.g., where did you park your car today versus yesterday?). This type of mnemonic discrimination is thought to rely on pattern separation, in which unique representations are generated for each event (see Yassa & Stark, 2011). Computational models of hippocampal function have proposed that pattern separation is mediated by the dentate gyrus (McClelland, McNaughton, & O'Reilly, 1995; Treves & Rolls, 1994; Norman & O'Reilly, 2003). In support of this view, electrophysiological studies in rodents have revealed that neurons within the dentate gyrus alter their firing rates in response to minor changes in input events (i.e., the testing environment; Leutgeb, Leutgeb, Moser, & Moser, 2007; Neunuebel & Knierim, 2014). Similarly small changes in inputs (i.e., images of highly similar objects) have also elicited differential activity within the dentate gyrus in functional neuroimaging studies in humans, consistent with the role of the dentate in pattern separation

(Bakker, Kirwan, Miller, & Stark, 2008; Lacy, Yassa, Stark, Muftuler, & Stark, 2011).

Importantly, the dentate gyrus operates within a broader network of medial temporal lobe (MTL) regions and their connections. The dentate gyrus primarily receives inputs (e.g., highly processed sensory information) from entorhinal cortex via the perforant path (Witter, 2007). Entorhinal cortex receives its input from neocortex via the cingulum bundle (Jones & Witter, 2007), whereas the hippocampus receives additional input from subcortical regions via the fornix (Amaral & Cowan, 1980; Swanson & Cowan, 1977). Thus, differences in pattern separation ability could be observed not only from a disruption of processing within dentate gyrus itself, but also from disrupted transfer of information via the perforant path and other MTL tracts (cingulum, fornix).

A noninvasive technique for assessing these white matter tracts in humans is diffusion tensor imaging (DTI), in which the rate of molecular water diffusion can be used to identify the orientation and “integrity” of white matter microstructure (e.g., axonal size and density, degree of myelination, coherence of fiber orientation; Beaulieu, 2002; Le Bihan, 2003). Using ultra-high in-plane resolution DTI (hrDTI), we previously calculated perforant path integrity as the amount of diffusion signal parallel to an anatomically-constrained prototypical perforant path within

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parahippocampal white matter (Yassa, Mattfeld, Stark, & Stark, 2011; Yassa, Muftuler, & Stark, 2010). In healthy older adults, this measure of perforant path integrity was positively related to a behavioral index of pattern separation (i.e., mnemonic discrimination; Yassa et al., 2011), measured as the ability to discriminate highly similar lure objects from repeated objects in the Mnemonic Similarity Task (MST; Kirwan & Stark, 2007; Stark, Yassa, Lacy, & Stark, 2013). More recently, we used normal resolution DTI to show that integrity of the fornix (identified using traditional tractography methods) was also related to mnemonic discrimination (measured using the MST) in adults across the lifespan (Bennett, Huffman, & Stark, 2014).

The current study aimed to assess the specificity of the perforant path integrity–mnemonic discrimination relationship relative to other cognitive constructs and white matter tracts in 112 healthy adults (20–87 years). In addition to using measures of mnemonic discrimination from the MST for comparisons to our earlier work, mnemonic and executive functioning constructs were identified using a Principal Components factor analysis of thirteen MST and neuropsychological test measures. Furthermore, we introduce a novel method for assessing tract integrity, in which integrity metrics (diffusion, anisotropy) were calculated from fibers identified as running parallel to a prototypical tract orientation, after estimating multiple (two) fiber populations per voxel. This is especially important for the perforant path whose smaller fibers traverse parahippocampal white matter, which is primarily comprised of the hippocampal cingulum. It is predicted that perforant path integrity will be particularly sensitive to the factor capturing mnemonic discrimination. The mnemonic discrimination factor is also expected to relate to integrity of addition MTL tracts (fornix), but not the non-MTL control tract (corpus callosum).

2. Method

2.1. Participants

A lifespan sample of 112 healthy adults aged 20–87 years (51.7 ± 19.0 years, 69 female) were recruited from the University of California, Irvine and nearby Orange County communities. Prior to participation, all individuals were screened for health conditions that may interact with their neurological status (e.g., dementia, stroke, etc.), use of psychoactive medication (e.g., neuroleptics, sedatives, etc.), and contraindications for magnetic resonance imaging (MRI) scanning (e.g., having ferrous metal implants, being claustrophobic). All participants provided informed consent and were compensated for their time. The University of California, Irvine Institutional Review Board approved the experimental procedures.

2.2. Imaging data acquisition

Participants were scanned using a Philips Achieva 3.0 Tesla MRI system with an eight channel SENSE receiver head coil. Fitted padding was used to minimize head movements.

Twelve ultra-high in-plane resolution diffusion weighted echo planar imaging runs were acquired using the following parameters: TR/TE = 2717/67 ms, flip angle = 90°, SENSE factor = 2.5, FOV = 59 × 170 × 170 mm, 15 coronal slices, and 0.664 × 0.664 × 3 mm spatial resolution with 1 mm gap. Each run contained a single non-diffusion weighted volume ($b = 0$) and 32 volumes with diffusion weighting ($b = 1200$ s/mm²) applied in non-collinear directions. An ultra-high in-plane resolution T2 weighted fast spin echo scan was also acquired using identical parameters, except TR/TE = 3000/80 ms and no SENSE factor was

applied. Both the DTI and T2 scans were centered and oblique oriented along the length of the hippocampus.

2.3. Imaging data analysis

2.3.1. Preprocessing

Diffusion weighted data were pre-processed separately for each participant. To correct for head movement, diffusion weighted volumes with the same gradient direction were aligned across runs and then aligned to the first non-diffusion weighted volume using Advanced Normalization Tools (ANTS; Avants, Tustison, & Song, 2009). A single diffusion tensor model, adjusted for slice angulation and other imaging settings (e.g., gradient overplus, slice orientation, patient orientation, etc.; Farrell et al., 2007), was then independently fit to each voxel using FMRIB Software Library's (FSL) dtifit (Behrens et al., 2003), with a binary mask limiting tensor fitting to brain space. For each voxel, the modeled tensor was characterized by a primary, secondary, and tertiary diffusion direction. Dtifit provided separate output files for the vectors (eigenvectors: V1, V2, V3) and rates of diffusion (eigenvalues: L1, L2, L3) corresponding to these modeled tensor directions, as well a voxel-wise map of FA.

Given our interest in parahippocampal white matter that contained more than one fiber population (i.e., the perforant path and hippocampal cingulum), two diffusion tensor models were estimated for each voxel using FSL's bedpostx (Behrens et al., 2003). The output of bedpostx included vectors indicating the mean diffusion direction of primary (dyads1, DY1) and secondary (dyads2_thr0.05, DY2) fibers within each voxel (see Fig. 1).

2.3.2. Tract isolation

The likelihood that a modeled fiber was part of a given tract was assessed by calculating the dot product between the prototypical tract (PT) and the modeled fiber vectors (DY) for each voxel using the following equation: $PT \cdot DY = |(X_{PT} \times X_{DY}) + (Y_{PT} \times Y_{DY}) + (Z_{PT} \times Z_{DY})|$. These calculations were conducted separately for each prototypical tract (perforant path, PP; hippocampal cingulum; fornix; corpus callosum), in the left (l) and right (r) hemisphere for bilateral tracts, and for the primary (DY1) and secondary (DY2) modeled fiber vectors (e.g., lPP-DY1, rPP-DY1, lPP-DY2, and rPP-DY2 for the perforant path).

The prototypical perforant path (PP) was hypothesized to run at a 45° angle within coronal slices (i.e., from entorhinal cortex to the subiculum; see Fig. 1), which corresponds to $X_{PP} = 0.5$, $Y_{PP} = 0$, and $Z_{PP} = 1$ for the left perforant path, and $X_{PP} = 0.5$, $Y_{PP} = 0$, and $Z_{PP} = -1$ for the right perforant path. Fibers most consistent with the perforant path were isolated by thresholding PP-DY at 50% of the maximum value (0.56).

For bilateral hippocampal cingulum and fornix, the prototypical tracts were hypothesized to run through-plane within coronal slices (i.e., 0° angle from anterior to posterior MTL and fornix body, respectively), which corresponds to $X_{PT} = 0$, $Y_{PT} = 1$, and $Z_{PT} = 0$. The prototypical corpus callosum (CC) was hypothesized to run through-plane within sagittal slices (i.e., 0° angle from left to right), which corresponds to $X_{CC} = 1$, $Y_{CC} = 0$, and $Z_{CC} = 0$. Fibers most consistent with these larger tracts were isolated by thresholding PT-DY at 90% of the maximum value (0.90).

After identifying voxels that survived PT-DY thresholding, the tracts were further limited to standard anatomical masks (JHU-ICBM-labels-1 mm) that were aligned to each participants' diffusion space via the high-resolution T2 image. The same standard hippocampal cingulum mask was used for the perforant path and hippocampal cingulum. Non-white matter voxels were then excluded by thresholding FA maps at 0.2, as were the two most anterior and posterior slices (due to scanner-related distortions).

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