Structural connectivity between the memory and oculomotor systems changes with age

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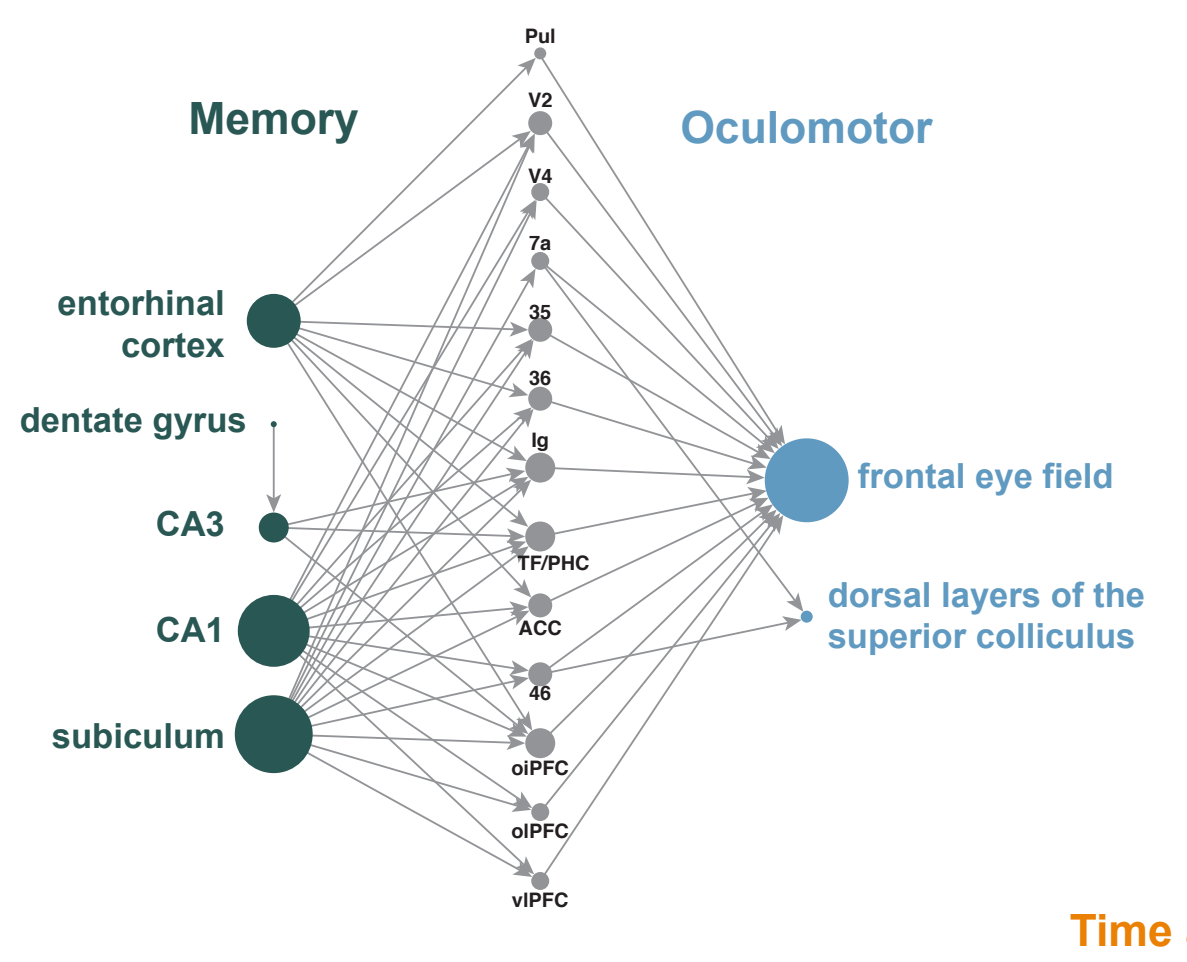
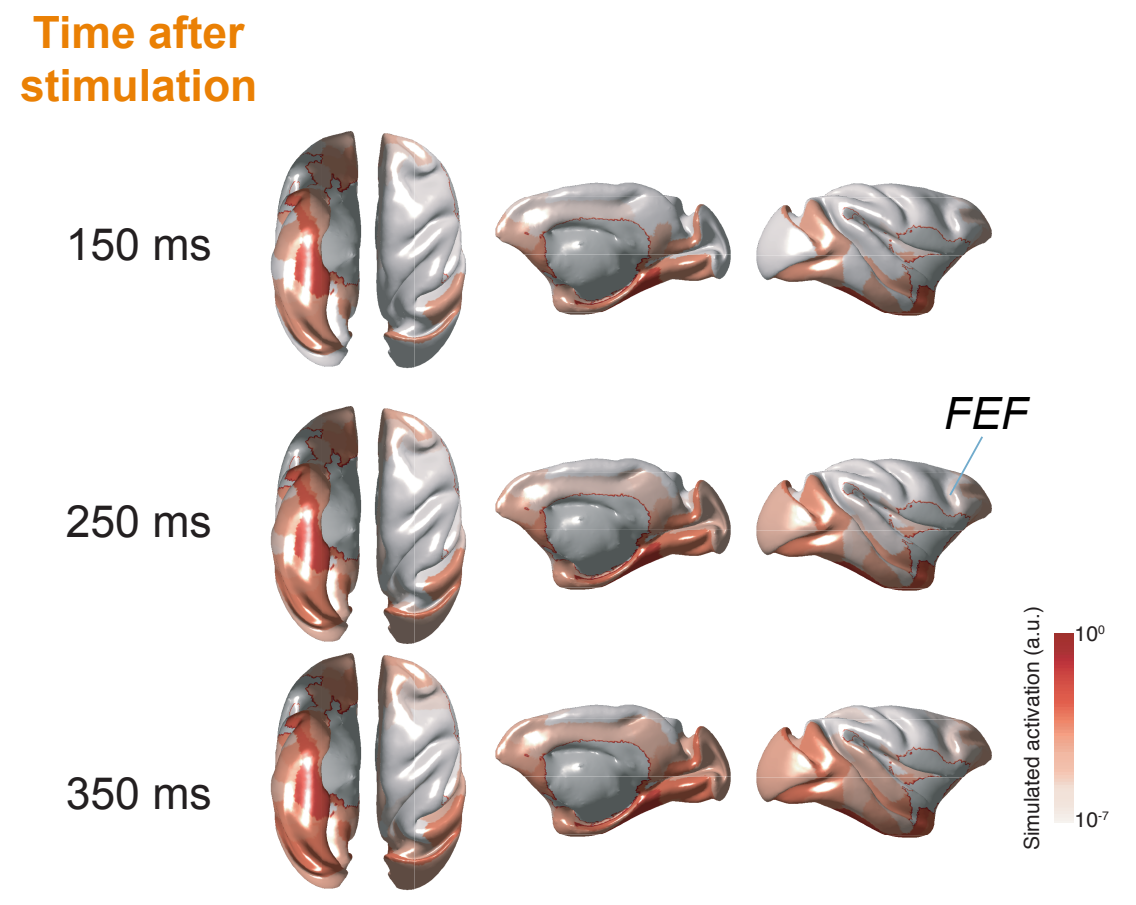
INTRODUCTION

Memories influence how we view the world by guiding our eye movements. Investigations of structural connectivity (SC) in macaques suggest that memory-guided eye movements may be mediated by indirect anatomical connections between the memory and oculomotor systems [1]. Simulations that track activity dissipation from memory system regions provide additional support for the involvement of a network that bridges the memory and oculomotor systems [2].



left: Shortest paths *from* hippocampal subregions *to* oculomotor control areas in the macaque. No direct anatomical connections are known to exist from hippocampus to oculomotor control areas in the macaque. Instead a set of polysynaptic pathways may mediate their interactions. Figure adapted from [1].



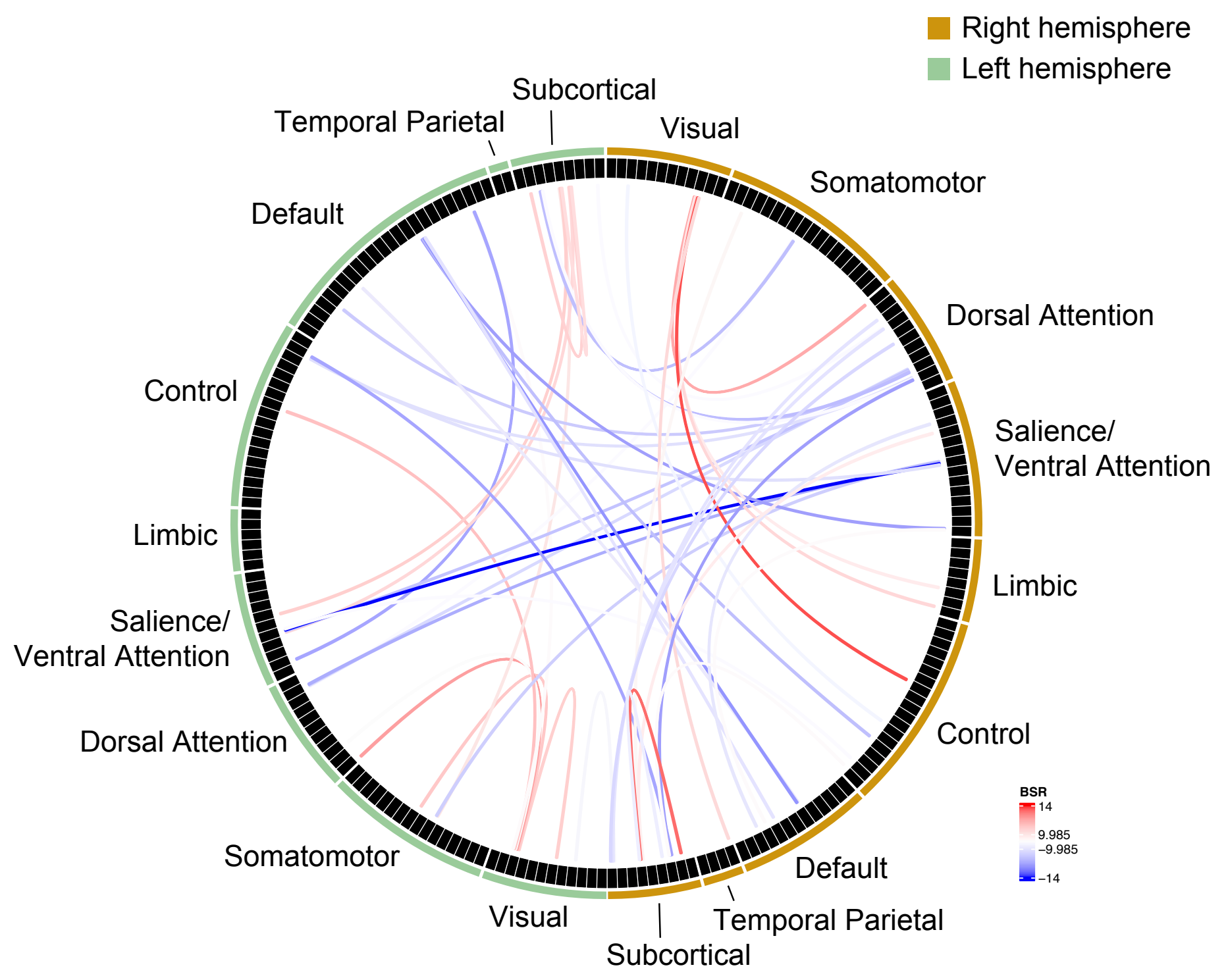
right: Simulations in TheVirtualBrain of a macaque cortical network suggested that activity from hippocampal subregions could reach frontal eye fields (FEF) inside the time it takes to generate a saccade. The example here shows dissipation of activity following stimulation of CA1. Figure adapted from [2].

SC between the memory and oculomotor systems has yet to be examined in humans. Of particular interest are the connections between hippocampus (HC) and the frontal eye fields (FEF), regions critical to memory processing and oculomotor control, respectively. To address this gap, we examined the SC between the HC and FEF in humans.

Memory-guided visual behavior also changes with age and may be due to concomitant changes in SC between the memory and oculomotor systems. We also examined whether there are age-related changes in the SC between HC and FEF with age.

RESULTS

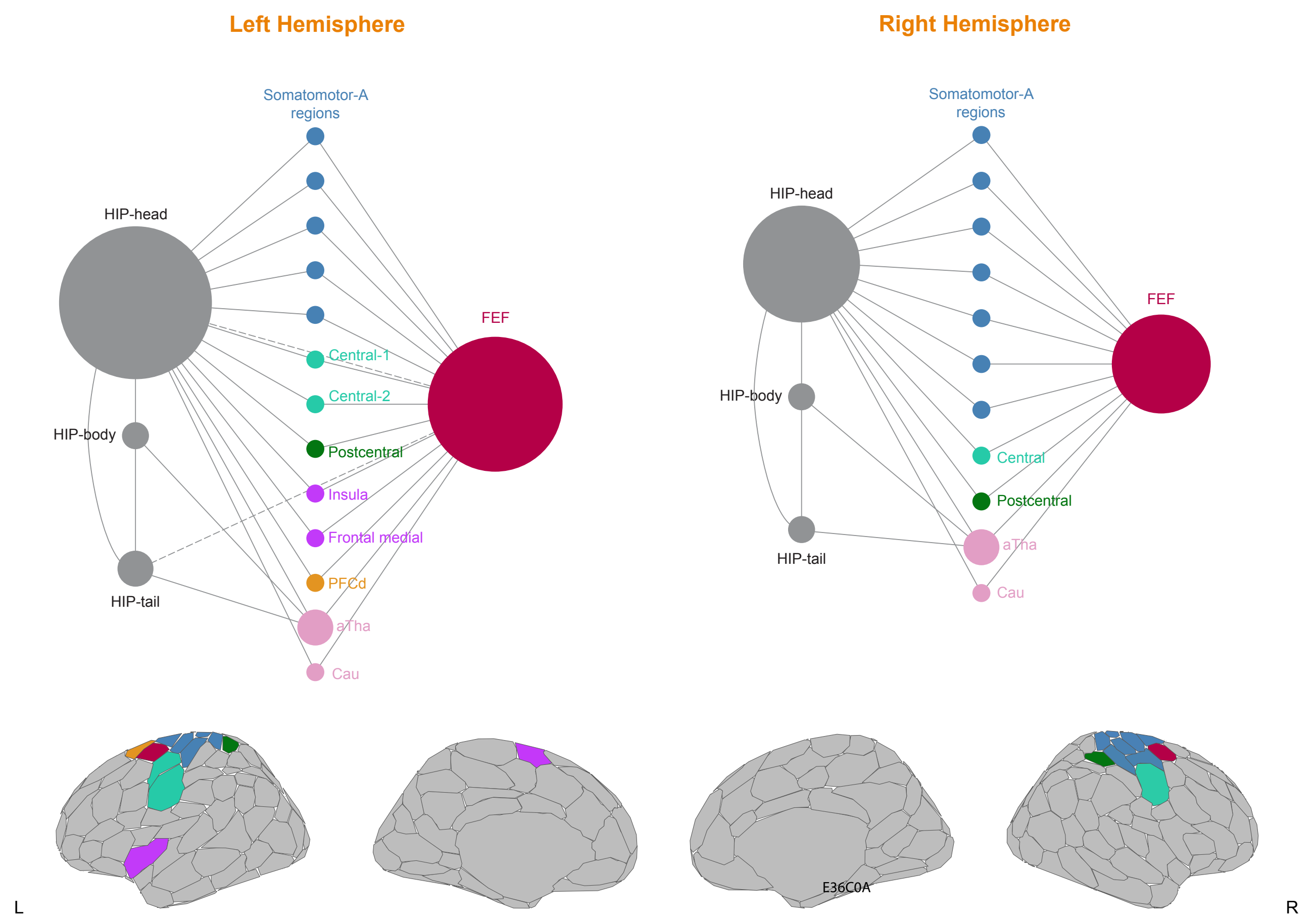
1. Whole-brain structural connectivity in the Cam-CAN cohort changes with age



Using all available Cam-CAN data, a multivariate PLS analysis showed a change in connectivity strength with age ($r = 0.82$; $p < 0.001$). Intrahemispheric connections were both strengthened (*red*; 53.0% of changed connections) and weakened (*blue*; 47.0%) with increasing age. Interhemispheric connections that varied with age were nearly all weakened (85.3%).

The 50 most reliable connections are visualized above. BSR: bootstrap ratio. Cortical region labels follow the resting-state networks named in [6].

2. A network of regions may mediate the interactions between HC and FEF in humans

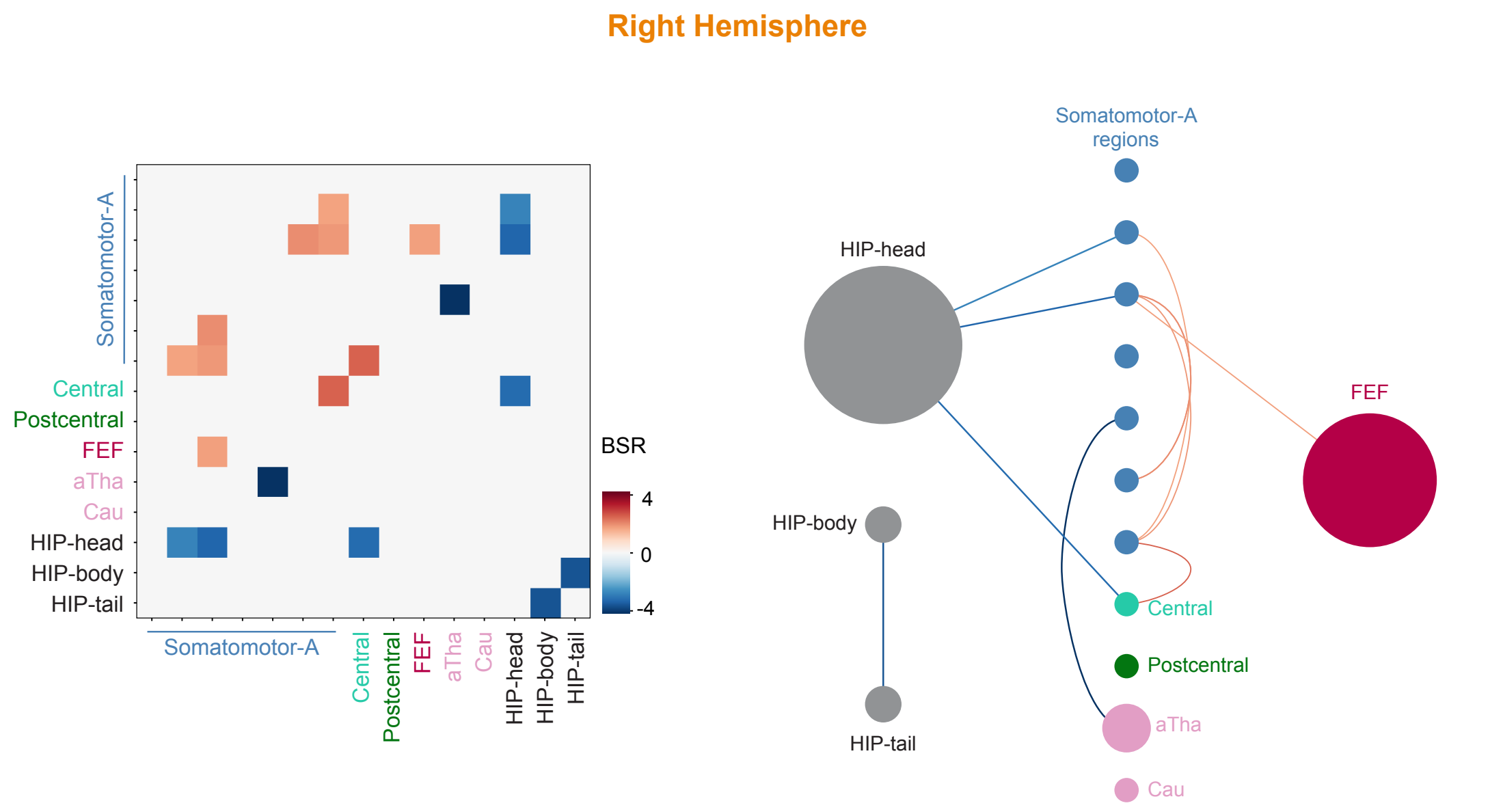


top: Using data from the manually-QC'd younger group, we identified a network of regions connecting the hippocampus and FEF in humans. These pathways involved somatomotor regions, central regions, insula, frontal medial cortex, dorsal prefrontal cortex, anterior thalamus, and caudate. Node size is scaled by node degree. Connections between the intermediary regions are not depicted.

bottom: Cortical intermediary regions are depicted on the brain surface. Regions are coloured by resting-state network assignment [6] and match those from the top figures. Subcortical regions are not depicted.

There was a weak but consistent direct connection between HC and FEF in the left hemisphere. However, the FEF parcels we used, especially in the left hemisphere, may extend into dlPFC.

3. Structural connectivity of the HC-FEF network changes with age



Using only data from the manually QC'd subset, multivariate PLS analyses revealed one significant latent variable for the right hemisphere showing a difference in SC between the younger and older groups ($p = 0.005$). A weakening of connections (*blue*) was observed between the HIP-head and intermediary regions, while a strengthening connections (*red*) occured among somatomotor regions and FEF. Only reliable changes (bootstrap ratios ≥ 2 or ≤ -2) are depicted in the figures above.

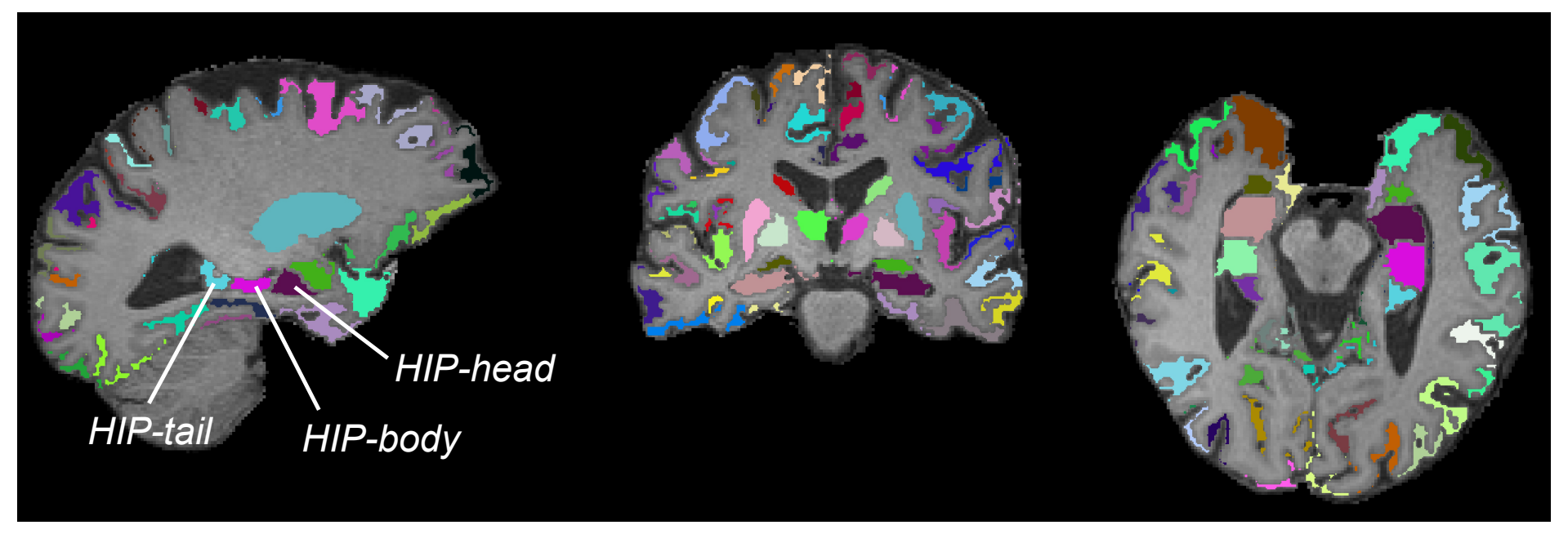
No significant differences between the younger and older groups were detected in the left hemisphere.

METHODS // MATERIALS

Whole-brain structural connectivity was estimated using diffusion-weighted imaging data from the Cambridge Centre for Aging and Neuroscience cohort (18-87 years, N = 628) [3]. Fibre orientations were modelled using FSL's *bedpostx* tool and probabilistic tractography was performed using *probtrackx* as we have previously described [4,5]. SC was calculated as the probability of connection (or 'weights') between 218 regions of interest (200 cortical [6], 18 subcortical [7]).

Quality Assurance of Hippocampal Segmentations

A subsample of the Cam-CAN cohort was pseudorandomly selected for manual quality control (QC) checks. 40 participants (20 female) from the youngest two deciles and 40 participants (20 female) from the oldest two deciles were selected.These two subsets were considered the «younger» and «older» groups, respectively. Two expert raters (NMZ & AK) visually inspected the parcellation of hippocampus into three subregions (HIP-head, HIP-body, HIP-tail) as well as the parcellation of parahippocampal gyrus and assigned a score ranging from 1 (perfect, or near-perfect parcellation) to 5 (completely incorrect parcellation). Data were excluded from further analysis if scores were ≥4. The remaining sample consisted of 34 younger (18-36 years, mean: 27.8, sd: 5.6) and 26 older (69-87 years, mean: 77.8, sd: 5.2) participants.



right: An example Cam-CAN participant from the older group with well-segmented hippocampal subregions.

Network Analyses & Statistical Modelling

The *Brain Connectivity Toolbox* [8] was used to identify the shortest paths between HC and FEF in the manually-QC'd younger subsample [Result #2]. A multivariate Partial Least Squares analysis [9] was performed to relate SC with age in both the full sample and whole-brain connectome [Result #1], as well as the manually-QC'd subset's subnetwork of regions connecting HC and FEF [Result #3]. Statistical significance was determined using permutation tests (1000 permutations) and reliability of the detected patterns was estimated by bootstrap sampling (500 bootstraps).

DISCUSSION

Our findings show that, in humans, the HC and FEF are structurally connected via a set of polysynaptic pathways. Unlike in the macaque, there was a weak direct connection in our sample between the hippocampus (head and tail) and the FEF. The directionality of this connection cannot be inferred from tractography. The FEF parcels in our study, especially that in the left hemisphere, may include some dlPFC. A larger sample, and a more robust definition of FEF, will help elucidate whether species differences exist in the network that bridges the memory and oculomotor systems.

Our findings also show that, with increasing age, connections between the HC and intermediary regions weaken while those between the intermediary regions and FEF strengthen. This is consistent with the shift away from hippocampally-mediated viewing with age [10].

These anatomical connections offer a potential neural substrate for the interaction between the memory and oculomotor systems, and for the declining influence of memory on viewing with age.

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