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Differential effect of age on posterior and anterior hippocampal functional connectivity

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ABSTRACT

Aging is associated with declines in cognitive performance and multiple changes in the brain, including reduced default mode functional connectivity (FC). However, conflicting results have been reported regarding age differences in FC between hippocampal and default mode regions. This discrepancy may stem from the variation in selection of hippocampal regions. We therefore examined the effect of age on resting state FC of anterior and posterior hippocampal regions in an adult life-span sample. Advanced age was associated with lower FC between the posterior hippocampus and three regions: the posterior cingulate cortex, medial prefrontal cortex, and lateral parietal cortex. In addition, age-related reductions of FC between the left and right posterior hippocampus, and bilaterally along the posterior to anterior hippocampal axis were noted. Age differences in medial prefrontal and inter-hemispheric FC significantly differed between anterior and posterior hippocampus. Older age was associated with lower performance in all cognitive domains, but we observed no associations between FC and cognitive performance after controlling for age. We observed a significant effect of gender and a linear effect of *COMT* val158met polymorphism on hippocampal FC. Females showed higher FC of anterior and posterior hippocampus and medial prefrontal cortex than males, and the dose of val allele was associated with lower posterior hippocampus – posterior cingulate FC, independent of age. Vascular and metabolic factors showed no significant effects on FC. These results suggest differential age-related reduction in the posterior hippocampal FC compared to the anterior hippocampus, and an age-independent effect of gender and *COMT* on hippocampal FC.

Introduction

Advanced age is associated with low performance on multiple cognitive tasks (Salthouse, 2010), and magnetic resonance imaging (MRI) has been used to explore the neural correlates of this cognitive decline (for example: (Grady, 2012; Gunning-Dixon and Raz, 2000; Raz et al., 1998)). Numerous brain characteristics, such as regional brain volumes, structural and diffusion properties of the white matter and task-related activation, exhibit significant age differences and have been linked to cognitive performance, see (Fjell et al., 2014; Kennedy and Raz, 2015) for reviews. Since the introduction of MRI measures of resting brain activity (resting state MRI or rsMRI; (Biswal et al., 1995; Raichle et al., 2001)), various measures of functional connectivity within and among brain networks have been used to assess age-related differences on a brain network level.

The core assumption behind applying functional connectivity measures to the study of cognitive aging is that even subtle disruption of physical connections and relatively minor damage to the brain's regional integrity may affect the flow of information across the brain, which can manifest their effect in age-related differences in functional connectivity (Ferreira and Busatto, 2013). Measures of resting state functional connectivity reflect coherence between temporal fluctuations in the blood oxygen level dependent (BOLD) signal across brain regions organized into distinct networks (Damoiseaux et al., 2006; van den Heuvel et al., 2008; Zuo et al., 2010).

In the extant studies of age-related differences in resting state functional connectivity, the most consistent finding is the association between advanced age and lower functional connectivity within the default mode network (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Ferreira and Busatto, 2013). Default mode network activity is commonly linked to a variety of cognitive processes such as episodic memory, self-referential processing, and mind wandering (Buckner et al., 2008; Raichle et al., 2001), with a positive relationship reported between strength of default mode connectivity and performance on tasks of memory and executive function (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Wang et al., 2010).

Even though both independent component analysis (ICA) and seed-based analyses of the default mode network have consistently revealed age-related differences in functional connectivity, there is no consensus regarding the role of the hippocampus within the default mode

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network. Consequently, age-related differences in hippocampal functional connectivity remain unclear. Some studies examining age effects on default mode connectivity did not include the hippocampus (Bluhm et al., 2008; Damoiseaux et al., 2008), while others varied considerably in the exact demarcation of the region in question. For example, some (Andrews-Hanna et al., 2007) found lower connectivity in older adults in a posteriorly hippocampal region of interest (ROI), whereas others found either no significant connectivity differences (Koch et al., 2010) or increased functional connectivity (Salami et al., 2014) with older age in more anteriorly located ROIs. These discrepancies in reported findings may, at least partly, be explained by differences in hippocampal ROI selection, since hippocampal connectivity patterns are known to vary across hippocampal regions (Kahn et al., 2008; Zarei et al., 2013). The posterior hippocampus is part of the functional pathway that, via the cingulum bundle, connects to parahippocampal, retrosplenial, posterior cingulate, precuneus, lateral parietal and medial prefrontal cortices—all areas of the default mode network. In contrast, the anterior hippocampus belongs to the functional pathway that via the uncinate fasciculus is connected with the amygdala, perirhinal/entorhinal cortices, and the anterior and lateral temporal lobes (Kahn et al., 2008; Poppenk and Moscovitch, 2011; Ranganath and Ritchey, 2012).

The main goal of this study is to address these discrepancies by determining the effect of age on posterior versus anterior hippocampal functional connectivity to default mode brain regions, and the relationship with cognitive performance, in an adult life-span sample. Based on the extant research outlined above, we hypothesized lower functional connectivity of the posterior hippocampus with older age, and either no age-related differences (Koch et al., 2010) or an increase in connectivity with age (Salami et al., 2014) for the anterior hippocampus.

As characteristics of participants vary across studies, another potential source of discrepancy among studies could be unaccounted variability in the samples with regards to gender, vascular risk burden and genetic risk factors, all of which can affect brain structure and function (Ferreira and Busatto, 2013; Jagust, 2013; Raz and Rodrigue, 2006). Thus, an additional, exploratory aim of this study was to determine the effect of several age-related and age-independent risk factors on hippocampal functional connectivity and cognitive performance. Among the former are risk factors such as vascular and metabolic risk (Friedman et al., 2014; Zhou et al., 2010) whereas the latter include gender and genetic variants that are associated with risk for age-related cognitive and physiological impairments, such as Alzheimer's disease, diabetes, inflammation and probable dopamine availability in the synapse (for examples see (Barnett et al., 2008; Damoiseaux et al., 2012)).

Methods

Participants

Adult volunteers were recruited from the Metro Detroit, Michigan area through advertisements in local newspapers and flyers for an ongoing longitudinal study of cognitive and neural correlates of aging. Structural and functional MRI data were available on 167 adults (60 men, 107 women) age 18–83 years (mean age 49.1 ± 18.0 years). A subset of this sample, 91 adults aged 18–78 years (mean age 42.2 ± 17.6 years; 33 men, 58 women), completed cognitive testing. The Wayne State University Institutional Review Board approved the study and signed informed consent was obtained from all participants. Participants spoke English as their first language and were right-hand dominant (score over 75% on Edinburgh Inventory, (Oldfield, 1971)). They were screened with a health questionnaire for neurological, psychiatric, cardiovascular, and endocrine diseases, diabetes, cancer, and a history of loss of consciousness for more than 5 min. In addition, participants were screened for dementia (Mini-Mental State Exam, MMSE ≥ 26; (Folstein et al., 1975)) and depression (Center for Epidemiological Study Depression questionnaire, CES-D ≤ 16; (Radloff, 1977)). There was no relationship between age and MMSE ($r = -0.053$, $p = 0.498$), but older participants had more years of formal education ($r = 0.173$, $p = 0.025$).

Data acquisition

MRI data

Imaging was performed at the MRI research facility at Wayne State University on a 3-Tesla Siemens Verio (Siemens Medical AG, Erlangen, Germany) full-body magnet with a 12-channel head coil. The scan session included resting state functional MRI and anatomical MRI. For the resting state functional scan, 200 volumes of 43 axial slices were acquired sequential using a T2*-weighted echo planar sequence with the following parameters: repetition time (TR) = 2500 ms, echo time (TE) = 30 ms, flip angle = 90°, pixel bandwidth = 2298 Hz/pixel, GRAPPA acceleration factor PE = 2, field-of-view = 210 mm, matrix size = 64 × 64, and voxel size = 3.3 × 3.3 × 3.3 mm. Participants were instructed to lie still with their eyes open. For the anatomical scan a 3D T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence was acquired with the following parameters: TR = 1680 ms, TE = 3.51 ms, inversion time (TI) = 900 ms, flip angle = 9.0°, pixel bandwidth = 180 Hz/pixel, GRAPPA acceleration factor PE = 2; field-of-view = 256 mm, matrix size = 384 × 384, and voxel size 0.67 mm × 0.67 mm × 1.34 mm.

Cognitive data

Cognitive performance was assessed using a comprehensive battery of cognitive tests, including: letter comparison, pattern comparison, Woodcock-Johnson-R Memory for Names (immediate and delayed); Stroop, Wisconsin Card Sorting Test (WCST), size judgment span, listening span, spatial recall, and Cattell Culture Fair Test (see (Raz et al., 2009), for a detailed description of the cognitive battery).

Vascular and metabolic risk data

We collected common indicators of vascular and metabolic risk: blood pressure, frequency of exercise, smoking, and waist-to-hip ratio. In addition, a phlebotomist collected blood samples from all participants following a 12-h overnight fast. The Detroit Medical Center hospital laboratory analyzed these samples to determine levels of cholesterol, glucose and triglycerides.

Genetic data

DNA extraction and genotyping were performed on material obtained from buccal cell cultures that were collected in mouthwash samples. DNA was isolated with Gentra Autopure LS under the standard buccal cell protocol. The Wayne State University Applied Genomics Technology Center performed DNA isolations and genotyping assays using an Applied Biosystems 7900. DNA sequencing reactions were carried out using the 0.5X protocol for ABI PRISM BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems). The sequencing extension products were purified utilizing Sephadex, and analyzed on an ABI PRISM 3700 DNA analyzer with a 50-cm capillary array. Genetic variants associated with increased risk for Alzheimer's disease, diabetes, synaptic dopamine degradation and pro-inflammatory response were determined, including: *APOE*, *CLU*, *TOMM157580*, *TOMM157581*, *TOMM207*, *TOMM5900*, *GCK*, *G6PC2*, *G6PC2*G231A, *TCF7L2*, *IL-1β* C-511T, *IL*-6 C-174G and *TNFα* G308A, and *COMT* val158met.

Data analysis

MRI data

Image preprocessing was carried out using tools from FMRIB's Software Library (FSL, version 4.1; (Smith et al., 2004)). For the resting state data the following pre-statistics processing was applied: motion correction (Jenkinson et al., 2002); removal of non-brain structures (Smith, 2002); spatial smoothing using a Gaussian kernel of 6 mm full width