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Increased sensitivity to age-related differences in brain functional connectivity during continuous multiple object tracking compared to resting-state

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A B S T R A C T

Age-related differences in cognitive agility vary greatly between individuals and cognitive functions. This heterogeneity is partly mirrored in individual differences in brain network connectivity as revealed using resting-state functional magnetic resonance imaging (fMRI), suggesting potential imaging biomarkers for age-related cognitive decline. However, although convenient in its simplicity, the resting state is essentially an unconstrained paradigm with minimal experimental control. Here, based on the conception that the magnitude and characteristics of age-related differences in brain connectivity is dependent on cognitive context and effort, we tested the hypothesis that experimentally increasing cognitive load boosts the sensitivity to age and changes the discriminative network configurations. To this end, we obtained fMRI data from younger (n=25, mean age 24.16 ± 5.11) and older (n=22, mean age 65.09 ± 7.53) healthy adults during rest and two load levels of continuous multiple object tracking (MOT). Brain network nodes and their time-series were estimated using independent component analysis (ICA) and dual regression, and the edges in the brain networks were defined as the regularized partial temporal correlations between each of the node pairs at the individual level. Using machine learning based on a cross-validated regularized linear discriminant analysis (rLDA) we attempted to classify groups and cognitive load from the full set of edge-wise functional connectivity indices.

While group classification using resting-state data was highly above chance (approx. 70% accuracy), functional connectivity (FC) obtained during MOT strongly increased classification performance, with 82% accuracy for the young and 95% accuracy for the old group at the highest load level. Further, machine learning revealed stronger differentiation between rest and task in young compared to older individuals, supporting the notion of network dedifferentiation in cognitive aging. Task-modulation in edgewise FC was primarily observed between attention- and sensorimotor networks; with decreased negative correlations between attention- and default mode networks in older adults. These results demonstrate that the magnitude and configuration of age-related differences in brain functional connectivity are partly dependent on cognitive context and load, which emphasizes the importance of assessing brain connectivity differences across a range of cognitive contexts beyond the resting-state.

Introduction

Individual life-span trajectories in brain and cognition are shaped by a dynamic interplay between genetic and environmental factors (Lindenberger, 2014). Aging confers a notable increase in inter-individual variability in cognitive functions (Buckner, 2004; Singh-Manoux et al., 2012), and developing sensitive and specific *in vivo* biomarkers for identification of individuals at risk for cognitive impairment and dementia is a key challenge for clinical neuroscience.

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The brain is intrinsically organized into neuronal networks or nodes of which continuous cross-talk enables cognition and complex behaviors (Sporns et al., 2004). Functional connectivity (FC) measured by functional magnetic resonance imaging (fMRI) refers to the synchronization between nodes, reflecting an organizational principle of the brain (Van Den Heuvel and Pol, 2010). In line with this system-level view of brain function, aging studies converge on less specialized and segregated brain networks, supporting the theory of cognitive and neuronal dedifferentiation in aging (Baltes and Lindenberger, 1997; Chan et al., 2014; Daselaar et al., 2005; Lindenberger, 2014; Park et al., 2012).

Age-related FC differences have been extensively studied, implicating a range of networks including the executive control (ECN), dorsal attention (DAN), default mode (DMN), frontoparietal (FPN) and hippocampal networks (Salami et al., 2014; Voss et al., 2010; Zhang et al., 2014), and links between DMN connectivity and cognitive aging (Andrews-Hanna et al., 2007; Sambataro et al., 2010) corroborate the notion of network-level vulnerability to advancing age (Mowinckel et al., 2012; Salami et al., 2012).

In line with the selective vulnerability of brain networks, age-related cognitive decline is not uniform across domains (Glisky, 2007). Whereas crystallized functions including vocabulary and general knowledge remain relatively unaffected, a commonly reported impairment relates to deficient selective attention (Quigley and Müller, 2014) which manifests as reduced ability to selectively attend to and ignore information based on relevance (Kensinger and Corkin, 2009; Murray and Kensinger, 2012). Whereas resting-state fMRI has provided an opportunity to test specific hypotheses regarding the underlying brain connectivity alterations, the selective cognitive vulnerability suggests that attention-demanding tasks may comprise a more sensitive and informative context for the study of age-related brain network alterations. Thus, in order to characterize the brain functional connectomic signature of cognitive aging in different cognitive contexts, we compare fMRI brain connectivity indices obtained during rest and during two load levels of a continuous multiple object tracking (MOT) task (Pylyshyn and Storm, 1988) between young and older healthy adults.

MOT requires the subject to attend to multiple target items as they move among distractor items, which is a basic feature of sustained multifocal visual attention (Cavanagh and Alvarez, 2005). Alnæs et al. (2015) reported widespread connectivity modulations during MOT in young adults, and machine learning revealed high classification accuracy when discriminating between task and rest, demonstrating successful decoding of cognitive load using FC features. Here, we utilize a similar decoding approach to describe the neuronal characteristics of cognitive aging by comparing two groups of healthy adults at both ends of the adult lifespan. We hypothesized that (1) multivariate classification would yield robust discrimination between resting state and data collected during MOT as well as between younger and older adults, reflecting age and cognitive context related changes in brain network configuration. Higher task classification accuracy in young compared to older adults would support the notion of cognitive and neuronal dedifferentiation in aging. Additionally, we anticipated stronger group differences with higher load, resulting in improved group classification with increasing load. On edge-level, we hypothesized (2) that the most discriminative edges for rest and task are found in connections between attention networks and somatosensory and motor nodes (Alnæs et al., 2015; Tomasi et al., 2014). With regards to age-related edgewise effects in response to attentional demand and keeping with the theory of dedifferentiation, we hypothesized a system-level loss in network segregation, reflected in decreased FC within modular networks and in particular within the DMN as well as increased connectivity between large-scale brain networks, in particular during continuous tracking, which would support a relative inability to selectively inhibit competing neural processes during task engagement.

Finally, since any effects on edgewise functional connectivity may be partly driven by nodal increases or decreases in activity, we probe temporal variability on node level by computing the standard deviation of signal amplitude (SDSA) (Garrett et al., 2010). Brain signal variability has been shown to reveal distinct patterns not captured by mean-based analyses (Garrett et al., 2011), and increased signal variability is thought to be indicative of a more sophisticated and complex neural machinery (McIntosh et al., 2008), offering greater dynamic range and facilitating the brain's ability to explore different network states. When applied to aging studies, reduced SDSA has proved to be a better predictor of advancing age and poorer task performance than the mean measure (Grady and Garrett, 2014). Additionally, in a study investigating age-related variability changes in response to cognitive demand, Garrett et al. (2012) observed a broad increase in SDSA on task compared to fixation for both age groups, the magnitude and spatial extent of this variability increase was comparatively reduced for the older group. Based on this, we hypothesize (3) task related modulations of signal variability that is network selective, reflected in increased and decreased SDSA in task-positive and task-negative/irrelevant networks, respectively. Further, reflecting reduced dynamic repertoire in response to cognitive state-transition, we anticipate group differences in signal variability manifested as diminished task-related SDSA changes for older compared to younger adults.

Materials and methods

Sample

We recruited 26 young and 26 older adults through a newspaper ad and social media. The sample is overlapping with a previous publication (Dørum et al., 2016) reporting results from the blocked MOT runs (see below). All subjects provided an informed consent and underwent neuropsychological screening (details below). Participants reported normal or corrected-to-normal vision. Exclusion criteria included estimated IQ < 70, previous history of alcohol- and substance abuse, history of neurologic or psychiatric disease, medications significantly affecting the nervous system and counter indications for MRI. All participants were self-sufficient and living independently, and reported no reason to suspect marked cognitive decline or undiagnosed dementia.

From the full dataset, we excluded participants due to excess in-scanner motion where image artifacts persisted after running FSL FIX (FMRIB's ICA-based Xnoiseifier) (n=2), as well as due to chance-level or below-chance level performance on the one load condition MOT task (n=3), yielding a final sample of 47 subjects, including 25 young (mean age: 24.2 years, SD: 5.1, 68% females) and 22 old individuals (mean age: 65.1, SD: 7.5, 55% females).

Screening and neuropsychological assessment

Participants completed the matrices and vocabulary subtests from the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). Results from the subtests were converted to standardized scores from which full scale IQ (FSIQ) was estimated. Two subjects were native foreign language speakers and thus not adequately able to perform the vocabulary subtest, and their FSIQ was calculated based on matrix reasoning.

fMRI paradigms

All participants underwent one resting state run and two versions of MOT, including one blocked and two continuous tracking runs, performed in the MRI scanner during the same session (Alnæs et al., 2015). Here we report data from the continuous MOT runs (Supplementary material). The level of attentional demand was set at two load conditions – load 1 (L1) and load 2 (L2) requiring the participants to track one or two targets respectively during the task. We restricted the load level to a maximum of 2 to ensure that both groups were able to perform at a high level.