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Older but still fluent? Insights from the intrinsically active baseline configuration of the aging brain using a data driven graph-theoretical approach

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ABSTRACT

A major part of our knowledge about the functioning of the aging brain comes from task-induced activation paradigms. However, the aging brain's intrinsic functional organization may be already a limiting factor for the outcome of an actual behavior. In order to get a better understanding of how this functional baseline configuration of the aging brain may affect cognitive performance, we analyzed task-free fMRI data of older 186 participants (mean age = 70.4, 97 female) and their performance data in verbal fluency: First, we conducted an intrinsic connectivity contrast analysis (ICC) for the purpose of evaluating the brain regions whose degree of connectedness was significantly correlated with fluency performance. Secondly, using connectivity analyses we investigated how the clusters from the ICC functionally related to the other major resting-state networks. Apart from the importance of intact fronto-parietal long-range connections, the preserved capacity of the DMN for a finely attuned interaction with the executive-control network and the language network seems to be crucial for successful verbal fluency performance in older people. We provide further evidence that the right frontal regions might be more prominently affected by age-related decline.

Introduction

The process of growing old is characterized by changes in cognitive performance (Hedden and Gabrieli, 2004; Reuter-Lorenz et al., 2000; Park and Reuter-Lorenz, 2009; Salthouse, 1996; Singer et al., 2003; Spreng et al., 2010a; Turner and Spreng, 2012), which are preceded or accompanied by structural alterations in the brain like progressive gray matter atrophy or loss of white matter integrity (Fjell et al., 2009; Good et al., 2001; Raz et al., 1997; Raz et al., 2005; Salat et al., 2004; Sowel et al., 2003). Functional neuroimaging methods like PET or fMRI were able to introduce another and potentially more optimistic aspect. A number of studies using task-induced fMRI reliably found that older adults often showed different, mainly spatially extended activation patterns but were still able to perform at the same high level as young adults. This observation was interpreted as demonstrating that the aging brain has still preserved a certain degree of functional plasticity. Because of that plasticity it may be able to functionally compensate for already manifest age-related gray matter and white matter degeneration and thus retain the performance level for a time. There exists already a number of theories (HAROLD Cabeza, 2002; PASA Davis et al., 2008; CRUNCH Reuter-Lorenz and Cappell, 2008; STAC Reuter-Lorenz and Park, 2014) that all try to subsume these age-related differences in brain activity observed in a large number of task-induced fMRI studies under an overarching principle.

The majority of studies exploring the activation pattern of the aging brain have used fMRI or PET in the context of task-induced activation paradigms. In this study, we will use task-free fMRI data instead of task-related fMRI because of the following reasons. First, to thoroughly comprehend the meaning of an activation pattern of a brain actively engaged in a demanding task, one has likewise to apprehend the functional starting base of that activity, since our brain is never truly at rest. Even when a person is lying relaxed in the scanner and thinking of nothing in particular, her/his brain is intrinsically highly active, systematically and highly dynamically creating different activity patterns that look very similar to the activation patterns we see in task-induced fMRI paradigms (Cordes et al., 2000; Damoiseaux et al., 2006; De Luca et al., 2006). This dynamic spontaneous connectivity is the functional foundation from which the brain generates goal-oriented behavior and the efficiency of its intrinsic organization may be a limiting factor that determines the outcome of an actual behavior (Sadaghiani and Kleinschmidt,

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2013). Comprehending the specific characteristics of the aging brain's intrinsically active functional baseline might therefore help us to get a better understanding of how it is still able to perform a cognitive demanding task despite structural loss. Second, a further advantage of task-free fMRI is that it allows to avoid potential confounds and limitations encountered in task-based approaches like practice effects or performance anxiety (Simpson et al., 2001). Thirdly, several papers have shown that intrinsic connectivity networks (ICN) are a good predictor for the underlying anatomical network organization (Collin et al., 2014; Kolchinsky et al., 2014; van den Heuvel and Sporns, 2013). Taken together, task-free fMRI provides promising opportunities for investigating the functional topology of the brain and has been widely used to study differences between populations.

Given that healthy aging is associated with a substantial change in verbal fluency, we are interested to examine the potential relationship between the intrinsic functional network structure and verbal fluency proficiency in the aging brain. In particular, we are interested to identify potential compensation or adaption strategies of the aging brain. To that aim we analyzed task-free fMRI data of a large sample of 186 older adults in combination with their verbal fluency data. Several studies have been published so far employing task-induced MRI studying age- and performance-related associations between verbal fluency performance and brain activation patterns (Birn et al., 2010; Destrieux et al., 2012; Fu et al., 2006; Marsolais et al., 2014; Meinzer et al., 2009; Meinzer et al., 2012a; Nagels et al., 2012; Persson et al., 2004; Persson et al., 2007). In these studies young adults generally show a clear leftward activation pattern, encompassing frontal regions like the inferior and middle frontal gyrus, medial frontal gyrus, cingulate cortex and superior temporal gyrus during the performance of verbal fluency tasks (Meinzer et al., 2009). In contrast, older participants recruit not only the right-sided homologs in the middle and inferior frontal gyrus, but additionally activate the left superior frontal gyrus, the right lingual gyrus, and the right precentral gyrus (Meinzer et al., 2009).

Successful performance of tasks of verbal fluency requires the combination of two fundamental cognitive functions, executive-control and language (Shao et al., 2014). The two cognitive functions have quite different trajectories across the life-span. While the perception and production of language are relatively well preserved far into very old age, executive functions are known to suffer from age-related decline earlier in the process (Glisky, 2007). Therefore, the combination of these two cognitive functions makes verbal fluency, i.e. the ability to fluently produce speech while following some production constraints, ideal to gain a better understanding of the mechanisms that allow the aging brain to perform still at a high level but in a different manner from the young brain.

There exist two different forms of verbal fluency: Semantic fluency demands that one fluently names as many words as possible from the same semantic category, e.g. animals or fruits, during a fixed time period. On the other hand, phonemic or lexical fluency requires the tested person to name as many words as possible beginning with the same letter during a fixed period of time. Older participants tend to show significantly worse performance in semantic fluency compared to young adults (Clark et al., 2009). Concerning phonemic fluency, the age-related differences are much less pronounced (Meinzer et al., 2009; Meinzer et al., 2012a; Persson et al., 2004; Persson et al., 2007) although phonemic fluency is always rated as the more difficult task regardless of the participant's age.

In order to be unbiased and receptive to unexpected discoveries, we pursued a purely data driven approach. From previous studies using intrinsic connectivity data we know that one of the aging brain's characteristic features is a general reduction of connectedness, especially the decline or even disruption of long-range connections among regions situated in different brain lobes (Andrews-Hanna, et al., 2007; Meunier et al., 2009). Based on these findings we hypothesized that the preserved degree of connectedness of the brain regions genuinely involved in such a demanding cognitive task like verbal fluency has to be a limiting factor that determines the performance of the old brain. For that reason we performed an Intrinsic Connectivity Contrast (ICC) analysis (Martuzzi et al., 2011). The ICC analysis is based on the graph theoretical concept of “degree” and therefore apt to measure the connectedness of regions. In comparison to other graph theoretical analyses (GTA) it has the advantage that it does not require a priori assumptions about possible regions or networks of interest and works on the single voxel-level so that it is apt to detect very small and unexpected effects. To the best of our knowledge, this study is the first to apply the ICC approach in correlation with cognitive performance in a population of older adults. Finally, for the purpose of relating the regions highlighted by the ICC analysis to other major intrinsic connectivity networks (ICN) and to better understand their meaning in the context of the underlying functional baseline configuration we computed a connectivity analysis.

Methods

Participants

Behavioral and MRI data from 186 older adults (mean age = 70.4; SD = 4.8; 97 females) were taken from the first wave of the LHAB (Longitudinal Healthy Aging Brain) database, which is currently being built at the International Normal Aging and Plasticity Imaging Center (INAPIC, University of Zurich, Switzerland) (Zöllig et al., 2011). Participants were right-handed and native Swiss-German or German speakers. The 12-Item Short-Form Health Survey (SF-12) was administered to assess physical and mental health. The self-reported mean physical health composite score in our sample was 50.8 (SD = 7.2) which is well above the US norm mean of 43.9 (age group between 65 and 74 years). The self-reported mean mental health composite score in our sample was 55.0 (SD = 6.0) which is slightly above the US norm mean of 51.6 points (age group between 65 and 74 years).

Besides the standard exclusion criteria relevant in the context of MRI assessments, the following exclusion criteria were applicable for the current study: (a) history or current diagnosis of psychiatric or neurologic diseases (e.g. Parkinson's disease, Alzheimer's dementia, multiple sclerosis, migraine), (b) an MMSE score of 26 or lower, (c) medical conditions such as diabetes, tinnitus, and diseases of the hematopoietic system.

All participants gave informed consent for participation of the longitudinal project under the approval of the local ethics committee and in accordance with the declaration of Helsinki.

At the first time-point of data collection in 2011, 230 older adults were enrolled in the LHAB project, but only the data of 186 subjects (mean age = 70.4; SD = 4.8; 89 men and 97 women) could be used in this study: The MRI datasets of 9 participants were incomplete, 31 subjects had to be excluded because of motion artifacts over 2 mm, and one participant showed a pathological high white matter lesion load. Another participant was excluded because of a diagnosis of type II diabetes shortly after the first time of assessment. Finally, the data of two other participants were not analyzed because they scored in 15% of all tests significant lower (> 3 SD) than the rest of the study sample.

Neuropsychological data

The LHAB database project comprises annual assessments of brain structure and resting-state function and a broad testing battery to probe cognitive and motor functions. The assessment of semantic and phonemic fluency performance is part of the regular LHAB cognitive testing battery.

Semantic fluency

The semantic fluency performance was examined using a standard German word fluency test (RWT: Regenburger Wortflüssigkeitstest, Aschenbrenner et al., 2000). In this test, participants have two minutes