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The impact of age on prefrontal cortex integrity during spatial working memory retrieval

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ABSTRACT

Healthy aging is accompanied by a decline in spatial working memory that is related to functional cerebral changes within the spatial working memory network. In the last decade, important findings were presented concerning the location (e.g., prefrontal), kind (e.g., 'underactivation,' 'overactivation'), and meaning (e.g., functional deficits, compensation) of these changes. Less is known about how functional connections between specific brain regions are affected by age and how these changes are related to behavioral performance. To address these issues, we used functional magnetic resonance imaging to examine retrieval-related brain activation and functional connectivity in 18 younger individuals and 18 older individuals. We assessed working memory with a modified version of the Corsi Block-Tapping test, which requires the storage and reproduction of spatial target sequences. Analyses of group differences in brain activation and functional connectivity included comparisons between younger individuals, older individuals, older high-performers, and older low-performers. In addition, we conducted a functional connectivity analysis by using a seed region approach. In comparison to younger individuals, older individuals showed lower right-hemispheric dorsolateral prefrontal activation and lower functional connectivity between the right dorsolateral prefrontal cortex and the bilateral orbitofrontal cortex. Older high-performers showed higher right dorsolateral and anterior prefrontal cortex activation than older low-performers, as well as higher functional connectivity between these brain regions. The present results suggest age-related reductions of prefrontal activation during spatial working memory retrieval. Moreover, task-related functional connectivity appears to be lower in older adults. Performance accuracy in older adults is associated with right dorsolateral and anterior prefrontal cortex activation, and with the functional connection between these regions.

1. Introduction

Healthy aging is accompanied by an accretive working memory decline (e.g., Park et al., 2002). Reasons for this decline are local gray matter and white matter changes (Good et al., 2001; Kennedy & Raz, 2009; Montembeault et al., 2012; Rabbitt et al., 2008) that particularly affect the frontal lobe (Raz, 2008; Raz et al., 1997; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003) and comprise the degeneration of neurons, a reduction of dendrites and synapses, as well as a decreased length of myelinated axons in the aging brain (Fjell & Walhovd, 2010). Possibly triggered by this age-related gray and white matter degeneration, healthy aging is associated with working memory related functional cerebral changes (Cabeza et al., 2004; Nagel et al., 2009; Park & Reuter-Lorenz, 2009; Reuter-Lorenz et al., 2000; Reuter-Lorenz & Park, 2010; Reuter-Lorenz & Sylvester, 2005; Sander, Lindenberger, & Werkle-Bergner, 2012). In fact, in the last decade there has been a lot of evidence for altered activation patterns during working memory processing in older individuals. Nevertheless, controversies remain concerning the location, extent, and interpretation of these changes. Numerous studies reported prefrontal 'overactivation' or recruitment of additional brain regions in older adults as a compensatory mechanism for age-related working memory decline (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008;

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Gutchess et al., 2005; Reuter-Lorenz et al., 2000; Reuter-Lorenz & Lustig, 2005). The most popular model concerning neural compensation is the *Hemispheric Asymmetry Reduction in Older Adults* (HAROLD) model (Cabeza, 2002). The HAROLD model postulates more bilateral activation of prefrontal brain regions in older individuals to compensate for age-related neural deficits. Other explanations for prefrontal overactivation or recruitment of additional brain structures are neural inefficiency (Rypma, Berger & D'Esposito, 2002; Zarahn, Rakitin, Abela, Flynn, & Stern, 2007) or reduction of regional specificity, also referred to as dedifferentiation of cortical subregions (Park et al., 2004; Rajah & D'Esposito, 2005; Zarahn, Rakitin, Abela, Flynn, & Stern, 2007).

A mediating factor is certainly performance accuracy. Prefrontal overactivation or increased bilaterality in the presence of an age-related performance breakdown would argue for neural inefficiency, dedifferentiation of cortical subregions, or failed compensation. By contrast, overactivation or increased bilaterality in older individuals, at an equivalent performance level to that of younger individuals, may be a sign of successful compensation. However, whereas there are different possible explanations for cerebral overactivation or bilaterality, prefrontal 'underactivation' in the aging brain was predominantly attributed to functional deficits (Johnson, Mitchell, Raye, & Greene, 2004; Thomsen et al., 2004): older adults recruit the same brain region during a working memory task but show lower activation intensity. This lower intensity is often associated with poorer performances and therefore points towards a working memory dysfunction (Bennett, Rivera, & Rypma, 2013; Cabeza et al., 2004; Cappell, Gmeindl, & Reuter-Lorenz, 2010; De Beni & Palladino, 2004; Holtzer et al., 2009; Jonides et al., 2000; Mattay et al., 2006; Nagel et al., 2009; Rypma & D'Esposito, 2000).

Reuter-Lorenz and Cappell (2008) integrated the variable findings by suggesting that the kind of activation differences between older and younger adults is strongly dependent on the cognitive demands of the applied task (*Compensation-Related Utilization of Neural Circuits Hypothesis,* CRUNCH). In comparison to younger adults, older adults show comparable performances at lower demand levels but more intense or bilateral prefrontal activation. This indicates a compensatory recruitment of neural resources as a response to limited working memory capacity. At high task demands, by contrast, older adults show poorer working memory performances accompanied by decreased prefrontal activation, which most likely reflects limited resources and failed neural compensation (Bennett et al., 2013; Cappell et al., 2010; Mattay et al., 2006; Nagel et al., 2009; Reuter-Lorenz & Park, 2010; Schneider-Garces et al., 2010). Another approach, which assembles the divergent findings, refers to a functional dorsolateral–ventrolateral organization of the prefrontal cortex (D'Esposito, Postle, Ballard, & Lease, 1999; Owen, 1997; Owen, Evans, & Petrides, 1996; Owen et al., 1999; Petrides, 1995; Wagner, Maril, Bjork, & Schacter, 2001) and region-specific changes with advancing age. Initially, it was proposed that aging affects dorsolateral parts of the prefrontal cortex, whereas the ventrolateral prefrontal cortex is relatively spared (Rypma & D'Esposito, 2000; Rypma, Prabhakaran, Desmond, & Gabrieli, 2001). Rajah and D'Esposito (2005) expanded their assumptions by attributing bilateral ventrolateral prefrontal activation changes to the dedifferentiation of cortical function, right dorsolateral and anterior prefrontal activation changes to functional deficits, and left dorsolateral and anterior prefrontal cortex activation changes to functional compensation. Contrary to a dorsolateral–ventrolateral prefrontal cortex organization, recent research suggests a hierarchical rostro-caudal distinction of control functions in the frontal lobe with parallel dorsal and ventral processing streams (Badre & D'Esposito, 2009; Blumenfeld, Nomura, Gratton, & D'Esposito, 2013). According to this distinction, rostral parts are associated with higher-level cognitive control, whereas caudal parts are rather related to spatial maintenance (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Nee et al., 2013). However, both approaches particularly highlight the role of anterior parts of the dorsolateral prefrontal cortex in top-down working memory control.

As all of these approaches suggest, prefrontal brain areas are differentially affected by age. However, ambiguity remains as to how aging impacts the functional connection between these regions. Some studies point towards a reduction of cortical connectivity in older individuals (Campbell, Grady, Ng, & Hasher, 2012; Klostermann, Braskie, Landau, O'Neil, & Jagust, 2012; Madden et al., 2010; Nagel et al., 2011; Rieckmann, Karlsson, Fischer, & Bäckman, 2011; Steffener, Habeck, & Stern, 2012). This reduction most likely points towards a growing working memory control dysfunction with advancing age (Montembeault et al., 2012; Sambataro et al., 2010; Sander et al., 2012). By contrast, other studies reported increased bilateral connectivity in older adults which supports the assumption of compensatory processing through enhanced cognitive control (Grady et al., 2010; Rieckmann et al., 2011). As for the valid interpretation of age-related differences in brain activation, it is necessary to analyze the mediating impact of performance accuracy in order to explain these discrepancies. For example, lower prefrontal functional connectivity associated with lower performance accuracy would argue for deficient control processes. By contrast, higher connectivity at an equivalent performance level would point towards successful compensation.

To address these issues, we used functional magnetic resonance imaging (fMRI) to examine brain activation and functional connectivity during spatial working memory retrieval in older and younger individuals. We analyzed the mediating impact of performance accuracy by comparing the brain activation and functional connectivity of older high-performers and older low-performers. In the context of functional frontal cortex organization, aging should particularly affect the rostral parts of the dorsolateral prefrontal cortex (Rypma & D'Esposito, 2000; Rypma et al., 2001) and their functional connections to other working memory related brain regions (Nagel et al., 2011). Thereby, successful compensatory processing of older individuals should be reflected by increased or bilateral activation (i.e., HAROLD; Cabeza, 2002) and connectivity (Grady et al., 2010), whereas working memory deficits in older individuals should be associated with decreased activation (i.e., CRUNCH; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2010) and decreased connectivity (Jolles, van Buchem, Crone, & Rombouts, 2013; Nagel et al., 2011).

2. Materials and methods

2.1. Participants

The present study included a group of 18 younger individuals and a group of 18 older individuals without differences in gender or education (Table 1). All participants were right-handed, with normal or corrected-to-normal vision. Participants were recruited by local advertising in newspapers. None of the participants had a documented diagnosis of neurological or psychiatric disease in the past.

Moreover, cognitive deficits in older individuals (one standard deviation below population mean) that might have pointed towards a neurodegenerative disorder were excluded by a neuropsychological test battery assessing different cognitive subfunctions as episodic memory, semantic memory, executive functioning, working memory capacity, processing speed, and spatial abilities. The test battery included the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), a German version of the Rey auditory verbal learning test (RAVLT; Müller Hasse-Sander, Horn, Helmstaedter, & Elger, 1997), a 15-items version of the Boston naming test (BNT; Kaplan, Goodglass, & Weintraub, 1983), a category fluency task (animal fluency; Lezak, Howieson, & Loring, 2004), four items for digit-word transformation (DemTect; Kessler, Calabrese, Kalbe, & Berger, 2000), digit and spatial span tasks forwards and backwards, the trail making test (TMT; Reitan, 1955; Tombaugh, 2004), and the clock drawing test (Shulman, Gold, Cohen & Zucchero, 1993; Schroder, Hasse-Sander, Müller, Horn, & Moller, 1999). Before the experiment started, subjects were informed about the specific experimental procedure and provided a written declaration of consent. The