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Working memory performance is related to intrinsic resting state functional connectivity changes in community-dwelling elderly cohort

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ABSTRACT

Characterization of normal age-related changes in resting state brain networks associated with working memory performance is a major prerequisite for studying neurodegenerative diseases. The aim of this study was to investigate the relationship between performing a working memory task (under MRI) and resting-state brain networks in a large cohort of healthy elderly subjects ($n = 337$).

Functional connectivity and interactions between networks were assessed within the default mode (DMN), salience (SN), and right and left central executive (CEN) networks in two groups of subjects classed by their performance (low and high).

The low performance group showed lower functional connectivity in both the DMN and SN, and higher functional connectivity in the right and left CEN compared to the high performance group. Overall the functional connectivity within the DMN and the CEN were correlated.

The lower functional connectivity within the DMN and SN in the low performance group is suggestive of altered attentional and memory processes and/or altered motivation. The higher functional connectivity within the CEN could be related to compensatory mechanisms, without which the subjects would have even lower performances. The correlation between the DMN and CEN suggests a modulation between the lower functional connectivity within the DMN and the higher functional connectivity within the CEN when performance is reduced.

Finally, this study suggests that performance modifications in healthy elderly subjects are associated with reorganization of functional connectivity within the DMN, SN, and CEN.

1. Introduction

Resting state functional magnetic resonance imaging (fMRI) studies in the field of aging have raised significant interest since the activation of specific networks engaged under resting conditions have been associated with increased rates of mild cognitive impairment (Koch et al., 2010; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005; Sorg et al., 2007) and Alzheimers (Wang et al., 2006; Wu et al., 2011). Resting-state networks could also

Abbreviations: CEN, central executive network; DMN, default mode network; DR, degree of representativity; DU, degree of unicity; P, performance between low and high levels of difficulty (one and six letters); RT_{L1}, mean correct response time in level 1 (one letter); RT_{L6}, mean correct response time in level 6 (six letters); SN, salience network.

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underlie a broad range of functions (memory, attention, motor, and sensory), involved in working memory (Fox & Raichle, 2007; Fox et al., 2005; Greicius, Krasnow, Reiss, & Menon, 2003; Sala-Llonch et al., 2012; Uddin & Menon, 2010). Indeed, short-term memory is impaired in Alzheimer's disease and at the earliest stages of the disease (Baddeley & Hitch, 1974; Huntley & Howard, 2010).

Age-related cognitive deficits have been associated with atrophy, amyloid protein deposition, accumulation of white matter hyperintensities, reduced glucose metabolism and modifications of the resting state networks (prefrontal cortex, precuneus, parietal lobule, cingulate cortex) (Benson et al., 1983; Birdsill et al., 2014; Buckner et al., 2005; Hafkemeijer, van der Grond, & Rombouts, 2012; Minoshima et al., 1997; Serra et al., 2011; Solé-Padullés et al., 2009). In addition to exploring the role of resting-state networks in dementia and cognitive decline, the relationship between resting state fMRI and working memory performances merits further investigation in non-pathological aging to improve our understanding of the neural bases underlying working memory processes.

Three main brain networks involved in resting-state and working memory tasks have been identified in the literature: the central executive network (CEN), the salience network (SN), and the default mode network (DMN) (Chen et al., 2013; Menon & Uddin, 2010; Smith et al., 2014; Weissman-Fogel, Moayedi, Taylor, Pope, & Davis, 2010).

The spatial distribution of the CEN is composed of the dorsolateral prefrontal cortices and the posterior parietal cortices (Liao et al., 2010; Menon & Uddin, 2010; Seeley et al., 2007; Weissman-Fogel et al., 2010). This network could be involved in cognitive processing for working memory, judgment, decision-making, and attention (Asplund, Todd, Snyder, & Marois, 2010; Corbetta & Shulman, 2002; Curtis & D'Esposito, 2003; Koechlin & Summerfield, 2007; Miller & Cohen, 2001).

The SN includes the limbic and paralimbic structures especially the bilateral insula and anterior cingulate (Cabeza & Nyberg, 2000; Heine et al., 2012; Rytty et al., 2013). These regions are involved in emotional, sensory, working memory, and attentional processes (Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; Cabeza & Nyberg, 2000; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Crottaz-Herbette & Menon, 2006; Johnson et al., 2006; Seeley et al., 2007; Taylor, Seminowicz, & Davis, 2009).

The last network, the DMN, involves the posterior cingulate gyrus, the inferior parietal lobules, and the medial prefrontal cortex (Greicius et al., 2003; Uddin, Clare Kelly, Biswal, Castellanos, & Milham, 2009; Wu et al., 2011). The specific role of the DMN has yet to be fully elucidated. It seems to be involved in behavioral planning, self-evaluation, and memory encoding (Damoiseaux et al., 2006; Greicius, Srivastava, Reiss, & Menon, 2004; Koch et al., 2010; Raichle et al., 2001; Sestieri, Corbetta, Romani, & Shulman, 2011).

These three networks have been shown to work simultaneously, particularly during working memory tasks. Sridharan et al. have shown that the anterior insula induces an increased activation in CEN and decreased activation in DMN during resting-state (Sridharan, Levitin, & Menon, 2008). Furthermore, a negative correlation has been reported between DMN and CEN activations while a positive correlation has been exhibited between SN and CEN activations during working memory tasks and even at rest (Bressler & Menon, 2010; Chen et al., 2013; Di & Biswal, 2013, 2014; Habeck et al., 2005; Menon & Uddin, 2010; Orliac et al., 2013; Palaniyappan & Liddle, 2012; Pochon et al., 2002; Seeley et al., 2007). In other words, when the SN and CEN show an increased activation, the DMN typically exhibits a decreased activation. Therefore, the SN could initiate a switch between the CEN and the DMN. These interactions at rest could be essential to promote efficient cognitive processing during cognitive tasks.

Resting state fMRI studies have also reported altered functional connectivity in each of these three networks in cognitively healthy elderly individuals. These studies showed lower functional connectivity within the DMN associated with decreased performance during working memory and executive tasks (Andrews-Hanna et al., 2007; Duchek et al., 2013). A similar lower functional connectivity has been reported in the SN (Duchek et al., 2013; Onoda, Ishihara, & Yamaguchi, 2012). Another study revealed higher functional connectivity within the right CEN associated with lower working memory performances (Sala-Llonch et al., 2012). The authors suggest that this finding could be ascribed to compensatory processes involved is case of impaired working memory.

However, these studies involved small numbers of subjects ($n < 73$) and did not focus on the interaction between these three networks, which is essential if we are to understand the neural basis of working memory.

We hypothesized that individuals with low working memory performance would exhibit lower functional connectivity within both the DMN and SN and higher functional connectivity within the CEN compared to individuals with higher performance. With this in mind, we aimed to investigate the relationship between working memory task performances and functional connectivity within the CEN, SN, and DMN, and the interaction between these networks during resting-state fMRI in a large cohort of healthy elderly subjects.

2. Methods

2.1. Subjects

The data was derived from the ongoing prospective Montpellier-Three-City study (The 3C Study Group, 2003) in which 2259 volunteers (recruited from the electoral rolls), aged 65 year-old and over, underwent standardized neurological examinations in a dedicated clinical research facility. The clinical examinations were undertaken at baseline (1999–2001) and 2, 4, 7, 10 and 12 years. At 12-year follow-up, participants who were free of dementia and had a Mini Mental State Examination MMSE (Folstein, Folstein, & McHugh, 1975) score over 24 were invited to undergo an MRI and complementary clinical examination as part of the CRESCENDO (Cognitive REServe and Clinical ENDOphenotype) study ($n = 380$) (Charroud et al., 2015). The clinical examination was carried out approximately 8 months before the MRI examination. The diagnosis of dementia was based on a 3-step procedure. First, trained psychologists administered a battery of neuropsychological tests detailed elsewhere (Akbaraly et al., 2009). Second, all the participants were examined by a neurologist. Finally, an independent committee of neurologists reviewed all potential cases of dementia to obtain a consensual diagnosis according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition. Similar procedures were performed at each phase over the 12-years of follow-up for incident dementia screening. Cases of AD were classified according to the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984) and cases of mixed/vascular dementia according to the National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche en l'Enseignement en Neurosciences criteria (Román et al., 1993).

The study protocol was approved by the ethics committee of the University-Hospital of Bicêtre, and written informed consent was obtained from each participant. Characteristics of the 380