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Regional brain shrinkage and change in cognitive performance over two years: The bidirectional influences of the brain and cognitive reserve factors

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ABSTRACT

We examined relationships between regional brain shrinkage and changes in cognitive performance, while taking into account the influence of age, vascular risk, Apolipoprotein E variant and socioeconomic status. Regional brain volumes and cognitive performance were assessed in 167 healthy adults (age 19–79 at baseline), 90 of whom returned for the follow-up after two years. Brain volumes were measured in six regions of interest (ROIs): lateral prefrontal cortex (LPFC), prefrontal white matter (PFw), hippocampus (Hc), parahippocampal gyrus (PhG), cerebellar hemispheres (CbH), and primary visual cortex (VC), and cognitive performance was evaluated in three domains: episodic memory (EM), fluid intelligence (G_f), and vocabulary (V). Average volume loss was observed in Hc, PhG and CbH, but reliable individual differences were noted in all examined ROIs. Average positive change was observed in EM and V performance but not in G_f scores, yet only the last evidenced individual differences in change. We observed reciprocal influences among neuroanatomical and cognitive variables. Larger brain volumes at baseline predicted greater individual gains in G_f, but differences in LPFC volume change were in part explained by baseline level of cognitive performance. In one region (PFw), individual change in volume was coupled with change in G_f. Larger initial brain volumes did not predict slower shrinkage. The results underscore the complex role of brain maintenance and cognitive reserve in adult development.

1. Introduction

Human aging is accompanied by shrinkage of the brain parenchyma (Kemper, 1994; Raz and Kennedy, 2009) and declines in cognitive performance (Cattell, 1943; Salthouse, 2010). However the trajectories of age-related change vary among individuals (Raz et al., 2010), brain regions (Fjell et al., 2009; Persson et al., 2014; Raz et al., 2005; Resnick et al., 2003) and cognitive domains (De Frias et al., 2007; Ghisletta and Lindenberger, 2003; Rabbitt, 1993).

Although the observed pattern of age-related change may in part depend on the sample characteristics and the time window of longitudinal assessment, age-related changes in the brain and cognition follow, on average, a reasonably consistent pattern. Brain shrinkage appears especially significant in medial temporal lobe (MTL) structures and tertiary association cortices, i.e., regions that are particularly important for support of age-sensitive cognitive functions. In contrast, sensory cortical regions, such as the visual cortex, evidence lesser age-related change (see Raz and Kennedy, 2009 for a review). Aging is characterized by a complex pattern of cognitive stability, growth and decline, and studies conducted over the past eight decades suggest significant heterogeneity of age-related change across cognitive domains (Cattell, 1943; Ghisletta et al., 2012; Miles, 1934; Rabbitt, 1993).

Cattell (1943), in refining Spearman's (1904) concept of general intelligence, postulated the existence of two broad types of abilities: fluid and crystallized. Fluid abilities have been viewed as rapidly growing until mid-twenties, stabilizing thereafter, steadily declining into the seventh decade of life, and accelerating their decline into senium (Cattell, 1943). In contrast, crystallized abilities continue to improve throughout childhood and adulthood, with gradual declines becoming apparent only during the latest part of the lifespan (Cattell, 1943; Finkel et al., 2003; Flicker et al., 1993; Ghisletta and Lindenberger,

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2003; Horn and Cattell, 1967; McArdle et al., 2002; Rabbitt, 1993; Rabbitt et al., 2004). Research conducted after Cattell's initial proposal suggests a more refined structure of abilities and their response to aging, with the rates of change varying across cognitive domains. Working memory, episodic memory, processing speed and spatial reasoning exhibit particular sensitivity to aging, whereas vocabulary and verbal comprehension are spared until the end of life (Flicker et al., 1993; Ghisletta et al., 2012; Hultsch et al., 1992; Rabbitt et al., 2004; Small et al., 2011a).

In light of the surveyed findings in the brain and cognitive aging, it is plausible that brain changes play an important role in cognitive declines. Indeed, devolution of cognitive performance into dementia appears to follow prolonged deterioration of structural and functional characteristics of relevant brain structures (Mortamais et al., 2013; Mungas et al., 2002; Tosto et al., 2014). However, the associations between normal brain aging and cognitive development in late adulthood are not unequivocally established. One of the most prominent reasons for inconsistency is the reliance on cross-sectional design in the majority of investigations (but see Cohen et al., 2001; Kramer et al., 2007; Raz et al., 2008; Rusinek et al., 2003). Cross-sectional methodology precludes gauging individual differences in change of the brain and cognition and examining the associations between the two (McArdle and Nesselroade, 1994). Moreover, cross-sectional design impedes evaluation of neural mediators of cognitive decline in age-heterogeneous samples and is ineffectual for generating hypotheses about brain-cognition relationships over time (Hofer and Sliwinski, 2001; Lindenberger et al., 2011; Maxwell and Cole, 2007; Raz et al., 2013). Longitudinal studies of non-demented adults show that global deterioration of the brain expressed in ventricular expansion (Grimm et al., 2012; McArdle et al., 2004) as well as regional changes such as shrinkage of the hippocampus (Kramer et al., 2007; Rusinek et al., 2003) lead to declines in episodic memory.

It is important to emphasize, however, that associations between brain and cognition may not be unidirectional (see Salthouse, 2011 for a relevant discussion). Indeed, whereas among older adults smaller gross brain volume has been linked to decline in fluid intelligence (Rabbitt et al., 2008), variations in prefrontal volume are related to age differences in fluid reasoning and in more specific cognitive functions such as strategic control of episodic memory (Euston et al., 2012; Kane and Engle, 2002; Rajah and D'Esposito, 2005). Functional and structural imaging studies reveal the importance of the cerebellar cortices in multiple cognitive operations (Stoodley, 2012). Longitudinal evidence further links higher fluid intelligence and episodic memory scores to lesser shrinkage of the MTL (Borghesani et al., 2012; Raz et al., 2008; Rodrigue and Raz, 2004), and higher general cognitive ability measured in youth predicts larger brain volumes in old age (Royle et al., 2013). Thus, assessment of bidirectional influences between the brain and cognition is necessary for understanding neural substrates of cognitive aging.

Chronological age is associated with multiple factors that shape individual trajectories of age-related change in the brain and cognition, and these factors have been hypothesized to distinguish between successful and typical aging (Rowe and Kahn, 1987). The concept of brain reserve has been advanced to explain individual differences in resilience to trauma and neurodegeneration by greater initial number of neurons and synapses (Katzman et al., 1988) as well as greater gross brain volume (Satz, 1993). Numerous cardiovascular and pro-inflammatory risk factors have been implicated in exacerbating the neural and cognitive declines observed in normal aging (Anstey and Christensen, 2000; Bettcher and Kramer, 2014; Convit et al., 2003; Ghisletta et al., 2014; Persson et al., 2014; Raz et al., 2005, 2010, 2013; Whalley et al., 2004).

In addition, socio-economic status (SES), which reflects multiple inter-related variables such as individual and parental education, income, and occupational attainment, has been proposed as a significant mediator of individual differences in cognitive change throughout the lifespan (Renner et al., 2012; Tucker and Stern, 2011; Vance, 2012; Whalley et al., 2004). The importance of SES-related characteristics for successful aging has been emphasized in developing a concept of cognitive reserve, and positing that higher educational and professional attainment early in life serve as a buffer against age-related cognitive declines (Stern, 2002). Although the extant literature does not present a consensus on the effects of these modifiers of aging, it is important to consider them while studying the relationship between brain shrinkage and cognitive change in healthy adults.

Our main objective in this research was to examine the relationship between previously reported regional heterogeneity of brain shrinkage (Persson et al., 2014) and change in performance in age-sensitive cognitive domains. In this hypotheses-driven study, we selected brain regions of interest (ROI) based on their theoretical and empirical relevance for the studied cognitive domains. The selection included ROIs with known relevance to age-sensitive cognitive functions: lateral prefrontal cortex (LPFC), prefrontal white matter (PFw), hippocampus (Hc), parahippocampal gyrus (PhG) and the cerebellar hemispheres (CbH), as well as a control region, primary visual cortex (VC), which we expected to show lesser age-related change and lesser relevance to age-sensitive cognitive skills (Buckner, 2013; Cabeza and Nyberg, 2000; Small et al., 2011b).

We chose two age-sensitive cognitive constructs, episodic memory (EM) and fluid ability (G_f), and one construct, vocabulary (V), which represents a crystallized ability that is relatively unaffected by aging. To examine changes in regional brain volumes and cognitive performance, we used latent change score models to assess mean change and variance in change. Further, we evaluated bidirectional lags between baseline levels and subsequent changes in brain volumes and cognitive performance scores. Finally, we tested the role of putative modifiers of change in the brain and cognition by adding cardiovascular risk, genetic variant associated with dementia risk, and socioeconomic status in addition to chronological age as determinants of individual differences in neuroanatomical and cognitive changes.

2. Methods

2.1. Participants

The data were collected in a major metropolitan area in the Midwestern USA. Volunteer participants across the adult lifespan were recruited through media advertisements and flyers. Persons who reported a history of cardiovascular, neurological or psychiatric disease, head trauma with loss of consciousness in excess of five minutes, thyroid dysfunction, diabetes mellitus, or history of drug and alcohol abuse, were excluded from the study. Participants with a reported diagnosis of hypertension who were taking prescription medication (e.g., beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors or potassium-sparing diuretics) were included in the study. Participants who reported taking anti-seizure medication, anxiolytics or antidepressants were excluded. Persons suffering from claustrophobia were advised not to participate in the study.

All participants were screened for dementia using the Mini-Mental State Examination (Folstein et al., 1975) with a cut-off of 26 (87%) correct responses, and for depression using the Center for Epidemiological Studies Depression Inventory (CES-D; Radloff, 1977), with a cut-off score of 15. All participants were right-hand dominant, as indicated by a score above 75% on the Edinburgh Handedness Questionnaire (Oldfield, 1971). One hundred sixty-seven persons were recruited for the study and assessed at baseline; 90 of them returned for cognitive and MRI evaluation. The average interval between assessments was two years and 24 days. A detailed description of the recruitment and attrition can be found in Persson et al. (2014); Fig. 1). Descriptive statistics for demographic indicators and blood markers are presented in Table 1.

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