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Differential brain shrinkage over 6 months shows limited association with cognitive practice

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ABSTRACT

The brain shrinks with age, but the timing of this process and the extent of its malleability are unclear. We measured changes in regional brain volumes in younger (age 20–31) and older (age 65–80) adults twice over a 6 months period, and examined the association between changes in volume, history of hypertension, and cognitive training. Between two MRI scans, 49 participants underwent intensive practice in three cognitive domains for 100 consecutive days, whereas 23 control group members performed no laboratory cognitive tasks. Regional volumes of seven brain structures were measured manually and adjusted for intracranial volume. We observed significant mean shrinkage in the lateral prefrontal cortex, the hippocampus, the caudate nucleus, and the cerebellum, but no reliable mean change of the prefrontal white matter, orbital-frontal cortex, and the primary visual cortex. Individual differences in change were reliable in all regions. History of hypertension was associated with greater cerebellar shrinkage. The cerebellum was the only region in which significantly reduced shrinkage was apparent in the experimental group after completion of cognitive training. Thus, in healthy adults, differential brain shrinkage can be observed in a narrow time window, vascular risk may aggravate it, and intensive cognitive activity may have a limited effect on it.

1. Introduction

Aging is accompanied by profound changes in brain structure and function, but the pace of change varies significantly across brain regions and is characterized by substantial individual differences (for reviews see Kemper 1994; Hedden and Gabrieli 2004; Raz & Rodrigue, 2006). Reliable volume reduction in multiple cortical, subcortical, and cerebellar regions as well as thinning of the cerebral cortex have been observed *in vivo* in many samples, with various analytical tools, and on different imaging platforms (Fjell et al., 2009; Pfefferbaum, Sullivan, Rosenbloom, Mathalon, & Lim, 1998; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010; Raz, Rodrigue, Kennedy, Dahle, et al., 2003; Raz, Rodrigue, Kennedy, Head, et al., 2003; Raz et al., 2004, 2005; Resnick, Pham, Kraut, Zonderman, & Davatzikos 2003; Scahill Fjell et al., 2003). In healthy individuals, regional changes in brain volume have been detected within time spans from five (Driscoll et al., 2009; Pfefferbaum et al., 1998; Raz et al., 2005; Rusinek et al., 2003) to less than two (Fjell et al., 2009; Raz et al., 2010) years to 6 months (Murphy et al., 2010), and in the hippocampus, reliable shrinkage was noted within a span of 4 months (Lövdén et al., 2012). However, the localization and extent of regional change vary across studies and even across different samples studied in the same laboratory (e.g., Raz et al., 2005 vs. Raz et al., 2010). Moreover, the samples in which the changes were observed cover different parts of the adult age span and vary in the mean age by more than two decades (e.g., from 52 years in Raz et al., 2005 to 76 years in Murphy et al., 2010). Notably, changes in brain structure are not limited to older adulthood. Shrinkage of at least some brain regions (e.g., HC) has been observed in younger adults (Delisi et al., 1997; Lövdén et al., 2012; Raz et al., 2005; Scahill et al., 2003), although not at the same rate as noted after the sixth decade of life (Raz et al., 2005).

Age-related shrinkage of the brain is not benign, and persons who evidence significant reduction in local brain volumes display reduced cognitive performance (Rodrigue and Raz, 2004; Raz et al.,

Abbreviations: HC, hippocampus; DLPFC, dorsolateral prefrontal cortex; OF, orbitofrontal cortex; VC, primary visual (pericalcarine) cortex; CD, caudate nucleus; CB, cerebellum; FW, prefrontal white matter.

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2008) and run increased risk of developing dementia (Murphy et al., 2010). Because brain shrinkage and its effects on cognition vary substantially among individuals, it is important to determine the factors that affect the rate of decline. An example of such moderator of brain decline is arterial hypertension (Salerno et al., 1992; Strassburger et al., 1997), a common vascular risk factor that increases the rate and widens the spread of shrinkage across the brain (Raz, Rodrigue, Kennedy, & Acker, 2007; Raz et al., 2005, 2008).

Once age-related shrinkage of the brain is observed, it is only natural to ask what can be done about it. To date, several interventions aimed at slowing age-related brain change yielded mixed results. Whereas treating accelerators of brain aging, such as hypertension, does not slow the rate of decline (Jennings et al., 2012), other interventions such as aerobic exercise (Erickson et al., 2011) inspire cautious optimism regarding the malleability of the aging brain. One increasingly popular approach to combatting age-related brain shrinkage is perceptual-motor and cognitive training. Intensive practice on perceptual-motor and cognitive tasks of a wide range of complexity may result in significant enlargement of circumscribed brain regions and changes in white matter diffusion properties in young adults (Draganski et al., 2004, Draganski, Gaser, Kempermann, Kuhn, Winkler & Büchel 2006; Mackey, Whitaker, & Bunge, 2012; Schmidt-Wilcke, Rosengarth, Luerding, Bogdahn, & Greenlee, 2010; Takeuchi et al., 2010). Most important, older brains show practice-related improvements in gray matter volume (Boyke, Driemeyer, Gaser, Büchel, & May, 2008; Lövdén et al., 2012) and regional white matter integrity (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010) as well, albeit not always and not to the same extent as the younger brains do (e.g., Wenger et al., 2012).

These findings suggest that intensive and systematic cognitive training may slow down the advancement of brain aging. However, even in younger adults the evidence of experience-induced change is far from overwhelming and significant methodological problems persist to dampen the enthusiasm about the findings. According to a recent review, 80% of extant studies of experience-dependent changes in brain structure relied on voxel-based morphometry (VBM) and a minority use other semi-automated approaches such as FreeSurfer (Thomas & Baker, 2012). Systematic comparisons between VBM and manual morphology (Allen, Bruss, Mehta, Grbowski, Brown & Damsio, 2008; Kennedy et al., 2009) provide ample basis for caution in interpreting differences between groups and conditions revealed by VBM. On the other hand, hypothesis-driven intervention studies with manual measurements are rare and thus far have been limited to investigation of one or two regions of interest (ROIs, e.g., Lövdén et al., 2012). In general, the hypothesis-free approach taken by the vast majority of the extant studies is problematic, especially when only small clusters of voxels that showed longitudinal change are compared between the training group and the controls (Thomas & Baker, 2012). Notably, among the extant studies of structural plasticity, only two (Lövdén et al., 2012; Wenger et al., 2012), conducted on the same sample, compared practice-related changes in younger and older adults, and most have not evaluated the critically important group × time interaction (Thomas & Baker, 2012). In addition, with a couple of notable exceptions, intervention studies of structural change relied on small samples, with a median size of 38 and a range of 11–120 participants (Thomas & Baker, 2012, Table 1). In summary, Thomas and Baker (2012) concluded that in studies of experience-based change in brain structure, the effects are small, highly localized, poorly replicated, transient, and restricted to younger adults.

In this study, we addressed four questions, while trying to take into account threats to validity outlined by previous studies and summarized in Thomas and Baker (2012). First, we inquired whether differential age-related shrinkage in healthy young and old adults happens fast enough to be noticed within a 6-month time window. In pursuit of that objective, we selected regions that have been shown to change in relatively short periods (the prefrontal cortex, the hippocampus, the cerebellum, and the caudate nucleus) and a control region that evidenced no significant shrinkage in previous longitudinal studies – the primary visual cortex. Second, we examined if individuals reliably differ in their rates of brain shrinkage, even when observed over relatively short intervals. The third question was whether vascular risk moderates age-related declines in brain volume. Based on the reviewed evidence, we expected vascular risk to exacerbate shrinkage of the gray matter in the prefrontal cortex and the hippocampus. The fourth objective was to evaluate whether persons who undergo intensive cognitive intervention show lesser regional brain shrinkage than their counterparts who do not participate in the program. We addressed these questions by examining short-term changes in the regional brain volumes of healthy adults who participated in intensive training of multiple cognitive skills. We hypothesized that healthy adults, especially the older among them, would show significant shrinkage within 6 months at least in the brain regions with established vulnerability, such as the hippocampus, the prefrontal cortex, and the cerebellum. We expected to observe significant individual differences in the rate of change, and we hypothesized that persons with hypertension would show greater shrinkage than their normotensive peers would. Finally, we expected that the brains of people who underwent intensive cognitive practice would evidence lesser shrinkage than those of the control group participants. We expected to observe the benefits of practice in the regions with known associations to higher cognitive activities that are tapped by the cognitive tasks employed in this study: episodic memory, working memory and perceptual speed. Thus we selected the hippocampus, in which extensive training related to high memory load is believed to induce functional, metabolic and structural changes (Groussard et al., 2010; Maguire et al., 2000; Mårtensson et al., 2012; Roche et al., 2009), the prefrontal cortex that showed changes after memory, attention and working memory training (Engvig et al., 2010; Hoekzema et al., 2011; Mårtensson et al., 2012), and the cerebellum which evidenced structural growth after working memory training (Hoekzema et al., 2011).

Table 1
Longitudinal change in regional cerebral volumes: a summary of the univariate latent change models.

ROI	Baseline mean	Mean change baseline – follow-up	Baseline, variance	Variance of change baseline – follow-up	Annual% change
Hippocampus	3551	−50*	170,709*	15,048*	−1.42
Lateral prefrontal cortex	10,569	−104*	3,813,815*	77,429*	−2.51
Orbital frontal cortex	4924	−33	1,031,243*	44,333*	−0.83
Primary visual cortex	3026	−7	200,748*	5195*	−0.48
Caudate	4160	−39*	412,269*	7988*	−1.21
Cerebellum	59,703	−494*	40,457,233*	650,285*	−1.86
prefrontal white	19,656	80	10,247,462*	433,687*	1.28

Notes: All volumes are in mm^3, adjusted for intracranial size.
* $p < 0.05$.