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Consistent neuroanatomical age-related volume differences across multiple samples

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Abstract

Magnetic resonance imaging (MRI) is the principal method for studying structural age-related brain changes *in vivo*. However, previous research has yielded inconsistent results, precluding understanding of structural changes of the aging brain. This inconsistency is due to methodological differences and/or different aging patterns across samples. To overcome these problems, we tested age effects on 17 different neuroanatomical structures and total brain volume across five samples, of which one was split to further investigate consistency (883 participants). Widespread age-related volume differences were seen consistently across samples. In four of the five samples, all structures, except the brainstem, showed age-related volume differences. The strongest and most consistent effects were found for cerebral cortex, pallidum, putamen and accumbens volume. Total brain volume, cerebral white matter, caudate, hippocampus and the ventricles consistently showed non-linear age functions. Healthy aging appears associated with more widespread and consistent age-related neuroanatomical volume differences than previously believed.

Keywords: MRI morphometry; Age; Cortex; White matter; Cerebellum; Ventricles; Hippocampus; Amygdala; Thalamus; Basal ganglia

1. Introduction

Brain changes are inevitable in aging. Still, core questions remain a matter of debate: What structures change, when do they start aging, at what rates, and are some structures spared? Many cross-sectional studies have demonstrated neuroanatomical age-related volume differences *in vivo* by the use of magnetic resonance imaging (MRI) (Allen et al., 2005; Blatter et al., 1995; Courchesne et al., 2000; Fotenos et al., 2005; Good et al., 2001; Head et al., 2004, 2005; Jernigan et al., 1991, 2001; Luft et al., 1999; Mu et al., 1999; Raz et al., 2000, 2004a,b, 2005, 2007; Raz and Rodrigue, 2006; Salat et al., 2004; Sullivan et al., 1995, 2004; Taki et al., 2004; Tisserand et al., 2002; Walhovd et al.,

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2005a). Some structures are found to decline substantially, while others appear better preserved (Raz and Rodrigue, 2006). Different age trajectories have been observed, with some brain areas declining linearly from early in life, whereas others continue to increase in volume before eventually beginning to deteriorate (Allen et al., 2005; Good et al., 2001; Luft et al., 1999; Raz et al., 2004b; Walhovd et al., 2005a). Unfortunately, the results diverge much across studies, and differences in segmentation procedures and demarcation criteria complicate comparisons. Discrepant findings have been reported for most structures. Adding to this problem, in most studies only a few structures are segmented, making it difficult to assess the relative vulnerability of different structures to age.

The aim of the present paper was to overcome these problems. Data from five samples (one split-half making a total of six groups for analysis) were processed with the same segmentation tools, and the stability of age effects across samples was assessed for 16 subcortical structures as well as cortical volume and total brain volume. Three questions were asked: (1) Which structures show significant age-related volume differences across samples? (2) Which structures undergo the most prominent age-related changes, and which are relatively preserved? (3) Which structures are volumetrically changed in a linear fashion, and which show curvilinear (quadratic) age relationships?

Main findings from previous MRI studies on age-related differences in neuroanatomial volumes are summarized in the following. Further reviews can be found elsewhere (Raz and Rodrigue, 2006). It should be noted that the vast majority of studies reviewed below are of a cross-sectional nature, and unless longitudinal designs are explicitly noted, what is observed are age differences, rather than age changes. There is consensus that gray matter (GM) volume/thickness is smaller with higher age (Blatter et al., 1995; Courchesne et al., 2000; Fotenos et al., 2008; Good et al., 2001; Jernigan et al., 1991, 2001; Murphy et al., 1996; Pfefferbaum et al., 1994; Raz et al., 1997; Resnick et al., 2000; Salat et al., 2004; Sullivan et al., 1995, 2004; Walhovd et al., 2005a), and that this effect is seen early in life (Courchesne et al., 2000; Giedd, 2004; Giedd et al., 1999, 1996; Lebel et al., 2008). Based on cross-sectional investigations, there generally appears to be somewhat greater GM loss in the cortex than in subcortical structures (Jernigan et al., 2001; Walhovd et al., 2005a). However, a longitudinal study has indicated at least as much shrinkage of the caudate and cerebellum as in the lateral frontal and orbitofrontal cortex (Raz et al., 2005). Aging of different parts of the cortex is highly heterogeneous, and cortical volume is included in the present study mainly to allow comparisons with subcortical structures. Detailed analyses of cortical thickness are reported elsewhere (Fjell et al., in press).

Less consistent results have been reported for the relationship between age and white matter (WM) volume. Some studies have found no age differences (Abe et al., 2008; Blatter et al., 1995; Good et al., 2001; Jernigan et al., 1991; Pfefferbaum et al., 1994; Sullivan et al., 2004), while others have found that total WM volume is negatively related to age (Allen et al., 2005; Guttmann et al., 1998; Jernigan et al., 2001; Walhovd et al., 2005a). Samples of varying ages may be a reason for the discrepant findings, and studies including the oldest participants tend to report age effects. One study (Courchesne et al., 2000) reported white matter to be negatively related to age only from 70 years of age onwards, and this age range has not been consistently included in aging studies. Jernigan and colleagues (Jernigan et al., 2001; Jernigan and Gamst, 2005) found that despite its later onset, white matter loss was more rapid than gray matter loss, and ultimately exceeded it. In recent years, there has been increased focus on the possibly curvilinear nature of age change in WM volume (Allen et al., 2005; Jernigan and Gamst, 2005; Walhovd et al., 2005a), with gains until middle age followed by later decrease. Non-linear fits tend to significantly increase the proportion of variance in WM volume explained by age. As for gray matter, results indicate somewhat less age-related loss in deep subcortical regions than in the cerebral lobes (Jernigan et al., 2001). For instance, although some decline has also been observed in brainstem volume (Walhovd et al., 2005a), several studies have reported no effect of age on volume of the pons (Luft et al., 1999; Raz et al., 1998, 2001, 1992; Van Der Werf et al., 2001).

In the following, age effects on different subcortical brain structures from 31 cross-sectional studies are reviewed (details are presented in Table 1). All studies tested effects of age on the volume of at least one of the subcortical structures/compartments included in the present study, and a short presentation of the main results from this literature is given below:

Hippocampus: The variability among studies is high. Nine of 15 studies reviewed here found that hippocampus shrank with age (Allen et al., 2005; Greenberg et al., 2008; Jernigan et al., 2001; Lupien et al., 2007; Mu et al., 1999; Raz et al., 2004a; Scahill et al., 2003; Schuff et al., 1999; Walhovd et al., 2005a), while five found no change (Du et al., 2006; Liu et al., 2003; Sullivan et al., 1995, 2005; Van Petten, 2004). In one study, age effects on hippocampal volume were found for men but not women (Pruessner et al., 2001). In addition, age effects on hippocampal volume normalized to global GM loss were not observed in a very large study (Good et al., 2001). Notably, three of the studies found non-linear effects of age (Allen et al., 2005; Lupien et al., 2007; Walhovd et al., 2005a), and one longitudinal study reported accelerated age-related hippocampal shrinkage (Raz et al., 2005). Part of the discrepant findings may thus stem from failure to account for non-linearity.

Amygdala: There have been fewer studies of age effects on the amygdala, but in sum, the reports indicate smaller age effects on the amygdala than on the hippocampus. Three studies found smaller volume of amygdala with higher age (Allen et al., 2005; Mu et al., 1999; Walhovd et al., 2005a), while two did not (Jernigan et al., 2001; Pruessner et al.,