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The effects of aging and Alzheimer's disease on cerebral cortical anatomy: Specificity and differential relationships with cognition

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ABSTRACT

Although both normal aging and Alzheimer's disease (AD) are associated with regional cortical atrophy, few studies have directly compared the spatial patterns and magnitude of effects of these two processes. The extant literature has not addressed two important questions: 1) Is the pattern of age-related cortical atrophy different if cognitively intact elderly individuals with silent AD pathology are excluded? and 2) Does the age- or AD-related atrophy relate to cognitive function? Here we studied 142 young controls, 87 older controls, and 28 mild AD patients. In addition, we studied 35 older controls with neuroimaging data indicating the absence of brain amyloid. Whole-cortex analyses identified regions of interest (ROIs) of cortical atrophy in aging and in AD. Results showed that some regions are predominantly affected by age with relatively little additional atrophy in patients with AD, e.g., calcarine cortex; other regions are predominantly affected by AD with much less of an effect of age, e.g., medial temporal cortex. Finally, other regions are affected by both aging and AD, e.g., dorsolateral prefrontal cortex and inferior parietal lobule. Thus, the processes of aging and AD have both differential and partially overlapping effects on specific regions of the cerebral cortex. In particular, some frontoparietal regions are affected by both processes, most temporal lobe regions are affected much more prominently by AD than aging, while sensorimotor and some prefrontal regions are affected specifically by aging and minimally more by AD. Within normal older adults, atrophy in aging-specific cortical regions relates to cognitive performance, while in AD patients atrophy in AD-specific regions relates to cognitive performance. Further work is warranted to investigate the behavioral and clinical relevance of these findings in additional detail, as well as their histological basis; ROIs generated from the present study could be used strategically in such investigations.

Introduction

The dementia of Alzheimer's disease is diagnosed when an individual loses independent functioning as a result of impairments in multiple domains of cognitive function (McKhann et al., 1984). These symptoms are thought to be a direct reflection of the loss of function of multiple brain systems for memory, executive function, visuospatial function, language, praxis, and other abilities, and are thought to result, at least in part, from the accrual of pathologic alterations in multiple regions of cerebral cortex (Arnold et al., 1991; Brun and Gustafson, 1976). Analyses of in vivo neuroimaging data demonstrate anatomic and physiologic abnormalities preferentially affecting limbic and heteromodal association cortices (Chetelat et al., 2005; Lerch et al., 2005; Scahill et al., 2002; Thompson et al., 2001; Whitwell et al., 2008). Recently developed computational analytic techniques have enabled the identification of a reliable "cortical signature" of specific regions that undergo atrophy in mild and prodromal AD (Bakkour et al., 2009; Dickerson et al., 2009b). The degree to which this signature atrophy pattern is expressed correlates with symptom severity (Dickerson et al., 2009b), predicts future decline in prodromal patients (Bakkour et al., 2009), and is detectable in cognitively normal individuals with preclinical AD (Dickerson et al., 2011, 2012).

This pattern of AD-related anatomical abnormalities is identified in comparison to cognitively intact individuals of similar age, which presumably controls for atrophy associated with the aging process. Yet it is known that aging itself is associated with regionally specific

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atrophy of the cerebral cortex, most prominently affecting prefrontal, lateral parietal, and sensorimotor regions (Allen et al., 2002, 2005; Brickman et al., 2007; Fjell et al., 2009b; Jernigan et al., 1991b, 2001; Kalpouzos et al., 2009; Raz et al., 1997, 1998, 2004, 2005; Resnick et al., 2003; Salat et al., 2004; Taki et al., 2004; Tisserand et al., 2002; Walhovd et al., 2005). However, a number of inconsistencies are present in the literature regarding the regions within the cerebral cortex that undergo the most substantial atrophy in normal aging, some of which may relate to technical issues related to MRI data acquisition and analytic methodology, and some of which may relate to sample-specific factors such as the presence of subclinical pathology (Raz and Rodrigue, 2006).

Despite observations that aging and AD exert regionally specific effects on the cerebral cortex, and studies demonstrating dissociations between aging and AD in analyses focusing on particular regions of interest (Dickerson et al., 2009a; Head et al., 2005), there has been relatively little comparative investigation of the spatial topographies of these processes surveying the entire cortex (Driscoll et al., 2009; Fjell et al., 2009a, 2010a; Jernigan et al., 1991a,b; McDonald et al., 2009; Ohnishi et al., 2001; Raji et al., 2009). In keeping with the methods at the time, the earlier studies (Jernigan et al., 1991a,b) focused on measurements of the volume of relatively large lobular cortical regions of interest, summarizing for example the parietal cortex and superior occipital cortex as a single measure, the superior posterior region. Ohnishi et al. (2001) performed a very early voxel-based morphometry study directly comparing aging vs. AD and identified several regions as being atrophic in normal aging, including prefrontal and lateral and medial parietal cortex, while the hippocampal formation and MTL cortices were relatively more prominently affected in AD. Raji et al. (2009) found similar results, with the additional observation of relatively prominent primary sensorimotor atrophy in normal aging which had not been observed by the prior studies. In addition, conflicting with Ohnishi, Raji et al. (2009) found that both aging and AD affected the hippocampal body and entorhinal cortex. The first study directly comparing cortical thickness between normal aging and AD focused on a frontostriatal network of regions which was relatively more atrophic in normal aging than a MTL network of regions which was relatively more atrophic in AD (Fjell et al., 2010a). In addition, atrophy of the MTL network was related to cerebrospinal fluid levels of amyloid-β and tau, but the frontostriatal network was not. This study did not compare amyloid-negative older adults to younger adults nor investigate the relationships of structural measures to cognition. Longitudinal investigations, while having the potential to resolve some of the conflicting data identified via the aforementioned cross-sectional studies, have to date only begun to provide novel insights as well as raising additional questions on this point, in part because of the relatively short duration of the initial reports (Driscoll et al., 2009; McDonald et al., 2009).

The existing data leave several important questions only partially answered, which we aimed to address here. First, with a few important exceptions mostly examining specific regions (Raz and Rodrigue, 2006; Rodrigue and Raz, 2004), much of the prior work reporting on differences in cortical structure between older and younger adults has not specifically investigated the relationship of age-related atrophy to cognitive test performance. Second, and perhaps most importantly, to our knowledge there have been no studies published to date that have compared cortical thickness in amyloid-negative cognitively intact older adults to that of young adults. Many cognitively intact older adults harbor AD pathology that is asymptomatic at the time of assessment (Hulette et al., 1998; Price and Morris, 1999; Troncoso et al., 1996). The development of molecular imaging techniques to identify the presence of fibrillar amyloid deposits has demonstrated that approximately 20–30% of cognitively intact adults over the age of 65 harbor silent brain amyloid (Becker et al., 2011; Jack et al. 2012; Mintun et al., 2006; Mormino et al., 2009; Morris et al., 2009), which is thought to be evidence of preclinical AD (Sperling et al., 2011). To date, although there are a growing number of investigations of the localization of cortical atrophy in cognitively normal individuals with brain amyloid (Becker et al., 2011; Chetelat et al., 2010; Dickerson et al., 2009b; Fjell et al., 2010b; Rodrigue et al., 2012), there has been essentially no work to our knowledge on the localization of cortical atrophy in cognitively normal older adults without evidence of brain amyloid, who presumably are experiencing brain changes associated with "normal" aging in the absence of AD pathology. Additional considerations include the following. Although temporal lobe regions, particularly the MTL, appear to be more prominently affected by AD than aging and frontal regions show the opposite pattern, the topography of overlap and lack of overlap in parietal regions is less consistent. Moreover, while the topographic patterns have received investigation, the relative magnitude of atrophy within distinct and overlapping cortical regions has not been reported. Finally, to date, the existing datasets have not been used to generate specific quantitative imaging biomarker summary measures that can be applied to new populations.

In the present study, we set out to systematically compare the spatial topography of cortical atrophy in AD with that of normal aging. Based on our and others' prior work using similar methods of measurement (Dickerson et al., 2009a, 2009b, 2011, 2012; Fjell et al., 2009b; Fjell et al., 2010a; Salat et al., 2004), we hypothesized that there are some cortical regions, such as those in the medial, ventral, and lateral temporal lobe, where the thickness of the cortical ribbon is predominantly affected by AD but much less so by normal aging. Other cortical regions, such as the sensorimotor cortices, were predicted to undergo atrophy in normal aging without appreciable additional atrophy in AD. Finally, frontoparietal cortices were predicted to show a more complex pattern in which some regions are affected much more by one process than the other (e.g., precuneus in AD; inferior frontal gyrus in aging), and some regions are affected by both (e.g., inferior parietal lobule, superior frontal gyrus). To investigate these hypotheses, we further performed specific focused measures of regional cortical thickness across the spectrum of age and AD dementia (young adult/older cognitively intact adult/older adult with mild AD) to determine the localization and relative magnitude of regional atrophy.

We believe there are three major novel contributions of the present work. First, we focused on a group of cognitively intact older adults without brain amyloid in order to determine whether cortical regions thought to be vulnerable to normal aging are substantially affected by aging even in the absence of cerebral amyloid. Second, we specifically examined the relationships of cortical thickness within age- vs. AD-vulnerable regions to cognitive test performance. Finally, in part to lay the foundation for future studies, we generated summary measures of the set of regions identified as being relatively AD-specific vs. those identified as being relatively aging-specific; these summary measures could be used in an unbiased fashion in future studies of normal aging or clinical or preclinical AD.

Participants and methods

Primary sample: participants, clinical assessment, and MRI data acquisition

A primary sample of 257 paid participants (age 18 to 96) was employed in this study. Data from subsets of the participants have been published in previous studies and are available as part of the OASIS sample (http://www.oasis-brains.org/) (Marcus et al., 2007). Four additional samples which are not part of the OASIS sample were also used in this study; one of these samples is described under the amyloid-negative section immediately below. The other three samples, used in the analysis of the similarity of cortical maps described at the end of the Participants and methods section, are detailed in a prior publication (Dickerson et al., 2009b).

Young adults were recruited from the community at Washington University. Non-demented and demented older adults were recruited from the ongoing longitudinal sample of the Washington University AD Research Center (ADRC). All procedures were approved by Washington University's human subjects committee. At study enrollment,