NeuroImage 146 (2017) 90–99

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Genetic and environmental influences on cortical mean diffusivity

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ARTICLE INFO

Keywords:
Mean diffusivity
Magnetic resonance imaging
Cortex
Twins
Heritability

ABSTRACT

Magnetic resonance imaging (MRI) has become an important tool in the early detection of age-related and neuropathological brain changes. Recent studies suggest that changes in mean diffusivity (MD) of cortical gray matter derived from diffusion MRI scans may be useful in detecting early effects of Alzheimer's disease (AD), and that these changes may be detected earlier than alterations associated with standard structural MRI measures such as cortical thickness. Thus, due to its potential clinical relevance, we examined the genetic and environmental influences on cortical MD in middle-aged men to provide support for the biological relevance of this measure and to guide future gene association studies. It is not clear whether individual differences in cortical MD reflect neuroanatomical variability similarly detected by other MRI measures, or whether unique features are captured. For instance, variability in cortical MD may reflect morphological variability more commonly measured by cortical thickness. Differences among individuals in cortical MD may also arise from breakdowns in myelinated fibers running through the cortical mantle. Thus, we investigated whether genetic influences on variation in cortical MD are the same or different from those influencing cortical thickness and MD of white matter (WM) subjacent to the cortical ribbon. Univariate twin analyses indicated that cortical MD is heritable in the majority of brain regions; the average of regional heritability estimates ranged from 0.38 in the cingulate cortex to 0.66 in the occipital cortex, consistent with the heritability of other MRI measures of the brain. Trivariate analyses found that, while there was some shared genetic variance between cortical MD and each of the other two measures, this overlap was not complete (i.e., the correlation was statistically different from 1). A significant amount of distinct genetic variance influences inter-individual variability in cortical MD; therefore, this measure could be useful for further investigation in studies of neurodegenerative diseases and gene association studies.

1. Introduction

Magnetic resonance imaging (MRI) measures of brain structure and function provide *in vivo* biomarkers to assess alterations associated with normal aging, disease onset and progression, as well as treatment efficacy. A substantial portion of the variance in MRI measures is under genetic control (Blokland et al., 2012; Eyler et al., 2011b; Kremen et al., 2010; Panizzon et al., 2009, 2012; Rimol et al., 2010). However, different MRI sequences and outcome metrics may provide unique information (Panizzon et al., 2009) and, thus, independent contributions to understanding disease state, risk, or progression. Recent studies have supported the strong potential for diffusion MRI (dMRI) to provide a sensitive marker of early disease onset or risk that may be independent from commonly used morphological metrics within the gray matter, such as cortical thickness. Metrics from dMRI provide an index of microstructural properties of the brain by measuring the degree and direction of movement of water molecules (Beaulieu, 2002), and strong relationships have been found between age and these microstructural properties of both white and gray matter (Abe et al., 2008; Benedetti et al., 2006; Salat et al., 2005).

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http://dx.doi.org/10.1016/j.neuroimage.2016.11.032
Received 15 April 2016; Accepted 12 November 2016
Available online 15 November 2016

Recent studies have found that the dMRI metric of mean diffusivity (MD), the average diffusion across all directions, may be a sensitive marker of neuronal damage in both cell bodies and axonal fibers. Changes in MD may result from a breakdown of cytoarchitectural barriers such as cell membranes that restrict water diffusion, or from a shift in the concentration of water between intra- and extracellular spaces (Neil et al., 2002; Sundgren et al., 2004; Van Camp et al., 2012). Altered MD within white and gray matter has been found in various diseases, including multiple sclerosis (Cercignani et al., 2001), Huntington's disease (Van Camp et al., 2012), Creutzfeld-Jakob disease (CJD; Demaerel et al., 1999; Ukisu et al., 2005; Zerr et al., 2009), and mild cognitive impairment (MCI; Fellgiebel et al., 2004; Kantarci et al., 2001; Ray et al., 2006). Such altered microstructure may presage future changes in cognition or morphological measures of the brain that are commonly used to assess disease progression. Indeed, baseline MD predicts later decline in episodic memory (Müller et al., 2005) and progression from MCI to Alzheimer's disease (AD; Douaud et al., 2013; Fellgiebel et al., 2006; Kantarci et al., 2005; Müller et al., 2005; Scola et al., 2010). Furthermore, MD alterations have been found in presymptomatic carriers of familial AD gene mutations (Fortea et al., 2010; Ryan et al., 2013) and in cognitively normal adults with evidence of amyloid deposition (Molinuevo et al., 2014). Thus microstructural changes may provide a useful marker for risk of future neurodegeneration, and in many of these studies, gray matter MD provided higher classification accuracy than did gray matter volume.

While most of the studies assessing the utility of dMRI-derived measures have focused on white matter or subcortical gray matter structures such as the hippocampus, cortical measures of dMRI have great potential to provide a unique marker of integrity. In contrast to WM, where motion tends to be restricted along the direction of axonal bundles, MD may be the most relevant dMRI measure in the cortex because water diffusion in gray matter (GM) is presumably isotropic (at least at conventional dMRI resolution). Altered cortical MD has been studied in the context of AD, as AD pathophysiology is highly associated with degeneration in cortical GM (Braak and Braak, 1991, 1996, 1998; Jack et al., 2013, 2008). Adults with either MCI or high genetic risk for AD show increased cortical MD compared to cognitively normal adults (Fellgiebel et al., 2004; Jacobs et al., 2013; Ray et al., 2006; Scola et al., 2010; Weston et al., 2015). Measures of cortical MD are also able to successfully discriminate the subtler differences between AD and dementia with Lewy bodies (Kantarci et al., 2010), and cortical MD begins to increase more generally in middle age (Ni et al., 2010). While the dMRI measures of white matter have been found to be heritable (Chiang et al., 2009; Kochunov et al., 2010), the genetic and environmental influences on cortical MD have yet to be elucidated.

Alterations in dMRI-derived measures within WM related to age, injury, or disease are often thought to reflect myelin damage and/or axonal injury, with supporting evidence coming from histological and lesion studies (Beaulieu, 2002, 1996; Concha et al., 2010; Fraidakis et al., 1998; Pierpaoli et al., 2001; Song et al., 2003, 2002, 2004; Sun et al., 2005). However, the neuroanatomical underpinnings of cortical MD remain unclear. Differences in MD have been proposed to reflect "expansion of the extracellular space corresponding to a decrease in membrane density due to cell degeneration" (Douaud et al., 2009). In this case, cortical MD may be directly related to cortical thickness in that accumulating microstructural damage could eventually manifest as macrostructural changes (i.e., reduced thickness). It is also possible that changes in cortical MD partially reflect contributions of myelinated fibers coursing through the cortical mantle. For instance, AD has been proposed as a response precipitated by age-related breakdowns in myelination (Bartzokis, 2011). The patterns of neurofibrillary changes related to AD appear in late myelinating cortical regions (Braak and Braak, 1996, 1998; Braak et al., 2000), and intracortical myelin may be particularly susceptible to such degeneration (Bartzokis, 2011; Bartzokis et al., 2007). Prior studies have found that changes in WM signal intensity subjacent to the cortex underlie age-related declines in white/gray contrast (Salat et al., 2009), and that MRI signal within cortical voxels may be partially influenced by intracortical myelin (Eickhoff et al., 2005; Paus, 2005). Therefore, factors that influence cortical MD may be similar to those influencing measures of MD sampled in proximal locations of WM if changes in myelination underlie variation in both measures.

Prior studies have found substantial genetic influences on most MRI measures of brain structure, including cortical thickness (Kremen et al., 2010; Panizzon et al., 2009; Rimol et al., 2010) and surface area (Eyler et al., 2011b; Winkler et al., 2012). Diffusion properties of the brain, particularly in WM, also appear to be heritable (Chiang et al., 2009; Kochunov et al., 2010). Elucidating the heritability of cortical MD will provide support for its biological relevance and to determine its usefulness in future gene association studies. It is also possible to calculate genetic correlations, which is the amount of shared genetic influences between structures or imaging modalities. Genetic correlations between structures have been used to provide insight into the structural organization of the brain (Chen et al., 2013, 2012; Eyler et al., 2011a). Examining the genetic correlation of cortical MD with other imaging phenotypes can determine whether this measure constitutes a unique imaging phenotype. For example, cortical thickness and surface area are both heritable but have little genetic overlap (Panizzon et al., 2009; Winkler et al., 2010), indicating that these measures capture unique neuroanatomical information. Such information can serve to sharpen the imaging phenotypes used in genetic studies and, in the case of cortical MD, determine whether it is worthwhile to collect dMRI in addition to more commonly acquired measures of brain structure such as cortical thickness.

In the present study, we employed classical twin methods in a large sample of middle-aged twins to determine genetic and environmental contributions to cortical MD. The twin model also allows us to investigate environmental and genetic correlations between cortical MD and both cortical thickness, a putative measure of cellular macrostructure, and WM MD subjacent to the cortical mantle, a microstructural measure of myelinated axons. The genetic correlation indicates the degree to which there are shared or distinct genetic influences on individual variations in these imaging measures.

2. Methods

2.1. Participants

Participants were from wave 2 of the Vietnam Era Twin Study of Aging (VETSA) project (Kremen et al., 2013, 2006). VETSA participants comprise a national, community-dwelling sample of male-male twins who are similar to American men in their age range with respect to health and lifestyle characteristics based on Center for Disease Control and Prevention data (Schoeneborn and Heyman, 2009). All served in the military service sometime between 1965 and 1975, but nearly 80% reported no combat exposure.

The VETSA2 MRI component included 447 subjects using standard MRI exclusion criteria (e.g., no metal in the body). Of these, diffusion data from 47 subjects and structural MRI data from 41 subjects was either missing or excluded due to poor quality (e.g., movement, artifacts, etc.). Subjects were included in the study if they had useable data from at least one modality. This resulted in a final sample of 420 subjects, 364 of whom had both structural and diffusion data available. The sample had a mean age of 61.8 years (range 56–66; SD=2.6), was primarily Caucasian (91.4%) and had a mean education of 13.8 (SD=2.1) years. The twin models were based on 96 monozygotic (MZ) pairs, 67 dizygotic (DZ) pairs and 94 unpaired individuals (i.e., participants whose co-twin either was not scanned or whose data was not useable). Members of each twin pair were scanned on the same magnet.

The study was approved by the Institutional Review Boards at the