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Microstructural changes and atrophy in brain white matter tracts with aging

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Abstract

Diffusion tensor (DT) magnetic resonance imaging (MRI) tractography was used to investigate microstructural and volumetric abnormalities of the major brain white matter (WM) tracts with aging in 84 healthy subjects. Linear relationships were found between age and mean diffusivity (MD) increase and fractional anisotropy (FA) decrease in all WM tracts, except the right cingulum and bilateral uncinate, where a linear correlation with age was found for FA only. Quadratic model fitted better MD and FA values of several tracts, including the corpus callosum, limbic pathways, and bilateral association, and corticospinal tracts. Age-related MD and FA abnormalities were associated with radial diffusivity increase in all WM tracts, while axial diffusivity changes were characterized by a considerable variation from a tract to another. A linear negative relationship with age was found for the volumes of the left cingulum and fornix, while the quadratic model fitted better age-related volume loss of corpus callosum and right inferior fronto-occipital fasciculus. Diffusion tensor magnetic resonance imaging may shed light into the complex pathological substrates of WM changes with aging.

Keywords: Aging; White matter tracts; Diffusion tensor MRI; Tractography; Atrophy

1. Introduction

Early diffusion tensor (DT) magnetic resonance imaging (MRI) studies of normal aging focused on 2 indexes (Madden et al., 2009a): mean diffusivity (MD), which is the average of the 3 eigenvalues of the DT and measures the magnitude of water molecule diffusion, and fractional anisotropy (FA), which is defined as a coefficient of variation of the eigenvalues and is an index of the degree of directionality of water diffusivity (Basser et al., 1994; Pierpaoli et al., 1996). However, the assessment of individual eigenvalues is likely to contribute to a better understanding of the pathological substrates associated with aging (Bennett et al., 2009; Burzynska et al., 2009; Davis et al., 2009; Madden et al., 2009b; Sullivan et al., 2010; Vernooij et al., 2008; Zahr et al., 2009; Zhang et al., 2008). The first eigenvalue is called axial diffusivity (diffusion parallel to the axon fibers; AD), whereas the second and third eigenvalues can be averaged and expressed as radial diffusivity (diffusivity perpendicular to the axonal fibers; RD) (Basser et al., 1994; Pierpaoli et al., 1996). Axonal damage, as occurs in secondary degeneration, is likely to result in decreased AD values (Pierpaoli et al., 2001), while myelin breakdown is associated with an increased RD and a normal AD (Pierpaoli et al., 2001; Song et al., 2002, 2003). More recently, a

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method to obtain estimates of white matter (WM) fiber bundle volumes using DT MRI has been developed (Pagani et al., 2007). This approach provides an index of atrophy derived from the transformation between an FA atlas (resuming average morphometry of a reference population) and individual subjects' FA maps (Pagani et al., 2007).

The assessment of the extent of age-related intrinsic changes and volume loss of specific WM pathways is likely to be more informative than that of global WM involvement (Johansen-Berg and Behrens, 2006). The location of WM abnormalities can be inferred from the analysis of regions of interest, voxel-wise comparisons, or projecting diffusion values onto a tract-based template (Madden et al., 2009a). All these approaches, however, make assumptions on the anatomy of the damaged WM tracts. An alternative strategy is to use DT MRI tractography to segment individual WM tracts (Johansen-Berg and Behrens, 2006). To date, only a few studies used quantitative DT MRI tractography to test the effect of aging on brain WM structures (Davis et al., 2009; Fjell et al., 2008; Madden et al., 2009b; Sullivan et al., 2010; Zahr et al., 2009), and only 1 tractography study reported AD and RD values of all the main cerebral WM tracts in adults between 20 and 81 years (Sullivan et al., 2010). The effect of age on DT MRI metrics (i.e., increased MD and decreased FA) varied from a fiber bundle to another, and was associated consistently with an increase in RD values in most WM tracts (Sullivan et al., 2010), thus suggesting demyelination as the most likely substrate of age-related WM abnormalities (Pierpaoli et al., 2001; Song et al., 2002, 2003). The volume loss of specific WM pathways with aging has never been assessed.

In this study, we investigated comprehensively the microstructural and volumetric abnormalities of the major inter- and intrahemispheric WM tracts with aging, using DT MRI tractography, in a large sample of healthy subjects spanning from the adolescence to the adult age range. Fiber bundles examined were the corpus callosum, limbic pathways (i.e., fornix and cingulum), major bilateral association tracts (i.e., uncinate, inferior fronto-occipital [IFO], inferior longitudinal [ILF], and superior longitudinal [SLF] fasciculi), and corticospinal tract (CST). Our main aims were to assess whether: (1) aging has an effect on different structural brain WM measures, such as diffusivity properties and regional atrophy; (2) the effect of age on WM tract abnormalities, if any, is linear or nonlinear; and (3) there is a relationship between microstructural and volumetric age-related abnormalities within each WM tract. We hypothesized that WM tracts would differ with respect to age-related changes in diffusivity properties and volume (Burzynska et al., 2009). In particular, we expected that the interhemispheric, limbic, and frontal association pathways would be the most damaged with aging. On the basis of cross-sectional (Bartzokis et al., 2001; Bartzokis, 2004; Courchesne et al., 2000; Jernigan et al., 2001) and longitudinal (Raz et al., 2005) studies showing that WM integrity and volume continue to increase into middle ages, remain relatively stable up to age of 40 to 50 years, and then undergo a steep decline, we also predicted that the quadratic function would improve the relations of diffusivity and volumetric age-related changes in most of the WM tracts. Another central question is whether WM diffusivity changes are independent of the corresponding fiber bundle atrophy (Fjell et al., 2008; Hugenschmidt et al., 2008). Diffusivity changes are related to several aspects of the WM microstructure, some of which are likely to also affect volume, e.g., degree of myelination and axonal degeneration (Basser et al., 1994; Pierpaoli et al., 1996). However, it is also expected that diffusivity metrics may be early markers of loss of tissue integrity that only at a later stage will be detectable by volumetric WM measures (Fjell et al., 2008; Hugenschmidt et al., 2008).

2. Methods

2.1. Subjects

Subjects were recruited by means of advertisements distributed in the community. All subjects were assessed clinically by an experienced neurologist. Participants were excluded if they had: (1) a history of major neurological, psychiatric, or cardiovascular diseases, or any other major systemic condition; (2) a history of alcohol or drug abuse; (3) an abnormal neurological examination; and (4) a WM hyperintensity (WMH) grade greater than 2 at the Wahlung rating scale score (Wahlund et al., 2001). Eight-four healthy volunteers (48 women and 36 men, mean age 44 years, range 13–70 years) were enrolled. Eighty-one subjects (96.4%) were right-handers and 3 subjects (3.6%) left-handers according to the 10-item version of the Edinburgh Handedness Inventory Scale (Oldfield, 1971). The main demographic characteristics of the subjects in each age group have been reported elsewhere (Pagani et al., 2008). Approval was received from the local ethical standards committee on human experimentation and written informed consent was obtained from all subjects participating in the study.

2.2. MRI data acquisition

Using a 1.5-T scanner (Avanto, Siemens, Erlangen, Germany), the following scans of the brain were obtained: (1) dual-echo (DE) turbo spin echo (SE), and (2) pulsed-gradient spin echo single shot echo-planar (PGSE-SS-EPI). Further details regarding the magnetic resonance (MR) acquisition protocol are reported elsewhere (Pagani et al., 2008).

2.3. MRI data analysis

All MRI analysis was performed by a single experienced observer, blinded to subjects' identity. WMHs, if any, were identified on dual-echo scans, and the WMH loads measured using a local thresholding segmentation technique