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REVIEW

DISCONNECTED AGING: CEREBRAL WHITE MATTER INTEGRITY AND AGE-RELATED DIFFERENCES IN COGNITION

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Abstract—Cognition arises as a result of coordinated processing among distributed brain regions and disruptions to communication within these neural networks can result in cognitive dysfunction. Cortical disconnection may thus contribute to the declines in some aspects of cognitive functioning observed in healthy aging. Diffusion tensor imaging (DTI) is ideally suited for the study of cortical disconnection as it provides indices of structural integrity within interconnected neural networks. The current review summarizes results of previous DTI aging research with the aim of identifying consistent patterns of age-related differences in white matter integrity, and of relationships between measures of white matter integrity and behavioral performance as a function of adult age. We outline a number of future directions that will broaden our current understanding of these brain–behavior relationships in aging. Specifically, future research should aim to (1) investigate multiple models of age–brain–behavior relationships; (2) determine the tract-specificity versus global effect of aging on white matter integrity; (3) assess the relative contribution of normal variation in white matter integrity versus white matter lesions to age-related differences in cognition; (4) improve the definition of specific aspects of cognitive functioning related to age-related differences in white matter integrity using information processing tasks; and (5) combine multiple imaging modalities (e.g., resting-state and task-related functional magnetic resonance imaging; fMRI) with DTI to clarify the role of cerebral white matter integrity in cognitive aging.

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Abbreviations: AD, axial diffusivity; DTI, diffusion tensor imaging; FA, fractional anisotropy; FLAIR, fluid-attenuated inversion recovery; fMRI, functional MRI; HARDI, high angular resolution diffusion imaging; MD, mean diffusivity; PCA, principal component analysis; RD, radial diffusivity; WML, white matter lesions.

Key words: white matter integrity, diffusion tensor imaging, aging, cognition, magnetic resonance imaging, disconnection.

Contents

INTRODUCTION

The broad array of human information processing abilities that we categorize as perception, attention, and memory are the result of coordinated processing among distributed brain regions (Mesulam, 1990; McIntosh, 2000). Disruptions to communication within these neurocognitive networks lead to cognitive dysfunction recognized as neurological disease (Geschwind, 1965a,b; Catani and Ffytche, 2005; Filley, 2005). But disconnection may also lead to measurable variations in performance that are well below the threshold for neurological disease.

In healthy aging, for example, behavioral research has long established that age-related declines occur in fluid (speed-based) measures, whereas crystallized (knowledge-based) measures are relatively preserved (Craik and Salthouse, 2008). More recently, neuroimaging research has revealed corresponding changes in the aging brain, including decreases in the integrity of the white matter that can occur in the absence of specific neurological disease. These recent findings have created a central role for the concept of cortical disconnection, via age-related declines in white matter integrity, in the cognitive neuroscience of aging

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(O'Sullivan et al., 2001; Bartzokis, 2004; Charlton et al., 2006; Andrews-Hanna et al., 2007; Salat, 2011).

Diffusion tensor imaging (DTI) is ideally suited for the study of cortical disconnection as it provides indices of structural integrity within interconnected neural networks. DTI measures the diffusion, or movement, of molecular water (Basser et al., 1994; Pierpaoli and Basser, 1996; Johansen-Berg and Behrens, 2009). Within fluid-filled spaces of the brain (e.g., ventricles), diffusion is nearly unbounded and thus non-directional (i.e., isotropic). Similarly, within the gray matter, diffusion is relatively isotropic as a result of non-uniform restriction of molecular movement by microstructures such as cell bodies and dendrites. In contrast, diffusion within the white matter is more directional (i.e., anisotropic). In the white matter, microstructures such as axonal cell membranes, myelin sheaths, and neurofilaments restrict molecular movement such that the primary direction of diffusion runs parallel to axons (Pierpaoli et al., 1996; Beaulieu, 2002; Le Bihan, 2003).

Integrity of white matter structures can be inferred from DTI-based measures of the rate and directionality of associated molecular diffusion. For example, fractional anisotropy (FA) is a scalar measure that indexes the anisotropic, or restricted, fraction of total diffusion. Higher FA values (i.e., closer to 1) reflect increased diffusion directionality, independent of the rate of diffusion, which is characteristic of diffusion along the length of white matter axons. Mean diffusivity (MD) indexes the average rate of diffusion, independent of the directionality. Lower MD values within the white matter are characteristic of regions where neural microstructures (e.g., axonal cell membranes, myelin sheaths, and neurofilaments) displace intra- and extra-cellular water.

White matter integrity can be further characterized by measuring the rate of diffusion along the primary (axial diffusivity, AD) and secondary (radial diffusivity, RD) axes of diffusion ellipsoids that summarize diffusion properties of each voxel. Animal studies have provided support for the notion that AD is sensitive to axonal differences and RD is sensitive to myelin changes (Song et al., 2003, 2005; Sun et al., 2006, 2008). In turn, these findings have guided interpretations of similar patterns in human studies (Bennett et al., 2010; Burzynska et al., 2010). For example, age-related damage to both axon fibers and the surrounding myelin sheaths is suspected when older adults show increases in FA that are accompanied by increases in both RD and AD. In contrast, more specific disruption of myelin is inferred when age-related RD increases occur in the absence of AD increase. These interpretations of the neurobiological substrates of AD and RD are limited when not considered in the context of the orientation of the principal diffusion direction (Wheeler-Kingshott and Cercignani, 2009). However, the utility of diffusivity measures (MD, AD, and RD) is strengthened by the notion that they may be more sensitive to white matter integrity differences than their more commonly used counterpart, FA. That is, in some cases, complementary changes in both AD and RD may lead to FA being relatively unchanged.

Beyond the measurement of white matter properties, DTI provides a basis for the anatomical reconstruction of white matter tracts throughout the brain. An illustration of these major white matter pathways is presented in Fig. 1. DTI tractography (or fiber tracking) algorithms estimate connections among interconnected voxels by propagating from a specified source region or between source and target regions. This reconstruction may be conducted in the native anatomical space of each participant, or in an averaged space that normalizes the anatomy across individual participants. Tractography and other voxel-wise analyses of DTI data have further variants, each with advantages and disadvantages, though a comparison of these different methodologies is beyond the scope of this article (Mori and van Zijl, 2002; Wakana et al., 2004; Catani and Ffytche, 2005; Catani, 2006; Smith et al., 2006; Nucifora et al., 2007; Jones, 2008). Tractography is emerging as an informative method for characterizing the major pathways of the white matter in the brain. It is important to note, however, that tractography and related DTI indices are measures of water diffusion and thus are indirect measures of structural connectivity (Jones et al., 2013). Further, structural and functional connectivity are not identical, because strong functional connections may exist between regions with limited structural connections (Honey et al., 2009).

Researchers frequently use DTI to study age-related differences in cerebral white matter integrity, as well as the relationships between measures of white matter integrity and behavioral performance as a function of adult age. The technology of DTI and related techniques, such as q-ball imaging and high angular resolution diffusion imaging (HARDI) continues to evolve, providing improved resolution of the orientation of white matter pathways (Tuch et al., 2003; Koenig et al., 2013; Nagy et al., 2013; Zhan et al., 2013). The majority of the research to date, however, addressing the relation of white matter integrity to age-related differences in cognition, has used conventional DTI and fiber tractography. The current review aims to summarize consistent patterns of results across these studies, discuss interpretations that can be drawn from DTI studies of cognitive aging and their limitations, and outline future directions that will broaden our current understanding of these brain–behavior relationships in aging.

WHITE MATTER INTEGRITY DECLINES IN AGING

Age-related declines in cerebral white matter integrity are well-documented, and the number of DTI investigations addressing age-related integrity differences is growing rapidly (Sullivan and Pfefferbaum, 2006, 2007; Wozniak and Lim, 2006; Malloy et al., 2007; Minati et al., 2007; Madden et al., 2009a, 2012; Salat, 2011; Carmichael and Lockhart, 2012). Across studies, the predominant findings are decreased FA and increased MD as a function of increasing adult age, suggesting an age-related decline in the composition and integrity of the