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Review

Aging of cerebral white matter

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ABSTRACT

White matter (WM) occupies a large volume of the human cerebrum and is mainly composed of myelinated axons and myelin-producing glial cells. The myelinated axons within WM are the structural foundation for efficient neurotransmission between cortical and subcortical areas. Similar to neuron-enriched gray matter areas, WM undergoes a series of changes during the process of aging. WM malfunction can induce serious neurobehavioral and cognitive impairments. Thus, age-related changes in WM may contribute to the functional decline observed in the elderly. In addition, aged WM becomes more susceptible to neurological disorders, such as stroke, traumatic brain injury (TBI), and neurodegeneration. In this review, we summarize the structural and functional alterations of WM in natural aging and speculate on the underlying mechanisms. We also discuss how age-related WM changes influence the progression of various brain disorders, including ischemic and hemorrhagic stroke, TBI, Alzheimer's disease, and Parkinson's disease. Although the physiology of WM is still poorly understood relative to gray matter, WM is a rational therapeutic target for a number of neurological and psychiatric conditions.

Contents

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1. Introduction

The central nervous system (CNS) has long been divided into gray and white matter based on the appearance of human brain tissue at autopsy. Gray matter is mainly composed of neuronal cell bodies, dendrites, axons, and glial cells and serves to process electrical and chemical signals for the purpose of interneuronal communication. White matter (WM) is mostly composed of bundled myelinated or unmyelinated axons and myelin-producing glial cells, among other glial cell types. WM volume has expanded during primate evolution (Hofman, 2014) such that WM occupies almost 50% of total cerebral volume in humans (Zhang and Sejnowski, 2000). In turn, most of the space within WM (up to 87%) is occupied by myelinated axons (Wang et al., 2008). WM is essential for the transmission of electrical signals across different brain regions, and WM malfunction can therefore lead to serious neurobehavioral and cognitive impairments (Bennett and Madden, 2014).

As with other organs, the brain undergoes a series of structural and functional changes during the aging process. Longitudinal and cross-sectional imaging studies have reported smaller global brain volumes (Driscoll et al., 2009; Seidler et al., 2010), reduced cortical thickness (Salat et al., 2004), and expansion of the ventricular system (Scahill et al., 2003) in the brains of older adults. Cerebral pathologies such as WM lesions, infarction, and cerebral microbleeds are also more common in older brains (Salat et al., 2004). As anatomical structure reflects physiological function, it is not surprising that many brain functions are also affected by aging. For example, declines in motor abilities (Seidler et al., 2010), sensory function (Brodoehl et al., 2013), and cognitive skills have all been observed with natural aging. Along with these functional declines, the cerebral levels of neurotransmitters such as dopamine (Wenk et al., 1989), acetylcholine (Gottfries, 1990), serotonin (Gottfries, 1990), and norepinephrine (Mei et al., 2015), and neurotrophic factors such as brain-derived neurotrophic factor (BDNF) (Terry et al., 2011) and nerve growth factor (NGF) (Zeng et al., 2011) are dramatically reduced in aging brains.

Although a number of age-related cerebral changes have been identified, the identity of those changes directly responsible for age-related declines in function remains controversial. It was previously held that the functional decline in aging brains was associated with significant and progressive neuronal loss in gray matter (Colon, 1972). However, this view has been challenged by Pakkenberg and Gundersen, who used an unbiased stereological approach to estimate the precise number of cortical neurons in three dimensions (Pakkenberg and Gundersen, 1997). They reported only 10% loss in the total number of neurons in the cortex of both sexes from 20 to 90 years of age. Subsequent studies further confirmed that the age-related decline in cognitive function is not accompanied by robust neuronal loss (Morrison and Hof, 1997). Instead, normal aging led to a reduction in WM volume by as much as 28% (Pakkenberg and Gundersen, 1997). With the advent of advanced imaging methods (to be discussed in Section 2), particularly diffusion tender imaging (DTI), higher resolution visualization of WM pathways has become possible. Thus, many studies have explored WM alterations in aging brains and have identified WM atrophy (Lemaitre et al., 2005), WM tract disruption (Shenkin et al., 2005), vessel impairments (Pantoni, 2002), increased inflammation (Sloane et al., 1999), and loss of myelination (Marner et al., 2003). More importantly, these age-related changes have been associated with functional deficits, such as sensorimotor (Fleischman et al., 2015) and cognitive impairments (Kohama et al., 2012) and psychiatric disorders (Fields, 2008). Indeed, age-related changes in WM have been shown to influence the pathogenesis and progression of many brain diseases.

In this review, we summarize current knowledge of age-related structural and functional alterations of WM and speculate on the underlying mechanisms. We also discuss the influence of age-related changes in WM on the progression of various neurological conditions, including stroke, traumatic brain injury (TBI), Alzheimer's disease (AD), and Parkinson's disease (PD). Despite progress in our understanding of WM structure and function, the physiology and pathology of WM changes with aging are still poorly understood compared to gray matter because of the greater historical emphasis on neurons. Nevertheless, it has become evident that WM is a valid therapeutic target for a number of brain injuries and disease states.

Search criteria

In the present review, PubMed was used to systematically identify studies investigating WM alterations in normal aging and various pathological contexts, including stroke, TBI, neurodegenerative diseases, MS, and schizophrenia. The search strategy was restricted to original studies and reviews published in English up to August 30, 2016. Search terms included (i) aging, older adults, or elderly; (ii) cerebral; brain; (iii) magnetic resonance imaging (MRI), fluid-attenuated inversion recovery (FLAIR), diffusion tensor imaging (DTI), positron emission tomography (PET), functional MRI (fMRI); (iv) Stroke; ischemia; hemorrhage; intracerebral hemorrhage (ICH) intraventricular hemorrhage (IVH); subarachnoid hemorrhage (SAH); Alzheimer disease (AD); Parkinson's disease (PD); Huntington's disease (HD); multiple sclerosis (MS); schizophrenia. The selected studies were screened for content to assure compliance with the aforementioned inclusion/exclusion criteria. A total of 199 publications were examined in this manner.

2. Emerging neuroimaging tools to detect age-related white matter alterations

In the middle of the 20th century, magnetic resonance imaging (MRI) measurements were developed as neuroimaging tools to identify and study WM alterations. The field of MRI has exploded since its introduction and MRI is now used to aid in clinical diagnoses.

Traditional MRI methods include T1-weighted sequences and T2-weighted sequences. T1-weighted sequences are often used to acquire high-resolution structural images of brain anatomy that typically maximize the contrast between gray matter, WM, and cerebrospinal fluid (CSF), and can thereby reveal the sizes of cortical and subcortical structures. In contrast, T2-weighted sequences are useful in detecting pathological lesions, such as damaged WM. For example, edema often accompanies pathological lesions and presents as a hyperintensity in T2 sequences. FLAIR (fluid-attenuated inversion recovery) MR images are T2-weighted

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