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Review

Genetics of ageing-related changes in brain white matter integrity – A review

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ABSTRACT

White matter (WM) plays a vital role in the efficient transfer of information between grey matter regions. Modern imaging techniques such as diffusion tensor imaging (DTI) have enabled the examination of WM microstructural changes across the lifespan, but there is limited knowledge about the role genetics plays in the pattern and aetiology of age-related WM microstructural changes. Family and twin studies suggest that the heritability of WM integrity measures changes over the lifespan, with the common DTI measure, fractional anisotropy (FA), showing moderate to high heritability in adults. However, few heritability studies have been undertaken in older adults. Linkage studies in middle-aged adults suggest that specific regions on chromosomes 3 and 15 may harbour genetic variants for WM integrity. A number of studies have investigated candidate genes, with the *APOE ε4* polymorphism being the most frequently studied. Although these candidate gene studies suggest associations of particular genes with WM integrity measures in some specific brain regions, the findings remain inconsistent due to differences in their methodologies, samples and the outcome measures used. The *APOE ε4* allele has been associated with decreased WM integrity (FA) in the cingulum, corpus callosum and parahippocampal gyrus. Only one genome-wide association study of global WM integrity measures in older adults has been published, and reported suggestive single nucleotide polymorphisms await replication. Overall, genetic age-related WM integrity studies are lacking and a concerted effort to examine the genetic determinants of age-related decline in WM integrity is clearly needed to improve our understanding of the ageing brain.

1. Introduction

White matter (WM) comprises long myelinated axons generally regarded as passive routes connecting grey matter regions to permit flow of information across brain regions that form brain networks (Fields, 2008). The importance of WM was not fully realised until studies investigating the role of brain structure and function in psychiatric disorders and cognition were undertaken in the last two decades (Filley, 2010; Thomason and Thompson, 2011). Additionally, recent developments in imaging technology have enabled a greater understanding of the anatomy and physiology of WM. This has led to an increase in studies investigating WM and its relationship with development, ageing and health.

The human brain is not completely developed at the time of birth. Brain volume increases from birth to young adulthood, remaining stable until middle age and decreasing thereafter (Brickman et al., 2011; Kochunov et al., 2012). There are early and late myelinating regions of the brain and even the thickness of WM fibres varies in early and late myelinating regions (Thomason and Thompson, 2011). The anterior regions of the adult brain have more unmyelinated axons compared to the posterior regions (Lamantia and Rakic, 1990). Ageing leads to degeneration of WM and thus decline in its integrity (Sullivan and Pfefferbaum, 2006). Histological studies in animals and humans have been used to examine age-related WM microstructural changes. These studies report age-related reduction in the number of myelinated fibres and alterations of the myelin sheath (Meier-Ruge et al., 1992; Peters, 2007; Tang et al., 1997). A variety of cerebrovascular changes also possibly contribute to the ageing-related WM microstructural changes observed (Back et al., 2011; Brown and Thore, 2011). Studies have also indicated that the observed age-related WM decline is not uniform (Sala et al., 2012). The late myelinating regions of the brain are more susceptible to atrophy in normal ageing than early myelinating regions (Bartzokis, 2004). Various patterns of WM degeneration have been observed such as an anterior–posterior gradient (Davis et al., 2009; Head et al.,

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2004; Sullivan and Pfefferbaum, 2006) or a superior–inferior gradient (Sullivan et al., 2010a,b) indicating a complex pattern of WM degeneration.

Of the various non invasive in vivo imaging technologies available, diffusion tensor imaging (DTI) is a sensitive and sophisticated technique to study WM integrity. DTI is based on measuring the diffusion of water molecules in brain tissues in the presence of a magnetic field (Basser et al., 1994; Pierpaoli and Basser, 1996) and it provides quantitative three dimensional analyses of WM microstructure. DTI analyses can be undertaken on specific regions of interest (ROIs), the whole brain or by tract-based analysis. DTI yields various measures of WM integrity including fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) (Appendix 1), of which FA is most commonly used. A number of studies have examined the relationships between these different DTI measures and histological findings (e.g. cell counts, staining, and manual tracing of axon tracts) from post-mortem brain (e.g. Budde and Frank, 2012; Hansen et al., 2011). This research suggests that the different DTI measures may be differentially sensitive to levels of myelination (FA and RD), axonal density/diameter (FA), axonal damage or loss (AD) (Bastin et al., 2009; Beaulieu, 2002; Budde et al., 2007; Song et al., 2003, 2005). However, the specific microstructural correlates of DTI measures are still not completely understood (Alger, 2012; Seiler et al., 2012) and many of these studies did not specifically investigate age-related changes. In the future, in addition to validating DTI measurement, histological/DTI studies may lead to a better understanding of the relationships between DTI measures and the underlying tissue characteristics.

DTI studies report a general increase in MD and RD and a decrease in FA with advancing age in several brain regions (Head et al., 2004; Pfefferbaum et al., 2005). However, AD varies with the WM region studied (Bennett et al., 2010; Burzynska et al., 2010; Madden et al., 2009; Zhang et al., 2010). These age-related changes may be due to alterations in WM microstructural properties such as damage and loss of myelin (Pakkenberg et al., 2003; Peters, 2002), or changes in brain water content, axonal density, diameter and inflammation. Macrostructural properties such as the topography of crossing fibres (Giorgio et al., 2008; Mori and Zhang, 2006; Sala et al., 2012) may also contribute to the observed DTI changes.

WM plays a key role in the co-ordination, integration and the efficient information transfer between various grey matter cortical regions. During ageing, there is degeneration of WM, which decreases this efficiency and the functionality of the brain. Indeed, age-related cognitive decline may be due to the degeneration of WM tracts (Grady et al., 1994; Greenwood, 2000). Study of the age-related micro structural changes observed in WM by DTI and related measures will assist in a greater understanding of the relationships between brain structure, function and disease.

Genetics may play a role in WM integrity changes observed with ageing. Heritability studies can provide evidence for the role that genetics plays in WM integrity across the lifespan. Even though the development of both WM and GM may share common genes, those related to myelin formation and oligodendrocyte signalling may act uniquely on WM, suggesting that the development and degeneration of WM may be at least be partially independent of GM. Although ageing-related atrophy is observed for both WM and GM, it is yet unclear whether WM atrophy leads to GM atrophy or vice versa or both. Hence, elucidation of the genes involved in WM integrity may clarify the relationship between WM and GM development and atrophy. It will also increase our knowledge of the role that genetics plays in WM integrity and age-related decline. This review summarises the previous findings on the genetics of WM integrity and provides suggestions for future research.

1.1. Method

Studies related to the genetics of WM integrity were retrieved in PubMed®, published until April 2012, using search criteria based on combinations of the following keywords: white matter integrity, DTI, micro structural changes, healthy, children, young, ageing or age-related or elderly or older or adults, linkage, gene* or genetics, heritability, association, and genome wide association studies (GWAS). Further reports were identified by hand-searching the citations of the retrieved references. From the results obtained, studies were retained for the review if they met the following criteria: were published in English in a peer-reviewed journal; were carried out on healthy individuals; were original investigations of genetic factors; had examined WM integrity using DTI; and the age group was specified. Conference abstracts were excluded.

2. Genetics

Although WM integrity in older adults has been extensively studied and reviewed (Madden et al., 2012), the role that genetics plays in WM integrity and decline has been less frequently examined in this age group. Hence, here we present the genetic studies undertaken across the lifespan.

2.1. Heritability/genetic correlation

Heritability is the proportion of the observed variation in a particular trait that can be attributed to inherited genetic factors. It is measured by estimating the relative contributions of genetic and non-genetic factors to the total variation of that trait in a population. A trait with heritability (h^2) less than 0.30 can be considered as low, between 0.30 and 0.60 as moderate and above 0.60 as highly heritable. A number of studies have examined the heritability of FA, AD and RD across the lifespan (Table 1).

2.1.1. FA

The heritability (h^2) of FA in several brain regions was observed to be low in children (Brouwer et al., 2010) whereas it was moderate to high in young healthy adults (Chiang et al., 2009b, 2011b; Jahanshad et al., 2010). An extended family study also demonstrated moderate heritability for FA of the whole brain ($h^2 = 0.52$) (Kochunov et al., 2010). In addition, FA of the corpus callosum was moderately to highly heritable ($h^2 = 0.49$–0.67) in older male twins (Pfefferbaum et al., 2001). High FA heritability for earlier developing WM regions compared to late developing regions has also been observed in a voxel-wise study (Lee et al., 2009) but was not demonstrated in a recent tract-wise heritability study (Kochunov et al., 2010). Also, the heritability of FA was greater in males, and in adolescence compared to early adulthood (Chiang et al., 2011b).

2.1.2. RD and AD

In children, both RD and AD were observed to be moderately to highly heritable ($h^2 = 0.30$–0.64) in the majority of WM tracts (Brouwer et al., 2010). In adults, the heritability of RD was observed to be moderate ($h^2 = 0.37$), whereas AD did not show significant heritability, suggesting a minor role of genetic factors for this trait (Kochunov et al., 2010).

The results from these studies suggest that the heritability of the most commonly used DTI measure, FA, is low in children while it is moderate to high in adults. An opposite pattern was observed for AD where heritability was moderate to high in children and not significant in adults. RD was observed to be heritable across the lifespan. A strong caveat is that relatively few studies have been undertaken in older adults. Studies using larger cohorts would provide a more accurate and better estimate of the heritability of DTI measures.