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SHORT REVIEW

White Matter and Cognitive Decline in Aging: A Focus on Processing Speed and Variability

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Abstract

White matter (*WM*) change plays an important role in age-related cognitive decline. In this review, we consider methodological advances with particular relevance to the role of WM in age-related changes in processing speed. In this context, intra-individual variability in processing speed performance has emerged as a sensitive proxy of cognitive and neurological decline while neuroimaging techniques used to assess WM change have become increasingly more sensitive. Together with a carefully designed task protocol, we emphasize that the combined implementation of intra-individual variability and neuroimaging techniques hold promise for specifying the WM-processing speed relationship with implications for normative and clinical samples. (*JINS*, 2014, *20*, 262–267)

Keywords: Reaction time, Information processing, Intra-individual variability, Diffusion tensor imaging, Dementia, Depression

INTRODUCTION

The relationship between age-related change in white matter (WM) and cognitive decline is becoming ever-more established (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Madden et al., 2012). Reflecting this, the *disconnection hypothesis* postulates a causal role for WM decline in disrupting information flow within neural networks in healthy aging as well as in age-related neurocognitive disorders, such as Alzheimer's disease (Bartzokis, 2004; O'Sullivan et al., 2001). However, the relationship between WM and cognition is lacking both in specificity and detail (Brickman et al., 2011). This selective review aims to emphasize several recent methodological developments, which are important in the continued elucidation of the role of age-related WM change in cognition and its wider implications in health and disease.

DETAILING THE LINK BETWEEN WHITE MATTER AND PROCESSING SPEED

Capturing Processing Speed Changes

Selective cognitive decline is a robust phenomenon in aging (Craik & Salthouse, 2008). Although well-practiced abilities and acquired knowledge show little decline until very late in life, mechanisms that underlie the efficiency of cognition, such as processing speed, executive function, and episodic memory, follow a linear decline that may start already in young adulthood (Hedden & Gabrieli, 2004; Salthouse, 2009, 2010; although see Nilsson, Sternang, Ronnlund, & Nyberg, 2009). Processing speed appears to be particularly sensitive to age and mediates at least some of the age-related declines in higher-level cognition (Salthouse, 1996b; Verhaeghen & Salthouse, 1997). Salthouse (1996b) proposed that reduced processing speed represents a core deficit in aging, which has stimulated a great interest in methods that can maximize the information gained from processing speed tasks (Balota & Yap, 2011).

One important development in the characterization of processing speed is the increased appreciation of intra-individual variability of reaction times (RT) at a trial-to-trial level (*RT inconsistency*; Dykiert, Der, Starr, & Deary, 2012; Hultsch & Macdonald, 2004). Above and beyond the average slowing of RTs (Verhaeghen & Salthouse, 1997), RT inconsistency increases reliably in old age (Hultsch, MacDonald, & Dixon, 2002; MacDonald, Hultsch, & Dixon, 2003; Verhaeghen & Salthouse, 1997). The importance of RT inconsistency as a cognitive construct has been demonstrated by evidence linking it to impairments in overall cognitive ability (Hultsch et al., 2002; MacDonald et al., 2003), physical function (Strauss, MacDonald, Hunter,

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Moll, & Hultsch, 2002), and even to impending death (MacDonald, Hultsch, & Dixon, 2008). Consequently, RT inconsistency has been proposed to reflect a measure of general neurological integrity at a biological level (Hultsch & Macdonald, 2004; Li, Lindenberger, & Sikstrom, 2001) and of general processing efficacy, including attentional and executive control, at a cognitive level (Duchek et al., 2009; Schmiedek, Oberauer, Wilhelm, Suss, & Wittmann, 2007).

The measurement of RT inconsistency warrants some methodological consideration. Since changes in RT inconsistency in aging are often accompanied by an average slowing of RTs, it is important to ensure that any RT inconsistency increase is not driven by changes in average RT (Hultsch et al., 2002). The coefficient of variation, which constitutes the intra-individual standard deviation divided by the intra-individual mean, has emerged as the standard measure of RT inconsistency (Jackson, Balota, Duchek, & Head, 2012). However, the suitability of this approach can be questioned based on the usual positive skew of RT distributions and the inherent assumption of distributional symmetry in the standard deviation (Balota & Yap, 2011).

By fitting empirical RT data to an Ex-Gaussian function, it is possible to characterize dissociable components of the distribution and thereby capture RT inconsistency more fully (Hultsch & Macdonald, 2004). Relative to other Ex-Gaussian parameters (*mu, sigma*), the parameter that describes the "slow tail" of the distribution (*tau*) appears to be a better predictor of general processing efficacy, as measured by tasks of working memory, reasoning and processing speed (Schmiedek et al., 2007), and to better discriminate between age groups (Spieler, Balota, & Faust, 1996; West, Murphy, Armilio, Craik, & Stuss, 2002). Individual components of the distribution can also be studied directly by rank ordering and plotting RTs for individual participants as a function of condition, as in Quantile and Vincentile plots (Balota & Yap, 2011). It is important to emphasize, however, that only computationally explicit models can be assumed to be commensurate with well-defined cognitive processes (Matzke & Wagenmakers, 2009; see diffusion model by Ratcliff, Van Zandt, & McKoon, 1999).

Capturing White Matter Changes

WM has been identified as an important contributor to processing speed slowing in aging (Madden et al., 2004). Whereas gray matter consists mainly of neuronal cell bodies, WM consists mainly of neuronal projections, which are coated with myelin to ensure efficient neural communication (Madden, Spaniol, et al., 2009). Consequently, WM decline could contribute to a breakdown of the efficacy of neural communication and, ultimately, speed of processing.

Further to a reduction of WM volume (Jernigan et al., 2001; Raz et al., 2005), old age is associated with an increased prevalence of white matter hyperintensities (WMH), which are best detected as areas of brightness on FLAIR magnetic resonance imaging (de Groot et al., 2000). The increase in WM hyperintensity prevalence has primarily been observed in periventricular and frontal areas (Raz, Rodrigue, Kennedy, & Acker, 2007; Ylikoski et al., 1995) and has shown robust associations with age-related cognitive decline (Gunning-Dixon & Raz, 2000). In the context of processing speed specifically, negative associations have been demonstrated with speeded performance in older adults (Bunce et al., 2007; de Groot et al., 2000).

An important limitation of volumetric and lesion techniques is that inferences are limited to regions affected by atrophy or WMH. Diffusion tensor imaging (DTI) provides a sensitive measure of microstructural properties and spatial organization of WM even when no significant disease is present (Madden, Bennett, & Song, 2009). Fractional anisotropy (FA) represents the most common DTI index and approximates the ratio between diffusion of water molecules parallel to the tract (axial diffusivity) and perpendicular to the tract (radial diffusivity). In line with the lesion findings, DTI investigations have revealed an age-related reduction of FA, particularly in frontal and parietal tracts, with greater effects in anterior compared to posterior segments within the fiber tracts (Davis et al., 2009; Gunning-Dixon et al., 2009). A link between WM microstructure and cognitive decline has also been demonstrated, with particularly consistent effects in the domains of processing speed and executive function (Madden, Bennett, et al., 2009).

Beyond average processing speed, RT inconsistency increases have been proposed to reflect the increased neural noise and less distinct cortical representations that could result from WM decline (MacDonald, Li, & Backman, 2009). Indicative of such a relationship, RT inconsistency appears to follow a U-shaped function across the lifespan (Williams, Strauss, Hultsch, & Hunter, 2007), which approximates the inverted U-function of WM volume (Gogtay et al., 2004). Furthermore, both reduced WM volume and an increased prevalence of WMH in older adults have been associated with measures of increased RT inconsistency, independent of mean RT, with promising results for the *tau* parameter of the Ex-Gaussian distribution (Bunce et al., 2007; Jackson et al., 2012; Walhovd & Fjell, 2007). Support for RT inconsistency as a reliable proxy of WM integrity across the lifespan has also started to emerge in DTI investigations (Fjell, Westlye, Amlien, & Walhovd, 2011; Tamnes, Fjell, Westlye, Ostby, & Walhovd, 2012).

Importantly, histopathological studies validate the neuroimaging findings by demonstrating age-related alterations in several aspects of WM, including axons, myelin and glia (Peters, 2002). However, since such cellular components are not easily distinguished *in vivo*, the relative influence of the neurobiological mechanisms underlying DTI and WM hyperintensity findings remains largely unknown (Assaf & Pasternak, 2008; Maillard et al., 2012). Some mechanistic information may be provided by the radial diffusivity measure in DTI, which has been linked to myelin-related effects in animal studies (Song et al., 2002). In aging, FA reductions are commonly accompanied by more prominent changes in radial diffusivity relative to axial diffusivity (Bennett, Madden, Vaidya, Howard, & Howard, 2010; Davis et al., 2009) and

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indices of myelin breakdown, including radial diffusivity, have been found to be closely related to processing speed (Jacobs et al., 2013; Lu et al., 2013; although see Burgmans et al., 2011). Thus, although a mechanistic account for the WM change that underpins age-related slowing is largely incomplete, demyelination represents a likely contributor.

The Issue of Causality

As the evidence above suggests, correlational data often represent the primary means of investigating interrelations of age, brain structure and cognition. Although a correlation cannot prove causation, the *implications* of causal hypotheses can be examined with correlational data (Salthouse, 2011). In the present context, the disconnection hypothesis represents the dominant causal hypothesis and postulates that WM changes mediate age-related cognitive decline (O'Sullivan et al., 2001). According to the Age-Brain-Cognition triangle proposed by Salthouse (2011), the implication of such a hypothesis would be a reduction or elimination of the correlation between age and processing speed when variation in WM is statistically controlled. Consistent with this, a reduction in age-related variance of processing speed has been demonstrated when a WM index is added to hierarchical regression models (Rabbitt et al., 2007; Salami, Eriksson, Nilsson, & Nyberg, 2012). Similarly, structural equation modeling has provided support for a mediating role for WM in age-related slowing (Burgmans et al., 2011; although see Charlton et al., 2008).

Although promising, an important caveat of mediation analyses is that because causality cannot be tested directly, examination of competing models is critical for enhancing confidence in the hypothesized model (Penke & Deary, 2010; Salthouse, 2011). For example, WM-cognition relationships are commonly reduced when age is controlled (Madden et al., 2012), which would be suggested by a model in which WM and cognition are coincidentally related given independent relations to age. Examination of competing models is therefore critical for evaluating the plausibility of the causal connections postulated by the disconnection hypothesis.

The Issue of Specificity

The widespread WM change in aging necessarily has broad effects on cognition (Gunning-Dixon & Raz, 2000). Nevertheless, the anterior-posterior gradient in WM decline and the particularly close relationship between WM and processing speed and executive function in old age suggest a degree of specificity (Davis et al., 2009; Madden et al., 2012). Comprehensive cognitive test batteries therefore remain essential for testing the domain specificity of any detected WM relationship. In the case of RT inconsistency, further mapping of the relationships with other domains has particular importance given its proposed role as a proxy of general processing efficacy (Schmiedek et al., 2007).

Another important consideration is the degree to which a chosen processing speed task measures processing speed *per se* (Albinet, Boucard, Bouquet, & Audiffren, 2012). The nature of the processing speed tasks in the context of age-related WM changes has ranged from visuospatial processing (Kerchner et al., 2012) to psychomotor function (Charlton et al., 2008) and various higher-order cognitive functions (Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2013). Although this demonstrates the reliability of age-related slowing, it does not specify processing speed as the driving factor (Cepeda, Blackwell, & Munakata, 2013).

Fundamental processing speed is defined as the speed at which other cognitive operations can be executed, which indicates an independence from higher-level cognitive operations and motor operations (Salthouse, 1996a). The age-related declines in executive function and motor speed (Joy, Fein, Kaplan, & Freedman, 2000; Salthouse, 1993) and their associations with WM (Gunning-Dixon & Raz, 2000; Sachdev, Wen, Christensen, & Jorm, 2005), therefore, make a strong case for controlling for such confounding factors. When such separation is lacking, as in the case of complex processing speed tasks, WM findings may reflect associations with executive function rather than fundamental processing speed *per se* (Salami et al., 2012). Similarly, since most tests of processing speed involve a motor response, motor slowing is likely to contribute to demonstrated relationships.

To capture processing speed independently of motor speed and executive processes, multiple speeded tasks can be combined in a composite score (Salthouse, 1996a). By analyzing the commonalities of tasks with variable methodologies (e.g., motor requirements) and scope (e.g., cognitive load/domain), the contributions from individual task demands are minimized in favor of the processing speed component of interest (Cepeda et al., 2013). An alternative or complementary approach is to include additional task conditions to allow processing speed to be dissociated from confounding variables by a method of subtraction. As an example, the digit-symbol substitution test can be divided into influences of motor speed, perceptual speed, memory and higher-level coding processes (Joy et al., 2000; Joy, Kaplan, & Fein, 2004). Demonstrating the relevance of subtraction in the present context, Madden, Spaniol, et al. (2009) demonstrated that the mediating role of WM was limited to a decisional component in a task-switching paradigm. Thus, to situate processing speed and RT inconsistency within the broader cognitive hierarchy and to evaluate their potential superiority over other cognitive variables in indicating age-related WM change tasks selection will be of utmost importance.

CLINICAL IMPLICATIONS

The value of a detailed description of the cognitive consequences of age-related WM changes extends to age-related neurocognitive disorders, such as dementia and depression (Madden et al., 2012). WM hyperintensities have not only been linked with global functional decline in old age but also with an increased risk of dementia and late-life depression (Debette & Markus, 2010; Firbank et al., 2012; Inzitari et al., 2009). Interestingly, increased RT inconsistency appears to

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be a feature of both depression and dementia (Kaiser et al., 2008; Tse, Balota, Yap, Duchek, & McCabe, 2010). In dementia, RT inconsistency predicts cognitive impairment over a five year period (Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010) and has been found to be more reliable than average RT in delineating groups with different levels of cognitive impairment (Dixon et al., 2007; Strauss, Bielak, Bunce, Hunter, & Hultsch, 2007). Moreover, recent evidence has indicated that changes in RT inconsistency in the early stages of dementia may be particularly well captured by the tau parameter of the Ex-Gaussian distribution (Jackson et al., 2012; Tse et al., 2010). Considering the brevity of RT tasks, a promising possibility therefore is to use RT inconsistency clinically to gain information about WM decline (Bunce et al., 2013) and to predict subsequent cognitive decline (Bielak et al., 2010).

CONCLUSION

In this review, we have offered a response to what has been identified as an imperfect relationship between WM and cognition (Brickman et al., 2011). RT inconsistency, particularly when captured by an Ex-Gaussian distribution, has been highlighted as a sensitive indicator of WM integrity and DTI has shown particular promise in allowing for a sensitive assessment of age-related WM change and its relationship with cognition. Along with the challenging issue of causality, the importance of an improved specification of fundamental processing speed and its place within the broader cognitive hierarchy has also been emphasized. The potential of WM changes as an early marker of cognitive decline in healthy aging as well as in age-related neurocognitive conditions highlights the importance of specificity, both in relation to the characterization of the WM changes and how such changes can be reliably detected by means of cognitive testing. By careful methodological consideration, the information gained from investigations of WM-cognition relationships can be maximized to advance our understanding of what underpins age-related cognitive decline in health and disease.

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