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Age related differences in reaction time components and diffusion properties of normal-appearing white matter in healthy adults

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ABSTRACT

Deterioration of the white matter (WM) is viewed as the neural substrate of age differences in speed of information processing (reaction time, RT). However, the relationship between WM and RT components is rarely examined in healthy aging. We assessed the relationship between RT components derived from the Ratcliff diffusion model and micro-structural properties of normal-appearing WM (NAWM) in 90 healthy adults (age 18–82 years). We replicated all major extant findings pertaining to age differences in RT components and WM: lower drift rate, greater response conservativeness, longer non-decision time, lower fractional anisotropy (FA), greater mean (MD), axial (AD) and radial (RD) diffusivity were associated with advanced age. Age differences in anterior regions of the cerebral WM exceeded those in posterior regions. However, the only relationship between RT components and WM was the positive association between DR in the body of the corpus callosum and non-decision time. Thus, in healthy adults, age differences in NAWM diffusion properties are not a major contributor to age differences in RT components. Longitudinal studies with more precise and specific estimates of regional myelin content and evaluation of the contribution of age-related vascular risk factors are necessary to understand cerebral substrates of age-related cognitive slowing.

1. Introduction

Advanced age is reliably associated with reduced speed of processing (Cerella, 1985; Salthouse, 1991), but the neural underpinnings of that association remain unclear. Drawing on the findings that link response slowing to diffuse axonal injury (e.g., Felmingham et al., 2004), many studies attempted to demonstrate the association between age-related differences in integrity of the cerebral white matter and age-related slowing (see Gunning-Dixon and Raz, 2000; Madden et al., 2009a for reviews). To date, the overwhelming majority of studies that examined relationships between speed of processing and diffusion properties of white matter have used mean or median reaction time (RT) on a variety of cognitive and perceptual tasks as the main indicator of speed of processing. However, most do not take into account heterogeneity of RT that usually shows markedly non-Gaussian distribution, and has been long conceptualized as complex phenomena comprised of multiple components (Salthouse, 1981) In addition, procedures based on indices of central tendency, such as Donders' subtractive method (Donders, 1969) and Sternberg's additive-factor method (Sternberg, 1969) do not take into account RT distribution and assume no temporal overlap between stages-an assumption that is virtually impossible to sustain.

Many approaches have been proposed to address the heterogeneous nature of RT and quantify its components. Although ex-Gaussian function fits RT data well, its parameters do not reflect clearly interpretable mental process (Matzke and Wagenmakers, 2009). Notably, all traditional methods do not take into account speed-accuracy trade-offs, which is especially important in study of age-related differences because older adults tend to emphasize accuracy more than younger adults do (Salthouse, 1979). The mathematical model proposed by Ratcliff (1978) was designed to overcome these limitations. Ratcliff's diffusion model successfully accounts for all aspects of RT data and decomposes them into meaningful mental processes: rate of information acquisition, response conservativeness and time spent on non-decision processes (Ratcliff and McKoon, 2008).

At the time of this writing, there is only one study of the associations between white matter properties and two of three RT components derived from the diffusion model: drift rate and non-decision time (Madden et al., 2009b). That study has several limitations. First, the diffusion parameters were estimated with a simplified version of the diffusion model (EZ), which was designed only for exploratory purposes and did not provide precise

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parameter estimates (Ratcliff, 2008a). Second, only two relatively small extreme-age groups were compared, and age-related differences were not investigated across the adult life span. Third, that study evaluated only two RT components, drift rate and non-decision time, while the neuroanatomical substrates of response conservativeness remained unexamined. Finally, in assessing the associations of RT components with the white matter indices, the study did not separate white matter hyperintensities (WMH) from the normally appearing white matter and thus confounded the influence of these breaches on the diffusion parameters of white matter. Because WMH burden increases with age, is associated with age-related slowing (Gunning-Dixon and Raz, 2000), has substantially altered diffusion properties (Maillard et al., 2013) and may account for a significant share of age-related differences in diffusion indices (Davis et al., 2012, Vernooij et al., 2008), controlling for the effects of WMH is essential for understanding the relationship between diffusion parameters of white matter and RT components.

To address these limitations, we investigated the relationship between age related differences in diffusion properties of the cerebral white matter and three RT components derived from the Ratcliff diffusion model: the rate of information accumulation (drift rate), response conservativeness (boundary separation), and non-decision time by taking the following approach. First, we applied the full diffusion model to decompose RT into three components as specified in the Ratcliff model. Second, we studied healthy adults spanning a wide age range. Third, we used the indices of white matter diffusion derived from diffusion tensor imaging (DTI) data restricted to normal appearing white matter after removing the WMH. Fourth, we used tract-based spatial statistics (TBSS, Smith et al., 2006), to identify multiple white matter pathways: the superior longitudinal fasciculus, the uncinate fasciculus, the cingulum adjacent to cingulate gyrus portion, the genu, body, and splenium of the corpus callosum, and the anterior, and posterior limb of the internal capsule. Our selection of pathways was based on the extant literature. White matter integrity in anterior and superior regions contributed to perceptual speed (Bucur et al., 2008; Kennedy and Raz, 2009; Turken et al., 2008). DTI parameters of uncinate fasciculus were associated with performance on tasks assessing executive functioning in older adults (Davis et al., 2009), suggesting this tract might be involved in response conservativeness. Frontal-striatum network was implicated in cognitive control (Liston et al., 2006), and the latter had been shown to play a role in response conservativeness (Dutilh et al., 2012; Saunders and Jentzsch, 2012). DTI parameters in the cingulum were associated with information processing speed (Sasson et al., 2012). FA in the posterior region was associated with sensory-motor responses (Sullivan et al., 2001). We also took care in selecting the skeleton locations that would be the least sensitive to multiple threats to validity of the TBSS analytic approach used in this study. Specifically, we avoided potentially relevant regions, such as fornix, because of its particular sensitivity to misregistration and noise (Smith et al., 2006; Bach et al., 2014). We modeled the relationships between RT parameters and white matter diffusion features in a structural equations modeling (SEM) path analysis framework, a multivariate approach that takes into consideration the mutual influence among the predictors and assessing the unique contribution of predictors to criteria. The extant studies indicate that anterior white matter regions and tracts evidence greater age-elated differences in comparison to posterior regions (the anterior–posterior gradient of aging hypothesis) (Head et al., 2004; Madden et al., 2009a), and the connections between high-order association cortices are more relevant to speed of information processing than to motor speed (Kennedy and Raz, 2009; Kerchner et al., 2012; Madden et al., 2009a). We therefore expected that age-related differences in two decision components of RT (drift rate and response conservativeness) would correlate with diffusion properties of anterior rather than posterior white matter, and would be related to the indices of white matter organization in the association and commissural rather than projection fibers. In contrast, we hypothesized age-related differences in non-decision time to show stronger associations with white matter diffusion properties in posterior rather than anterior regions, and in projection rather than association or commissural fibers.

2. Method

2.1. Participants

Participants were healthy community volunteers from the Metro Detroit area who were enrolled in a longitudinal study of healthy aging. They were recruited through advertisements in the local media and screened via a telephone interview and an extensive health questionnaire. Participants were ineligible if they reported history of cardiovascular disease, neurological or psychiatric conditions, head trauma with loss of consciousness for more than 5 min, treatment for drug and alcohol problems, or a habit of taking more than three alcoholic drinks per day. Persons with diagnosis of diabetes or thyroid dysfunction were also excluded from the study, as were those taking any anxiolytics, antidepressants or anti-seizure medication. None of the participants resided in a nursing home or an assisted-living facility.

All participants had corrected visual acuity of 20/50 or better (Optec 2000 apparatus; Stereo Optical, Chicago, IL) (ICO, 1984) without color blindness, and hearing of 40 dB or better for frequencies of 500–4000 Hz (MA27 audiometer; Maico, Eden Prairie, MN) (WHO, 1991); all were native English speakers, with a minimum of a high school education (or a GED diploma), and were consistently right-handed as determined by Edinburgh Handedness Questionnaire (Oldfield, 1971) score of 75% and above. To screen for dementia and depression, we used the Mini-Mental State Examination (MMSE: Folstein et al., 1975), with a cut-off of 26 (O'Connor et al., 1989) and depression questionnaire (CES-D; Radloff, 1977), with a cut-off of 15 (Burns et al., 2002). The participants provided written informed consent in accord with the guidelines of Wayne State University Institutional Review Board. In addition, for this study, the participants were screened for history of hypertension and were excluded if they were taking anti-hypertension medication. Participants who had no MRI data due to either being claustrophobic or having metallic implants were not included in this study.

Although the initial sample consisted of 100 participants, four participants had low rate of usable RT data identified by exponentially weighted moving average (EWMA) method (less than 90%) and the RT data of six participants did not fit the diffusion model. Thus, the total sample with complete data consisted of 90 healthy normotensive adults (90% of the original sample), 18–82 years of age. The excluded participants did not differ from the remaining sample on age ($t=-1.30$, $p=0.22$), education ($t=-0.54$, $p=0.60$), sex ratio ($\chi^2=-0.05$, $p=0.83$), and ethnic origin ($\chi^2=-0.15$, $p=0.70$) and thus were considered missing at random. Sample demographic information is presented in Table 1.

2.2. Reaction time task and analysis

2.2.1. Reaction time task

RT data were collected from a two-choice letter discrimination task (Thapar et al., 2003). Participants were seated in front of a 19-in. liquid crystal display (LCD) computer monitor in a quiet room. They were asked to sit comfortably and lean back in the chair. The