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White matter hyperintensities are associated with visual search behavior independent of generalized slowing in aging

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ABSTRACT

A fundamental controversy is whether cognitive decline with advancing age can be entirely explained by decreased processing speed, or whether specific neural changes can elicit cognitive decline, independent of slowing. These hypotheses are anchored by studies of healthy older individuals where age is presumed the sole influence. Unfortunately, advancing age is also associated with asymptomatic brain white matter injury. We hypothesized that differences in white matter injury extent, manifest by MRI white matter hyperintensities (WMH), mediate differences in visual attentional control in healthy aging, beyond processing speed differences. We tested young and cognitively healthy older adults on search tasks indexing speed and attentional control. Increasing age was associated with generally slowed performance. WMH were also associated with slowed search times independent of processing speed differences. Consistent with evidence attributing reduced network connectivity to WMH, these results conclusively demonstrate that clinically silent white matter injury contributes to slower search performance indicative of compromised cognitive control, independent of generalized slowing of processing speed.

1. Introduction

Consistent, gradual differences in cognition are commonly found among elderly individuals even in the absence of clinical diseases such as Alzheimer's disease, and are frequently ascribed to “normal” or cognitively healthy aging (Grady & Craik, 2000; Salthouse, 2009). Researchers have attributed cognitive differences with advancing age to multiple, possibly overlapping factors; some argue that global processing speed reductions explain a majority of cognitive impairment, while others attribute aging-related impairments to declines in prefrontal function and brain network connectivity (Greenwood, 2000; Nordahl et al., 2006; Salthouse, 1996; Salthouse, 2000; West, 1996). These speed and disconnection hypotheses are not mutually exclusive, yet they generate specific predictions regarding the effects of brain structural differences in healthy aging on cognition. If declines in processing speed predominantly explain cognitive differences, little to no residual performance differences should remain once generalized slowing is factored out (Salthouse, 1996; Salthouse, 2000). If some cognitive differences remain independent of speed differences, however, other hypotheses related to connection efficacy and degraded information transfer would contribute explanatory power to cognitive differences in healthy aging.

Advancing age also is associated with a variety of other disease processes, including clinically asymptomatic cerebrovascular disease (CVD), that can impact the results of cognitive tasks aimed at understanding specific differences in brain systems affected with age. White matter abnormalities linked to cardiovascular risk factors and CVD, such as white matter hyperintensities (WMH) seen on brain magnetic resonance images (MRI), increase with age and are correlated with declines in processing speed and cognitive control (DeCarli et al., 1995; DeCarli, Fletcher, Ramey, Harvey, & Jagust, 2005a; Gunning-Dixon & Raz, 2000; Mayda, Westphal, Carter, & DeCarli, 2011); previous research has shown that WMH are associated with frontal lobe and executive dysfunction

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regardless of where in the brain they are located (Tullberg et al., 2004). Recent research in our laboratory suggests at least some cognitive differences in healthy aging result from asymptomatic CVD contributing to altered connection efficacy and degraded information transfer between prefrontal systems and their cortical targets (Mayda et al., 2011; Nordahl et al., 2006). Yet the specific role of CVD-related degradations in network information transfer in terms of neurobiological and cognitive differences in healthy aging has not been fully explored. Previous aging studies showed correlations of WMH with fluid intelligence or neuropsychological measures (van den Heuvel et al., 2006; Rabbitt et al., 2007; Raz, Rodrigue, Kennedy, & Acker, 2007), but used broad-domain tools assessing global cognitive function rather than detailed cognitive neuroscience methods designed to tease apart distinct components of cognition, or utilized qualitative and semi-quantitative WMH measures. Additional studies have examined visual attentional search performance in relation to white matter integrity with diffusion tensor imaging (DTI), and have found that visual search performance was related to white matter tract integrity, but excluded participants with conditions such as diabetes or hypertension that contribute to white matter pathology, limiting generalizability to the full range of age- and CVD-related cognitive differences (Madden et al., 2004; Bennett, Motes, Rao, & Rypma, 2012).

One possible role of CVD in cognitive aging could be that WMH contribute to cognitive impairments by leading to generalized perceptual and motor slowing, affecting multiple cognitive domains. There is evidence suggesting that WMH affect frontal-subcortical systems associated with balance and motor speed (Poggesi et al., 2013). Other evidence, from previous studies of cognitively healthy older adults (OA), finds that the extent of white matter injury may affect speed and mediate cognitive differences in aging (Andrews-Hanna et al., 2007; Head, Rodrigue, Kennedy, & Raz, 2008; Madden et al., 2004; Nordahl et al., 2006; O'Sullivan et al., 2001; Smith et al., 2011; Sullivan et al., 2001; Ziegler et al., 2010). Another possibility is that WMH also affect cognition through injury to distributed cortical networks necessary for specific cognitive functions, such as cognitive control, independent of generalized slowing. This latter hypothesis is supported when generalized reductions in processing speed cannot address certain findings, such as associations between impaired structural connectivity (e.g. WMH) and *improved* cognitive performance or increased task-related activations (Cabeza, 2002; Greenwood, 2007; Mayda et al., 2011). This hypothesis is also consistent with findings that impaired prefrontal connectivity impacts cognitive control across several domains, including visual attention and working memory, in a manner separable from age-related processing speed differences (Braver & Barch, 2002; Rush, Barch, & Braver, 2006). The use of WMH as a proxy for injury to connectivity within broadly-distributed cognitive systems is supported by previous findings: WMH may detrimentally affect cognition by impairing neural transmission and intraneuronal connectivity (Gunning-Dixon & Raz, 2000), and WMH are associated with impaired activation of prefrontal systems under cognitive demand and altered connection efficacy of prefrontal systems (Mayda et al., 2011; Nordahl et al., 2006). The specific impacts of CVD-related white matter injury on processing speed and cognitive differences in healthy aging have received little study yet are crucial to understanding mechanisms of cognitive decline. Examining the role of CVD in cognitive decline in healthy aging has public health implications; early and aggressive treatment of vascular risk factors may deter brain injury and cognitive decline, and might suggest cognitive benefits of speed-preserving interventions.

Therefore we conducted a study to directly test whether individual differences in white matter injury in cognitively healthy aging, measured by WMH, contribute to differences in cognitive control independent of age-related generalized slowing. We designed a cognitive control paradigm (a visual search task where attentional control is controlled by working memory) emphasizing coordination of distributed frontoparietal control systems with visual cortex (Corbetta & Shulman, 2002; Kastner & Ungerleider, 2000). Our approach was designed to dissociate two visual search components: a generalized processing speed component reflecting time to conduct basic bottom-up search sensory and motor processing, and a top-down control component that augments basic search strategies.

We hypothesized that, among both young adult (YA) and OA subjects, search slope (the increase in log-normalized reaction time [ln RT] with additional distracters) would increase with task difficulty. In addition, we hypothesized that OA would show higher search intercepts (ln RT in each condition with no distracters present) than YA, representing age-related generalized slowing. We further hypothesized that, among OA, greater extent of WMH would be associated with impaired performance in this cognitive control task beyond generalized slowing (measured by a main effect of WMH volume producing increasingly longer ln RTs, controlling for baseline search intercept), explaining, in part, network disconnection leading to declines in cognitive performance in cognitively healthy older adults.

2. Method

2.1. Participants

Forty cognitively healthy OA and twenty YA were recruited. OA, aged 65–89 years and in stable health, were cognitively healthy controls (free of cognitive impairment or dementia) from the UC Davis (UCD) Alzheimer's Disease Center (ADC) participant pool, who received detailed neuropsychological testing to determine the clinical diagnosis of cognitively healthy or "normal," as described previously (He et al., 2012). OA participants possessed a range of whole-brain WMH volumes similar to the larger cognitively healthy aging population, enabling examination of the role of white matter injury previously linked to aging and CVD processes in cognition (Carmichael et al., 2010). YA aged 18–30 were recruited from UCD. All participants were right-handed, free of major illness, and not taking medications thought to affect cognition; all had normal or corrected-to-normal visual acuity and color vision, consented to participation, and received compensation. No participants were excluded based on gender, race, or ethnicity. The UCD Institutional Review Board approved the project. Procedures took 60–90 min with breaks as necessary. Two OA were excluded who did not complete testing, yielding 38 OA for study. One YA subject was excluded due to task non-compliance, yielding 19 YA.

2.2. Neuropsychological testing

Participants performed several standard neuropsychological tests reported in Table 1. OA performed more poorly than YA but exhibited no clinically significant cognitive impairment.

2.3. Cognitive control task

Participants performed a computerized cue-guided search task (Carlisle, Arita, Pardo, & Woodman, 2011; Wolfe, Horowitz, Kenner, Hyle, & Vasan, 2004; Woodman, Luck, & Schall, 2007) with 3 conditions requiring varying levels of top-down and bottom-up attentional control (Fig. 1), using Presentation® (v14.9, www.neurobs.com). Participants were required to report which of two targets (left- or right-oriented C, each presented in 50% of trials) was present in a set of distracters (up- and down-oriented C's) while reaction time (RT) was measured. Each C was 2.1° in diameter with a .41° gap, in an 8.6°-diameter ring. A central fixation cross began each trial (1000 ms), followed by a color cue indicating target color (1000 ms), then the search array (4000 ms). All stimuli were viewed against a black background on a 15.6″ screen at a 70 cm distance. There were 3 cue/stimulus colors (red, green, and blue, each presented randomly on 1/3 of trials), and three different conditions (Feature, Mixed, and Identity search).

2.3.1. Feature search condition

The target appeared in the cued color and all distracters (if present) were in one of the other two colors (randomly determined). Minimal top-down control should