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AGE-RELATED INCREASES IN RIGHT FRONTAL ACTIVATION DURING TASK SWITCHING ARE MEDIATED BY REACTION TIME AND WHITE MATTER MICROSTRUCTURE

Z. ZHU,[a*] J. G. HAKUN,[a] N. F. JOHNSON[a] AND B. T. GOLD[a,b,c*]

[a] *Department of Anatomy and Neurobiology, University of Kentucky, Lexington, KY 40536, USA*

[b] *Magnetic Resonance Imaging and Spectroscopy Center, University of Kentucky, Lexington, KY 40536, USA*

[c] *Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA*

Abstract—Age-related increases in right frontal cortex activation are a common finding in the neuroimaging literature. However, neurocognitive factors contributing to right frontal over-recruitment remain poorly understood. Here we investigated the influence of age-related reaction time (RT) slowing and white matter (WM) microstructure reductions as potential explanatory factors for age-related increases in right frontal activation during task switching. Groups of younger (*N* = 32) and older (*N* = 33) participants completed a task switching paradigm while functional magnetic resonance imaging (fMRI) was performed, and rested while diffusion tensor imaging (DTI) was performed. Two right frontal regions of interest (ROIs), the dorsolateral prefrontal cortex (DLPFC) and insula, were selected for further analyses from a common network of regions recruited by both age groups during task switching. Results demonstrated age-related activation increases in both ROIs. In addition, the older adult group showed longer RT and decreased fractional anisotropy in regions of the corpus callosum with direct connections to the fMRI ROIs. Subsequent mediation analyses indicated that age-related increases in right insula activation were mediated by RT slowing and age-related increases in right DLPFC activation were mediated by WM microstructure. Our results suggest that age-related RT slowing and WM microstructure declines contribute to age-related increases in right frontal activation during cognitive task performance. Published by Elsevier Ltd. on behalf of IBRO.

*Corresponding authors. Address: Department of Anatomy and Neurobiology, University of Kentucky College of Medicine, Lexington, KY 40536-0298, USA. Tel: +1-859-323-4813; fax: +1-859-257-6700.
E-mail addresses: zude.zhu@uky.edu (Z. Zhu), brian.gold@uky.edu (B. T. Gold).

Abbreviations: ANOVAs, analyses of variance; BOLD, blood-oxygen-level dependent; CC-Body, body of the corpus callosum; CC-Genu, genu of the corpus callosum; DB, digit span backward; DF, digit span forward; DLPFC, dorsolateral prefrontal cortex; DTI, diffusion tensor imaging; EPI, gradient-echo planar imaging; FA, fractional anisotropy; fMRI, functional magnetic resonance imaging; FMRIB, Functional MRI of the Brain software library; FWE, familywise error-rate; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; ROIs, regions of interest; RT, reaction time; TE, echo time; TR, repetition time; WM, white matter.

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INTRODUCTION

Human aging is associated with altered brain activation patterns on a number of cognitive tasks. Alterations in brain activation associated with aging tend to be especially pronounced on tasks that emphasize cognitive control processes (Drag and Bieliauskas, 2010). Cognitive control refers to a set of processes that enable humans to flexibly shape thoughts and behavior in order to accomplish internal goals (Miller and Cohen, 2001). One way to explore this cognitive ability is by using the task switching paradigm, in which participants are required to perform two separate tasks in isolation (non-switch condition) or switch between the two tasks (switch condition). The requirement to switch between tasks tends to prolong reaction time (RT), with this effect being especially pronounced in older adults (Kray and Lindenberger, 2000).

Young adults typically recruit a distributed set of brain regions, prominently involving frontoparietal regions, during task switching (Kim et al., 2012) and other forms of cognitive control tasks (Badre and Wagner, 2006; Cole and Schneider, 2007; Neumann et al., 2008). While a variety of age-related alterations in brain activation during cognitive control tasks have been reported, among the most common appears to be increased activation of the frontal cortex (DiGirolamo et al., 2001; Drag and Bieliauskas, 2010; Spreng et al., 2010; Gazes et al., 2012; Di et al., 2014). In particular, older adults are often found to show greater activation than younger adults in right frontal regions (reviewed in Dennis and Cabeza, 2008; Reuter-Lorenz and Park, 2010).

Despite the relative ubiquity of age-related right frontal over-recruitment, little is known about the factors that contribute to this phenomenon. Among the many neurocognitive changes associated with aging, two that hold high potential as contributors to age-related brain activation increases are RT slowing and white matter (WM) microstructure reductions. Both RT and WM microstructure have potentially high explanatory value as proxy variables of age-related blood-oxygen-level dependent (BOLD) activation increases because they change significantly with age, and have been found to correlate with BOLD activation magnitudes. For example, RT slowing is the most frequently reported age-related performance change (Salthouse, 1993, 1996), and many studies have revealed RT and BOLD magnitude relationships in older adults (Rypma et al., 2007; Davis et al., 2008; Gazes et al., 2012).

The microstructure of cerebral WM represents a potential contributor to age-related increases in brain activation because it consists of well-myelinated axons that transmit signals between different functional regions of the brain (Burzynska et al., 2011). Diffusion tensor imaging (DTI) provides an *in vivo* method for estimating WM microstructure by measuring the diffusion of water molecules in neural tissue (Basser and Pierpaoli, 1996; Le Bihan, 2003). For example, fractional anisotropy (FA) is a scalar value that describes the fraction of diffusion and its directionality. Age-related FA declines are well-established (Sullivan and Pfefferbaum, 2006; Madden et al., 2012), and may influence BOLD activation (Bennett and Madden, 2013). Specifically, the orientation of axons and their myelin sheaths running in parallel bundles facilitates the diffusion of the water molecules preferentially along their main direction. Thus, lower FA values may suggest reduced signaling/information flow across WM tracts (Pierpaoli and Basser, 1996). This could result in an increase in synaptic activity and BOLD response at the local level as a compensatory response to disconnection from a larger neuronal circuitry.

While a growing number of studies have begun to explore relationships between RT and WM microstructure or between one of these neurocognitive variables and frontal activation (reviewed in Bennett and Madden, 2013), few have explored the potential contributions of both RT and WM microstructure to age-related frontal over-recruitment. Such investigations have the potential to broaden our understanding of age-related increases in frontal recruitment, which may have implications for testing the efficacy of cognitive intervention programs in aging. In the present study, we first identified brain regions showing sensitivity to task switching across younger and older adult groups. Subsequent analyses focused on two right hemisphere regions that showed sensitivity to task switching and are also often over-recruited by older adults in cognitive control tasks (the right dorsolateral prefrontal cortex (DLPFC) and right insula). Correlation analyses explored potential associations between BOLD magnitudes in these regions and both RT and WM microstructure. Where correlations were observed, we conducted mediation analyses to determine if age-related over-recruitment in these right frontal regions could be explained by RT and/or WM microstructure. We hypothesized that increased brain activation in older adults compared to younger adults may be better explained by cognitive slowing and WM microstructure than chronological age. We reported the significant models due to space limitation.

EXPERIMENTAL PROCEDURES

Participants

A total of 65 healthy adults (32 younger adults, 33 older adults) participated in the present study. Written informed consent was obtained from each participant, and the study was approved by University of Kentucky Institutional Review Board. Participants were recruited from the Lexington community and from the University of Kentucky via flyers and newspaper advertisements. Participants were community-dwelling individuals who were native English speakers with normal or corrected-to-normal visual acuity. Exclusionary criteria for the study included the following: color blindness, a major head injury, stroke, a neurological or psychiatric disorder, high blood pressure, hypercholesterolemia, diabetes, heart disease, the use of any psychotropic drugs, or the presence of metal fragments and/or metallic implants contraindicated for magnetic resonance imaging (MRI).

Task switching performance is known to be correlated with intelligence and digit span (Kray and Lindenberger, 2000). The task switching paradigm employed in the present study involved non-verbal, perceptual switching. Thus, the Cattell Culture Fair (CCF) Intelligence Test (Cattell and Cattell, 1960) was used as a measure of intelligence because it assesses non-verbal intelligence associated with perceiving inductive relationships in shapes and figures. Digit span forward (DF) and backward (DB) were assessed with The Digit Span Subtests of the Wechsler Memory Scale (WMS III) (Wechsler, 1997). Totals for the DF and DB sets were based on the number of trials that were accurately reported in the correct order.

These cognitive tests were administered for potential use as covariates in our analyses in the event of significant group differences. However, there was no significant difference between younger and older groups in male/female ratio ($X^2 = 1.85$, $p = 0.17$), years of education [t (63) = 0.20, $p = 0.84$], IQ [t (61) = 1.20, $p = 0.24$], DF [t (61) = 0.32, $p = 0.75$], DB [t (61) = 0.35, $p = 0.73$] (Table 1). Thus, we did not include these demographic or cognitive test scores as covariates in subsequent analyses.

Task and procedure

Participants completed a color-shape task switching paradigm (Fig. 1). The stimuli consisted of two possible shapes (circle or square), in one of two possible colors (red or blue), presented in the center of the screen. The cue was presented for 150 ms and was followed immediately by the stimulus for 2650 ms. A fixation cross then appeared for 200 ms prior to the next cue word. A block design was employed which included four types of blocks: shape, color, switch (shape/color) and baseline fixation [in which participants focused their vision on a central cross hair (+)]. In the shape block, participants decided if a stimulus was a circle or square. In the color block, participants decided if a stimulus was red or blue. In the switch block, participants alternated between shape and color decisions. Participants were asked to press a response (left or right) button to indicate whether the stimulus was red or blue, or if it was a circle or square, depending upon the cue word. Participants were asked to respond as quickly and accurately as possible.

Task blocks were 60 s in duration, and fixation blocks were 30 s in duration. There were three runs. Each run