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Dynamic range in BOLD modulation: lifespan aging trajectories and association with performance

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ABSTRACT

Alteration of dynamic range of modulation to cognitive difficulty has been proposed as a salient predictor of cognitive aging. Here, we examine in 171 adults (aged 20–94 years) the effects of age on dynamic modulation of blood oxygenation–level dependent activation to difficulty in parametrically increasing working memory (WM) load (0-, 2-, 3-, and 4-back conditions). First, we examined parametric increases and decreases in activation to increasing WM load (positive modulation effect and negative modulation effect). Second, we examined the effect of age on modulation to difficulty (WM load) to identify regions that differed with age as difficulty increased (age-related positive and negative modulation effects). Weakened modulation to difficulty with age was found in both the positive modulation (middle frontal, superior/inferior parietal) and negative modulation effect (deactivated) regions (insula, cingulate, medial superior frontal, fusiform, and parahippocampal gyri, hippocampus, and lateral occipital cortex). Age-related alterations to positive modulation emerged later in the lifespan than negative modulation. Furthermore, these effects were significantly coupled in that greater upmodulation was associated with lesser downmodulation. Importantly, greater fronto-parietal upmodulation to difficulty and greater downmodulation of deactivated regions were associated with better task accuracy and upmodulation with better WM span measured outside the scanner. These findings suggest that greater dynamic range of modulation of activation to cognitive challenge is in service of current task performance, as well as generalizing to cognitive ability beyond the scanner task, lending support to its utility as a marker of successful cognitive aging.

1. Introduction

As we age, most fluid cognitive functions decline, including one of the most fundamental cognitive skills, working memory (WM) (Babcock and Salthouse, 1990; Park et al., 2002; Salthouse, 1994; Van der Linden et al., 1994). Both manipulation of items in WM (Dobbs and Rule, 1989) and the updating of this information (Artuso et al., 2016; Clarys et al., 2009; Hartman et al., 2001; Van der Linden et al., 1994) decline with increasing age. The *n*-back paradigm has been widely utilized in behavioral and functional magnetic resonance imaging (fMRI) studies of WM (Owen et al., 2005; Rottschy et al., 2012), as it requires participants to monitor and flexibly update items kept in WM, and because WM load can be parametrically increased to examine change in blood oxygenation–level dependent (BOLD) response to increasing cognitive demand. WM robustly engages regions of bilateral dorsolateral prefrontal cortex, posterior parietal cortex (PPC), cingulate gyrus, and lateral cerebellar cortex (Cabeza and Nyberg, 2000). The *n*-back task consistently activates regions of the cognitive control network: premotor, middle frontal gyrus, anterior cingulate gyrus, and PPC (Owen et al., 2005). In younger adults, increasing WM load is associated with increasing modulation of activation in these fronto-parietal regions (Manoach et al., 1997).

Parametric *n*-back tasks have been utilized across various populations and contexts (Braver et al., 1997; Callicott et al., 1999; Choo et al., 2005; Cohen et al., 1997; Druzgal and D'Esposito, 2001; Jansma et al., 2004; Jonides et al., 1997) including the study of normal aging (Cappell et al., 2010; Heinzel et al., 2014, 2016; Mattay et al., 2006; Nagel et al., 2009; Nyberg et al., 2009; Rypma and D'Esposito, 2000; Sala-Llonch et al., 2012; Schulze et al., 2011). In general (with the exception of Kaup et al. (2014) and Wishart et al. (2006)), aging studies rely on comparison of extreme

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age groups (i.e., young vs. old) to examine age differences in modulation to increasing WM load, rather than examining the entire adult lifespan. These comparisons find unilateral prefrontal cortex response in younger adults, but bilateral frontal activation in older adults, with some studies finding greater activation in old compared to younger adults, at lower (e.g., 1-back and 2-back) WM loads (Mattay et al., 2006; Prakash et al., 2012; Reuter-Lorenz et al., 2000; Schneider-Garces et al., 2010). These extreme age group comparisons, however, omit 2 important portions of the lifespan, namely middle-age and very old adulthood. In a growing number of recent studies (Ankudowich et al., 2016; Chan et al., 2014; Grady et al., 2006; Kennedy et al., 2015; Kwon et al., 2016; Park et al., 2013; Rieck et al., 2017), middle age has been illustrated to be an essential piece of information in determining when functional brain changes occur in adulthood. Structurally, the fronto-parietal regions included in the canonical WM network are known to degrade with age around this time in both gray and white matter (Kennedy and Raz, 2009; Raz et al., 2005), and these declines are related to poorer cognition (Kennedy and Raz, 2009; Raz and Rodrigue, 2006).

Recent research has pinpointed middle age as a time when important functional changes in modulation to difficulty appear (Kennedy et al., 2015; Rieck et al., 2017). Using a spatial distance judgment paradigm, Rieck et al. (2017) found reduction in dynamic range of BOLD modulation to parametrically increasing difficulty in both fronto-parietal upmodulation (i.e., the ability to increase activation from easier to more difficult conditions) and in downmodulation (i.e., ability to increase deactivation from easier to more difficult conditions) of deactivated regions (such as ventromedial prefrontal cortex) with age. This reduced dynamic range was evident in early middle age for downmodulated regions, but not evident until older age in upmodulated brain regions, suggesting that these modulatory processes follow different aging trajectories. Interestingly, it is increasingly hypothesized that these processes are not independent, but act in synergy. Turner and Spreng (2015) have hypothesized that aging brings about an increased coupling of activation of these “default” (i.e., medial frontal, anterior and posterior cingulate, and hippocampal formation) and “executive” (i.e., dorsolateral prefrontal, posterior parietal, and cingulate) systems, or Default-Executive Coupling Hypothesis of Aging, possibly as an adaptive support for declining fluid abilities with aging. Rieck et al. (2017) found significant coupling of upmodulated and downmodulated regions, in that individuals who showed greater modulation in one direction also showed greater modulation in the other direction. Interestingly, greater coupling was associated with higher fluid intelligence. To be able to interpret the nature of alterations in BOLD data, that is, whether they are beneficial, detrimental, or unrelated to performance, these differences need to be yoked to cognition, ideally to both task performance during scanning and to measures of related cognitive processes assessed outside of the scanner (Grady, 2012).

Here, we aimed to address these issues in the existing literature by examining the full adult lifespan, with substantial sample size, utilizing a richer parametric increase in WM load than generally used to determine the nature of age-related alterations in dynamic range by yoking BOLD modulation to task performance and out-of-scanner cognition. Thus, the current study sought to characterize age-related differences in modulation to parametrically increasing WM load in a large lifespan sample of healthy adults. Specifically, we aimed to examine when in the lifespan alterations to upmodulation and downmodulation occur, whether and how these shifts in dynamic range are coupled, and whether they are related to task performance and generalize to WM beyond the scanner environment. To test this, 171 individuals aged 20–94 years underwent fMRI scanning during a digit *n*-back paradigm with blocks of incrementally increasing WM load: 0-, 2-, 3-, and 4-back, allowing us to model both age and WM load as continuous variables. We hypothesized that both positive and negative modulation to difficulty would decrease with age, that this modulation would be significantly coupled, and that greater dynamic range of modulation would be associated with better WM, both during scanning and on a test of WM span.

2. Methods

2.1. Participants

Participants consisted of 171 individuals aged 20–94 years (mean age = 53.03 ± 19.13 years; 100 women; 71 men) recruited from the greater Dallas metro area via media advertisements and flyers. All participants received compensation for their time. Prior to enrollment, participants completed a health history screening, telephone, and in-person interviews. All individuals were screened against neurological, psychiatric, metabolic, and cardiovascular disease (except for controlled essential hypertension, $n =$ 35), head trauma with loss of consciousness, diabetes, and cognition-altering medications. To screen for dementia and depression exclusion, participants completed the Mini–Mental State Examination (MMSE; Folstein et al., 1975) and the Center for Epidemiologic Study Depression Scale (Radloff, 1977), with cutoffs <26 and ≥16, respectively (mean Mini–Mental State Examination = 29.04 ± 0.87, range 26–30; mean Center for Epidemiologic Study Depression Scale = 4.19 ± 3.79, range 0–16). Participants were fluent English speakers, right-handed, had a minimum of high school education or equivalent (mean education = 15.60 ± 2.47 years), and had normal or corrected-to-normal vision (at least 20/40); when necessary vision was corrected to normal using MRI compatible lenses during the scanning session. See Table 1 for breakdown of sample demographics by age group. Note, however, that age was sampled and analyzed as a continuous variable, unless specified otherwise. All participants provided written informed consent in accord with the University of Texas at Dallas and the University of Texas Southwestern Medical Center institutional review board guidelines.

2.2. Cognitive measures

On 2 separate days, prior to the MRI session, participants underwent extensive cognitive testing spanning a number of cognitive domains (as in Rieck et al., 2017). Because our fMRI task was focused on the domain of WM, in this study we focused on a similar out-of-scanner cognitive task: the Wechsler Adult Intelligence Scale–Digit Span subtest (Wechsler, 2008). There are 3 subsections of the digit span (DS)—forward, backward, and sequencing—that increment in difficulty, and thus, we use the more taxing span, Sequencing, for analysis in this study to best mirror the difficult nature of the *n*-back task implemented.

Table 1
Participant demographics by age group

Age	*N* (M/F)	Edu (SD)	MMSE (SD)	CES-D (SD)
Younger (20–35)	42 (18/24)	15.62 (2.17)	29.19 (0.94)	4.48 (3.62)
Middle (36–55)	47 (21/26)	15.28 (2.52)	29.26 (0.87)	4.98 (4.48)
Older (56–69)	38 (16/22)	15.84 (2.34)	28.89 (0.76)	3.40 (2.93)
Oldest (70–94)	44 (16/28)	15.73 (2.82)	28.77 (0.83)	3.77 (3.73)
Total	171 (71/100)	15.60 (2.47)	29.04 (0.87)	4.19 (3.79)

Key: CES-D, Center for Epidemiologic Study–Depression Scale; Edu, years of education; F, female; M, male; MMSE, Mini–Mental State Examination; SD, standard deviation.