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ORIGINAL ARTICLE

Greater BOLD Variability is Associated With Poorer Cognitive Function in an Adult Lifespan Sample

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Abstract

Moment-to-moment fluctuations in brain signal assessed by functional magnetic resonance imaging blood oxygenation level dependent (BOLD) variability is increasingly thought to represent important "signal" rather than measurement-related "noise." Efforts to characterize BOLD variability in healthy aging have yielded mixed outcomes, demonstrating both age-related increases and decreases in BOLD variability and both detrimental and beneficial associations. Utilizing BOLD mean-squared-successive-differences (MSSD) during a digit *n*-back working memory (WM) task in a sample of healthy adults (aged 20–94 years; $n = 171$), we examined effects of aging on whole-brain 1) BOLD variability during task (mean condition MSSD across 0–2–3-4 back conditions), 2) BOLD variability modulation to incrementally increasing WM difficulty (linear slope from 0–2–3-4 back), and 3) the association of age-related differences in variability with in- and out-of-scanner WM performance. Widespread cortical and subcortical regions evidenced increased mean variability with increasing age, with no regions evidencing age-related decrease in variability. Additionally, posterior cingulate/precuneus exhibited increased variability to WM difficulty. Notably, both age-related increases in BOLD variability were associated with significantly poorer WM performance in all but the oldest adults. These findings lend support to the growing corpus suggesting that brain-signal variability is altered in healthy aging; specifically, in this adult lifespan sample, BOLD-variability increased with age and was detrimental to cognitive performance.

Key words: aging, fMRI, MSSD, *n*-back, working memory

Introduction

Marked increases in intraindividual variability of cognitive performance across trials occurs with aging and is associated with poorer cognitive performance in both normal aging and in individuals with neurodegenerative or related disorders (for reviews, Hultsch et al. 2008; MacDonald et al. 2006). This pattern of increased variability of cognitive function has been attributed to increased noise in the system of an aging brain. Intraindividual variability of brain function, as measured by the blood oxygenation level dependent (BOLD) signal, has historically been considered as related to image acquisition or other non-neural nuisance effects (Smith et al., 2005); thus, traditional methods for examining the BOLD response have relied upon central tendency or mean parameters of interest. The central nervous system is inherently noisy (Faisal et al. 2008; Stein et al. 2005), consequently, variability in the BOLD signal is frequently considered "noise" to be accounted for, rather than a meaningful signal for study. There has been a recent shift in empirical work, however, suggesting that variability of the BOLD signal is meaningful in its own right, demonstrated in studies of development, aging,

disease status, task performance, and even pharmacological intervention (Garrett et al. 2010; McIntosh et al. 2010). Indeed, the variability of brain function may show utility as a novel individual difference measure in cognitive neuroscience (Mohr and Nagel 2010).

A handful of studies to date have examined BOLD variability in healthy aging individuals, utilizing mostly multivariate methods (Garrett et al. 2013; Grady and Garrett 2014 for reviews), and largely suggest that moment-to-moment fluctuations in BOLD variability are altered with increasing age and associated with cognitive performance as well as real-world cognitive outcomes. Compared to (and independent of) mean-BOLD amplitude, BOLD variability demonstrates 5 times greater power in predicting age, supporting the notion that BOLD variability contains unique and important age-related information (Garrett et al. 2010). Evidence also suggests differential regional BOLD variability is age-dependent, with older adults generally demonstrating lower BOLD variability cortically, but greater levels of BOLD variability subcortically, relative to younger adults, at least during cross-hair fixation (Garrett et al. 2010). In this early examination of BOLD variability, older relative to younger adults also displayed greater cortical BOLD variability in superior frontal and inferior temporal gyri and in the cerebellum (Garrett et al. 2010 Fig. 4A warm color scale), pointing against a strictly cortical versus subcortical aging-related delineation of BOLD variability differences. In another study, comparing task to fixation, older adults demonstrated greater BOLD variability than younger adults in primarily cortical regions, providing further evidence for age-related increases in variability (Garrett et al. 2013 Fig. 3A, cool scale regions). Similarly, at the network level, BOLD variability during resting state increased across the lifespan in the insula and ventral temporal regions, whereas regions in most other large-scale networks such as the thalamic, basal ganglia, visual, sensorimotor, central executive, and default mode networks, linear decreases were observed with increased age (Nomi et al. 2017). Thus, an admixture of age-related directionality has been reported, highlighting the importance of anchoring brain to behavior in the interpretation of these findings.

Some evidence suggests that these age-related differences in brain signal variability may be related to cognitive performance. Older age and greater BOLD variability in the nucleus accumbens have been associated with suboptimal financial decision-making performance (Samanez-Larkin et al. 2010); however, younger, faster, and more consistent cognitive performers demonstrated greater BOLD variability during perceptual matching, attentional cueing, and delayed match-to-sample tasks as compared to their older counterparts (Garrett et al. 2011). Finally, there is some limited evidence that suggests that BOLD variability may illustrate modulatory properties, and scale in response to increasing task difficulty (Garrett et al. 2015; younger adult placebo effects) and with the level of internal or external task demand, albeit less so in older, relative to younger, adults (Grady and Garrett 2018).

As it currently stands, it is unclear whether greater or lesser BOLD variability is detrimental or beneficial in the context of healthy cognitive aging. Interestingly, in a small group of healthy older individuals, lower memory scores and higher volume of white matter hyperintensities (WMH) were associated with greater BOLD variability in a mix of cortical and subcortical regions, including cerebellum, orbital frontal and superior temporal gyri and thalamus (Scarapicchia et al. 2018), suggesting that greater BOLD variability might be detrimental during aging. However, this seems to be in contrast to age-group comparison studies that indicate greater BOLD variability in younger, better cognitively performing adults (Garrett et al. 2011; for review see Grady and Garrett 2014). Potentially, instances of greater and lesser BOLD variability could occur differentially across the adult lifespan, vary by brain region or neural network, and may exhibit differential cognitive consequences among these. Further investigation of the association between BOLD variability and other well-known aspects of healthy aging is warranted. Establishing an adult lifespan trajectory of BOLD variability and its association with cognitive function will provide additional evidence for some of these questions and aid future investigations into pathological or disordered populations.

Previous work from our lab and others investigates how the aging brain responds functionally to incrementally increasing cognitive difficulty (e.g., Rieck et al. 2017; Kennedy et al. 2017; Hakun and Johnson 2017). Specifically, with increasing age, modulation of activation decreases in both fronto-parietal cognitive control regions as well as default mode regions, and this reduction in modulation is associated with poorer performance during the task, as well as poorer cognitive performance measured outside the scanner. Thus, dynamic modulation of (mean amplitude) BOLD in response to difficulty may be a reliable marker of healthy aging. However, it is unknown whether alterations in BOLD variability in response to cognitive challenge occur throughout the adult lifespan, or whether they relate to cognitive performance.

Therefore, the current study sought to investigate age-related differences in BOLD variability, as indexed by the mean square of successive differences (MSSD, von Neumann et al. 1941), during a digit *n*-back task (0-, 2-, 3-, 4-back) across an adult lifespan sample of healthy adults. Given the prevalence of bidirectional findings within normal aging, including increases in BOLD variability subcortically and at times in cortical regions (Garrett et al. 2010, 2013), coupled with the fact that increased variability within a system is generally detrimental (e.g., in the cognitive aging literature and in AD, Scarapicchia et al. 2018), we hypothesized that BOLD variability would mirror behavioral intraindividual variability and increase across the adult lifespan, or be bidirectional, demonstrating different patterns in subcortical regions compared to cortical regions. Additionally, we hypothesized that BOLD variability would up-modulate in response to increasing difficulty (i.e., WM load), and these modulatory effects would depend upon age (Garret et al. 2015; Garrett et al. 2011; Grady and Garrett 2018). Finally, we expected that age-related increases in BOLD variability would be associated with poorer cognitive function, as measured by in-scanner task accuracy and outside-of-scanner WM ability.

Materials and Methods

Participants

Study participants included 171 healthy individuals aged 20–94 (mean age = 53.03 ± 19.13 years; 100 women, 71 men), who were part of a larger study recruited from the greater Dallas-Fort Worth metro area (Kennedy et al. 2017). Participants were screened against neurological, psychiatric, metabolic, cardiovascular disease (except for controlled essential hypertension, $n = 32$), head trauma with loss of consciousness, diabetes, and cognition-altering medications. Participants completed the Mini Mental State Examination (MMSE) (Folstein et al. 1975) and the Center for Epidemiological Study Depression Scale

Table 1 Participant demographics by age group

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

Notes: Edu, years of education; F, female; M, male; SD, standard deviation. Age is used as a continuous variable in all analyses, but is presented here in arbitrary age groups to provide demographic information throughout the sample.

(CES-D; Radloff, 1977), with exclusion cutoffs ≤ 26 and ≥ 16 (mean MMSE = 29.04 ± 0.87, mean CES-D = 4.19 ± 3.79) to screen against dementia and depression, respectively. Participants were fluent English speakers, right-handed, had a minimum of high school education or equivalent (mean education = 15.60 ± 2.47 years), and normal or corrected-to-normal vision (at least 20/40). See Table 1 for sample demographics by arbitrary age group for display purposes (age is treated as a continuous variable in all analyses). All participants provided written informed consent in accord with the University of Texas at Dallas and University of Texas Southwestern Medical Center review board guidelines and participants received compensation for their time.

Cognitive Measures

Prior to the scanning visit, participants completed a comprehensive cognitive examination that spanned multiple cognitive domains. In this report, we focused on WM span utilizing the Wechsler Adult Intelligence Scale-Digit Span subtest (WAIS-DS; Wechsler 2008) as a measure of WM. The task contains three subsections, requiring participants to listen to a string of digits and/or letters and then repeating them back in either Forward, Backward, or letter-number Sequencing order. For each of these three subtests, the total number of correct trials served as the index of performance.

Blood Pressure Measures

Participants' blood pressure was measured at each of the three study visits using brachial cuff automatic sphygmomanometers via a Panasonic EW3153 at each of the two cognitive sessions and a Welch Allyn Spot Vital Signs 420 TB at the MRI session. Each measurement was taken after the participant had been in a seated position for a minimum of 5 min, arm horizontal, and legs uncrossed. Systolic and diastolic pressure were recorded in mm/Hg, as well as heart rate (HR) in beats per minute (bpm). Mean HR was calculated as the average bpm across the three visits.

MRI Protocol

MRI Scan Acquisition

Participants were scanned on a single 3 T Philips Achieva scanner equipped with a 32-channel head coil using SENSE encoding. BOLD data were collected using a T2∗-weighted echo-planar imaging sequence with 29 interleaved axial slices per volume providing full brain coverage and acquired parallel to the AC-PC line, ($64 \times 64 \times 29$ matrix, $3.4 \times 3.4 \times 5$ mm^3, FOV = 220 mm^2, TE = 30 ms, TR = 1.5 s, flip angle = 60°). Cerebral blood flow (CBF) was estimated using arterial spin labeled images from a pcASL sequence (labeling time = 1516 ms, postlabeling delay = 1500 ms, labeling plane offset = 20 mm, two-dimensional pcASL readout parameters TR = 4460 ms, TE = 17 ms, $64 \times 64 \times 29$ matrix; voxel size = $3.44 \times 3.44 \times 5$ mm^3, FOV = 220 mm^2, EPI factor = 35, 35 label-control pairs, M0 image = mean of control images, 5:20 min). High-resolution anatomical images were also collected using a T1-weighted MP-RAGE sequence with 160 sagittal slices, $1 \times 1 \times 1$ mm^3 voxel size; $256 \times 204 \times 160$ matrix, TR = 8.3 ms, TE = 3.8 ms, flip angle = 12°.

Functional magnetic resonance imaging (fMRI) Task Procedure

The fMRI task in this study has been described in detail previously (Kennedy et al. 2017). In short, participants completed a digit *n*-back task, that required individuals to monitor the identity of a series of digits and to indicate with a button press whether the current digit on the screen was the same or different from the one presented *n* trials previously. Prior to each block, a cue indicated which type of *n*-back participants would complete: 0-, 2-, 3-, or 4-back. Digits ("2–9") were presented in six pseudo-counterbalanced blocks for 500 ms, with a 2000 ms interstimulus interval, using Psychopy v1.77.02 (Peirce 2007, 2009). There were three runs total, yielding a total functional scan time of about 20 minutes.

Task Pretraining Procedure

Just before entering the scanner, participants were trained on the functional task to ensure their understanding. Each level of difficulty was demonstrated by a trained lab member; following the demonstration participants completed a brief practice. After exposure to each level of difficulty, participants completed a practice that closely resembled the in-scanner experience to ensure comfort in responding to task stimuli.

fMRI Data Processing

Utilizing SPM8 (Wellcome Department of Cognitive Neurology, London, UK) and in-house Matlab R2012b (Mathworks, Natick, MA) scripts, data were preprocessed and statistically analyzed. Art Repair toolbox (Mazaika et al. 2007) was used to identify potential outliers in movement (>2 mm displacement) and intensity shift (>3% deviation from the mean in global intensity spikes) in the EPI images. Runs with >15% of total volumes (~40 volumes) marked as outliers for movement were excluded (excluded $n = 3$). In order to be included in the analysis, participants were required to have at least two runs (out of three runs total) with quality data. Three additional participants were excluded for the following reasons: poor T1 acquisition ($n = 2$), no response on >15% of trials ($n = 1$). Functional images were adjusted for slice acquisition time and motion correction (using six directions of motion-estimates from ArtRepair). Individual participant's T1-weighted images were used for coregistration

purposes, to align the functional maps to standardized MNI space and the resulting normalized images were smoothed with an isotropic 8 mm FWHM Gaussian kernel.

ASL Data Processing

Preprocessing of the CBF data first required the separation of labeled and control images. Next, a difference image was calculated for each of the labeled and control images. The difference images were utilized to calculate perfusion images with the Bayesian Inference for Arterial Spin Labeling MRI (BASIL) toolbox (Chappell et al. 2009), available from the FMRIB Software Library (fsl.fmrib.ox.ac.uk/fsl/fslwiki/BASIL). Resulting images represent blood flow in gray matter regions. Each CBF image was coregistered to the participant's T1-weighted image. Cortical parcels were obtained using Freesurfer v5.3 (Fischl and Dale 2000) for each individual for all cortical gray matter regions in the Desikan atlas (Desikan et al. 2006). Whole-brain CBF was calculated as the average CBF across these parcels. See Rodrigue et al. (2020) for further details on the ASL data processing.

Data Analysis Approach

fMRI first-level analyses

In-house MATLAB 2019a scripts were utilized to calculate MSSD within-voxel (e.g., for each of n images sum(($image_{n+1}$—$image_n$)^2)/n) for each level of n-back difficulty (0-, 2-, 3-, and 4-back) for each participant. First, white matter and CSF time series were extracted from each participant's unsmoothed functional volumes for each run. Next, a set of nuisance regressors for each run was created using the six motion parameters estimated from realignment, the white matter and CSF time series, the square of each of these time series, the derivative of the raw and squared derivative time series, and dummy-coded regressors indicating volumes flagged for excessive motion. The functional volumes were then regressed on the nuisance regressors to obtain the residual time series using SPM12. Finally, because each condition occurred noncontiguously, MSSD was calculated from the start of each task block. Two contrasts of interest were modeled for each participant: mean condition MSSD (averaging across all four conditions 0-, 2-, 3-, 4-back), and linear MSSD (slope of MSSD in response to increasing WM load from 0- to 4-back; contrast weights −2.25, −0.25, 0.75, 1.75) to capture the effects of task performance on variability and effects of difficulty on variability, respectively.

fMRI second-level analyses

Group-level regression models were constructed for the two contrasts of interest, with age as a continuous, mean-centered predictor of MSSD (either the mean of conditions or linear contrast of difficulty). Additionally, given the potential contribution of vascular signals to the estimation of BOLD variability, we additionally controlled for the influence of two major vascular factors, HR and cerebral perfusion, including them as covariates of no interest in both SPM models. Note that results from models run with and without these second-level covariates did not differ in the spatial location or extent. Voxelwise regression SPM maps were corrected with a height threshold of $P < 0.001$ and cluster correction of $P_{FWE} < 0.05$.

In addition to controlling vascular factors at the second level, physiological noise in BOLD signal can be estimated at the participant level. See Supplemental Figure 3 for the presentation of the results after applying first-level preprocessing noise reduction techniques (Independent Components Analysis Automatic Removal of Motion Artifacts [ICA-AROMA, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/OtherSoftware]; Physiologic EStimation by Temporal ICA [PESTICA, https://www.nitrc.org/projects/pestica]); as an attempt to "clean" the data at the participant level prior to the calculation of BOLD variability. These preprocessing steps result in highly similar results to the models using second-level covariates only (Supplemental Fig. 3) and do not appear to remove a significant amount of signal that might potentially be related to physiological noise. Therefore, results presented herein are those utilizing HR and CBF as covariates at the second level, without the additional first-level preprocessing.

Testing for MSSD Effects on Cognition

From voxelwise SPM models, participant-level estimates of significant MSSD effects were extracted from each cluster using MarsBaR toolbox v0.42 (Brett et al. 2002) to examine associations with cognitive function. General linear models were tested using these MSSD estimates, age, and their interaction as predictors of cognitive performance (task accuracy and Digit Span scores) using RStudio version 1.2.5033 (R Core Team 2019). Significant interactions between these continuous variables were probed with simple slopes analyses and the Johnson-Neyman procedure (Preacher et al. 2006) using the "interactions" package in RStudio (Long 2019). Graphs were created with the *ggplot2* package (Wickham 2016). The authors have made these data and associated code publicly available upon publication at https://osf.io/hvejn/?view_only=b2ac4d588ae14902b1e4d7147f94f423.

Partial Least Squares-Correlation (PLS-C)

Given that multivariate techniques have been frequently employed when examining age-related BOLD variability (e.g., Garrett et al. 2010, 2011), PLS-C was additionally utilized to further investigate the association between age and MSSD. PLS-C was conducted using the Command-Line PLS application (http://pls.rotman-baycrest.on.ca/) via Matlab 2019a. The first table contained 171 rows representing each participant and columns for each voxel of mean MSSD across WM task conditions, while the second table consisted of again 171 rows and one column of age. A correlation matrix between the two tables was calculated and then decomposed using singular value decomposition, resulting in a single latent variable (regular behavioral PLS method; Supplemental Fig. 2A for a flowchart of the PLS-C analysis steps). "Brain saliences" were the left singular matrix (U) and were determined significant if the absolute value of the bootstrap ratio from 1000 bootstrap iterations was greater than 3 (|BSR| > 3). "Brain scores" were calculated as the dot product of the first table and significant brain saliences within gray matter voxels.

Results

Task Performance

Accuracy and response time were recorded for all trials and performance differences across WM load levels and age has been reported for this sample previously in Kennedy et al. (2017). In brief, for accuracy, there were significant effects of age (F [1169] = 50.13, $P < 0.001$) and WM load (F [3507] = 280.11, $P < 0.001$), with accuracy declining as both age and WM load increased, qualified by a significant age × WM load interaction (F [3507] = 12.68, $P < 0.001$) indicating lower accuracy with

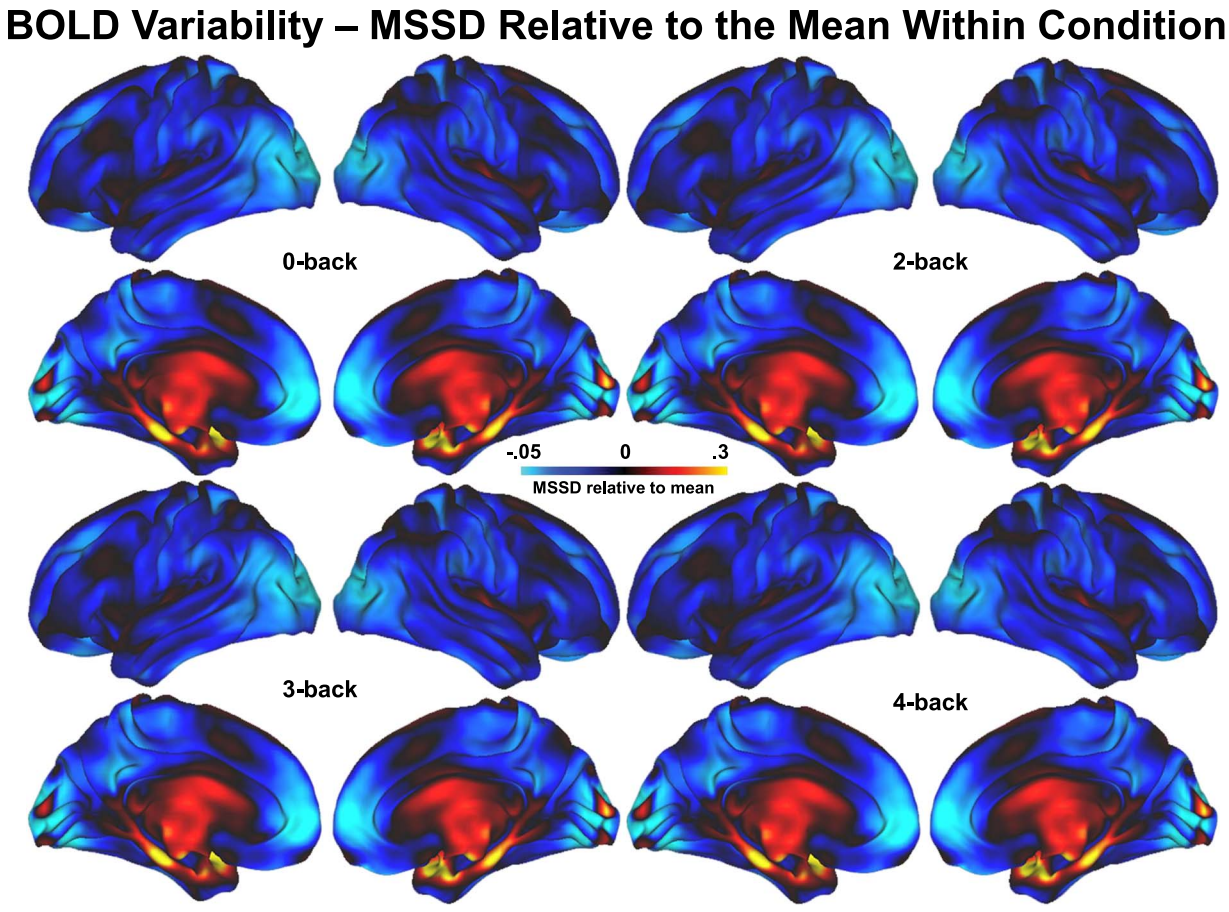

Figure 1. Regional BOLD variability relative to the mean for each of the *n*-back conditions. For each level of WM load, BOLD variability is displayed relative to the mean of MSSD within condition. Warm-colored voxels evidence greater BOLD variability for that condition, while cool-colored regions show lesser variability than the mean for that condition. Regions at the mean MSSD are shown in black.

increasing age and greater difficulty. Response time increased with increasing WM load (F [3507] = 335.95, $P < 0.001$), and age (F [1169] = 9.78, $P = 0.002$), and there was a trend for an age × WM load interaction (F [3507] = 2.40, $P = 0.067$).

Neuroimaging Results

Spatial Distribution of BOLD Variability during n-back Conditions

As a means of providing the spatial pattern of variability for each condition, voxel-wise variability was plotted relative to the condition mean across all participants, for each condition (0-, 2-, 3-, 4-back) in Figure 1. Warm color scale depicts the brain regions that demonstrate greater BOLD variability relative to the mean within the condition, while cool colors represent regions that evidence lesser BOLD variability, and voxels exhibiting the mean BOLD variability for that condition are presented in black. For example, medial frontal/frontal pole and lateral occipital cortices evidenced the least variability, relative to the mean, whereas medial temporal and subcortical variability was greater than the mean variability per condition for the whole lifespan sample.

Age-related BOLD Variability during n-back (Mean Condition MSSD)

The voxelwise multiple regression SPM model utilizing age as a continuous, mean-centered predictor of Mean Condition (across 0-, 2-, 3-, and 4-back) MSSD, controlling for vascular factors, resulted in widespread cortical and subcortical regions that evidenced greater BOLD variability with increasing age. Table 2 displays regional cluster information for mean MSSD. Figure 2A displays parametric maps of the gray matter regions that demonstrate significantly greater BOLD variability with increasing age, which included superior temporal, parahippocampal and fusiform gyri, superior parietal lobule, angular, precentral, superior frontal, middle frontal, and inferior frontal gyri, amygdala, nucleus accumbens, thalamus, and dorsal anterior cingulate cortex. Figure 2B illustrates the mean MSSD across all significant regions plotted against continuous age. No voxels evidenced lower MSSD with age in any condition. Age parametric maps are provided for each *n*-back condition in Supplemental Figure 1 and coordinates in Supplemental Table 1.

Partial Least Squares-Correlation (PLS-C) Analysis

To ease comparison to previous work that used a PLS approach to model BOLD variability, we also tested PLS-C model for the mean MSSD data (see Supplemental Fig. 2A). Significant brain scores, (i.e., BSR > 3 following 1000 bootstrap iterations), were positively associated with age (Supplemental Fig. 2B) in almost identical gray matter brain regions (Supplemental Fig. 2C) as found in the SPM analysis. This complimentary analysis provides supporting evidence for the univariate analyses

Table 2 Regions demonstrating age-related increases in BOLD variability (mean condition MSSD) during *n*-back conditions (0-, 2-, 3-, 4-back)

Cluster label	BA	*k*	X	Y	Z	*t*-value	Cluster- level $P_{FWE} < 0.05$
L/R fusiform gyrus	37	2418	−54	−54	−24	6.71	<0.001
			42	−72	−18	6.64	
R lateral cerebellum	52		48	−60	−36	6.16	
R parahippocampal gyrus	36	1756	21	−30	−9	6.56	<0.001
L amygdala	53		−24	3	−21	6.45	
R nucleus accumbens			15	6	−12	6.33	
L precentral gyrus	6	1055	−18	30	63	5.55	<0.001
R/L sup. parietal lobule	7		9	−66	72	5.50	
			−18	−51	81	5.26	
R mid. frontal gyrus	9	1111	42	18	33	5.19	<0.001
R precentral gyrus	6		30	−12	57	4.82	
R inf. frontal gyrus	45		51	27	12	4.78	
L anterior cingulate gyrus	24	243	−9	−9	30	5.18	<0.001
			−9	6	27	4.96	
			−15	24	15	4.70	
R anterior cingulate gyrus	24	106	15	24	15	5.17	0.007
			12	9	24	4.30	
			12	−12	30	4.17	
R/L thalamus	50	117	0	−15	6	5.09	0.004
			0	−6	3	5.00	
			−6	−21	12	4.15	
L insula	13	339	−42	−18	3	4.82	<0.001
L sup. temporal gyrus	22		−57	−36	9	4.79	
L insula	13		−36	−24	12	4.58	
L angular gyrus	39	285	−36	−51	42	4.67	<0.001
L postcentral gyrus	1		−33	−36	57	4.49	
L sup. parietal lobule	40		−45	−39	51	4.48	
L mid. frontal gyrus	9	208	−42	36	45	4.42	<0.001
L sup. frontal gyrus	8		−39	12	36	4.20	
			−45	18	45	4.10	
R mid. temporal gyrus	21	75	69	−36	3	4.03	0.032
R sup. temporal gyrus	22		69	−21	−6	3.83	
			51	−21	−15	3.42	

Note: BA, Brodmann area; L, left; R, right; sup., superior; mid., middle; inf., inferior.

reported above using SPM. Notably, both analytical methods result in widespread cortical and subcortical regions that evidence higher BOLD variability with increasing age, and no regions that evidence lower BOLD variability with increasing age.

Age-Related BOLD Variability Modulation to Difficulty (Linear Slope MSSD)

The voxelwise multiple regression SPM model testing age effects on BOLD variability modulation of MSSD in response to increasing WM load (controlling for vascular factors), identified a significant age × difficulty interaction in a cluster spanning left posterior cingulate, right precuneus, and right cuneus regions. See Table 3 for cluster information and Figure 3A for parametric map illustration. Greater BOLD variability modulation to difficulty was observed with increasing age (Fig. 3B). To probe the interaction between age and task difficulty on BOLD variability, Figure 3C plots the association between age and condition variability at each level of *n*-back difficulty. This figure illustrates that in this cluster, BOLD variability decreases with age during the easiest task condition (0-back) whereas at higher levels of WM load, BOLD variability increases with older age. In other words, younger adults display a pattern of decreasing variability or down-modulation as the task increases in difficulty, whereas this association flips across the lifespan where older adults exhibit increasing or up-modulation of BOLD variability as the task becomes more difficult. Although the slopes of BOLD variability across the lifespan do not significantly differ from zero, the pattern is suggestive of a differing association that tracks with difficulty.

Associations between Age-Related BOLD Variability and WM Performance

To test for associations between BOLD variability and WM performance, MSSD was extracted from the significant clusters from each of the two models (i.e., mean condition and linear slope MSSD). Clusters from the effect of age on mean condition BOLD variability were combined into one average MSSD variable, after the effects discussed below were found to be consistent across cortical and subcortical regions (given previous literature suggesting age-related differences in BOLD variability cortically vs. subcortically). The single significant cluster from the effect of age on BOLD variability modulation (i.e., in posterior cingulate/precuneus) was examined separately. GLMs were conducted to examine whether estimates of MSSD (from mean condition

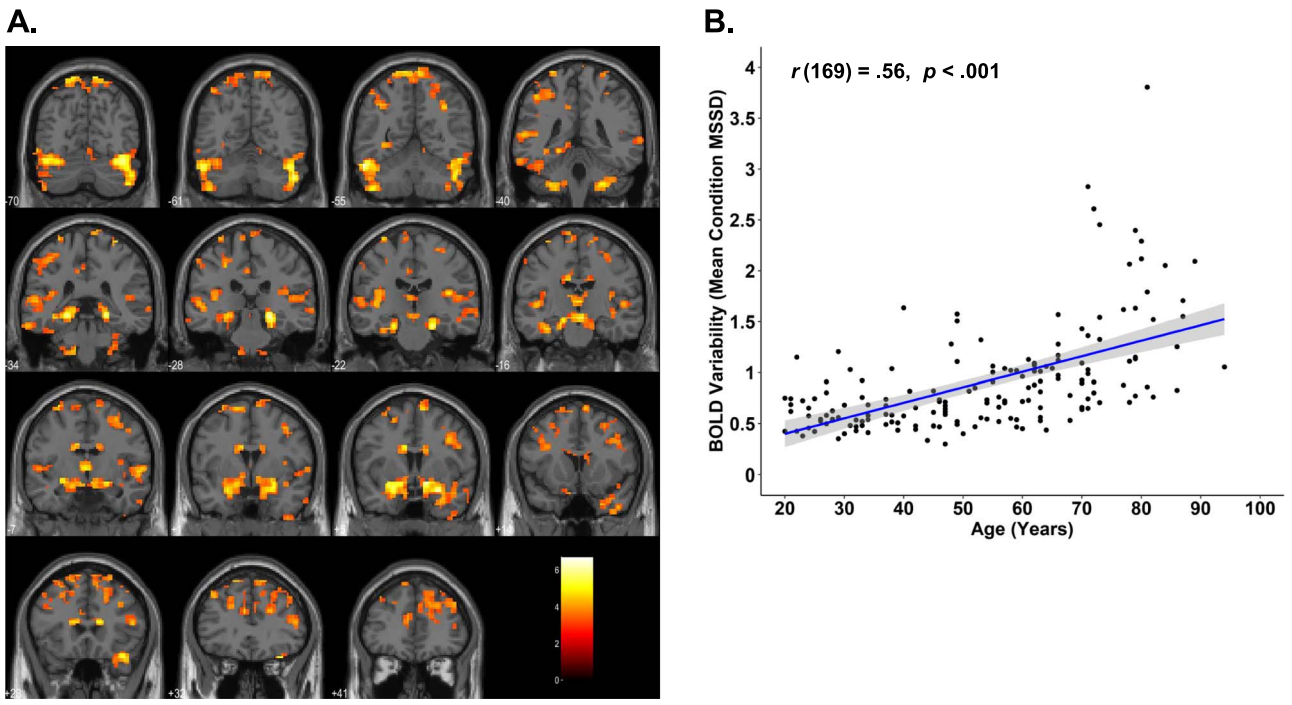

Figure 2. Effects of age on regional BOLD variability (mean condition MSSD) during *n*-back task. (A) Displays regions that are significantly increased in variability (greater MSSD) with increasing age during task conditions (mean MSSD during 0-, 2-, 3-, and 4-back), overlaid on coronal slices. Regions demonstrating increased age-related BOLD Variability (mean MSSD) include parahippocampal gyrus, amygdala, nucleus accumbens, fusiform gyrus, thalamus, superior parietal lobule, precentral, superior frontal, middle frontal, angular, superior temporal, and inferior frontal gyri, and dorsal anterior cingulate cortex. (B) Illustrates the slope of MSSD increase with age in these regions.

Table 3 Regions demonstrating age-related BOLD variability modulation in response to WM load (linear contrast of 0-, 2-, 3-, 4-back)

Cluster label	BA	k	X	Y	Z	t-value	Cluster- level $P_{FWE} < 0.05$
L posterior cingulate gyrus	31	46	−12	−57	27	4.34	0.026
R cuneus	19		15	−69	30	3.81	
R precuneus	7		3	−72	30	3.66	

or linear slope contrasts) predict WM accuracy during scanning and/or WM performance assessed by WAIS Digit span. All variables were continuous and mean-centered.

Accuracy During fMRI *n*-back Task

BOLD variability (mean condition MSSD)

A GLM was tested with age, mean condition MSSD, and their interaction term entered as predictors of mean task accuracy (across 0-, 2-, 3-, and 4-back conditions). There was a significant effect of Mean MSSD (F [1167] = 9.40, P = 0.003), as well as an age × mean MSSD interaction (F [1167] = 9.57, P = 0.002) on *n*-back accuracy. Simple slopes analyses and the Johnson-Neyman procedure were used to deconstruct the significant interaction (Preacher et al. 2006) and indicated a significant negative slope between accuracy and BOLD variability that weakened as age increased, suggesting greater variability is associated with lower accuracy in adults aged 20–66 years, after which the association becomes nonsignificant (see Fig. 4A).

BOLD Variability Modulation (linear slope MSSD)

A second GLM was tested with age, BOLD variability modulation MSSD (from posterior cingulate/cuneus), and their interaction as predictors of task accuracy. There was a significant effect of MSSD on *n*-back accuracy (F [1167] = 4.91, P = 0.03), and no significant age × MSSD interaction (F [1167] = 1.24, P = 0.27), indicating that greater BOLD variability modulation to difficulty was associated with poorer accuracy on the task, an association that was not age-dependent (see Fig. 4B).

Performance on Digit Span Test

BOLD variability (mean condition MSSD)

Three separate GLMs were conducted with age, mean condition MSSD, and their interaction, predicting digit span forward, backwards, and sequencing. There were no significant effects of Mean MSSD on digit span forward, (F [1167] = 0.01, P = 0.91), nor on sequencing: (F [1167] = 0.87, P = 0.35). However, there was a significant effect of mean MSSD (F [1167] = 11.00, P = 0.001), qualified by an age × mean MSSD interaction (F [1167] = 5.70,

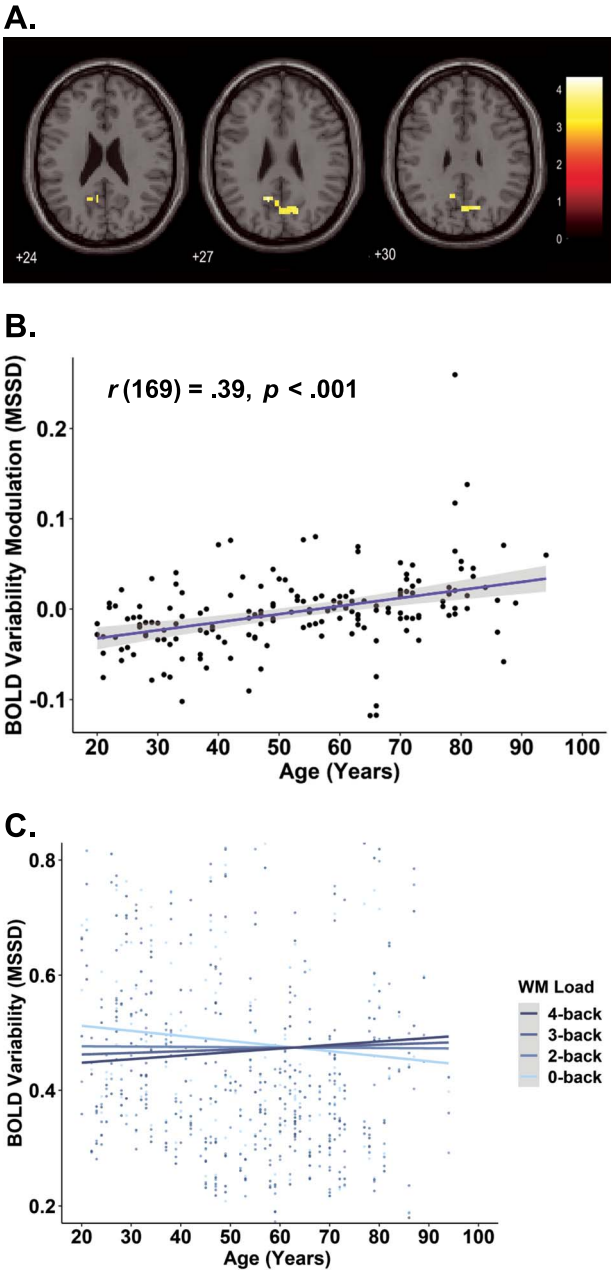

Figure 3. Effects of age on BOLD variability modulation to difficulty. (*A*) Displays regions that evidence a significant age-dependent increase in variability (greater MSSD) in response to difficulty (linear slope of 0-, 2-, 3-, and 4-back), overlaid on axial slices, including left posterior cingulate gyrus, right cuneus, and right precuneus. (*B*) Illustrates the slope of BOLD variability modulation increase with age in these regions. (*C*) Plots condition MSSD-age associations for each level of WM load. During the easiest condition (0-back), BOLD variability decreases across the lifespan, while the more difficult WM load conditions (2-, 3-, 4-back) exhibit increased MSSD with older age. To put it differently, younger adults evidence decreasing MSSD with increasing difficulty while older adults display the opposite, namely increasing BOLD variability with higher levels of difficulty. The slopes in 3C were estimated with full data, however for ease of illustration the data range is truncated.

$P = 0.02$) on digit span backwards. Simple slopes analysis indicated that greater mean BOLD variability was associated with poorer WM performance, from age 20 until 73, when the association becomes no longer significant (see Fig. 5A).

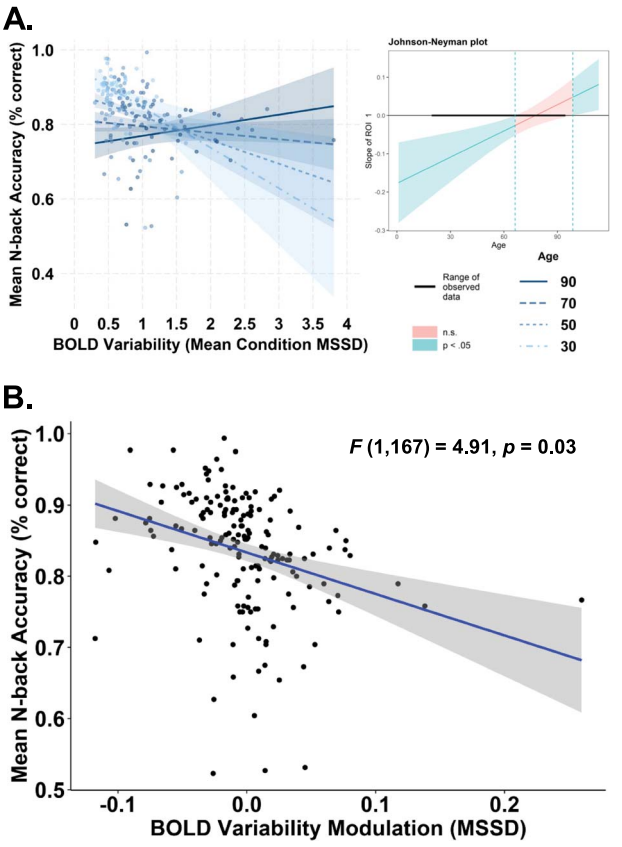

Figure 4. Association between age-related increased BOLD variability (mean condition MSSD and linear MSSD) and *n*-back task performance. (*A*) Illustrates the interaction among age, BOLD Variability (mean MSSD), and *n*-back task accuracy. The region of significance is indicated in the top right, with a significant association identified in ages 20–66. The plot on the left represents the slope between MSSD and accuracy for participants aged 30, 50, 70, and 90. (*B*) Illustrates the association between BOLD variability modulation and accuracy on the *n*-back task.

BOLD variability modulation (linear slope MSSD)

GLMs were created with age, linear MSSD, and their interaction, separately predicting digit span forward, backwards, and sequencing. A significant effect of linear MSSD emerged for digit span forward: (F [1167] = 4.69, P = 0.03), see Fig. 5B and a trend was observed for digit span backwards: (F [1167] = 3.41, P = 0.066), illustrated in Fig. 5C, such that greater BOLD variability modulation was associated with poorer digit span forward and backward performance, an association that did not depend upon age. There was an effect of BOLD variability modulation (F [1167] = 10.42, P = 0.002), as well as a significant age × BOLD variability modulation interaction (F [1167] = 5.55, P = 0.02) on digit span sequencing. Simple slopes estimation indicated that there was a significant slope between BOLD variability modulation and digit span sequencing performance between the ages of 20 and 66. Greater BOLD variability modulation to difficulty was associated with poorer sequencing performance, until the mid-60s, after which the association becomes nonsignificant (see Fig. 5D).

Discussion

The current study demonstrated that BOLD variability, on average across all participants within condition, evidenced

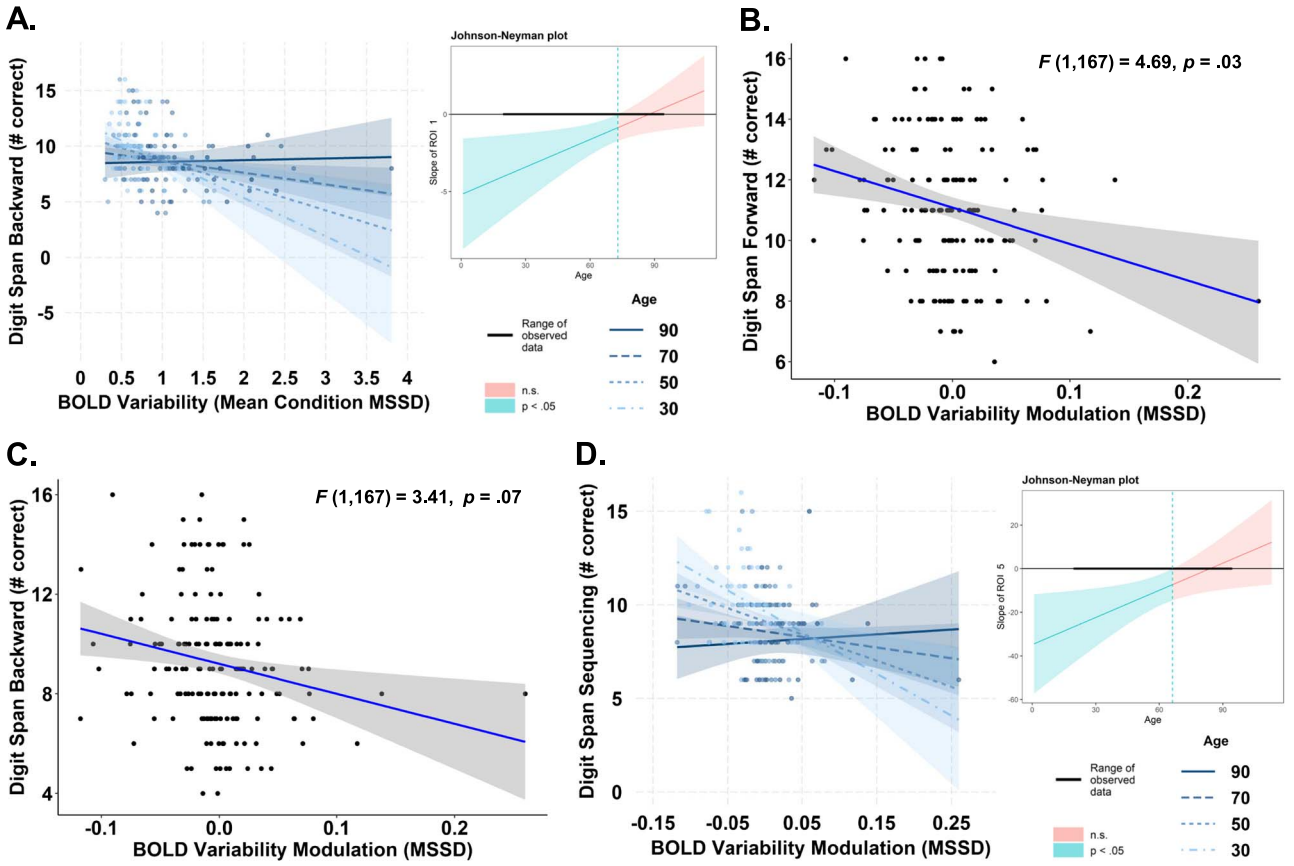

Figure 5. Association between age-related BOLD variability (mean condition MSSD and linear MSSD) and WM performance. (*A*) Illustrates the interaction among age, mean MSSD, and digit span backwards performance (number correct). The region of significance is demonstrated in the top right, with a significant association found for ages 20–73. The plot on the left illustrates the slope between MSSD and digit span performance for representative participants aged 30, 50, 70, and 90. The effect of BOLD Variability modulation on digit span forward (*B*) and backward (*C*) illustrate greater BOLD Variability Modulation demonstrating an association with poorer performance that did not depend upon age. (*D*) Exhibits the interaction among age, BOLD variability modulation and digit span sequencing performance. The region of significance is indicated in the top right, with a significant association identified in ages 20–66. The plot on the left represents the slope between BOLD variability modulation and number correct on sequencing for participants aged 30, 50, 70, and 90.

differential patterns across the cerebral cortex, with relatively greater BOLD variability in subcortical regions and relatively lesser BOLD variability in cortical regions (Fig. 1). However, both cortical and subcortical regions robustly demonstrated greater variability during the *n*-back task with increasing age, including in the superior temporal, parahippocampal and fusiform gyri, superior parietal lobule, angular, precentral, superior frontal, middle frontal, and inferior frontal gyri, amygdala, nucleus accumbens, thalamus, and dorsal anterior cingulate regions (Fig. 2*A*). Furthermore, this pattern of effects appears to be robust to analysis method, (PLS-C; Supplemental Fig. 2), and to controlling for potential vascular confounding effects (i.e., cerebral perfusion and HR).

The current study also demonstrated that BOLD variability modulates with difficulty. In posterior cingulate and precuneus regions, younger adults evidenced down-modulation of BOLD variability with increasing difficulty, while older adults demonstrate the opposite or up-modulation of BOLD variability with greater task difficulty (Fig. 3). Namely, during the 0-back, BOLD variability decreased across the lifespan in this sample while the opposite, increased BOLD variability with older age, was observed during the more difficult WM load conditions. Importantly, we also demonstrate that in both instances of age-related increases in variability (i.e., on the task overall, and in response to difficulty), increased variability was associated with both poorer accuracy during the task and on working memory (WM) measured outside of the scanning environment. Sampling individuals across the adult lifespan allowed for the investigation of when in the lifespan these variability effects were most related to cognitive performance (Figs 4 and 5). For individuals aged ~20–66 years old, greater BOLD variability was associated with poorer performance on both the in-scanner and outside-of-scanner WM assessments suggesting, as predicted, that this age-related BOLD variability increase is detrimental up until the mid-60. This age is representative of the mean age of the older group utilized in many previous investigations of age-related BOLD variability (Garrett et al. 2010; Garrett et al. 2013). For the oldest adults, variability was no longer predictive of performance, possibly due to the wide array of alterations that the brain has undergone by this stage of the lifespan (e.g., gray matter shrinkage, white matter connectivity degradation, white matter lesions, beta-amyloid, and iron deposition). If the current study had not incorporated middle-age and oldest-age spans, portions of the lifespan which are frequently overlooked

in studies of healthy aging, these differential age effects of BOLD variability would have been missed.

Some previous research has suggested that age-related variability patterns may be region-dependent, differing between cortical and subcortical areas, such that younger, better-performing adults typically demonstrate greater cortical BOLD variability, while older, slower performers evidence greater subcortical BOLD variability (Garrett et al. 2011). Indeed, the spatial pattern of age-related greater BOLD variability seen within the current adult lifespan sample was strikingly similar to the pattern seen in previous investigations in subcortical regions (Garrett et al. 2010; Garrett et al. 2011). However, whereas the subcortical pattern of greater variability in older adults appears highly consistent across studies, several studies have also observed selective cortical regions that demonstrate higher BOLD variability in older adults (e.g., in superior frontal and inferior temporal gyri and cerebellum; Garrett et al. 2010). Further, in individuals with probable AD, BOLD variability was higher in right-lateralized regions, including the superior frontal gyrus compared to healthy controls (Scarapicchia et al. 2018). Additionally, higher WMH burden was associated with greater cortical and subcortical BOLD variability in the healthy control group and was linked with poorer memory performance (Scarapicchia et al. 2018). Therefore, whereas it has been previously postulated that BOLD variability is greater in subcortical and lower in cortical regions, this is not consistently reported in the literature, and the findings appear to be more mixed with a lack of apparent regionally differential aging patterns.

Prior examinations of BOLD variability support the notion that this metric captures modulatory effects to *n*-back difficulty (Garrett et al. 2013; younger adults, placebo effects), from task compared to fixation (Garrett et al. 2011), and a gradation of increasingly variable response to rest, internal, and external task demands (Grady and Garrett 2018). Modulatory effects on BOLD variability are often observed in younger adults, but less so in older age groups. In the current study, in a focal region in the parietal lobe, we demonstrated that variability tracks with difficulty. These age-related differences in the modulation of BOLD variability in response to difficulty seem to be driven by differences between 0-back and the WM conditions. Here, older adults displayed up-modulation of BOLD variability with increasing difficulty, while younger adults displayed down-modulation with greater difficulty. This is generally supportive of previous investigations that observed the up-modulation of BOLD variability from control conditions to task conditions (Grady and Garrett 2014; Grady and Garrett 2018). Potentially, the present task samples difficulty levels beyond those that evidence modulation of BOLD variability, hence the observation that this effect may be driven by differences between task and control. This is in line with previous literature where younger adults modulated BOLD variability in response to *n*-back difficulty up until 2-back in a previous investigation (Garrett et al. 2015 placebo effects), whereas 2-back was the "easiest" level of WM load represented in the current study.

Currently, the potential mechanisms leading to age-related differences in BOLD variability are not yet established. Possibly, other age-related deficits such as declines in dopaminergic neuromodulation (Karrer et al. 2017) or age-related losses of structural integrity (Raz et al. 2005; Pur et al. 2019) may promote age-related differences in BOLD variability. Age-related declines in dopaminergic neuromodulation may lead to greater age-related BOLD variability, especially in subcortical regions (Guitart-Masip et al. 2016). One investigation demonstrated that BOLD variability during a spatial WM task was greater in subcortical regions with older age and slower responses, and further, was associated with lower D1 receptor density in the caudate and dorsolateral prefrontal cortex in a PET investigation (Guitart-Masip et al. 2016). Specifically, lower dopamine was associated with greater subcortical BOLD variability in regions including the hippocampus, amygdala, thalamus, caudate, and midbrain (even when controlling for age), while the majority of voxels in the neocortex were unrelated to D1 receptor density.

Notably, BOLD variability has also been studied across various disorders and disease states, with differences in BOLD variability evident between patient and healthy control groups. These differences have arisen in studies of attention deficit hyperactivity disorder (Depue et al. 2010; Sørensen et al. 2016; Mowinckel et al. 2017; Nomi et al. 2018), autism spectrum disorder (Dinstein et al. 2010; Dinstein et al. 2012), schizophrenia (Fryer et al. 2015; Xie et al. 2018), Parkinson's Disease (Zhu et al. 2019), 22q11.2 deletion syndrome (Zöller et al. 2017; Zöller et al. 2018), and Multiple Sclerosis (Petracca et al. 2017). Across studies, BOLD variability is altered (generally increased) in these patient groups compared to healthy controls, and further, alterations in BOLD variability are linked to the severity of disorder symptomatology.

Although the field is just beginning to investigate and understand BOLD variability in the context of healthy aging, examination of this metric in neurodegenerative conditions such as mild cognitive impairment and Alzheimer's disease (AD) may provide some relevant insight. Initial investigations have shown elevated physiological fluctuations in white matter (PFWM) (Makedonov et al. 2016), as well as greater BOLD variability in right-lateralized regions in those with AD compared to healthy adults (Scarapicchia et al. 2018). Heightened levels of PFWM and BOLD variability have been associated with negative outcomes such as lower levels of glucose metabolism and memory scores in those with probable AD (Makedonov et al. 2016), and even within the healthy control group, lower memory scores and higher volume of WMHs are seen with greater variability (Scarapicchia et al. 2018). Our findings, thus, support this notion that increased brain signal variability occurs in a less than optimal brain state.

Mounting evidence, including the current study, suggests a detrimental association between greater BOLD variability and age, given findings of higher WMH burden, poorer cognition, and financial decision making, and reduced D1 binding with greater BOLD variability (Samanez-Larkin et al. 2010; Guitart-Masip et al. 2016; Scarapicchia et al. 2018; Scarapicchia et al. 2019). However, there remain age-group comparison studies that indicated greater BOLD variability in younger, better cognitively performing adults compared to older adults (Garrett et al. 2011, 2013, 2015). These investigations posit that greater BOLD variability grants flexibility to switch between states, permitting greater dynamic range and allowing for favorable cognitive outcomes on the tasks at hand. It is plausible that both increases and decreases in BOLD variability may occur differentially across the adult lifespan and the consequence of these differences may vary by brain region or neural network. Longitudinal investigations of BOLD variability will allow for a clearer picture to emerge, which is currently underway in this sample.

Replication of the current study in a different lifespan sample is essential, as it is one of few examinations of whole-brain task-based BOLD variability in an adult lifespan cohort. Characterization of the lifespan trajectory of BOLD variability will allow for the further study of modifiers of BOLD variability, such

as genetic influences on the aging process (e.g., the resource-modulation hypothesis; Lindenberger et al. 2008), as well as other current guiding hypotheses of aging such as the CRUNCH model or STAC model (Reuter-Lorenz and Cappell 2008; Park and Reuter-Lorenz 2009), which may provide insight into potential mechanisms leading to age-related alterations in BOLD variability. Considerations for future examinations of age-related differences in BOLD variability include simultaneous recording of physiological signals during fMRI scanning to help more directly quantify and remove other contributing factors to the estimate of BOLD variability, including those of vascular nature at the participant level. The inclusion of HR measurement and ASL-based estimates of cerebral perfusion at the group-level did not influence the results of the present study; however, the BOLD variability body of literature would benefit from focused examinations of vascular (and other physiological sources of nonneural BOLD signal) contributions to the calculation of BOLD variability.

Conclusions

In sum, the present adult lifespan examination of BOLD variability provides evidence for greater age-related BOLD variability in widespread cortical and subcortical regions during *n*-back conditions, and more focal parietal regions that displayed age-dependent modulatory effects of difficulty on BOLD variability, controlling for two major vascular factors. Notably, greater age-related BOLD variability (both on average, and in response to task difficulty) were predictive of poorer *n*-back task accuracy and WM ability measured outside of the scanner up until older age. Overall, this study provides further evidence that greater age-related BOLD variability is associated with detrimental outcomes and may serve as a marker of decline in cognitive functioning that may be observed prior to oldest age (Samanez-Larkin et al. 2010; Guitart-Masip et al. 2016; Scarapicchia et al. 2018, 2019). Longitudinal examination of within-person change in variability across an adult lifespan sample will be a critical test for the replication of the current findings.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

Notes

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