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Abstract

Older adults tend to over-activate regions throughout frontoparietal cortices and exhibit a reduced range of functional modulation during WM task performance compared to younger adults. While recent evidence suggests that reduced functional modulation is associated with poorer task performance, it remains unclear whether reduced range of modulation is indicative of general WM capacity-limitations. In the current study, we examined whether the range of functional modulation observed over multiple levels of WM task difficulty (N-Back) predicts in-scanner task performance and out-of-scanner psychometric estimates of WM capacity. Within our sample (60–77 years of age), age was negatively associated with frontoparietal modulation range. Individuals with greater modulation range exhibited more accurate N-Back performance. In addition, despite a lack of significant relationships between N-Back and complex span task performance, range of frontoparietal modulation during the N-Back significantly predicted domain-general estimates of WM capacity. Consistent with previous cross-sectional findings, older individuals with less modulation range exhibited greater activation at the lowest level of task difficulty but less activation at the highest levels of task difficulty. Our results are largely consistent with existing theories of neurocognitive aging (e.g. CRUNCH) but focus attention on dynamic range of functional modulation as a novel marker of WM capacity-limitations in older adults.

Keywords

fMRI; modulation; working memory capacity; N-Back; aging

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1 INTRODUCTION

Human aging is associated with declines in working memory (WM) and alterations in brain function (Bopp & Verhaeghen, 2005; Braver & West, 2008; Cabeza & Dennis, 2012; Drag & Bieliauskas, 2010; Grady, 2012; Lustig, Hasher, & Zacks, 2007; Park & Hedden, 2001; Reuter-Lorenz & Park, 2010). During WM task performance older adults tend to exhibit similar spatial patterns of activation to younger adults, but show altered patterns of activation modulation including increased response magnitude at low levels of task difficulty ("over-activation") and a more rapid approach of asymptotic activation levels as task difficulty increases (Cappell, Gmeindl, & Reuter-Lorenz, 2010; Mattay et al., 2006; Nagel et al., 2011; Schneider-Garces et al., 2010). While these modulatory patterns have advanced neurocognitive compensation theory (e.g. the compensation-related utilization of neural circuits hypothesis; CRUNCH; Reuter-Lorenz & Cappell, 2008), recent evidence suggests that altered modulation patterns, such as a reduced modulatory range, may track closely with individual and age psychometric differences in WM function (Schneider-Garces et al., 2010).

WM processing is associated with activation of regions throughout frontoparietal cortices (e.g., bilateral dorsal and ventral prefrontal cortices, anterior cingulate cortex, superior and lateral parietal cortices; Nee et al., 2013; Owen, McMillan, Laird, & Bullmore, 2005; Rottschy et al., 2012; Wager & Smith, 2003). Regions throughout this network tend to exhibit an orderly parametric response to experimental manipulations of task difficulty including manipulation of set-size (# of items to be maintained in WM) and judgment difficulty (# of items to search through in continuous performance WM tasks; Owen et al., 2005; Rottschy et al., 2012). In addition, asymptotic levels of activation have been observed across various neuroimaging modalities (e.g., EEG, fMRI) at set-sizes that match behavioral estimates of WM span (# of items a participant is estimated to be able to maintain in WM; Linden et al., 2003; McCollough, Machizawa, & Vogel, 2007; Song & Jiang, 2006; Todd & Marois, 2004, 2005; Vogel & Machizawa, 2004; Xu & Chun, 2006).

Age-associated reductions in frontoparietal functional modulation range have been observed in studies of WM function involving span tasks (e.g. memory search task; Cappell et al., 2010; Schneider-Garces et al., 2010) and continuous performance task paradigms (e.g. N-Back task; Kaup, Drummond, & Eyler, 2014; Mattay et al., 2006; Nagel et al., 2011). It remains unclear whether declines in modulation range are due to general capacity limitations or distinct task-related impairments, as few studies have linked in-scanner modulation range with out-of-scanner psychometric measures. It is also unknown whether functional modulation range, like other neurocognitive functional markers such as over-activation (Cabeza, Anderson, Locantore, & McIntosh, 2002; Colcombe, Kramer, Erickson, & Scalf, 2005; Dolcos, Rice, & Cabeza, 2002), differentiates between high and low performing older adults. Based on recent evidence from meta-analyses showing that WM paradigms such as the N-Back and span tasks involve an overlapping, core frontoparietal network (Rottschy et al., 2012), we hypothesized that frontoparietal modulation range may reflect individual differences in WM capacity (WMC) limitations among older adults.

WM is the stage in information processing theories of human cognition associated with short-term representation of active memory traces (Baddeley, 2003). WM is capacity-limited and generally limited to only a few units/chunks of information (Cowan, 2005, 2010; Luck & Vogel, 2013; Miller, 1956; M. L. Turner & Engle, 1986). However, considerable individual differences exist in the amount of information that can be actively maintained in WM, particularly under conditions of distraction (Conway, Kane, & Engle, 2003; Kane & Engle, 2003). While short-term representation in WM is supported by separable storage units (e.g. visual vs verbal buffers; Baddeley & Hitch, 1974), individual differences in WMC are thought to emerge primarily through differences in domain-general abilities associated with actively maintaining, updating, and retrieving memory traces (Alvarez & Cavanagh, 2004; Barrouillet, Bernardin, & Camos, 2004; Bays et al., 2009; Cowan, 1999, 2005; Engle, 2002; Kane & Engle, 2003; Luck & Vogel, 2013; Oberauer, Lewandowsky, Farrell, Jarrold, & Greaves, 2012; Unsworth, Fukuda, Awh, & Vogel, 2014). Such a domain-general component of WM has been corroborated by functional imaging evidence showing overlapping activation patterns across verbal and visual WM task conditions in the core frontoparietal network associated with span and N-back task performance (Rottschy et al., 2012). Domain-general declines in WM processing have been the focus of several theories of cognitive aging (Braver & West, 2008; Hasher & Zacks, 1988; Lustig et al., 2007) and may help explain declines across multiple domains of cognition (Braver & West, 2008; Kennedy, Partridge, & Raz, 2008; Lustig et al., 2007; Park et al., 1996; Park & Hedden, 2001; Salthouse, 1990).

In the current study, we investigated domain-general WM function by examining composite estimates of frontoparietal functional modulation range and WMC through performance of visual and verbal versions of N-Back (in-scanner) and complex span tasks (out-of-scanner). Critically, previous research shows that performance on N-Back and span tasks is largely uncorrelated (sharing only a much as 2-5% variance; Kane, Conway, Miura, & Colflesh, 2007; Redick & Lindsey, 2013; Roberts & Gibson, 2002). However, latent estimates of performance on N-Back and complex span tasks covering multiple stimulus modalities were shown to be highly correlated in a previous study (Schmiedek, Hildebrandt, Lövdén, Lindenberger, & Wilhelm, 2009). Here we sought to determine whether functional modulation range in the core frontoparietal WM network, similarly, serves as an indicator of domain-general WMC in older adults.

Fifty-three participants between the ages of 60–77 years old participated in an fMRI scanning session where they performed visual and verbal N-Back task conditions and a separate cognitive assessment session where they completed visual and verbal complex span tasks (Operation Span and Symmetry Span). We first examined individual differences in functional modulation across levels of the N-Back task by fitting a parametric contrast to functional activation across all four levels of both task conditions (visual and verbal). After determining which regions scaled parametrically with increases in task demand we examined whether modulation range was associated with individual differences in conditional activation, performance during the N-Back task, and individual differences in psychometric WMC.

2 METHODS

2.1 Participants

A total of 53 right-handed healthy older adults participated in the study (24M/29F; age range = 60–77, mean age = 66.62, age SD = 4.15). Written informed consent was obtained from each participant under an approved University of Kentucky Institutional Review Board protocol. Participants were recruited from the community and were financially compensated. Exclusionary criteria for the study included the following: color blindness, major head injury, stroke, neurological or psychiatric disorder, high blood pressure, diabetes, heart disease, the use of psychotropic drugs, and or the presence of metal fragments and/or metallic implants contraindicated for MRI. Two participants were excluded from analyses involving N-Back task performance due to missing data (<70% of trials were recorded during 2-Back and 3-Back conditions).

2.2 Materials and Procedure

2.2.1 N-Back task—Participants completed a 4-level N-Back task (Compare, 1-Back, 2-Back, 3-Back) that included verbal (letters) and visual (faces) task conditions. During the Compare task condition participants judged whether two stimuli presented side-by-side (either two letters or two faces) were the same or different. During the 1-Back condition, participants were asked to judge whether the item on the current trial matches the item presented one item back in history. Similarly, the 2-Back and 3-Back conditions involved the same procedure as the 1-Back but varied with respect to how far back in the trial history (2- or 3-Back) comparisons were made (Figure 1). Responses were made using MRI compatible response button-boxes (one in each hand). Participants were asked to press the left button for "same" judgments and press the right button for "different" judgments. Participants were asked to respond as quickly and accurately as possible.

Task blocks were 40 seconds in duration (15 trials per block), and fixation periods were 17.5 seconds in duration. There were two runs. Each run began and ended with a fixation period (+ symbol presented centrally) and contained a total of 8 task blocks and 9 fixation periods. Each run contained two blocks of each N-Back level (including one block of each stimulus type). Each task block began with an instruction screen containing the task condition (e.g. "Compare", "1-Back") presented centrally for 2500ms. Following the instruction screen, stimuli were presented centrally for 2000ms each, separated by 500ms of fixation. Eight upper-case letters were included (B, F, K, H, M, Q, R, Y) in the verbal task and eight face stimuli were included in the visual task. Each face stimulus was a computerized drawing of a face containing only a circular face outline, eyes, eyebrows, and a mouth. Face stimuli each contained a different facial expression (based loosely on contemporary "emoji") and varied only in the length, curvature, or angle of the mouth and eye brow features (see Figure 1 for the complete set of faces). Each task block contained 4 target matching stimuli and 11 non-matching stimuli. The order of task blocks was pseudorandomly assigned and kept consistent across participants. Task blocks within each run alternated between verbal and visual N-Back tasks.

Task stimuli were generated by E-prime software (Psychology Software Tools, Inc, Pittsburgh, PA) and projected to a mirror mounted on the MRI head coil using an MRI compatible projector. Response time and accuracy for subject responses on each trial were recorded by the stimulus presentation program.

Prior to scanning, participants received task instructions along with 2 practice runs of each task condition before proceeding to the scanner. Participants were required to reach an accuracy criterion of 75% during Compare and 1-Back task practice. All participants reached this practice accuracy criterion.

2.2.2 Complex Span Tasks—Two automated complex span tasks (Operation Span and Symmetry Span) were administered together in a session separate from the scanning session. The Operation Span task measures the ability to store information in verbal working memory while processing additional information. Similarly, the Symmetry Span task measures the ability to store information in visual working memory while processing additional information. Each automated task contained self-guided instructions, practice, and timing parameters customized to the participant (for a full description of the development, parameters, and reliability of these automated procedures, see Conway et al., 2005; Redick et al., 2012).

Briefly, the Operation Span task involved memorizing a single letter at a time while performing interleaved arithmetic operations. After memorizing a set of letters and completing the interleaved arithmetic operations, participants were asked to recall all of the letters memorized throughout the current trial in order. Trials randomly varied in set-size. Set sizes (# of total letters memorized) ranged from 3–7 with three repetitions of each set size throughout the task. The total number of item-operation pairs was 75.

The Symmetry Span task involved memorizing highlighted locations in a 4×4 matrix one at a time while performing interleaved symmetry judgments on 8×8 mosaic pattern stimuli that were either symmetrical or non-symmetrical along the vertical axis. After memorizing a set of locations and completing the interleaved symmetry judgments, participants were asked to recall all of the spatial locations from the 4×4 matrices memorized throughout the current trial in order. Trials randomly varied in set-size. Set sizes (# of total locations memorized) ranged from 2–5 with three repetitions of each set size throughout the task. The total number of location-symmetry pairs was 42.

Both Operation Span and Symmetry Span were scored according to the partial-trial scoring method (Conway et al., 2005). The partial-trial scoring method involves counting each item recalled in the correct order from memory regardless of whether all items within a trial were recalled. A composite estimate of WMC was calculated by averaging performance on the Operation and Symmetry Span tasks. In order to account for differences in total potential span scores, span scores for each task were first z-scored and then z-scores were averaged.

2.3 Imaging Data Acquisition

Imaging data were collected on a 3T Siemens TIM scanner at the Magnetic Resonance Imaging and Spectroscopy Center of University of Kentucky. Two types of images were

collected for use in this study: 1) high-resolution T1-weighted image for functional image registration and 2) T2*-weighted images sensitive to the BOLD signal. High-resolution T1-weighted images were collected using an MPRAGE sequence (TR = 2100 ms; TE = 2.93 ms; FA = 12 degrees; resolution = 1 mm isotropic). Functional images were collected using a T2*-weighted gradient echo-planar sequence (TR = 2500 ms, TE = 30 ms, FA = 76 degrees, FOV = 224 mm^2, matrix = 64 × 64, resolution = 3.5 mm isotropic, 33 interleaved slices).

2.4 Functional Imaging Data Preprocessing

Imaging data were preprocessed and analyzed using FMRIB's Software Library (FSL) and fMRI Expert Analysis Tool (FEAT; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). Functional data were brain-extracted (i.e. skull-stripped) and motion-corrected to the median functional image using b-spline interpolation (4 degrees of freedom). The resulting functional images were high-pass filtered (100 s/cycle) and spatially smoothed [6mm full width at half maximum (FWHM), isotropic]. The anatomical volume was brain-extracted and registered to standard space T1 MNI 2 × 2 × 2mm template with FMRIB's Non-linear Image Registration Tool (FNIRT; Andersson, Jenkinson, & Smith, 2007). Each participant's median functional image was co-registered to their anatomical volume and warped to standard space using the non-linear warping matrix generated by the transformation of anatomical volume to standard space (Andersson et al., 2007). All resulting functional images were interpolated to 2 × 2 × 2mm resolution for group analysis in MNI standard space.

2.5 Functional Imaging Single-Subject Analysis

Functional data were first modeled at the individual subject-level by fitting a voxel-wise General Linear Model (GLM) to the BOLD data acquired for each run. The two runs were modeled separately and included task regressors for the visual and verbal Compare, 1-Back, 2-Back, and 3-Back blocks. Task regressors were modeled as a box-car function and convolved with a canonical double-gamma hemodynamic response function. Consistent with estimation of WMC, subject-level contrast maps for each level of the N-Back task were generated representing the average of visual and verbal N-Back task conditions at each level (e.g. average of visual and verbal 1-Back). A linear parametric contrast [−3, −1, 1, 3] was generated to detect regions that parametrically scaled in functional activation magnitude from Compare to 1-Back to 2-Back to 3-Back, respectively. In addition, a mean activation contrast was generated estimating average activation level across all task conditions. First-level contrast-maps for each N-Back condition, mean across all conditions, and parametric slope (the linear parametric contrast) from Compare to 3-Back were passed to a 2nd-level fixed effects model. In the 2nd-level model, subject-level contrast-maps were averaged across the two runs.

2.6 Functional Imaging Group Analysis

Parametric slope contrast maps from the 2nd level fixed effects model were entered into whole-group one-sample t-test where voxel-wise parametric increases in activation from the Compare to the 3-Back condition were explored. The whole-brain group-level parametric contrast was thresholded at voxel-wise FWE-corrected p < 0.05 (corresponding to voxel-

level threshold of Z > 4.7). Spherical ROIs (5mm radius) were centered on local peaks of clusters resulting from the one-sample t-test. Ten total ROIs were identified based on the peaks of clusters in frontal and parietal cortices (see Table 1). Subject-level parametric slopes, conditional means, and mean activation across all conditions for each ROI were estimated by calculating the average parameter estimate of all voxels falling within each spherical ROI mask. These parameter estimates were acquired from the individual results of the 2nd-level fixed effects model (where parameter estimates were averaged across runs). Frontoparietal slope and mean composites were created by first z-scoring the parameter estimates for each ROI obtained from the 2nd-level model and then averaging the z-scores across all ten ROIs. fMRI analysis results were rendered using Surf Ice by Chris Rorden (https://www.nitrc.org/projects/surface/).

3 RESULTS

3.1 N-Back Performance

Consistent with the imaging results, all behavioral analyses were conducted on average performance across visual and verbal N-Back conditions. The results of a 1×4 repeated measures ANOVA on accuracy indicated a significant main-effect of accuracy ($F(3,150) = 145.2$, MSE = 0.731, $p < 0.001$). Results of post-hoc comparisons revealed a significant reduction in accuracy between the Compare and the 1-Back task conditions ($t(50) = 5.09$, $p < 0.001$), 1-Back and 2-Back conditions ($t(50) = 7.91$, $p < 0.001$), and 2-Back and 3-Back conditions ($t(50) = 5.55$, $p < 0.001$; Figure 2A).

The results of a 1×4 repeated measures ANOVA on response time (RT) indicated a significant main-effect of RT ($F(3,156) = 65.14$, MSE = 597858.7, $p < 0.001$). Results of post-hoc comparisons revealed a significant increase in RT between the Compare and the 1-Back task conditions ($t(50) = -5.27$, $p < 0.001$) and between 1-Back and 2-Back conditions ($t(50) = -7.16$, $p < 0.001$). No significant increase in RT was observed between the 2-Back and the 3-Back conditions ($t(50) = -1.26$, $p = 0.21$; Figure 2B).

3.2 WMC and N-Back Performance

Performance on Operation Span (M = 46.4, SD = 13.0) and Symmetry Span tasks (M = 19.2, SD = 6.8) was significantly correlated ($r(53) = 0.41$, $p = 0.003$). Additional correlation analyses were run to examine whether WMC was related to performance during each condition of the N-Back task. The results of correlation analyses on accuracy revealed a significant correlation between WMC and accuracy during the Compare condition only ($r(51) = 0.30$, $p = 0.03$). No significant correlation was observed between WMC and the 1-Back ($r(51) = 0.23$, $p = 0.10$), 2-Back ($r(51) = 0.23$, $p = 0.10$) and 3-Back conditions ($r(51) = 0.05$, $p = 0.76$). No significant relationship was observed between WMC and RT during the Compare ($r(51) = -0.18$, $p = 0.20$), 1-Back ($r(51) = -0.24$, $p = 0.09$), 2-Back ($r(51) = -0.06$, $p = 0.69$), or 3-Back ($r(51) = 0.01$, $p = 0.94$) conditions.

3.3 Functional Activation during N-Back

The results of the group voxel-wise one-sample t-test performed on the parametric slope contrast revealed a significant linear increase in functional activation magnitude throughout

frontal and parietal cortices. The regions that scaled positively with increase in N-back difficulty included dorsal and ventral lateral prefrontal cortex including bilateral anterior insulae (AI) and bilateral middle and inferior frontal gyri (MFG/IFG), anterior cingulate cortex (ACC), and posterior parietal cortex including bilateral intraparietal sulci (IPS) and dorsal precuneus (PREC; Table 1). See Figure 3 for results of the group-level parametric slope contrast and location of cluster peaks used for the ROI analysis.

3.4 Parametric Slope and N-Back Conditional Activation

Parametric slope estimates across the 10 ROIs were highly correlated (ranging from 0.39-0.84, all p's < 0.004; M(*r-value*) = 0.57, sd(*r-value*) = 0.09). Reliability analysis suggested that parametric slope estimates across the 10 ROIs were highly reliable (Cronbach Alpha = 0.93), and therefore, a composite of parametric slope estimates across the 10 frontoparietal ROIs was constructed ("Frontoparietal Slope") for further analyses.

Individual differences in Frontoparietal Slope could emerge from a number of patterns of activation across levels of the N-Back task. For example, participants with overall shallower slopes may exhibit similar levels of functional activation during the easiest or most difficult task conditions while failing to modulate activation across task in a manner similar to participants with steeper slopes. In order to investigate how differences in Frontoparietal Slope were reflected in levels of conditional activation across the same ROIs we first conducted a median-split on Frontoparietal Slope, separating the sample into High and Low Slope groups.

After splitting the sample into High and Low Slope groups we compared mean functional activation magnitude across the 10 ROIs ("Frontoparietal Activation Magnitude") between groups at each level of the N-Back task. Note that a group × task condition interaction is statistically guaranteed by splitting the sample based on slope across task conditions. Therefore, only group contrasts at each level of the N-Back task were conducted to reveal the overall pattern of group differences as discussed above. Results of independent-samples t-tests on Frontoparietal Activation Magnitude revealed group differences during the Compare condition (t(51) = 3.53, p = 0.001), 2-Back condition (t(51) = −2.06, p = 0.045), and 3-Back condition (t(51) = −3.45, p = 0.001). No group difference was observed during the 1-Back condition (t(51) = 0.73, p = 0.47). Overall, this pattern of group differences revealed that individuals with shallower slopes showed generally greater activation during the least difficult task condition (Compare) and less activation during the most difficult task conditions (2-Back & 3-Back; Figure 4A).

3.5 Frontoparietal Slope, N-Back Performance, Age, and WMC

Results of correlation analyses of Frontoparietal Slope and performance on the N-Back revealed a significant correlation between Frontoparietal Slope and accuracy during the Compare (r(51) = 0.35, p = 0.01), 1-Back (r(51) = 0.31, p = 0.03), and 2-Back conditions (r(51) = 0.28, p = 0.046). No significant correlation was observed between Frontoparietal Slope and accuracy during the 3-Back condition (r(51) = −0.02, p = 0.91). No significant correlation between Frontoparietal Slope and RT was observed during any condition (all p's > 0.08).

The results of a correlation analysis on Age and Frontoparietal Slope revealed that Age was negatively correlated with Frontoparietal Slope (r(53) = −0.28, p = 0.04), suggesting that increases in Age were associated with a reduction in the range of functional activation observed across N-Back task conditions (Figure 5A). The results of a correlation analysis on Age and WMC revealed no significant relationship between Age and WMC (r(53) = −0.06, p = 0.68; Figure 5B).

Two analyses were conducted in order to address the central question of whether the range of functional modulation over levels of N-Back task difficulty was associated with individual differences in WMC. First, a significant positive correlation was observed between Frontoparietal Slope and WMC (r(53) = 0.30, p = 0.03; Figure 5C). Second, a multiple regression analysis was conducted on WMC entering Frontoparietal Slope as a predictor while controlling for individual differences in mean activation across task conditions and Age. Results of the multiple regression analysis revealed that Frontoparietal Slope was a significant predictor of WMC (standardized β = 0.35, p = 0.02) while controlling for mean activation (standardized β = −0.24, p = 0.08) and Age (standardized β = 0.06, p = 0.69).

4 DISCUSSION

Our current results show that patterns of functional activation magnitude regarded as the hallmark of CRUNCH (under- and over-activation during lower and higher difficulty task conditions, respectively), and typically observed in cross-sectional comparisons between older and younger adults, discriminate between older adults with higher and lower WMC. Functional modulation range during the N-Back was not only indicative of in-scanner N-Back performance, but moreover, individual differences in WMC as measured by a set of out-of-scanner tasks that are a standard of WMC assessment in psychometric research (Conway et al., 2005; Redick et al., 2012). Importantly, a significant relationship between range of functional modulation during the N-Back task and WMC was observed in the absence of significant relationships between N-Back and complex span task performance. We interpret these findings as suggesting that dynamic range of functional modulation may indicate WMC limitations that may not be reflected in task performance.

In addition to our current results, a growing body of evidence suggests that the ability to modulate functional activation in accordance with manipulations of task difficulty is a potentially important indicator of neurocognitive functioning in aging (Cappell et al., 2010; Hedden, Van Dijk, et al., 2012; Kaup et al., 2014; Kennedy et al., 2015; Mattay et al., 2006; Nagel et al., 2009, 2011; Park, Polk, Hebrank, & Jenkins, 2010; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Rieck, Rodrigue, Boylan, & Kennedy, 2017; Sambataro et al., 2010; Schneider-Garces et al., 2010). Importantly, these changes are not limited to "task-positive" brain networks such as the frontoparietal network investigated here, but also networks that show patterns of task-related deactivation (e.g., regions of the default-mode network; Brown, Hakun, Zhu, Johnson, & Gold, 2015; Park et al., 2010; Persson et al., 2007; Sambataro et al., 2010). Recent evidence suggests that modulation of task-positive and task-deactivated networks may be dynamically coupled (G. R. Turner & Spreng, 2015). Consistent with our current results, a recent study by Rieck and colleagues (2017) showed that modulatory coupling between task activated and deactivated networks is associated with individual

differences in fluid intelligence (Rieck et al., 2017), which is highly associated with WMC (Conway et al., 2003; Kane et al., 2004; Kyllonen & Christal, 1990; Unsworth et al., 2014). Together with our current results, these findings suggest that higher-order cognitive abilities such as WMC and fluid intelligence may be altered by age-related changes in the neurocognitive resources that underlie domain-general WM processes.

We observed that the slope of functional modulation across levels of the N-Back accounted for 9-11% of the variance in WMC (before/after controlling for age and mean activation magnitude). Importantly, this relationship was observed in the absence of significant relationships between performance on the N-Back and complex span tasks. However, it is important to note that the low correlation values between the N-Back and WMC estimates observed here are not anomalous, as the N-Back and WMC were, similarly, only weakly (2-5% shared variance) or uncorrelated in previous studies (Kane et al., 2007; Redick & Lindsey, 2013; Roberts & Gibson, 2002). Several explanations have been proposed to account for the lack of correlation between tasks such as differences in decision-related processes (familiarity- vs recollection-based decisions), as is described in more detail elsewhere (see Jaeggi, Buschkuehl, Perrig, & Meier, 2010). We can not rule out participant use of verbal strategies during the visual N-Back task conditions (e.g. naming the emotional expressions), which may have influenced the performance correlations observed here. Importantly, however, the observation that activation patterns during N-Back performance are predictive of WMC is consistent with the proposal that the tasks rely on common underlying processes (Schmiedek, Hildebrandt, Lövdén, Lindenberger, & Wilhelm, 2009).

The N-Back task is frequently utilized in applied cognitive neuroscience research due to its adaptability to the fMRI scanner environment, the ability to parametrically manipulate task demand by increasing the working memory load (increasing the "N"), and the surface validity of the relevant task-induced cognitive operations (e.g. updating, maintenance, resistance to proactive interference; Jaeggi et al., 2010). Meta-analysis of fMRI activation patterns during N-Back performance show that N-Back performance engages a similar set of brain regions distributed throughout dorsal and ventral frontoparietal cortices as observed here (Burgess, Gray, Conway, & Braver, 2011; Owen et al., 2005; Rottschy et al., 2012). In studies comparing younger and older adults, a clear pattern has emerged indicating that while frontoparietal activation magnitude scales parametrically with increase in the N-Back judgment in younger adults, older adults exhibit higher activation at lower levels of the N-Back and lower overall functional modulation (Burzynska et al., 2013; Nagel et al., 2011).

In our sample, decreases in range of modulation were observed over less than two decades in age range. Similar to a recent study by Nagel and colleagues (2011) we observed significant relationships between functional modulation and performance on the N-Back task (in the form of sub-group differences in accuracy between individuals with low and high slopes). However, the relationships observed in our primary analyses were between modulation range over all levels of the task and performance during COMPARE, 1-Back, and 2-Back conditions, where Nagel and colleagues observed a significant correlation between 3-Back performance and modulation from the 1-Back to 2-Back conditions (Nagel et al., 2011). A re-analysis of our own data replicated this relationship ($r = 0.32$, $p = 0.02$) such that

individuals who exhibited greater increases from the 1-Back to the 2-Back conditions exhibited higher accuracy during the 3-Back condition.

The specific cognitive mechanisms that drive individual variability in WMC-limitations remain widely debated, and much of the debate centers around whether capacity is limited more or less by processing or representational (i.e. storage) mechanisms. A common feature shared among domain-general descriptions of WMC is that individual differences are more likely to reflect differences in the ability to control WM processing and prioritization than the ability to passively store a certain quantity of information (Chun, 2011; Cowan, 1999, 2005; Engle, 2002; Kane & Engle, 2003; Oberauer et al., 2012; Unsworth et al., 2014). These controlled processing abilities include the ability to control and divide attention (Chun, 2011; Engle, 2002; Kane & Engle, 2003), the ability to actively remove irrelevant information (Oberauer et al., 2012), and the ability to efficiently retrieve from secondary memory (i.e. long-term memory or the periphery of the focus of attention in working memory; Mogle, Lovett, Stawski, & Sliwinski, 2008; Unsworth et al., 2014). Similarly, aging is associated with greater declines in controlled WM processing than passive short-term memory maintenance (Bopp & Verhaeghen, 2005; Braver & West, 2008; Hasher, Lustig, & Zacks, 2007; Park et al., 2002; Park & Hedden, 2001; although see Hale et al., 2011). Along with previous findings (Cappell et al., 2010; Schneider-Garces et al., 2010), our current study suggests that there may be neurocognitive contributions to WMC-limitations related to the ability to recruit functional regions distributed throughout frontoparietal cortices. These findings are consistent with recent neurocognitive theories of distributed WM and fit well with the presumed role of a frontoparietal brain network in controlled cognition (Christophel, Klink, Spitzer, Roelfsema, & Haynes, 2017; Cole, Repovš, & Anticevic, 2014; Hazy, Frank, & O'Reilly, 2007; Jurado & Rosselli, 2007; Niendam et al., 2012; G. R. Turner & Spreng, 2012; Vandierendonck, 2016; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008; Zanto & Gazzaley, 2013)

If range of functional modulation indeed reflects the ability to engage in controlled cognitive processing, then the consequences of this restricted range should be evident in other tasks and operations that rely on cognitive control. For example, we would expect individuals with a more restricted range of modulation to perform more poorly on dual tasks, divided/ selective attention tasks, task switching, and perhaps also daily activities such as driving or maintaining prospective memory performance under conditions of distraction (see also Braver & West, 2008). Here we examined a domain-general measure of N-Back performance but we propose that a multi-task domain approach (e.g. diversity-unity approach; Miyake et al., 2000; Miyake & Friedman, 2012) would serve to benefit future work in this area.

Age and WMC were each associated with frontoparietal functional modulation, but WMC and Age were not interrelated. WMC declines with age (Hale et al., 2011; Mccabe, Roediger III, Mcdaniel, Balota, Hambrick, 2010; Park et al., 2002), and despite observing a wide range in WMC and functional modulation we did not observe a significant relationship between age and WMC. We expect that this is primarily due to the limited age range present in our sample. However, it is important to note that a lack of correlation between WMC and Age confirms that the relationship between functional modulation and WMC was not driven

purely by age-related change in each variable (see also multiple regression results). Future studies would benefit from a broader age range, longitudinal follow-up, and lifespan approaches to the questions investigated here. In addition to a limited age range among older adults, we did not include a younger adult sample in our study. The focus of the current study on older adults was motivated by an extensive literature documenting patterns of age-related functional over-recruitment and recent evidence examining age-related changes in functional modulation. It is possible, however, that the modulation-WMC relationship may be age-invariant and therefore should be examined in future work. We note that age was negatively associated with modulation range in our sample, suggesting that this factor is sensitive to aging, but we cannot rule out modulation range as a general marker of cognitive ability throughout the adult lifespan (see Rieck et al., 2017). Lastly, a variety of age-related neurophysiological factors beyond chronological age may underlie individual differences in the ability to modulate functional modulation including changes in gray and white matter, neurovascular coupling mechanisms, and neurodegenerative pathology (Brown et al., 2015; Buckner, 2005; Burzynska et al., 2013; Drzezga et al., 2011; Girouard & Iadecola, 2005; Hakun, Zhu, Brown, Johnson, & Gold, 2015; Hedden, Mormino, et al., 2012; Hedden, Van Dijk, et al., 2012). Multi-modal imaging efforts could further our understanding of these neurocognitive relationships in future work.

5 CONCLUSIONS

Our current findings show that the dynamic range of functional modulation throughout a frontoparietal network of brain regions discriminates between older adults with higher and lower WMC. These findings extend previous cross-sectional evidence suggesting that brain functional modulation is a potentially important indicator of neurocognitive functioning in older adults. Future work should elucidate the specific mechanisms that underlie reduction of functional modulation in aging and examine the degree to which modulation is a determinant of other areas of cognitive ability and daily functioning.

Acknowledgments

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Highlights

- Older adults with greater modulation range exhibited better in-scanner performance

- Frontoparietal functional modulation predicted psychometric working memory capacity

- Modulation range decreased with age

- Older adults with lower modulation range showed "CRUNCH"-like pattern of activation
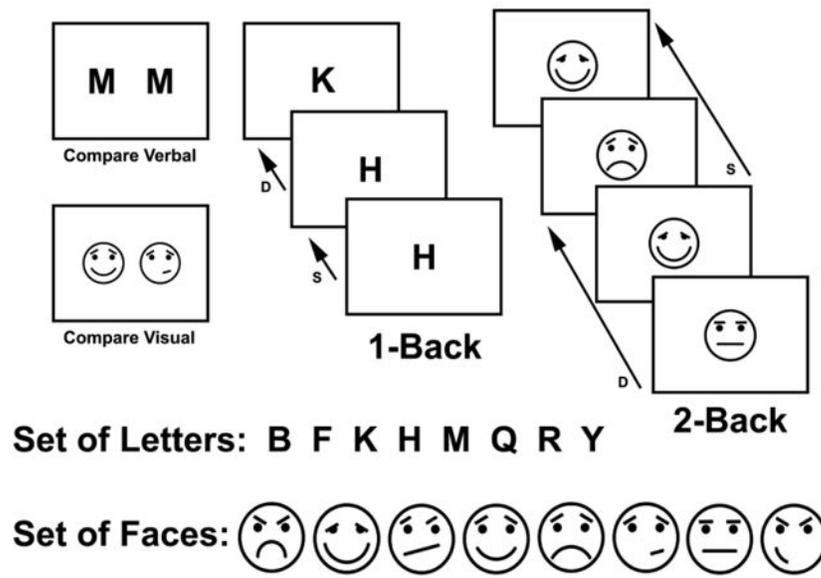
Figure 1. N-Back Task Design
(TOP) Example verbal and visual stimulus displays for the Compare, 1-Back, and 2-Back task conditions. 3-Back condition is not displayed. (BOTTOM) Complete set of letter and face stimuli. S = "same", D = Different".
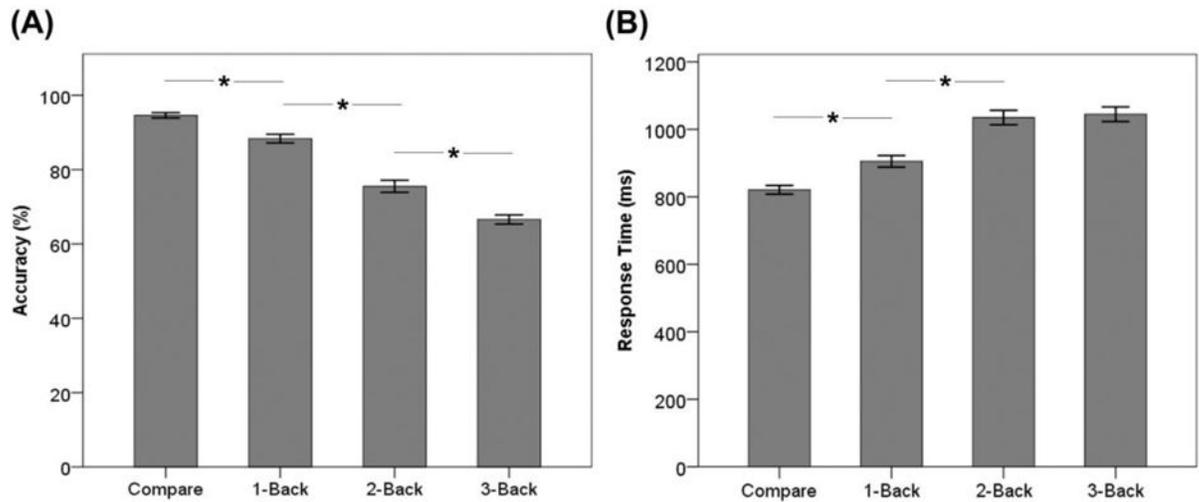
Figure 2. Accuracy and Response Time

(A) A significant reduction in accuracy was observed between each level of the task (B) A significant increase in RT was observed between the Compare and 1-Back conditions as well as the 1-Back and 2-Back conditions. RT did not increase between the 2-Back and 3-Back conditions.
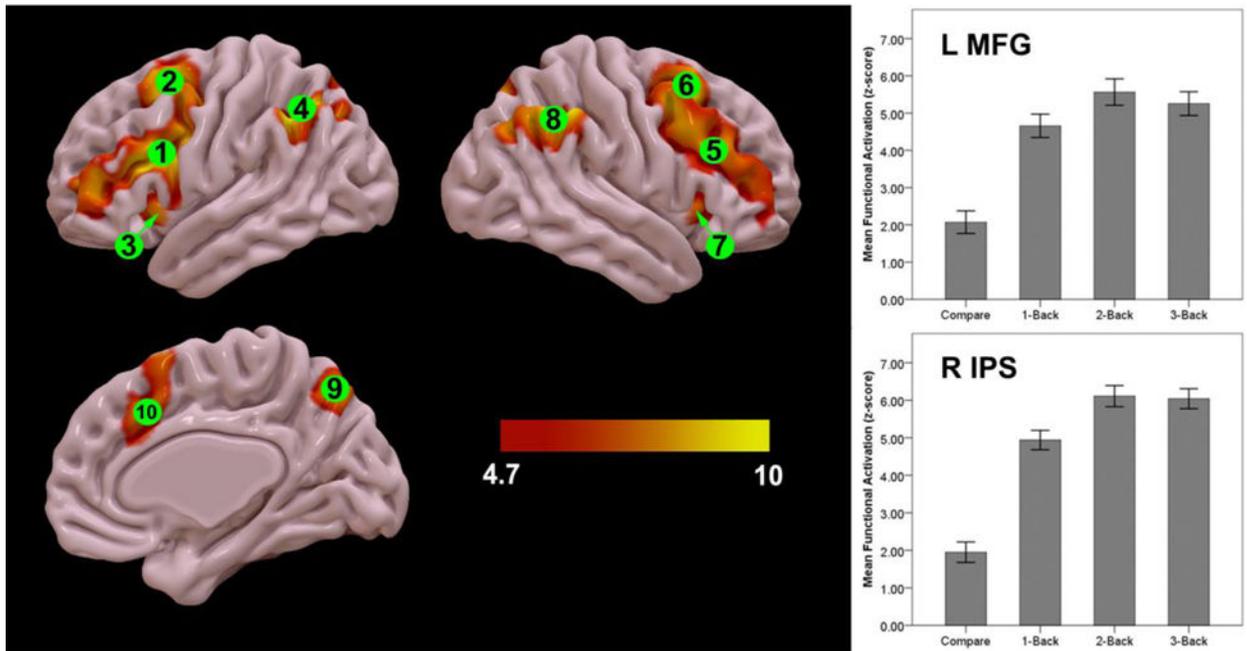
Figure 3. Regions Showing Significant Linear Increase in Functional Activation over Levels of N-Back Difficulty

(LEFT) Significant increases in functional activation magnitude were observed throughout frontal and parietal cortices. Green numbered circles indicate location of ROIs isolated for subsequent analyses. (RIGHT) ROI patterns of functional activation across N-Back task conditions across all participants. A similar pattern of activation to that depicted here for the L MFG and R IPS was observed across all 10 regions selected for further analysis. L MFG = left middle frontal gyrus; R IPS = right intraparietal sulcus. Numbering of ROIs in Figure match numbering in Table 1.
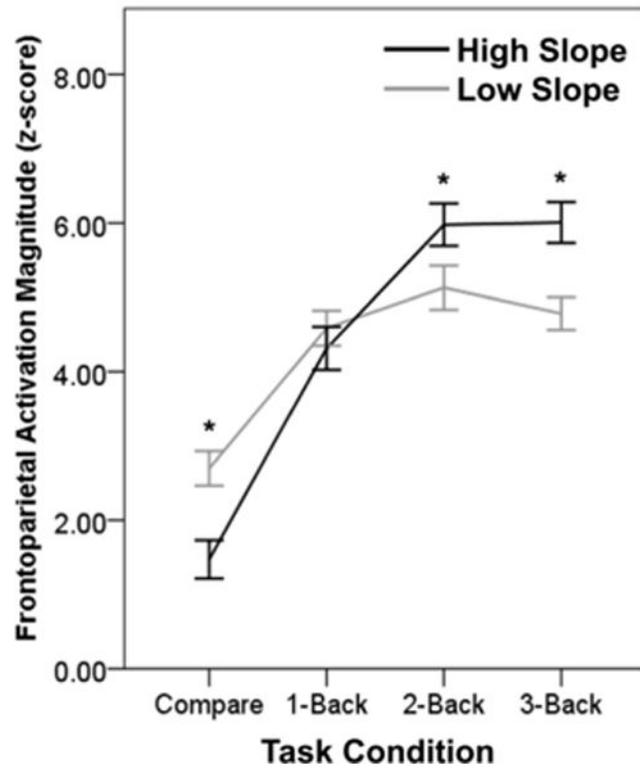
Figure 4. Frontoparietal Activation Magnitude by N-Back Task Condition
Individuals with lower modulation range showed generally higher levels of activation during the lowest level of task demand and lower levels of activation during the highest levels of task demand.
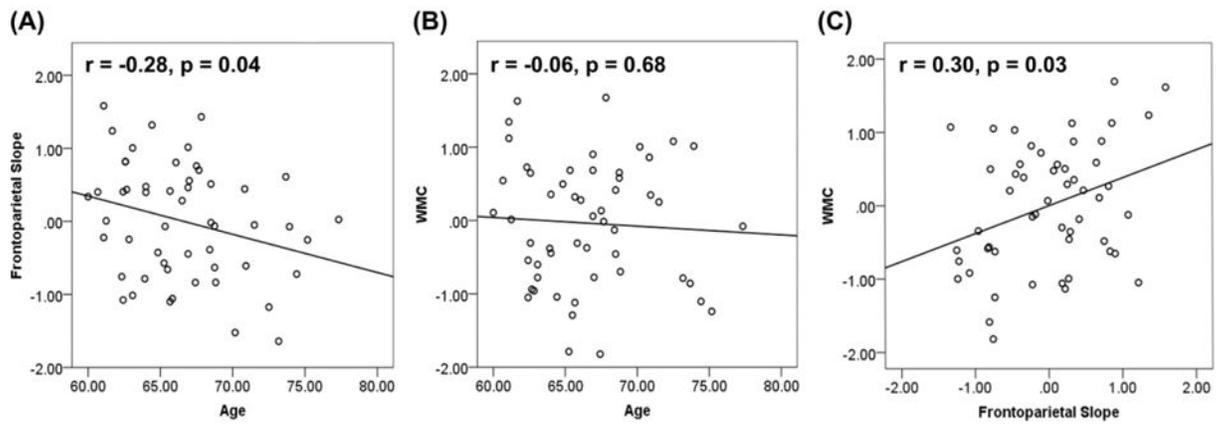
Figure 5. Relationships between Frontoparietal Slope, Age, & WMC
(A) Age was negatively associated with Frontoparietal Slope. (B) Age was not significantly associated with WMC. (C) Individual differences in Frontoparietal Slope significantly predicted WMC even after controlling for Age and mean functional activation magnitude.

ROI MNI Coordinates from Parametric Contrast and Conditional Means

Region	X	Y	Z	Mean Activation Magnitude (z - score)			
				Compare	1-Back	2-Back	3-Back
1. Left Middle Frontal Gyrus (L MFG)	−52	18	26	2.07	4.66	5.56	5.25
2. Left Superior Frontal Gyrus (L SFG)	−28	10	52	0.17	2.92	4.08	4.06
3. Left Anterior Insula (L AI)	−32	18	−4	3.35	5.00	6.12	5.75
4. Left Intraparietal Sulcus (L IPS)	−40	−56	44	1.35	4.18	5.36	5.18
5. Right Middle Frontal Gyrus (R MFG)	44	32	26	2.83	5.06	6.18	6.05
6. Right Superior Frontal Gyrus (R SFG)	28	8	54	1.81	4.51	5.85	5.96
7. Right Anterior Insula (R AI)	34	20	−2	4.13	5.72	6.73	6.37
8. Right Intraparietal Sulcus (R IPS)	46	−50	44	1.95	4.94	6.11	6.04
9. Dorsal Precuneus (PREC)	10	−74	48	0.28	2.34	3.22	3.15
10. Anterior Cingulate Cortex (ACC)	−6	18	40	2.55	5.02	6.29	6.14

NOTE: Numbers in the table correspond with numbering in Figure 2.