Performance level modulates adult age differences in brain activation during spatial working memory

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Working memory (WM) shows pronounced age-related decline. Functional magnetic resonance imaging (fMRI) studies have revealed age differences in task-related brain activation. Evidence based primarily on episodic memory studies suggests that brain activation patterns can be modulated by task difficulty in both younger and older adults. In most fMRI aging studies on WM, however, performance level has not been considered, so that age differences in activation patterns are confounded with age differences in performance level. Here, we address this issue by comparing younger and older low and high performers in an event-related fMRI study. Thirty younger (20–30 years) and 30 older (60–70 years) healthy adults were tested with a spatial WM task with three load levels. A region-of-interest analysis revealed marked differences in the activation patterns between high and low performers in both age groups. Critically, among the older adults, a more "youth-like" load-dependent modulation of the blood oxygen level-dependent signal was associated with higher levels of spatial WM performance. These findings underscore the need of taking performance level into account when studying changes in functional brain activation patterns from early to late adulthood.

aging | fMRI | premotor cortex | performance load

Working memory (WM), the process of holding information "on-line" to perform tasks in the absence of external cues (1, 2), is compromised in old age (3, 4). Spatial WM, which refers to the on-line retention of spatial memory contents, appears to be more affected in aging than verbal WM (5, 6). Furthermore, there are marked individual differences in WM performance (7–11) that seem to increase with age (12–14).

The neural network typically activated during spatial WM tasks involves lateral prefrontal cortex (PFC), premotor cortex (PMC), posterior parietal cortex (PPC), and temporal brain regions (15–19). fMRI studies reveal that decreased WM performance in older adults is paralleled by age-related changes in functional brain activation patterns (20–22).

In younger adults, activation of the WM network is affected by memory load (23–26). The load-dependent change of the blood oxygen level-dependent (BOLD) signal can be characterized as a dose–response function. Interestingly, the shape of dose–response functions differs among studies. Some researchers have reported monotonically increasing functions that are either linear (23) or nonlinear (27, 28). Others have found inverted U-shaped functions (24), where activation in dorsolateral PFC (DLPFC) increases with load up to a certain difficulty level, and then decreases.

Only a few studies have investigated the shape of dose–response functions in older adults (29–32). Mattay et al. (29) reported brain activations peaking at load three in younger and at load 1 in older adults during a spatial n-back task, and concluded that older adults reach their capacity limits at lower levels of difficulty than younger adults. By contrast, Petrella et al. (31) reported that activation in task-relevant regions increased with load in a delayed-recognition task among older adults as well. Conceivably, these discrepancies across studies reflect the dependency of the BOLD response on performance levels, which may have differed across studies, both within and across age groups. Indeed, there are individual differences in WM performance (7) that increase with age (13, 14, 33), and functional activation is associated with performance in both younger and older adults (30, 34–36). The modulation of age differences in memory-related brain activation patterns by performance levels has, however, only rarely been investigated, and when considered, it has been for long-term memory rather than WM (30, 32, 34, 35). Thus, performance heterogeneity in WM, which can be expected to be particularly high within samples of older adults, is often left unanalyzed (7), thereby confounding differences in BOLD responses across age groups with differences in performance level within age groups (37).

In this study, we tested 30 younger adults (mean age 25.6) and 30 older adults (mean age 64.1) with a spatial WM delayed matching task during fMRI scanning. We investigated the general hypothesis that performance modulates the BOLD response to a WM challenge in both younger and older adults. Furthermore, we hypothesized that the modulation differs between age groups, such that signal change increases linearly in young high performers and follows a quadratic pattern in old low performers, with young low and old high performers showing intermediate patterns (30).

Results

Behavioral Performance. ANOVA revealed significant age effects for accuracy, $F(1, 58) = 22.25$, $P < 0.01$, $\eta^2 = 0.28$, and correct response times, $F(1, 58) = 16.04$, $P < 0.01$, $\eta^2 = 0.27$. Similarly, the effects of load were statistically reliable both for accuracy, $F(2, 116) = 205.62$, $P < 0.01$, $\eta^2 = 0.78$, and correct response times, $F(2, 116) = 456.50$, $P < 0.01$, $\eta^2 = 0.89$ (see Fig. 1). Furthermore, the age × load interaction was reliable for both accuracy, $F(2, 116) = 7.28$, $P < 0.01$, $\eta^2 = 0.11$, and correct response times, $F(2, 116) = 5.53$, $P < 0.01$, $\eta^2 = 0.09$, with older adults showing a greater decline with load than younger adults.

We selected extreme groups of the 10 highest and 10 lowest performers for each age group based on their mean accuracy levels at loads 3 and 7. An ANOVA revealed no reliable difference in years of education between the four extreme groups (young high, young low, old high, old low: $F(1, 31) = 1.14$,

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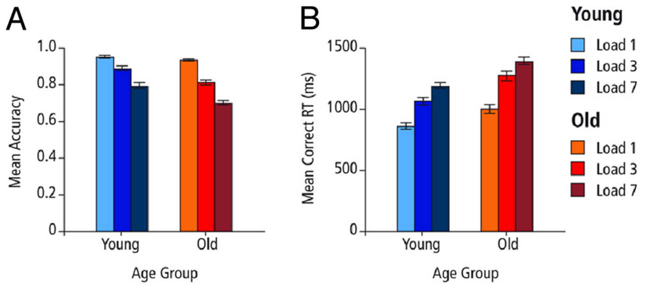

Fig. 1. Behavioral performance during the spatial WM task. (*A*) Accuracy. (*B*) Response times (RT) for younger and older adults at the three different load levels with significant effects of age, load, age × load ($P < 0.005$). Error bars represent ±1 SEM.

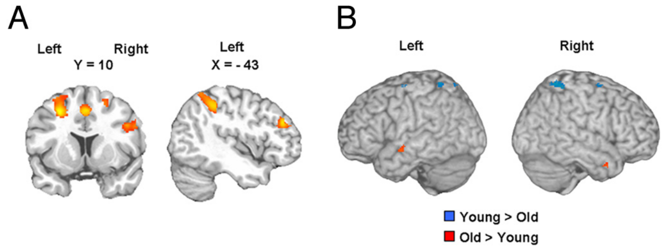

Fig. 3. Load and age group effects in the SWM network. Load 7 compared with load 1: (*A*) Conjunction of younger and older adults (colors range from light yellow, $z = 3.1$, to dark red, $z = 7$). (*B*) Load × age interaction (blue, young > old; red, old > young). Both common and age-specific increases in BOLD signal with load can be seen.

$P = 0.35$). We first conducted an age × performance × load repeated-measures ANOVA for accuracy and response times to test whether the difference between performance groups was reliably greater in one age group (the younger) than the other. This analysis revealed no reliable three-way interactions. For accuracy, the age × performance interaction was reliable [$F(1, 36) = 16.12$, $P < 0.01$, $\eta^2 = 0.31$], indicating that the performance effect differed between age groups. Also, the age × load [$F(2, 72) = 6.60$, $P < 0.01$, $\eta^2 = 0.16$] and performance × load group interactions [$F(2, 72) = 27.38$, $P < 0.01$, $\eta^2 = 0.43$] were reliable. These effects reflect greater change in accuracy with load in the old and in low performers. For response times, only the age × load interaction [$F(1, 36) = 6.60$, $P < 0.05$, $\eta^2 = 0.16$], was reliable. A two-way repeated-measures ANOVA testing the effects of performance and load separately in each age group revealed a significant performance level × load interaction in younger adults, $F(2, 36) = 15.46$, $P < 0.01$, $\eta^2 = 0.46$, reflecting an increase in group differences across load (Fig. 2 *Left*). The performance × load interaction was also significant in older adults, $F(2, 36) = 12.04$, $P < 0.01$, $\eta^2 = 0.40$ (Fig. 2 *Right*). For correct response times, the performance × load interaction was not significant in either age group ($P > 0.10$). As can be seen from Fig. 2, accuracy levels of young low performers were much lower than those of young high performers, such that the accuracy levels of young low performers fell in between those of old high and old low performers. In accordance with this observation, an independent samples *t* test confirmed that young low and old low performers did not differ significantly in their performance ($P > 0.05$).

Imaging Results. ***Voxelwise analysis.*** We investigated the effect of task load in the WM network by comparing load 7 against load

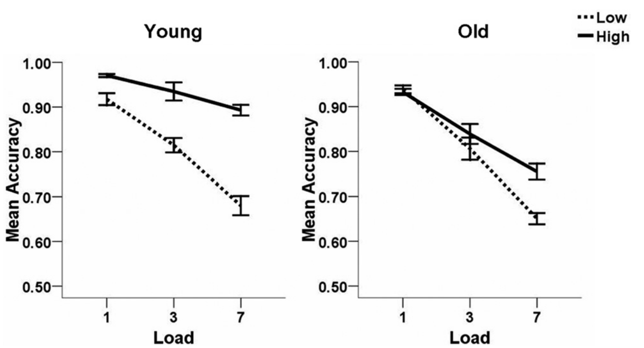

Fig. 2. Performance of the extreme groups. In each age group, the 10 highest- and 10 lowest-performing participants were selected based on mean accuracy at load 3 and load 7. (*Left*) Younger adults. (*Right*) Older adults. Error bars represent ±1 SEM.

1 separately for each age group (for peak activations see Table S1). A conjunction image was generated depicting regions where activation increased with task load in both younger and older adults. Common increases were observed in bilateral medial frontal gyrus, PMC, PPC, and visual cortex (Fig. 3*A*). We also obtained an age × load interaction, with older adults showing a greater increase of activation with load in right inferior frontal gyrus (IFG) and temporal regions, and younger adults showing more load-dependent activation in posterior parietal regions (Fig. 3*B*).

Region-of-interest (ROI) analysis. To examine the influence of age and performance group on BOLD signal changes in the spatial WM network under varying load conditions, we extracted percent signal change from ROIs in the left and right DLPFC, RDPMC, and PPC for both age groups and for high and low performers in each age group (for details on ROI locations see Table S2).

In the first step, we extracted percent signal change of younger and older participants. As can be seen in Fig. 4, in younger adults, the BOLD response increased from load 1 to 7 in all ROIs except right DLPFC. By contrast, in older adults, activation increased linearly only in left DLPFC and left PPC. Instead, in right DLPFC, bilateral PMC, and right PPC, activation did not change with load. These group differences were tested statistically by using a repeated-measures ANOVA testing the age × load interaction, and a second analysis testing the load effect within each age group. Instead of reporting the main effects from the omnibus test, polynomial contrasts are reported because they correspond directly to the hypotheses of this investigation. The first analysis revealed a trend toward a level × age × load interaction contrast in left PMC [linear contrast: $F(1/58) = 3.68$; $P = 0.06$; $\eta^2 = 0.06$; quadratic contrast: ns] and a reliable interaction contrast in right PMC [linear contrast: $F(1/58) = 4.23$; $P < 0.05$; $\eta^2 = 0.07$; quadratic contrast: ns].

The second repeated-measures ANOVA, testing the effect of load separately for each ROI and age group, revealed that in younger adults the BOLD response increased from load 1 to 7 in left DLPFC [linear contrast: $F(1, 29) = 7.74$; $P = 0.009$, $\eta^2 = 0.21$; quadratic contrast: ns], left PMC [linear contrast: $F(1, 29) = 12.24$; $P = 0.002$, $\eta^2 = 0.297$; quadratic contrast: ns], and right PMC [linear contrast: $F(1, 29) = 10.86$; $P = 0.003$, $\eta^2 = 0.27$; quadratic contrast: $F(1, 29) = 3.26$; $P = 0.08$, $\eta^2 = 0.10$]. In older adults, activation increased reliably in left DLPFC [linear contrast: $F(1, 29) = 6.62$; $P = 0.015$, $\eta^2 = 0.17$; quadratic contrast: $F(1, 29) = 3.6$; $P = 0.06$, $\eta^2 = 0.11$] and left PPC [linear contrast: $F(2, 58) = 5.34$; $P = 0.028$, $\eta^2 = 0.15$; quadratic contrast: ns], and increased at trend level in left PMC [linear contrast: ns quadratic contrast: $F(1, 29) = 3.41$; $P = 0.07$, $\eta^2 = 0.10$]. In right DLPFC, PMC and PPC, activation did not change significantly with load in the older sample.

Notably, the age effects reported above were qualified by differences between high and low performers within each age

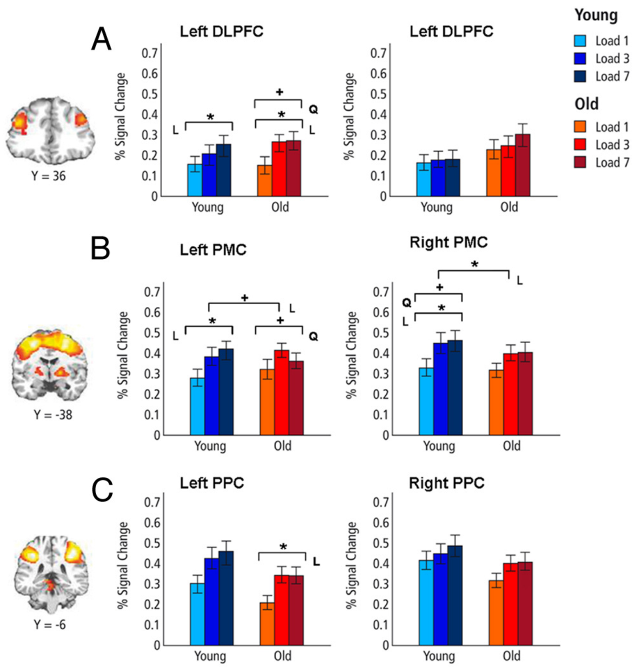

Fig. 4. ROI analysis for younger and older adults. BOLD signal changes in younger and older adults with load (younger adults, blue; older adults, red; lower task demand is represented by lighter colors). *, $P < 0.05$; +, $0.05 < P < 0.10$; L, linear contrast; Q, quadratic contrast. A monotonic increase of the BOLD response is seen in younger but not in older adults. Note that this pattern is modulated by performance (see Fig. 5).

group. As can be seen in Fig. 5, activation patterns were substantially modulated by performance level, both across and within age groups. In the young sample, the BOLD signal of high performers increased up to load 7 in left DLPFC and bilateral RDPMC and less so in right DLPFC and bilateral PPC. In the sample of old low performers, there was no increase in activation from load 3 to load 7 for any ROI. In fact, in old low performers, activation declined reliably in most ROIs after load 3. Thus, the compromised BOLD response at high load in the older sample was primarily driven by old low performers. In contrast, old high performers showed an increase of activation with load that resembled the pattern observed in younger adults. In both young low and old high performers, the change in BOLD with WM load was less pronounced than in the other two groups. In this context, it is important to consider the shape of the dose–response curves. A reliable change with load does not necessarily indicate better function. Instead, the response seems to follow an inverted U-shaped curve whereby the young low and old high performers are placed close to the apex, which is why there is no reliable load effect although performance is better than in old low performers, who showed a decline in BOLD response after the intermediate load condition.

To test the patterns for high and low performers in both age groups statistically, we first conducted a three-way repeated-measures ANOVA (age × performance × load) to test interactive effects of age and performance on the load-related BOLD response. This analysis revealed reliable contrast effects in left DLPFC [linear: $F(1, 36) = 6.6$, $P = 0.014$, $\eta^2 = 0.16$], right DLPFC [quadratic: $F(1, 36) = 4.3$, $P = 0.045$, $\eta^2 = 0.11$], left PPC [quadratic: $F(1, 36) = 4.4$, $P = 0.043$, $\eta^2 = 0.11$], and right PPC [quadratic trend: $F(1, 36) = 3.7$, $P = 0.062$, $\eta^2 = 0.09$]. We then ran two additional repeated-measures ANOVAs to test modulatory effects of performance on changes in BOLD signal separately for each age group, the first testing the performance × load interaction and the second testing the effect of load separately for each performance group. The first analysis revealed a significant interaction contrast in the young sample in left DLPFC [$F(1, 18) = 4.85$; $P = 0.041$, $\eta^2 = 0.22$]. In the older sample, the performance by load contrast interaction was reliable in right DLPFC [linear contrast: ns; quadratic contrast: $F(1, 18) = 4.99$; $P = 0.038$, $\eta^2 = 0.22$] and left PMC [linear contrast:

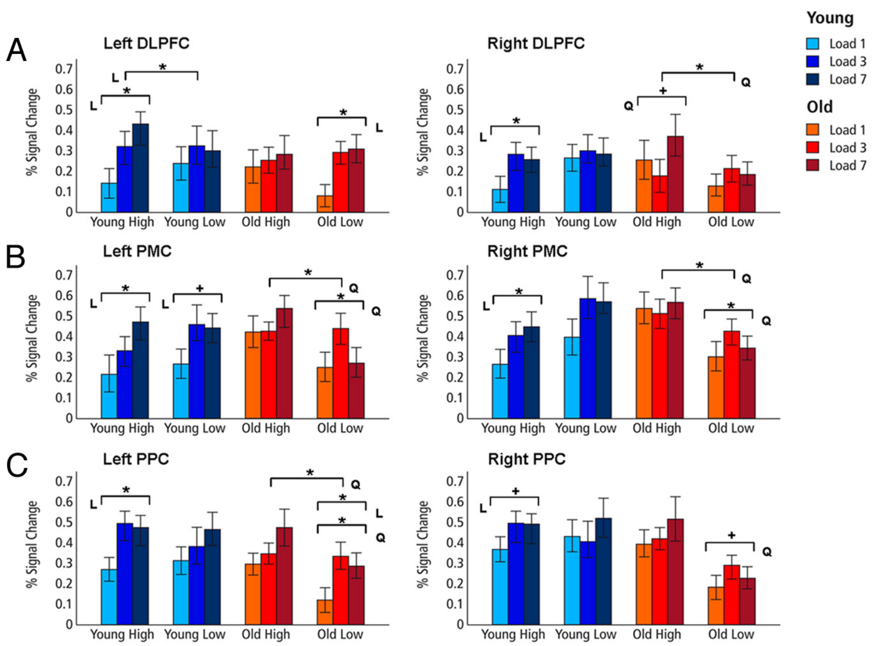

Fig. 5. ROI analysis for the extreme groups. BOLD signal changes in high- and low-performing younger and older adults across load (younger adults, blue; older adults, red; lower task demand is represented by lighter colors). *, $P < 0.05$; +, $0.05 < P < 0.10$; L, linear contrast; Q, quadratic contrast. There are marked differences in BOLD response between high and low performers within and across age groups as shown by reliable age × performance × load interactions in four of the six ROIs investigated here (see *Results* for details).

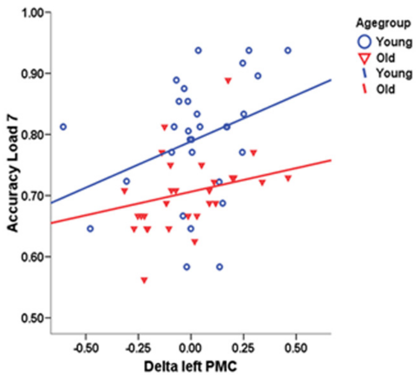

Fig. 6. Correlation of delta (BOLD signal change at load 7 minus load 3) with accuracy at load 7 in the left PMC ROI for younger adults and older adults.

ns, quadratic contrast: $F(1, 18) = 9.67$; $P = 0.006$, $\eta^2 = 0.35$]. The interaction reached trend level in right PMC [linear contrast: ns, quadratic contrast: $F(1, 18) = 3.84$; $P = 0.066$, $\eta^2 = 0.176$] and left PPC [linear contrast: ns; quadratic contrast: $F(1, 18) = 3.203$; $P = 0.09$; $\eta^2 = 0.15$]. Finally, we also compared statistically the patterns of young low and old high performers. When comparing the signals at loads 1, 3, and 7 between these two groups, we found no reliable group differences for any of the ROIs ($P > 0.05$).

The second analysis testing load contrasts in each performance group separately revealed reliable linear contrasts in all ROIs in young high performers [left DLPFC: $F(1/9) = 22.28$; $P < 0.001$; $\eta^2 = 0.712$; right DLPFC: $F(1/9) = 6.91$; $P = 0.027$; $\eta^2 = 0.43$; left PMC: $F(1/9) = 9.72$; $P = 0.01$; $\eta^2 = 0.519$; right PMC: $F(1/9) = 5.93$; $P = 0.038$; $\eta^2 = 0.40$; and left PPC: $F(1/9) = 14.35$; $P = 0.004$; $\eta^2 = 0.615$]. In right PPC, there was a trend level increase [$F(1/9) = 3.43$; $P = 0.097$; $\eta^2 = 0.28$]. By contrast, in young low performers there were no changes, except for a weak tendency in left PMC [$F(1/9) = 3.31$; $P = 0.10$; $\eta^2 = 0.27$].

In the sample of older adults, the repeated-measures ANOVA testing the load contrast in each performance group revealed no change in old high performers except for a quadratic trend level effect in right DLPFC [$F(1/9) = 3.86$; $P = 0.08$; $\eta^2 = 0.30$]. Thus, even though the BOLD response was greater overall in old high than in old low performers, there was no reliable increase of activation in this group. In old low performers, quadratic load contrasts were found to be reliable in most ROIs. There was a linear increase with load only in left DLPFC [$F(1/9) = 10.97$; $P = 0.009$; $\eta^2 = 0.55$] and reliable quadratic load contrasts in bilateral PMC [left PMC: $F(1/9) = 16.38$; $P = 0.003$; $\eta^2 = 0.65$; right PMC: $F(1/9) = 8.68$; $P = 0.020$; $\eta^2 = 0.49$]. In left PPC, the linear as well as the quadratic contrasts were reliable [$F(1/9) = 20.28$; $P = 0.001$ $\eta^2 = 0.69$ (linear); $F(1/9) = 5.69$; $P = 0.041$; $\eta^2 = 0.39$ (quadratic)]. In right PPC, the quadratic contrast was reliable at trend level [$F(1/9) = 3.86$; $P = 0.081$; $\eta^2 = 0.30$]. Quadratic contrasts in old low performers reflected an increase in activation from load 1 to 3 and decrease from load 3 to 7.

Correlation between load-dependent BOLD signal change and behavior. The correlation of the Δ-index (signal change at load 7 minus signal change at load 3) with accuracy at load 7 was statistically reliable in left PMC (Fig. 6) for both younger ($r = 0.42$; $P < 0.05$) and older ($r = 0.45$; $P = 0.01$) adults.

Discussion

We investigated whether and how the BOLD response to a WM challenge is modulated by performance in younger and older adults. We found that the dose–response functions differed between high and low performers within both age groups and particularly in older adults.

Behavioral research demonstrates individual differences in WM (7) that increase with age (33), but imaging studies on WM and aging typically do not consider within-age-group differences. The relatively large sample size of the present study allowed comparisons of dose–response functions across groups of low- and high-performing younger and older adults. These comparisons yielded several findings. A first key finding was the reliable increase in activation across load for all ROIs in the group of young high performers. In contrast, the BOLD response to load changes was less consistent in the other three groups. Apparently, the conjunction of being young and high-performing was associated with a superior ability to adaptively modulate brain activity to increasing cognitive demands. Second, there were pronounced differences in activation patterns between high and low performers within both age groups. Third, the modulation by performance was greater in older adults, where the compromised BOLD response observed in the full group was restricted to the group of low performers, who showed a drop of activation from load 3 to 7 in five of the six examined ROIs. In contrast, old high performers did not show such a drop. In both young low and old high performers, activation reached a plateau at load 3. Furthermore, in comparison with young high performers, young low were more similar in their performance to old high performers. The fact that dose–response functions of old high performers resembled those of the young suggests that similarity of functional activation patterns is related not only to chronological age, but also—and even more so—to performance level. Thus, in addition to and in interaction with age, performance level was strongly associated with demand-related modulations of the BOLD response. We add as a caveat that low performers contributed fewer data points to the analysis than high performers because we were able to exclude error trials, owing to the event-related design of the study.

In general, the shapes of the dose–response functions within each group were similar across DLPFC, PMC, and PPC, although there were some regional differences. Compared with the other groups, young high performers showed the most pronounced load–BOLD covariation in DLPFC, a region known to be critically involved in cognitive control (2, 38). Old low performers instead showed a decline after the intermediate load condition. The pattern of dose–response functions in PMC was similar to DLPFC (Fig. 5) and corresponded even more closely to behavioral performance. The PMC ROI was located in the rostrocaudal section of PMC, a region that is placed just in front of and slightly dorsal to the frontal eye fields (39) and has been implicated in spatial WM (15, 39–41). It appears to be involved in maintenance of locations and in attentional processes during spatial WM tasks and is sensitive to task load (19, 39). In PPC, a key region in spatial WM engaged in storage operations, item organization, and attention (19, 42), young adults showed large BOLD responses at all load levels. Older low performers showed reduced activation across load in this region. This pattern of results is in accordance with the suggestion that PPC is a key neural locus for capacity limitations in WM (19).Thus, despite apparent similarities across ROIs, the observed load-dependent activation changes in the different regions likely reflect load-dependent modulations in different cognitive processes, including attention, cognitive control, response preparation, and maintenance.

If activation patterns differ between performance groups, the question arises why these different patterns would lead to higher or lower performance. One difference in the dose–response functions of the performance groups may refer to the system's ability to respond adequately to a challenge (e.g., greater WM load). Activation typically increases with load, thus showing sensitivity to WM demand (18, 23). However, there seems to be a limit to such increases (43), and this limit has been suggested to reflect limitations in WM capacity (24, 44, 45). Specifically, failure in keeping PFC engaged appears to be the basis for capacity limitations (29, 46). The need to keep PFC sufficiently engaged seems to be an age-invariant characteristic limiting WM performance.

Previous findings regarding older adults' response to a WM challenge are contradictory, with some reporting a decreased response (29, 30), and others reporting no age-related decline in responsivity (31). The present study adds to this picture in two ways. First, as can be seen in Fig. 4, similar to Mattay et al. (29), we found differences in responsivity between age groups. Second, we provide evidence that the responsivity not only differs between age groups but also differs between high and low performers of the same age (Fig. 5), such that low performers reach their responsivity limits sooner than high performers, an effect that is particularly pronounced in older adults (as shown by the age × performance × load interactions). Thus, not only does performance modulate dose–response functions in most ROIs, but this effect is greater for older adults in the majority of ROIs. Old-age specific factors might dampen the responsivity of the BOLD response to WM challenge in older adults (36). First, because of age-related decline in processing efficiency, older adults might need to activate control regions already at a low load, so that activation cannot be much increased when task difficulty increases (47, 48). The present data suggest that young high performers do not require much prefrontal activation at low task demands and show an adaptive increase of activation as difficulty increases. Old high performers recruit PFC more extensively already at a low load and do not show much change with load, reflected in performance decreases compared with high-performing younger persons (Figs. 2 and 5). Old low performers do not seem to be able to recruit PFC control regions sufficiently. Second, physiological changes, which differ reliably between older individuals (49), may reduce the responsivity of PFC to a WM challenge. PFC regions are known to be particularly compromised in old age, reflecting senescent changes in neuroanatomy, such as gray- and white-matter losses (49), and neurochemistry, such as impaired dopaminergic neuromodulation (50).

We directly examined the relation of neural responsivity to WM performance by creating a difference score as an index of change in activation from load 3 to load 7, and relating this score to accuracy at load 7. If greater responsivity leads to better performance there should be a positive correlation between the difference score and accuracy. Critically, we found a positive correlation in PMC across both age groups, suggesting that responsivity in this region is closely linked to spatial WM functioning. Rostro-dorsal PMC is known to be involved in spatial memory and spatial attention (15, 39). Thus, as task difficulty increases, the use of PMC seems to become increasingly beneficial to performance. The observed correlation extends findings of a positive correlation between activity in the right PMC and WM performance under high-load conditions in younger adults (39).

The present data show that responsivity of the WM network to changing task demands is critical to successful task performance and that age differences in dose–response functions are modulated by performance. In a prior study on age differences in spatial WM, Mattay et al. (29) found an inverted U-shaped BOLD response in younger adults and a decreasing response in older adults across load. Probably, the younger adults in that study were placed at the top of the inverted U-shaped curve and older adults at the declining part. The present study adds to this evidence by demonstrating that the relative position on the curve is also determined by performance level within age group, particularly in older adults. Thus, some of the discrepant results in fMRI aging studies on WM may reflect differences in performance level, in addition to differences related to age. Given the marked heterogeneity in neuronal and behavioral aging (13, 49), it seems warranted to qualify statements about adult age differences in brain activation patterns in light of individual differences in performance within age groups. Hidden heterogeneity in activation patterns may lead to inadequate generalizations. For instance, in this study, the brain activation patterns observed in the full group of older adults (Fig. 4) did not provide a valid approximation of the patterns observed in older low and high performers.

It is debated whether the activation of additional brain regions in older participants is compensatory or dysfunctional depending on the specific site activated (34, 48, 51–53). Our results contribute to this debate, because older adults were able to attain levels of performance within the range of younger adults without showing signs of compensatory activation in the WM network. Put differently, showing a "youth-like" load-dependent modulation of the BOLD signal when being old was associated with higher levels of spatial WM performance.

Methods

Participants. Thirty younger and 30 older adults participated. The mean age of the younger sample was 25.6 years (SD = 3.0, 13 females), and the mean age of the older sample was 64.1 years (SD = 3.0, 13 females). Due to technical failure, additional demographic information of four young and one old participant was missing. Of the remaining 55 participants, years of education were 18.0 (SD = 2.9) for the younger adults and 16.2 (SD = 3.4) for the older adults. Participants were recruited from a database of the Max Planck Institute for Human Development in Berlin and via newspaper announcements and were paid for their participation. They were all right handed, had normal or corrected-to-normal vision, no history of neurological or psychiatric disease, and did not take psychiatric medication. The study was approved by the ethics committee of the Charité University Medicine, Berlin, and written consent was obtained from participants before investigation.

Behavioral Task. We used a spatial delayed-matching task, in which subjects saw points appearing on a screen. After a mask and a fixation delay, a probe point appeared. Participants had to indicate by a button press whether the location of the probe matched the location of one of the stimulus points they had seen in a given trial (for details, see *SI Methods* and Fig. S1).

Testing Procedure. Before entering the scanner, participants filled out a form for demographic information and received verbal instructions about the task and then practiced the task for up to three runs.

MRI Data Acquisition. Acquisition of imaging data were carried out by using standard procedures described in *SI Methods*.

Data Analysis. ***Behavioral data.*** Behavioral data were analyzed with ANOVAs using SPSS for Windows 15.0 (SPSS). Repeated-measures ANOVAs were conducted with age (young, old) as a between-subjects factor and load (one, three, seven points) as a within-subjects factor. Analyses were conducted separately for accuracy and response times. For the analysis of response times, trials <200 ms were discarded, and only correct responses were included in the analysis.

In a second step, participants were grouped based on their performance. The 10 highest and the 10 lowest performers were selected based on the mean of their performance level (accuracy) at load 3 and load 7. To examine group differences in task performance, first an age × performance × load repeated-measures ANOVA was conducted for accuracy and correct response times. Second, for each age group, a repeated-measures ANOVA (performance × load) was conducted. Finally, by using an independent samples t test, the accuracy of young low and old low performers was compared directly, because these groups had very similar performance levels.

MRI data. MRI data were analyzed by using a mixed-effects approach within the framework of the general linear model (GLM) as implemented in FSL. Each regressor of the GLM was set to model a whole trial, including encoding, maintenance, retrieval, and response with a duration of 7,000 ms. Group effects were computed by using the transformed contrast images in a mixed-effects model treating subjects as a random factor. A threshold of $z > 3.1$ ($P < 0.001$, cluster threshold of 20) was used for the exploratory whole-brain analysis. For FSL analysis details, see *SI Methods*.

The WM network was investigated in a voxel-based analysis by comparing load 7 with load 1 in both age groups. The load effect was assessed in two steps: First, we examined whether there were regions where both younger and older adults showed an increase with load. We computed a conjunction map of the load effects (load 7 compared with load 1) in the two age groups ($P < 0.001$, uncorrected) (see Table S1). Next, we tested whether there was a load × age interaction by contrasting the load effect maps of younger and older adults.

We conducted a ROI analysis, with ROIs in bilateral DLPFC, rostrodorsal PMC (RDPMC), and PPC. We defined the ROIs based on functional activation during spatial WM task performance. Within each age group, we calculated a contrast comparing WM task-related activation (mean of loads 1, 3, and 7) to fixation baseline. Based on this contrast, we then generated a conjunction map showing regions where the increase in BOLD signal was significant ($P = 0.005$, uncorrected) for all conditions in both younger and older adults. Finally, we defined ROIs by placing an 8-mm sphere around the peak activation in these regions (for MNI coordinates of ROIs, see Table S2). From these ROIs, percent signal change was extracted per subject for the three load conditions. Several repeated-measures ANOVAs were conducted to test age and performance group differences in signal change with load in these ROIs. For a detailed description of the analyses see *SI Methods*.

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1. Baddeley A (2003) Working memory: Looking back and looking forward. *Nat Rev Neurosci* 4:829–839.
2. D'Esposito M (2007) From cognitive to neural models of working memory. *Philos Trans R Soc* 362:761–772.
3. Babcock RL, Salthouse TA (1990) Effects of increased processing demands on age differences in working memory. *Psychol Aging* 5:421–428.
4. West RL (1996) An application of prefrontal cortex function theory to cognitive aging. *Psychol Bull* 120:272–292.
5. Park DC, et al. (2002) Models of visuospatial and verbal memory across the adult life span. *Psychol Aging* 17:299–320.
6. Jenkins L, Myerson J, Joerding JA, Hale S (2000) Converging evidence that visuospatial cognition is more age-sensitive than verbal cognition. *Psychol Aging* 15:157–175.
7. Conway ARA, Jarrold C, Kane MJ, Miyake A, Towse JN, eds. (2008) *Varitation in Working Memory* (Oxford Univ Press, New York).
8. Egan MF, et al. (2001) Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci USA* 98:6917–6922.
9. Meyer-Lindenberg A, et al. (2006) Impact of complex genetic variation in COMT on human brain function. *Mol Psychiatry* 11:867–877.
10. Miyake A (2001) Individual differences in working memory: Introduction to the special section. *J Exp Psychol* 130:163–168.
11. Hertzog C, Cooper BP, Fisk AD (1996) Aging and individual differences in the development of skilled memory search performance. *Psychol Aging* 11:497–520.
12. Baltes PB, Lindenberger U (1997) Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? *Psychol Aging* 12:12–21.
13. Nagel IE, et al. (2008) Human aging magnifies genetic effects on executive functioning and working memory. *Front Hum Neurosci*, 10.3389/neuro.09.001.2008.
14. Lindenberger U, et al. (2008) Age-related decline in brain resources magnifies genetic effects on cognitive functioning. *Front Neurosci* 2:234–244.
15. Courtney SM, Petit L, Maisog JM, Ungerleider LG, Haxby JV (1998) An area specialized for spatial working memory in human frontal cortex. *Science* 279:1347–1351.
16. D'Esposito M, et al. (1998) Functional MRI studies of spatial and nonspatial working memory. *Brain Res Cognit Brain Res* 7:1–13.
17. Goldman-Rakic PS (1987) *Circuitry of Primate Prefrontal Cortex and Regulation of Behavior by Representational Memory.* (Am Psychol Assoc, Bethseda).
18. Smith EE, Jonides J (1997) Working memory: A view from neuroimaging. *Cognit Psychol* 33:5–42.
19. Todd JJ, Marois R (2005) Posterior parietal cortex activity predicts individual differences in visual short-term memory capacity. *Cognit Affect Behav Neurosci* 5:144–155.
20. Rypma B, D'Esposito M (2000) Isolating the neural mechanisms of age-related changes in human working memory. *Nat Neurosci* 3:509–515.
21. Jonides J, et al. (2000) Age differences in behavior and PET activation reveal differences in interference resolution in verbal working memory. *J Cognit Neurosci* 12:188–196.
22. Reuter-Lorenz PA, et al. (2000) Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *J Cognit Neurosci* 12:174–187.
23. Braver TS, et al. (1997) A parametric study of prefrontal cortex involvement in human working memory. *NeuroImage* 5:49–62.
24. Callicott JH, et al. (1999) Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cereb Cortex* 9:20–26.
25. Jansma JM, Ramsey NF, Coppola R, Kahn RS (2000) Specific versus nonspecific brain activity in a parametric N-back task. *NeuroImage* 12:688–697.
26. Glahn DC, et al. (2002) Maintenance and manipulation in spatial working memory: Dissociations in the prefrontal cortex. *NeuroImage* 17:201–213.
27. Smith EE, Jonides J (1998) Neuroimaging analyses of human working memory. *Proc Natl Acad Sci USA* 95:12061–12068.
28. Cohen JD, et al. (1997) Temporal dynamics of brain activation during a working memory task. *Nature* 386:604–608.
29. Mattay VS, et al. (2006) Neurophysiological correlates of age-related changes in working memory capacity. *Neurosci Lett* 392:32–37.
30. Nyberg L, Dahlin E, Stigsdotter Neely A, Bäckman L (2008) Neural correlates of variable working memory load across adult age and skill: Dissociative patterns within the fronto-parietal network. *Scand J Psychol* 50:41–46.
31. Petrella JR, et al. (2005) Increasing memory load modulates regional brain activity in older adults as measured by fMRI. *J Neuropsychiatry Clin Neurosci* 17:75–83.
32. Rypma B, Eldreth DA, Rebbechi D (2007) Age-related differences in activation-performance relations in delayed-response tasks: A multiple component analysis. *Cortex* 43:65–76.
33. de Frias CM, Lovden M, Lindenberger U, Nilsson LG (2007) Revisiting the dedifferentiation hypothesis with longitudinal multi-cohort data. *Intelligence* 35:381–392.
34. Cabeza R, Anderson ND, Locantore JK, McIntosh AR (2002) Aging gracefully: Compensatory brain activity in high-performing older adults. *NeuroImage* 17:1394–1402.
35. Persson J, et al. (2006) Structure-function correlates of cognitive decline in aging. *Cereb Cortex* 16:907–915.
36. Grady CL, Yu H, Alain C (2008) Age-related differences in brain activity underlying working memory for spatial and nonspatial auditory information. *Cereb Cortex* 18:189–199.
37. Rugg MD, Morcom AM (2005) in *Cognitive Neuroscience of Aging*, eds Cabeza R, Nyberg L, Park D (Oxford Univ Press, New York).
38. Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. *Annu Rev Neurosci* 24:167–202.
39. Leung HC, Oh H, Ferri J, Yi Y (2007) Load response functions in the human spatial working memory circuit during location memory updating. *NeuroImage* 35:368–377.
40. Glabus MF, et al. (2003) Interindividual differences in functional interactions among prefrontal, parietal and parahippocampal regions during working memory. *Cereb Cortex* 13:1352–1361.
41. Rowe JB, Toni I, Josephs O, Frackowiak RS, Passingham RE (2000) The prefrontal cortex: Response selection or maintenance within working memory? *Science* 288:1656–1660.
42. Jonides J, et al. (1993) Spatial working memory in humans as revealed by PET. *Nature* 363:623–625.
43. Leung HC, Zhang JX (2004) Interference resolution in spatial working memory. *NeuroImage* 23:1013–1019.
44. Cowan N (2001) The magical number 4 in short-term memory: A reconsideration of mental storage capacity. *Behav Brain Sci* 24:87–114 and discussion, 114–185.
45. Luck SJ, Vogel EK (1997) The capacity of visual working memory for features and conjunctions. *Nature* 390:279–281.
46. Goldberg TE, et al. (1998) Uncoupling cognitive workload and prefrontal cortical physiology: A PET rCBF study. *NeuroImage* 7:296–303.
47. Reuter-Lorenz PA (2002) New visions of the aging mind and brain. *Trends Cognit Sci* 6:394.
48. Reuter-Lorenz PA, Lustig C (2005) Brain aging: Reorganizing discoveries about the aging mind. *Curr Opin Neurobiol* 15:245–251.
49. Raz N, et al. (2005) Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb Cortex* 15:1676–1689.
50. Bäckman L, Nyberg L, Lindenberger U, Li SC, Farde L (2006) The correlative triad among aging, dopamine, and cognition: Current status and future prospects. *Neurosci Biobehav Rev* 30:791–807.
51. Li SC, Sikstrom S (2002) Integrative neurocomputational perspectives on cognitive aging, neuromodulation, and representation. *Neurosci Biobehav Rev* 26:795–808.
52. Park DC, et al. (2004) Aging reduces neural specialization in ventral visual cortex. *Proc Natl Acad Sci USA* 101:13091–13095.
53. Rajah MN, D'Esposito M (2005) Region-specific changes in prefrontal function with age: A review of PET and fMRI studies on working and episodic memory. *Brain* 128:1964–1983.