

Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age

Melanie S. Höller-Wallscheid^{a,1}, Peter Thier^a, Jörn K. Pomper^a, and Axel Lindner^{a,1}

^aDepartment of Cognitive Neurology, Hertie-Institute for Clinical Brain Research, University of Tübingen, 72076 Tuebingen, Germany

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Elderly adults may master challenging cognitive demands by additionally recruiting the cross-hemispheric counterparts of otherwise unilaterally engaged brain regions, a strategy that seems to be at odds with the notion of lateralized functions in cerebral cortex. We wondered whether bilateral activation might be a general coping strategy that is independent of age, task content and brain region. While using functional magnetic resonance imaging (fMRI), we pushed young and old subjects to their working memory (WM) capacity limits in verbal, spatial, and object domains. Then, we compared the fMRI signal reflecting WM maintenance between hemispheric counterparts of various task-relevant cerebral regions that are known to exhibit lateralization. Whereas language-related areas kept their lateralized activation pattern independent of age in difficult tasks, we observed bilaterality in dorsolateral and anterior prefrontal cortex across WM domains and age groups. In summary, the additional recruitment of cross-hemispheric counterparts seems to be an age-independent domain-general strategy to master cognitive challenges. This phenomenon is largely confined to prefrontal cortex, which is arguably less specialized and more flexible than other parts of the brain.

working memory | subjective task difficulty | lateralization | prefrontal cortex | cognitive aging

Functional neuroimaging studies have demonstrated that elderly adults show a less lateralized activation pattern than young adults when completing the same cognitive tasks (1). For instance, this finding has been shown in experiments tapping working memory (WM), in which young adults recruit various brain areas unilaterally, but elderly subjects additionally activate corresponding regions in the other hemisphere (2–5). This phenomenon was termed “hemispheric asymmetry reduction in older adults” (HAROLD) by Cabeza (1) and seems to occur primarily in prefrontal areas of high-performing older adults (2). One of the most prominent interpretations of the HAROLD phenomenon suggests that it may be a mechanism specific to older adults, deployed to compensate age-related neurocognitive decline (2, 3).

The fact that older adults activate seemingly dormant non-specialized cross-hemispheric cerebral regions might seem at odds with the standard notion of a lateralized organization of human cerebral cortex (6–8). However, a contradiction arises only under the assumptions that there is strict lateralization with each member in a cross-hemispheric pair of a cortical region devoted to distinct functions and that specific tasks recruit only one member. Alternatively, Banich (9) and Belger and Banich (10) suggested that in most cases, both hemispheres can contribute to the processing of task-relevant information, but that they do so in different processing modes (e.g., left: verbal; right: spatial). Although the information-processing capacity supplied by the hemisphere with the task-related processing mode is sufficient for subjectively simple tasks, under more demanding circumstances, the task load can be distributed between the hemispheric modes. In this way, the brain can process an increased amount of information in an independent, parallel manner (9, 10).

Against this backdrop, an alternative interpretation of the HAROLD phenomenon is that it is a reflection of experimental

settings that were simply subjectively more difficult for the older subjects. Actually, in the studies that have shown the HAROLD phenomenon (2–5, 11), all subjects worked on the same memory tasks despite the fact that cognitive performance of older adults deteriorates, and WM is one of the most affected cognitive functions (12–14). This cognitive deterioration might make a task subjectively more demanding for older subjects, so that they need the recruitment of contralateral counterparts in prefrontal cortex to perform as well as the young subjects (14–16). However, the presence of bilateral activation patterns in the elderly does not necessarily mean that this mechanism is age-specific.

The idea that the provision of brain areas—including areas’ cross-hemispheric counterparts—reflects a general, age-independent support mechanism that kicks in when a task becomes subjectively demanding is the central tenet of the “compensation-related utilization of neural circuits hypothesis” (CRUNCH) (15). To date, it is unclear whether the bilateral recruitment of prefrontal areas during WM tasks represents an age-specific compensation mechanism or, alternatively, whether this phenomenon is also present in younger adults when coping with subjectively similarly demanding tasks—as posited by the CRUNCH concept. To distinguish between these alternatives, we asked whether the activation strengths in cross-hemispheric pairs of prefrontal areas differ between hemispheres of both young and old adults when we match the subjective difficulty of WM tasks, and task demands are high. We specifically focused on dorsolateral prefrontal cortex (DLPFC) and anterior prefrontal cortex (aPFC) because these areas have been shown to be bilaterally engaged in elderly adults during memory tasks (2, 11). We additionally considered ventrolateral prefrontal

Significance

One principle of human cerebral cortex is its lateralized functional architecture supporting processes such as language, precise motor control of the hands, and working memory. It has been shown that in elderly subjects such lateralized activations of dorsolateral and anterior prefrontal cortex vanish in working memory tasks, which is due to the corecruitment of corresponding regions in the other cerebral hemisphere. We show that such corecruitment of cross-hemispheric counterparts in prefrontal cortex is associated with subjectively demanding working memory tasks but not with age. This result suggests that prefrontal areas support us to maintain performance in challenging circumstances by additionally recruiting their non-specialized counterpart in the contralateral hemisphere.

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¹To whom correspondence may be addressed. Email: m.hoellerwallscheid@gmail.com or email@axel-lindner.info.

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cortex (VLPFC), an area whose left counterpart is known for the processing of language-based information (17) because it was suggested that certain language-based operations cannot be divided across the two hemispheres (10). Accordingly, we expected a left-lateralized activation pattern in VLPFC even in difficult tasks, whereas, following the notion of CRUNCH (15), we anticipated a bilateral activation pattern for DLPFC and aPFC in both young and old adults. Finally, we asked whether the recruitment of cross-hemispheric regions in prefrontal cortex is characteristic of specific WM domains or whether it operates in a domain-general fashion.

To address these questions, we used fMRI and compared blood oxygen level-dependent (BOLD) responses reflecting WM maintenance between several cross-hemispheric pairs of task-relevant regions of interest (ROIs) in groups of young and old adults. Both groups worked on verbal-, spatial-, and object-based WM tasks, which we designed to be highly demanding for every subject. Our results clearly indicate that in DLPFC and aPFC the simultaneous recruitment of cross-hemispheric counterparts during demanding WM tasks is present in both young and old subjects and in all WM domains. In a control experiment in which a group of young subjects worked on easy and difficult WM tasks in both the verbal and spatial domain, we found further evidence that also young individuals shift from a rather lateralized processing mode to a bilateral one when WM tasks get more difficult. Our results demonstrate that DLPFC is activated more strongly in the left hemisphere during easy WM tasks of both domains and that this lateralization pattern transforms into a bilateral recruitment in the more difficult task variants due to a stronger engagement of the right hemisphere. These activation patterns tend to be present also in aPFC.

Results

To quantify brain activity related to WM maintenance, we used three versions of a delayed match-to-sample task (18), in which subjects memorized either verbal-, spatial-, or object-based material (Fig. 1). We manipulated task difficulty within every WM domain by varying the memory load, which is the number of items to be remembered. To match levels of subjective task difficulty between young and old subjects, we first measured our subjects' WM spans outside the scanner. Then, based on the individual estimates of the WM span obtained in this pretest, we created memory load sets for the actual fMRI experiment for each subject and for each WM domain, separately. These sets typically consisted of the following five memory load levels: the load level that represented the individually estimated WM span—later on referred to as the central load level—plus two easier and two more difficult load levels (for further details, see *SI Materials and Methods, Creating Individual Load Sets*). This procedure should guarantee that task difficulty was comparable across individuals and age groups. We thereby considered all relative load levels as rather demanding because they closely ranged around the critical WM span of a subject. Moreover, all three WM domains and their five respective difficulty levels were presented in a randomly interleaved way. Participants could therefore not anticipate the load level of an actual trial and they had to be prepared for the most difficult tasks. For these reasons we expected a recruitment of the other hemisphere across all load levels to be likely.

Analyzing Objective Task Difficulty. To investigate whether younger and older adults worked on different objective difficulty levels in the fMRI experiment, we compared the mean central load levels (level 3) of young and old participants (Fig. 2A) by means of a two-way repeated measures ANOVA with the factors “age” (two levels: young vs. old) and “domain” (three levels: verbal vs. spatial vs. object). This analysis revealed that young subjects had higher mean central load levels and therefore could cope with objectively more difficult WM tasks than old subjects in all WM domains [main effect of age: $F(1,18) = 17.71$; $P = 0.001$]. This result is in accordance with previous reports showing that WM performance decreases with increasing age (12–14). Furthermore, the ANOVA yielded a main effect of domain [$F(2,36) = 18.21$; $P < 0.00001$], but no significant interaction between age and domain [$F(2,36) = 1.44$;

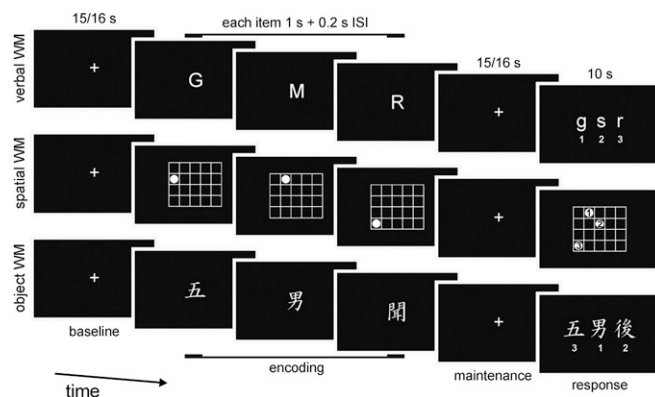


Fig. 1. The memory paradigm of the main fMRI experiment. Participants worked on delayed match-to-sample WM tasks. The items that had to be remembered in a trial were determined by the WM domain it belonged to (verbal: consonants of the Latin alphabet; spatial: dots within a grid; object: Japanese Kanji signs). This figure is an example of trials with a memory load of 3. Each trial started with a random baseline period (15 or 16 s), during which subjects were asked to maintain fixation on a white cross that was presented in the center of the otherwise black screen. In the encoding period, various randomly selected white WM items were centrally presented one after the other for 1 s each. There was an interstimulus interval (ISI) of 200 ms between items. During the random maintenance period (16 or 15 s), subjects again maintained fixation on a white fixation cross in the center of the screen while trying to keep the encoded items in memory. In the response period, we simultaneously showed all previously presented items of the encoding phase except for one, which was replaced with a novel item. The participants' task was to identify this new target item by verbally indicating its corresponding number.

$P = 0.250$]. Post hoc paired t tests revealed that across age groups, verbal tasks were objectively more difficult than spatial tasks [$t(19) = 4.40$; $P = 0.0003$; uncorrected; survives Bonferroni correction for multiple comparisons] and object tasks [$t(19) = 5.54$; $P = 0.00002$; uncorrected; survives Bonferroni correction for multiple comparisons], whereas spatial and object domains did not differ in objective difficulty [$t(19) = 1.10$; $P = 0.287$].

Analyzing the Success of Matching Subjective Task Difficulty. Our aim was to control for subjective task difficulty by using WM load sets for our subjects that had been created on the estimates of their individual WM spans. WM spans were assessed for each WM domain by means of a measurement termed “throughput.” This term, introduced by Schneider-Garces et al. (16), captures how many of the presented WM items a person is able to successfully keep in memory. The following Eq. 1 [adapted from Schneider-Garces et al. (16)] defines the throughput in our experiment as a function of the objective memory load, the subjective performance (hits) and chance level:

$$\text{throughput} = \frac{(\text{hits} - \text{chance level})}{(1 - \text{chance level})} \times \text{memory load.} \quad [1]$$

If a person answers a task perfectly (hits = 1), the throughput value will equal the memory load. The assumption is that the throughput increases with further increases in memory load until the person reaches his or her personal capacity limit, which is the WM span (Fig. 2B).

Throughput values were calculated for every load level according to Eq. 1, separately for each person and for each WM domain. Fig. 2C illustrates that the profiles of the throughput curves as function of the relative load levels look quite similar for young and old adults in the verbal WM domain: they increase with similar slopes up to the central load level before reaching a plateau. Hence, it seems that subjects in both age groups reached their WM spans equally fast and at the same relative load level, guaranteeing the same

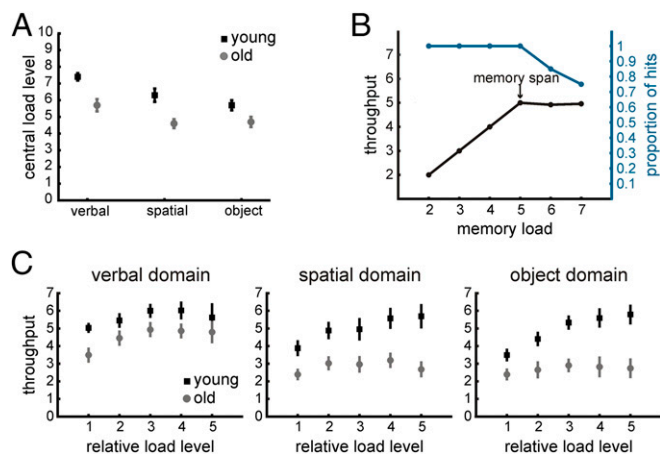


Fig. 2. Behavioral results. (A) To illustrate the objective difficulty of the tasks that were used in the main fMRI experiment, we present mean central load levels (the third relative load levels of the load sets) of the fMRI experiment and their SEs, separately for age groups (black: young, $n = 10$; gray: old, $n = 10$) and WM domains (verbal vs. spatial vs. object). (B) A fictitious example of how we defined a subject's WM span in the pretest. In this example, proportion of hits (blue) and throughput values (black) are displayed as a function of the memory load level. The fictitious subject answers all trials belonging to memory loads 2–5 correctly (proportion of hits = 1). This performance results in throughput values that equal the memory loads and expresses that the person stores all presented items and is able to memorize an increasing amount of information up to a memory load of 5. Here, the hit level drops and the WM span is reached because throughput saturates despite increasing memory load. (C) To demonstrate our subjects' behavioral performance in the main fMRI experiment, mean throughput values of this experiment and their SEs are shown, separately for age groups (black: young, $n = 10$; gray: old, $n = 10$), WM domains (left: verbal; center: spatial; right: object), and relative load levels (1–5).

subjective task difficulty despite the differences in objective task demands. Similar profiles of the throughput function of young and old subjects were also observed for the spatial domain; however, in the object domain the initial increase of the throughput curves seems to differ with age. To statistically examine whether we had indeed been successful in matching subjective task difficulty between age groups in the fMRI experiment, we tested whether the profiles of the throughput curves were comparable between young and old participants. We calculated two-way repeated measures ANOVAs with the factors age (two levels: young vs. old) and "load" (five levels: 1–5) on throughput values separately for each WM domain and examined whether the interactions between age and load were significant. The results indicate that we were successful in controlling for subjective task difficulty in the verbal [interaction age \times load: $F(1.9,34.3) = 0.38$; $P = 0.678$] and spatial [interaction age \times load: $F(2.6,46.3) = 2.65$; $P = 0.068$] domain because the interactions were not significant. In contrast, the way the throughput varied with load differed between young and old participants in the object domain [interaction age \times load: $F(2.6,46.6) = 5.71$; $P = 0.003$]. Inspection of Fig. 2C suggests that young subjects did not reach their capacity limits in the object domain, whereas old participants did.

Moreover, the ANOVAs revealed that, as expected, young participants achieved higher throughput values than old subjects in all WM domains by showing significant main effects of age [verbal: $F(1,18) = 5.75$, $P = 0.028$; spatial: $F(1,18) = 16.19$, $P = 0.001$; object: $F(1,18) = 20.51$, $P = 0.0003$]. Furthermore, the main effects of load expressed that throughput values significantly varied across relative load levels in all WM domains [verbal: $F(1.9,34.3) = 5.15$, $P = 0.012$; spatial: $F(2.6,46.3) = 7.14$, $P = 0.001$; object: $F(2.6,46.6) = 11.68$, $P = 0.00002$].

Analyzing fMRI Lateralization in Young vs. Old Subjects. The main purpose of our fMRI analyses was to investigate whether the BOLD-signal amplitudes of cross-hemispheric counterparts of task-relevant prefrontal and language-related areas differ during

WM maintenance in young and old subjects when they work on subjectively equally difficult tasks. We specifically focused on the prefrontal regions DLPFC [more posterior parts of Brodmann's area (BA) 46 and BA 9] and aPFC (most anterior part of BA 46 and BA 10) because they play a domain-general role in WM processes (19–22) and, more importantly, they showed age-related lateralization differences in previous work (2–5, 11). We further considered VLPFC (BA 44 and BA 45) because of its well-known left-lateralized processing of language-based information (17) in prefrontal cortex. It is an area that might potentially maintain its left-lateralized activation pattern even during demanding WM tasks (at least in the verbal domain) because it might process (phonetic) information that does not benefit from parallel bihemispheric processing in difficult situations (10). The two cross-hemispheric counterparts of each of these "main ROIs" were identified in each individual based on anatomical and functional criteria: cross-hemispheric pairs were identified by their anatomical location and by the presence of WM maintenance-related activity during the instructed delay of our stimulus sequence (see *Materials and Methods* for further details; also see Fig. S1). Because the same fMRI data set was used for ROI selection and for ROI analyses, we took specific care to meet the criteria described by Kriegeskorte et al. (23) to avoid circularity and an impact of biased activity estimates on our results (see also *SI Materials and Methods, Criteria to Avoid Circularity*).

Apart from our main ROIs (DLPFC, aPFC, and VLPFC), a number of additional brain areas did exhibit maintenance-related activity, namely anterior insula, dorsal premotor cortex/frontal eye fields (PMd/FEF), ventral premotor cortex (PMv), supplementary motor area (SMA), intraparietal sulcus (IPS), superior parietal lobule (SPL), calcarine sulcus, and lobule VI/crus1 of lobule VII of the cerebellum. Here, we also describe the results for these additional task-related areas, because they have been consistently reported to be involved in WM processes in young subjects (5, 16, 19, 20). However, we had no prior hypotheses with respect to their pattern of lateralization. Table S1 displays representative coordinates of all ROIs.

For every subject and for each ROI, we assessed the WM maintenance-related BOLD activity in the respective cross-hemispheric counterparts across a sphere of 3-mm radius in terms of the estimated percentage of BOLD-signal change (see *Materials and Methods* for further details). In cases in which the estimated percentage of BOLD-signal change was indistinguishable between both cross-hemispheric counterparts of an area in at least one WM domain, we refer to this area as "bilateral." In turn, an area is labeled as "unilateral" when one hemispheric counterpart is activated more strongly than the other in each WM domain. Accordingly, we grouped our ROIs in four respective categories: (i) "domain-general bilateral ROIs" (i.e., areas that showed a bilateral activation pattern across all WM domains); (ii) "domain-specific bilateral ROIs" (i.e., areas that were bilateral in at least one WM domain but unilateral in others); (iii) "domain-general unilateral ROIs" (i.e., the same pattern of unilateral activation was exhibited across all three WM domains); and (iv) "domain-specific unilateral ROIs" (i.e., lateralization was present throughout but the dominant hemisphere varied across WM domains). Note, however, that none of our ROIs fell in the latter category.

Domain-general bilateral ROIs. We first report the results of the prefrontal areas that had been shown to exhibit age-related differences in lateralization, namely DLPFC and aPFC. The averaged event-related time courses of the BOLD signals in these areas are depicted in Fig. 3A and B, respectively. Separate time courses are shown for the two hemispheres (brighter color: left hemisphere; darker color: right hemisphere), for young (upper rows) and old (lower rows) subjects, and for verbal (red), spatial (green), and object (blue) domains. These figures indicate that there was hardly any difference in activation between the cross-hemispheric counterparts of DLPFC and aPFC—in both age groups and in all three WM domains. To statistically test this impression, we first conducted—independently for each ROI and WM domain—three-way repeated-measures ANOVAs with the factors "hemisphere" (two levels: left vs. right),

age (two levels: young vs. old), and load (five levels: 1–5) on our estimates of percentage of BOLD-signal change during the WM maintenance phases (Fig. S2A and B). These analyses revealed that left and right hemispheres of DLPFC and aPFC were indeed similarly engaged in the maintenance phases in all three WM domains [absence of main effects of hemisphere in DLPFC: verbal: $F(1,18) = 0.27, P = 0.609$; spatial: $F(1,18) = 0.22, P = 0.649$; object: $F(1,18) = 0.83, P = 0.373$; absence of main effects of hemisphere in aPFC: verbal: $F(1,18) = 0.25, P = 0.624$; spatial: $F(1,18) = 0.13, P = 0.724$; object: $F(1,18) = 0.24, P = 0.633$]. Both areas are thus considered domain-general bilateral ROIs. Furthermore, the ANOVAs indicated that in both areas, the BOLD signal was significantly modulated by the load level in verbal and spatial domains during the maintenance period—as it was expected—but not in the object domain [main effects of load in DLPFC: verbal: $F(2.8,50.1) = 10.34, P = 0.00003$; spatial: $F(4,72) = 11.47, P < 0.00001$; object: $F(4,72) = 1.36, P = 0.255$; main effects of load in aPFC: verbal: $F(2.4,43.7) = 8.39, P = 0.0004$; spatial: $F(4,72) = 14.62, P < 0.00001$; object: $F(4,72) = 2.24, P = 0.073$]. The missing load effect in both ROIs in the object domain could refer to the fact that we were not successful in controlling subjective task difficulty in this domain (see above) and that load levels encompassed a difficulty range in which the BOLD-signal was not yet (young group) or no longer (old group) modulated by

the load level. Finally, the main effects of age and, most importantly, the interactions between age and hemisphere were not significant in DLPFC and aPFC in all three WM domains (all $P > 0.17$). Hence, in both prefrontal ROIs neither the age groups nor the hemispheres had any differential influence on BOLD-signal amplitudes in any of the three WM domains.

Our failure to reveal significant differences in activation strength between the hemispheric counterparts of DLPFC and aPFC does not allow us to conclude that these cross-hemispheric pairs were indeed equally activated. The reason is that we did not control for type II errors as strictly as for type I errors, a common tradeoff in orthodox statistics like in the ANOVAs performed here. To account for this limitation, we additionally calculated Bayes factors (24) to probe whether the two counterparts of our ROIs were similarly active (null hypothesis) in the maintenance phases of the memory tasks or not (alternative hypothesis) (also see *Materials and Methods*). Fig. 4A and B illustrate Bayes factors of DLPFC and aPFC for young and old subjects, respectively, separately for all WM domains (red: verbal; green: spatial; blue: object). A Bayes factor above 1 denotes evidence in favor of unilaterality, and a Bayes factor below 1 represents evidence in favor of bilaterality. Although the Bayesian approach typically refrains from using thresholds, Bayes factors that have values above 3 and below 1/3 provide substantial evidence for more unilateral vs. bilateral activation, respectively (25). In cases in which the

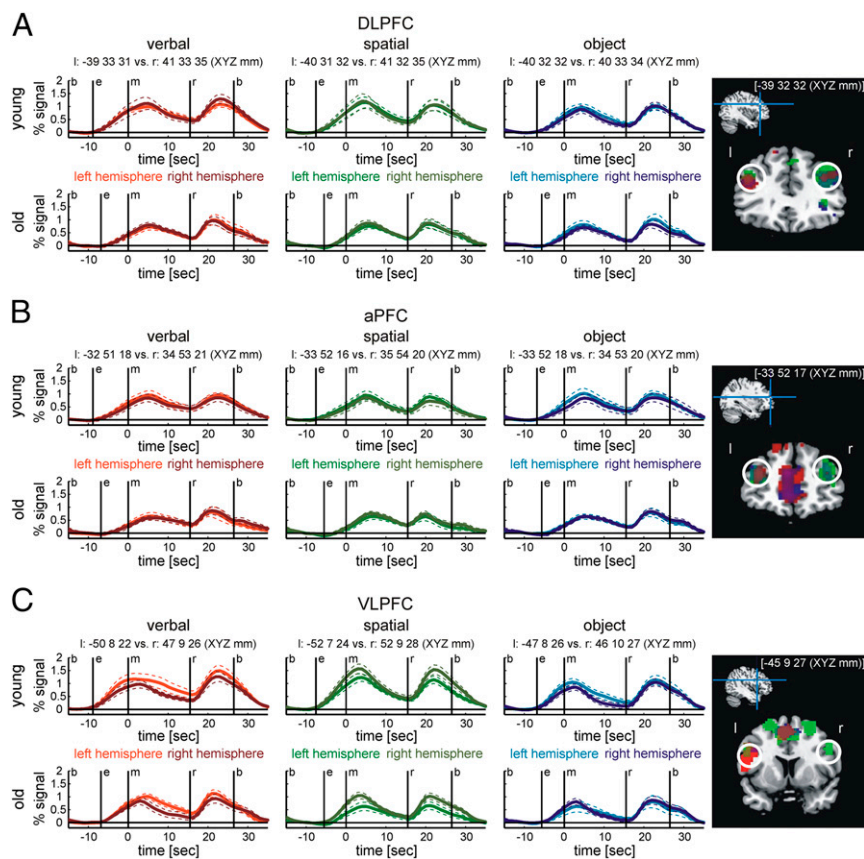


Fig. 3. Time-resolved fMRI activity in both hemispheres of young vs. old subjects in the main experiment. The time courses of the BOLD signals of DLPFC (A), aPFC (B), and VLPFC (C) are presented separately for the left (brighter color) and right (darker color) hemispheres, young subjects (upper rows, $n = 10$) and old subjects (lower rows, $n = 10$) and verbal (red), spatial (green), and object (blue) WM domains. Each time course refers to the across-subjects average of all trials of all five load levels. Dotted lines represent SEs. Vertical solid lines indicate the onsets of the individual phases of a trial: baseline (b), encoding (e), maintenance (m), response (r). Time courses are aligned to the onset of the maintenance phase. Consider that we did not extract time courses of a ROI from the same representative group coordinate of this ROI but from individual coordinates. The coordinates above the time courses are the mean coordinates of these individual coordinates. All coordinates are in Montreal Neurological Institute (MNI) space. Whereas DLPFC (A) and aPFC (B) represent domain-general bilateral ROIs, VLPFC (C) represents a domain-specific bilateral ROI. To illustrate the locations that we considered as DLPFC, aPFC, and VLPFC, we separately present the group maps for memory maintenance (EOI contrast; *Materials and Methods*) in the verbal (red), spatial (green), and object (blue) domains ($P < 0.00001$, uncorrected) and highlighted them with white circles. Note that colors mix additively when the same spots were activated in two WM domains, whereas dark reddish stains refer to spots that were recruited in all three domains. l, left; r, right.

Bayes factors equal 1, the experimental data are not sensitive enough to decide which lateralization pattern is more likely. The Bayes approach supported the preliminary conclusions suggested by the above-described ANOVA results: in all WM domains, left and right hemispheres were equally activated in DLPFC and aPFC in both young subjects (Bayes factors of DLPFC: verbal, 0.15; spatial, 0.33; object, 0.45; Bayes factors of aPFC: verbal, 0.29; spatial, 0.20; object, 0.52) and old subjects (Bayes factors of DLPFC: verbal, 0.32; spatial, 0.07; object, 0.31; Bayes factors of aPFC: verbal, 0.26; spatial, 0.33; object, 0.22). Note that in the object domain there is generally less evidence in favor of bilaterality in young compared with old subjects. This finding may reflect the abovementioned fact that young participants worked on object-based WM items that did not push them to their capacity limits as opposed to the other WM domains and to the group of older subjects.

In summary, all abovementioned results clearly speak in favor of the idea that bilateral activation patterns are associated with high WM task-demands in DLPFC and aPFC and are independent of age and WM domain. Because our analyses only considered activation in a relatively small area (a 3-mm radius sphere), there might still be differences in the spatial extent of activation across hemispheres. Therefore, we repeated our analyses while sampling from a larger area (a 9-mm radius sphere). The respective analyses led to the same principle findings (Table S2), suggesting that there are no differences in lateralization with respect to the spatial extent of activation in our prefrontal (and all other) ROIs. Finally, we tried to control for the fact that we had used the same dataset for both ROI definition and ROI analyses. To this end, we resorted to an a priori definition of the cross-hemispheric counterparts of our main ROIs based on previous WM research (20). This analysis again revealed the same pattern of hemispheric lateralization like the one obtained by our main analytical approach (Table S2).

Further areas that were engaged in WM maintenance and in which the main effect of hemisphere was not significant across all three WM domains were the anterior insula [verbal: $F(1,18) = 2.36, P = 0.142$; spatial: $F(1,18) = 0.86, P = 0.365$; object: $F(1,18) = 0.16, P = 0.698$], PMd [verbal: $F(1,18) = 0.01, P = 0.919$; spatial: $F(1,18) = 1.66, P = 0.213$; object: $F(1,18) = 1.53, P = 0.232$], and the calcarine sulcus [verbal: $F(1,18) = 0.0003, P = 0.988$; spatial: $F(1,18) = 0.64, P = 0.433$; object: $F(1,18) = 0.38, P = 0.548$]. Considering these results, the corresponding Bayes factors (Fig. S3 A and B) and the fact that we did not find any hemisphere \times age interactions in the respective ANOVAs (all $P > 0.10$), we assume that in addition to DLPFC and aPFC, the anterior insula, the PMd, and the calcarine sulcus are regions that exhibit a bilateral activation pattern during the maintenance phases of all three WM domains and thus reflect a domain-general bilaterality that is independent of age.

Domain-specific bilateral ROIs. Contrary to DLPFC and aPFC, we had predicted that VLPFC should rather exhibit a unilateral pattern of activation, at least in those WM domains that build on language-related processes. In fact, VLPFC—along with the SMA and the cerebellum—exhibited a unilateral pattern in the verbal and object domains but a more bilateral one in the spatial domain. Hence, these ROIs exhibited a domain-specific bilaterality. Whereas VLPFC and SMA showed stronger activation in the left than in the right hemisphere in the verbal domain [main effects of hemisphere in VLPFC: $F(1,18) = 16.82, P = 0.001$; in SMA: $F(1,18) = 31.58, P = 0.00003$] and in the object domain [main effects of hemisphere in VLPFC: $F(1,18) = 4.91, P = 0.040$; in SMA: $F(1,18) = 14.43, P = 0.001$] across age groups, right lobule VI/crus1 of lobule VII of the cerebellum was stronger activated than its left-hemispheric counterpart in these WM domains [main effects of hemisphere: verbal: $F(1,18) = 10.27, P = 0.005$; object: $F(1,18) = 6.25, P = 0.022$]. In contrast, the left and right cross-hemispheric counterparts were similarly engaged in all three ROIs in the spatial domain [main effects of hemisphere in VLPFC: $F(1,18) = 0.71, P = 0.410$; in SMA: $F(1,18) = 3.82, P = 0.066$; in cerebellum: $F(1,18) = 0.96, P = 0.341$]. Importantly, all effects were independent of age and thus identical across age groups (all interactions between hemisphere and age: $P > 0.24$). The Bayes factors of young and old

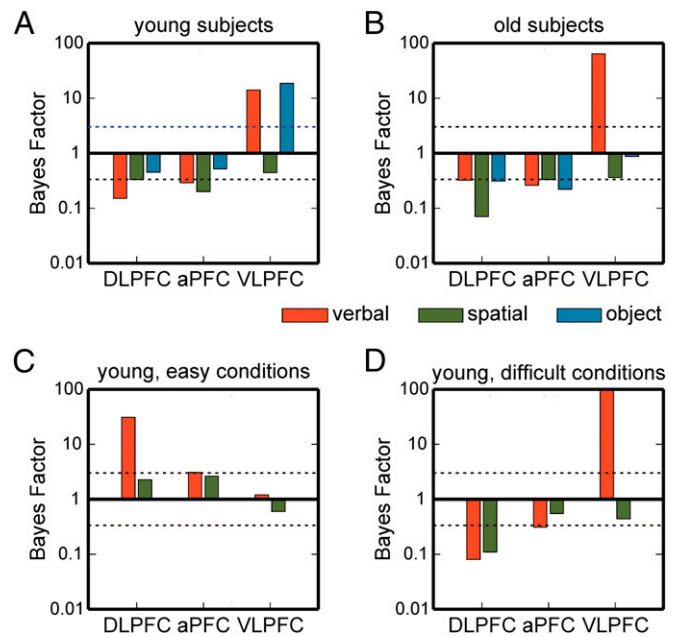


Fig. 4. Bayes factors of the main ROIs. Bayes factors of the 10 young (A) and 10 old (B) subjects of the main experiment are shown separately for DLPFC, aPFC, and VLPFC and WM domains (red: verbal; green: spatial; blue: object). Furthermore, we illustrate Bayes factors of the 11 young subjects of the control experiment for easy (C) and difficult (D) tasks, which are depicted for the same ROIs and separately for the verbal (red) and spatial (green) WM domain. A Bayes factor below 1 denotes evidence in favor of bilaterality, a Bayes factor above 1 represents evidence in favor of unilaterality, and a Bayes factor that equals 1 expresses that the experimental data are not sensitive enough to decide which lateralization pattern is more likely. The horizontal dashed lines represent the thresholds that provide—according to Jeffreys (25)—substantial evidence for unilateral (upper line, $y = 3$) vs. bilateral (lower line, $y = 1/3$) activation patterns. We logarithmized the y axis to ensure that the two thresholds have the same distance from 1. For better general visibility, we set the upper limit of the x axis to 100. As a consequence, the bar depicting the Bayes factor of VLPFC in the verbal domain was cut in D because its value amounts to 241 (compare Fig. S3). Note that, whereas VLPFC generally exhibited unilaterality in difficult conditions of the verbal domain, this pattern was less pronounced in the easy condition (C), which could relate to a floor effect, because the easy verbal task may have been too simple to drive left VLPFC.

subjects further support the aforementioned findings (Fig. S3 A and B). The time courses of the BOLD-signal changes (Fig. 3C) and the Bayes factors (Fig. 4 A and B) show that the activation in VLPFC matched our predictions.

Another brain region that exhibited domain-specific bilaterality was area SPL. ANOVAs of SPL showed no effects of hemisphere in the verbal [$F(1,18) = 0.33; P = 0.573$] and spatial [$F(1,18) = 1.60; P = 0.222$] domains, whereas they revealed a significant main effect of hemisphere in the object domain [$F(1,18) = 18.10; P = 0.0005$]. We did not find significant interactions between hemisphere and age in these ANOVAs (verbal and spatial: $P > 0.40$), apart from the object domain [$F(1,18) = 4.45; P = 0.049$]. The Bayes factors of young and old subjects further support these findings (Fig. S3 A and B). These statistical results suggest that, except for the object domain, the described lateralization patterns were similar in young and old subjects. Here, young subjects showed a stronger activation of the left hemisphere [$F(1,9) = 20.10; P = 0.002$; uncorrected; survives Bonferroni correction for multiple comparisons], whereas old subjects did not show this hemispheric difference [$F(1,9) = 2.32; P = 0.162$]. Because the object task was subjectively easier for young subjects (as described above), this result leaves ambiguous whether the difference in lateralization patterns in SPL in the object domain is a function of task difficulty or age.

Domain-general unilateral ROIs. The three-way repeated measures ANOVAs yielded significant main effects of hemisphere for all WM domains in PMv [verbal: $F(1,18) = 15.76, P = 0.001$; spatial: $F(1,18) = 14.20, P = 0.001$; object: $F(1,18) = 12.38, P = 0.002$] and in IPS [verbal: $F(1,18) = 23.59, P = 0.0001$; spatial: $F(1,18) = 10.88, P = 0.004$; object: $F(1,18) = 13.81, P = 0.002$], whereas, in each case, activation was stronger in the left hemisphere. Therefore, these areas are considered domain-general unilateral ROIs. The additional absence of significant interactions between the factors hemisphere and age (all $P > 0.35$) indicated that this hemispheric difference is independent of age. This conclusion is supported by Bayes factors of young and old subjects (Fig. S3 A and B). In sum, PMv and IPS are regions that maintain left-lateralized activation patterns during the maintenance phases of all three WM domains in the face of high subjective task loads and independently of age.

Changes in Prefrontal Lateralization with Task Difficulty. In our main experiment, bilateral recruitment of DLPFC and aPFC was present at all load levels in all three WM domains and in both age groups (Fig. S2 A and B). This result was not surprising because, as was mentioned above, all relative load levels closely ranged around a subject's WM span and participants could not anticipate the load level of the current trial and, thus, always had to be prepared for the highest load level. Either of the two factors could have triggered the recruitment of the other hemisphere irrespective of the actual load. To demonstrate that DLPFC and aPFC do in fact exhibit lateralized patterns of activity in easier versions of our WM tasks and to further substantiate the notion that young individuals also shift from a lateralized to a bilateral mode of prefrontal processing in difficult WM tasks, we conducted an additional control experiment in young adults. In this experiment, we used the same WM tasks as in our previous experiment but limited to the verbal and spatial domain (Fig. 1). In the control experiment, both verbal and spatial conditions consisted of one easy and one difficult load level. The experiment was conducted in four sessions and we tested only one experimental condition (e.g., verbal easy, etc.) per session to make it clear to the subjects whether any given trial would be easy or difficult.

The analysis of the hit rate showed that we were successful in creating an easy and a more difficult condition in both domains. Almost all trials were answered correctly in the easy conditions of the verbal domain (proportion of hits: mean, 0.996; SE, 0.005; throughput: mean, 2.980; SE, 0.021) and the spatial domain (proportion of hits: mean, 0.984; SE, 0.008; throughput: mean, 1.938; SE, 0.033). Secondly, the proportion of hits was significantly lower in the difficult conditions of both the verbal (proportion of hits: mean, 0.841; SE, 0.036; throughput: mean, 5.701; SE, 0.296) and spatial (proportion of hits: mean, 0.833; SE, 0.039; throughput: mean, 4.797; SE, 0.282) domain (both tests revealed almost the same statistical values: $U = -2.81, P = 0.005$; we conducted Wilcoxon tests because simple conditions were not normally distributed in both WM domains due to ceiling effects in performance).

Next, we investigated whether there is lateralized activation of DLPFC and aPFC in easy tasks that shifts to bilateral activation of corresponding counterparts in difficult tasks. To this end, we calculated two-way repeated-measures ANOVAs independently for DLPFC and aPFC and for the verbal and the spatial domain with the factors hemisphere (two levels: left vs. right) and load (two levels: easy vs. difficult) on the estimates of percentage of BOLD-signal change during the maintenance phase (compare Fig. S4) and also determined the corresponding Bayes factors. The ANOVAs revealed significant interactions between hemisphere and load in DLPFC in both the verbal [$F(1,10) = 6.79; P = 0.026$] and spatial [$F(1,10) = 5.88; P = 0.036$] domains. Bayes factors (Fig. 4 C and D) supported these findings (verbal easy: 30.94; verbal difficult: 0.08; spatial easy: 2.26; spatial difficult: 0.11). These results indicate that left DLPFC was more activated than its right counterpart in the easy conditions of verbal and spatial domains. This lateralization disappeared in the difficult conditions due to an increase in activation of the right hemisphere in both domains (compare Fig. S44). For aPFC, the hemisphere \times load interactions were not

significant [verbal: $F(1,10) = 2.13, P = 0.175$; spatial: $F(1,10) = 0.01, P = 0.940$; Fig. S4B]. However, at least in the verbal domain, the corresponding Bayes factors again indicated a unilateral lateralization pattern in the easy condition (verbal: 3.06; Fig. 4C) that transforms into a bilateral activation pattern in the difficult condition (verbal: 0.31; Fig. 4D), whereas a clear trend in the same direction was also present in the spatial domain (spatial easy: 2.63; spatial difficult: 0.55; Fig. 4 C and D). Further effects and the results of the ANOVAs of VLPFC and of all additional ROIs are in Table S3 (see Fig. S3 C and D for corresponding Bayes factors).

In summary, the findings of our control experiment support the notion that DLPFC and aPFC show left-lateralization during memory maintenance in easy WM tasks but which recruit their right-hemispheric counterpart when tasks get difficult. Our main experiment suggests that this support mechanism operates in a domain-general and age-independent manner.

Discussion

Our aim was to investigate whether bilateral activation patterns observed in prefrontal cortex during WM tasks are the result of an age-specific compensation mechanism or, alternatively, an age-independent strategy to cope with high task demands. In addition, we wanted to know whether these bilateral activation patterns are present across various WM domains, suggesting a domain-general support mechanism. Moreover, we asked whether recruiting cross-hemispheric counterparts is an option in principle available to any task-relevant brain area.

Previous work demonstrated that younger adults show unilateral activation of prefrontal cortical regions, whereas older adults exhibit a bilateral activation pattern of these areas during the execution of cognitive tasks in which objective task difficulty was kept constant across subjects and age groups (2–5). Because these bilateral activation patterns were found in high-performing older adults but neither in young adults nor in low-performing older individuals (2), Cabeza interpreted them as an age-specific compensation mechanism (2, 3). In our main experiment, we used a task that was subjectively very demanding and matched subjective difficulty across young and old participants. In these conditions, we saw bilateral activation patterns in DLPFC and aPFC in all investigated WM domains and in both age groups, suggesting that bilateral activation is not age-dependent. Our results are in agreement with the CRUNCH model which proposes that independently of age, neural activity increases in subjectively demanding tasks. This increase can be local but can also spread to other brain regions, including an area's cross-hemispheric counterpart (14, 15). A specific prediction of the CRUNCH model is that all differences in brain activation strength between age groups should disappear once subjective task difficulty is matched between age groups (16). The first evidence supporting this prediction came from an fMRI experiment by Schneider-Garces et al. (16). In this work, all young and old subjects worked on the same objective WM load sets in a verbal delayed match-to-sample task comparable to ours. Importantly, apart from WM load, Schneider-Garces et al. also considered individual WM span as a factor influencing brain activity. They demonstrated that the BOLD response was larger in older subjects when it was expressed as a function of WM load—both in single ROIs and after averaging all ROIs (considered as “total activation strength”). However, this age-related difference disappeared when total activation strength was expressed as a function of WM load, whereas WM load was adjusted as a function of subjects' WM spans. Unfortunately, these authors did not focus on differences in lateralization patterns in their analyses. Moreover, they did not report any results for DLPFC and aPFC although at least DLPFC should support WM tasks like the verbal task used in their study (5, 26). Going beyond Schneider-Garces et al., we directly tested whether or not individual ROIs were bilaterally activated in the face of challenging WM tasks, while also focusing on both DLPFC and aPFC. Furthermore, we assessed the lateralization patterns of our ROIs not only in a verbal task but also in spatial and object tasks. Our results indicate that bilateral activation patterns in DLPFC and aPFC do not represent an age-specific

compensation mechanism. Rather, the results speak in favor of a general age-independent support mechanism that compensates for task difficulty in a domain-general manner.

The Nature of an Age-Independent Compensation Mechanism. How might such a general cross-hemispheric support mechanism operate? Banich (9) suggested that the brain has at least two alternative cognitive strategies for the processing of most tasks because, with only a few exceptions, both hemispheres are capable of processing the same kind of information. However, they do so with a different degree of competence as each of them is specialized to process information in a particular mode (9, 10). According to Banich, the decision to recruit only one or both hemispheres to solve a task depends on the difficulty of the task as well as the costs associated with reintegrating the processed information from both hemispheres via the corpus callosum. Although the hemisphere with the specialized mode is adequate for processing easy tasks, the capacity of the brain can be boosted by distributing the information across the two hemispheres in demanding situations leading to a simultaneous and independent processing of the information in different modes (9, 10). Banich's group provided evidence for these assumptions on a behavioral level by showing that contrary to simple cognitive tasks, in difficult tasks, across-field processing—in which the relevant information to solve a task is distributed across left and right visual hemifields/hemispheres—has a behavioral advantage over within-field processing (10, 27). In agreement with Banich's idea and those behavioral results, we showed that lateralization patterns of the prefrontal areas DLPFC and aPFC depend on the difficulty of WM tasks: in the control experiment, both areas were unilaterally activated in young adults during easy WM tasks which is in agreement with former research (2, 5). In contrast, in our main experiment DLPFC and aPFC exhibited bilateral activation patterns in both young and old subjects and in either WM domain when subjective task difficulty was high. Moreover, our control experiment allowed us to directly demonstrate this change in lateralization as a function of task difficulty in DLPFC for both the verbal and the spatial domain by means of significant interactions between hemisphere and load (also compare the corresponding Bayes factors in Fig. 4 C and D). However, we failed to reveal such significant interactions between hemisphere and load in aPFC. This result was most likely due to the fact that—as opposed to the main experiment—there was a less pronounced bilaterality in aPFC in the difficult conditions of the control experiment (Fig. 4 C and D and Fig. S4). This finding may have been caused by the fact that in our control experiment we did not match task difficulty on an individual level and, as a consequence, some subjects might not have worked at their capacity limits. Thus, our control experiment was perhaps less reliable in prompting the recruitment of the other hemisphere to compensate for task difficulty—a recruitment that might also be triggered by varying levels of task difficulty as dependent on brain region (DLPFC vs. aPFC) and on compensatory function.

Clues about the nature of the prefrontal compensation mechanism might be derived from the pattern of lateralization revealed by our control experiment, namely a left-lateralized activation in easy tasks that was present in DLPFC and aPFC in both the verbal and the spatial domain. This pattern seemingly contrasts the results of Reuter-Lorenz and colleagues (5) which demonstrated in a delayed match-to-sample task left-lateralized activity for verbal WM but right-lateralized activity for spatial WM in DLPFC. Note, however, their short maintenance phase of 3 s did not allow to separately attribute lateralization to encoding, maintenance and/or retrieval processes (20) and the reported lateralization might have simply referred to a material-specific encoding or retrieval of the stimuli (28). In contrast, we here exclusively focused on lateralization during WM maintenance. To this end, we used comparatively long maintenance durations (~15 s) allowing us to conduct a time-resolved analysis and to specifically estimate fMRI activity of the maintenance phase without any confounding influences of the encoding and retrieval phases (29, 30). Current models of WM assume that DLPFC plays an executive role during such WM maintenance rather than being a mere content-specific buffer (29,

31, 32). Accordingly, lateralization during WM maintenance should rather refer to such executive operation than to the stimulus-material. In agreement with this proposal for instance Johnson et al. (33) have shown that the left and not the right DLPFC and aPFC are engaged in “refreshing” memory representations for WM maintenance—irrespective of the stimulus material that had to be memorized. Our left-lateralized activation patterns retrieved during the maintenance of verbal and spatial material in the control experiment could be interpreted accordingly, namely as a left-lateralized executive operation subserving the maintenance of WM across various WM domains. Moreover, as is suggested by our research, this executive operation could further demand an age-independent domain-general recruitment of the other hemisphere if tasks get more difficult.

Besides DLPFC and aPFC, also the anterior insula and PMd were consistently mapped across all WM domains (Table S1) while exhibiting bilaterality in a domain-general manner. Following the rationale of Craig (34), we hypothesize that the anterior insula might thereby support interoceptive meta-awareness, namely the “feeling-of-knowing.” Moreover, we interpret bilaterality in PMd/FEF as a reflection of attention (35), which belongs to the most basic executive processes that are required for WM operations (21, 31, 32).

The Unilateral Processing of Language-Based Areas. Belger and Banich (10) suggested that almost all tasks can be processed by both hemispheres in their specific modes, with the exception of certain phonetic tasks whose linguistic contents are assumed to be exclusively processed by the left hemisphere. Therefore, we asked whether bilaterality is a general mechanism that the brain developed to cope with challenging tasks, available not only to DLPFC and aPFC but also to other task-relevant brain regions—even to areas that are known for their highly lateralized processing of language-based information like Broca's area in VLPFC (17). Our results suggest that the answer to this question is no because in both age groups, VLPFC, SMA, and cerebellum maintained unilaterality in the verbal and object domains despite high task demands. As many of our participants reported that they had stored the object items partly by maintaining names which they had associated with them, we suspect that unilaterality in the object domain also refers to verbal mnemonic strategies. Besides VLPFC, the SMA and cerebellum may also be considered language-relevant areas because these areas are involved in preparing and executing speech as well as in verbal WM processes (21, 36). Furthermore, Broca's area (which overlaps with our left ROI in VLPFC) and left SMA are anatomically interconnected with right lobule VI and crus1 of the cerebellum (37, 38). The unilateral activation pattern of VLPFC, SMA, and cerebellum could reflect subvocal rehearsal during the maintenance phase of the verbal and object WM tasks (21, 39). Moreover, PMv showed stronger activation in the left hemisphere than in the right across all three investigated WM domains and in both age groups, a pattern consistent with the idea that left PMv plays a role in language (40). Because this unilateral lateralization pattern was not domain-specific for the verbal (and object) material but was also present in the spatial domain we assume that the function of a lateralized pattern of PMv during the maintenance phase of our study may reflect an unspecific preparation of the verbal report that was required during the response epochs of all three WM domains (40).

Putative Limitations. There were several limitations in the object-based WM task that could affect the interpretation of our experimental findings. First, many subjects maintained not only “pure” object information but resorted to a verbal mnemonic strategy, as reported by the majority of our subjects after the experiment. Second, subjective task difficulty was not successfully matched between young and old subjects: the object tasks were easier for the young than for the old subjects, which may have resulted from the fact that older adults learn new material more slowly (41). Future studies could also use Kanji signs but use new items in every trial to prevent learning effects. The shortcomings in the object domain offered us the possibility to see whether these “imperfections” are reflected in the activation of our ROIs in a meaningful way. For example, whereas the Bayes factors in DLPFC and in aPFC clearly

indicated bilaterality in young and old subjects in both verbal and spatial domains, in the object domain, there was less evidence for bilaterality in young compared with old subjects. The fact that the object domain was not as difficult for the young as for the old subjects might underlie this finding. Furthermore, we found a significant age \times hemisphere interaction in SPL in the object domain: whereas young subjects clearly showed a stronger activation of the left hemisphere, older subjects did not. This finding could suggest that beyond prefrontal cortex, SPL might also compensate for task-difficulty by recruiting its cross-hemispheric counterpart. This idea is also supported by the results of the control experiment, in which SPL showed unilateral activation in easy verbal tasks that shifted to a more bilateral pattern in difficult tasks (compare Fig. S3 C and D).

Another limitation might be the small number of subjects in our experiments (10 subjects per age group in the main experiment; 11 young subjects in the control experiment). Nevertheless, we think that our approach should have been sensitive enough to detect hemispheric differences in lateralization for the following reasons. First, former studies having reported the HAROLD effect also had a small n of ~ 10 subjects per age group and showed unilateral activation in young subjects (2–5). Second, we were able to find hemispheric differences in the 11 young subjects of our control experiment in DLPFC and aPFC when they worked on easy verbal and spatial tasks. This result shows that our paradigm was in principle suitable for detecting hemispheric differences. Third, we found an age \times hemisphere interaction in SPL in the object domain of the main experiment which indicates that we are able to show age group differences with our approach. Fourth, despite the small number of subjects we had a relatively high number of repetitions of trials in the main experiment (5 load levels \times 15 repetitions = 75 repetitions of difficult trials per WM domain; compare also *SI Materials and Methods, Procedures of the Main Experiment*) for the important within-subject comparison between activations of the hemispheres. Fifth, because the most important conclusion of our study builds on the finding that also young adults exhibit bilaterality during demanding tasks, we increased the n of the young group by combining the functional activation data of the difficult condition of the control experiment with the average activation (calculated across all five load levels) in the main experiment. Also with an n of 21, we did not find hemispheric differences for DLPFC [verbal domain: paired t test: $t(20) = 0.31$, $P = 0.761$; Bayes factor: 0.07; spatial domain: paired t test: $t(20) = 0.26$, $P = 0.801$; Bayes factor: 0.10] and aPFC [verbal domain: paired t test: $t(20) = 0.48$, $P = 0.637$; Bayes factor: 0.22; spatial domain: paired t test: $t(20) = 1.01$, $P = 0.324$; Bayes factor: 0.36] in young subjects.

Performance Difference Between Young and Old Subjects. Our data suggest that lateralization patterns are similar between young and old subjects when they work on tasks that are matched for subjective task difficulty. Consequently, the elderly use the same compensation mechanism as young subjects when handling demanding memory tasks. Why are their memory spans still lower than those of young adults despite this compensation mechanism? Clearly, our study cannot provide an answer to this question, but it is generally believed that such decreases in WM performance with age reflect neurocognitive decline (3, 42). In addition, we would like to also highlight a novel answer to this question, which is suggested by the research of Ramscar et al. (43), who expect even elderly adults without any morbid cognitive decline to perform worse in WM tasks than their younger counterparts. This decrease in performance would be simply due to computational limitations in handling the large amounts of information and knowledge that older adults keep accumulating during their life span.

Summary and Conclusions

In summary, we did not find any hemispheric differences in brain activation between younger and older adults in prefrontal cortex while they worked on WM tasks that were matched for subjective task difficulty. More specifically, we found that bilateral activation patterns of the prefrontal ROIs DLPFC and aPFC emerged across all WM domains in both young and old adults when they had to

maintain large amounts of information at their capacity limits. Furthermore, we were able to show that these prefrontal regions show unilateral recruitment in easy tasks which shifts to bilateral recruitment during difficult tasks. This finding speaks in favor of the idea that the recruitment of cross-hemispheric counterparts in prefrontal cortex represents a support mechanism that compensates for task demand rather than age. Moreover, we did not demonstrate bilaterality in all task-relevant ROIs. For instance, areas that probably dealt with language processes (VLPFC, SMA, lobule VI, and crus1 of lobule VII of the cerebellum and PMv) maintained a unilateral activation pattern even during very demanding WM tasks. In conclusion, activating the contralateral counterpart in the other hemisphere under demanding circumstances and across WM domains seems to be an age-independent support mechanism that is largely restricted to dorsolateral and anterior prefrontal cortex.

Materials and Methods

All participants gave written consent in accordance with the declaration of Helsinki, and the study was approved by the ethics committee of the University of Tübingen.

Subjects. Twelve young and 11 older subjects completed all sessions of the main experiment. We excluded two of the young participants and one of the older ones from data analysis due to strong movement artifacts in the fMRI recordings, lack of oral responses, or falling asleep during scanning, respectively. Consequently, we were left with 10 young subjects (3 males; age range: 19–27 y; mean age: 24.3 y; SD: 2.7 y) and 10 old subjects (4 males; age range: 59–70 y; mean age: 65.2 y; SD: 3.8 y) for our final analyses. All subjects were native German speakers and scored higher than 27 on the Mini-Mental State Examination (44). Young and old participants did not show significant differences (all $P > 0.45$) in the age-corrected scores of the applied subtests “picture completion,” “vocabulary,” “similarities,” “block design,” “arithmetic,” and “digit span” of the Wechsler Adult Intelligence Scale (45). One subject of each age group was regularly taking thyroxin, but no other participants were on any medication, suggesting that the BOLD signals were not modulated by drugs. Moreover, none of our subjects had any Japanese or Chinese language skills, which was important to ensure that the object items were perceived as objects and not linguistically based material. In the control experiment, we measured a total of 12 young subjects while ultimately including 11 subjects (6 males; age range: 21–30 y; mean age: 25.1 y; SD: 3.2 y) who had not participated in the main experiment. One subject was excluded due to strong movement artifacts. The subjects of both experiments had normal or corrected-to-normal visual acuity, were right-handed according to the Edinburgh Handedness Inventory (46), and participated in the experiments for monetary compensation, and none suffered from chronic, neurological, or psychiatric diseases.

Stimuli. We used consonants of the Latin alphabet (uppercase letters in the encoding phase and lowercase letters in the response phase) as memory items in the verbal domain. All letters were presented in “Arial” font and a 50-pixel font size. In the spatial domain, dots (\circ : 30 pixels) within a grid (192 \times 240 pixels) that consisted of 20 squares (4 rows \times 5 columns; each square: 48 \times 48 pixels) served as memory items. Twenty Japanese Kanji signs ($\sim 50 \times 50$ pixels) that had been randomly chosen from the Japanese Language Proficiency Test were the memory items in the object domain (Fig. S5). We displayed the numbers indicating the stimuli in the response phase in Arial font and a 30-pixel font size and the fixation crosses of the baseline and maintenance phases in a 50-pixel font size.

Procedure. The main experiment comprised five sessions, which were conducted on five separate days. On the first day, our subjects worked on six subtests of the German version of the Wechsler Adult Intelligence Scale (45), the Edinburgh Handedness Inventory (46), and the Mini-Mental State Examination (44). On the second day, we assessed our participants’ WM spans (Fig. 2B and *SI Materials and Methods, Creating Individual Load Sets and Procedures of the Main Experiment*). In the last three sessions of the study, subjects worked on individualized fMRI versions of the memory task (Fig. 1), while they were scanned using fMRI.

In the control experiment, we used an easy and a difficult version of the verbal and spatial WM tasks of the main experiment (Fig. 1). The respective load levels in the easy conditions were three items in the verbal domain and two items in the spatial domain. Load levels were chosen one item lower than those engaged in the study by Reuter-Lorenz and colleagues (5), who demonstrated lateralized activation of DLPFC in young subjects in both WM domains. For the

difficult conditions we used the average WM capacity of young subjects revealed in the verbal domain (load level: 7) and the spatial domain (load level: 6) in our main experiment (Fig. 2A).

Further information on the procedures, stimulus presentation, and data acquisition is detailed in the respective subsections of *SI Materials and Methods*.

Data Analysis. We statistically analyzed behavioral data using SPSS (version 22; IBM SPSS Statistics). To investigate whether our two age-groups differed in essential cognitive processes, we conducted six independent-samples *t* tests—one on each of the six age-corrected scores of the subtests of the Wechsler Adult Intelligence Scale. Functional data were analyzed using Statistical Parametric Mapping version 8 (SPM8, Wellcome Department of Cognitive Neurology, London) and SPSS (version 22; IBM SPSS Statistics). In the next sections, we explain in detail how we analyzed the fMRI data. For detailed information on the preprocessing of the fMRI data, see *SI Materials and Methods, Preprocessing of the Functional Data*.

First-Level Analysis. On the single subject level of our main experiment, we created a general linear model (GLM) with 45 regressors that were comprised of a combination of 15 memory conditions (3 WM domains \times 5 relative load levels) and 3 task phases (encoding period vs. maintenance period vs. response period). We convolved all 45 regressors with the default canonical hemodynamic response function offered by SPM. The movement parameters that were calculated during the realignment procedure served as covariates of no interest in this GLM. The fixation periods in the beginning of a trial and the intertrial intervals were not specifically modeled and were consequently treated as the baseline phase. For each subject, we generated 15 statistical *t*-contrast images—each of them representing 1 of the 15 memory conditions (3 WM domains \times 5 relative load levels) in the maintenance period (image set 1)—and 3 statistical *t*-contrast images—each of them representing 1 of the 3 WM domains in the maintenance period while considering all 5 load levels simultaneously (image set 2). All analyses described in the following were conducted independently for verbal, spatial, and object WM domains.

In the control experiment, we created a GLM on the single subject level with three regressors that comprised the encoding, maintenance, and response phases separately for every experimental condition (e.g., verbal easy). The further procedure was identical to the one described for the main experiment. For each subject, we generated four statistical *t*-contrast images separately representing the maintenance period of easy and difficult conditions of the verbal and the spatial domain.

Analyzing fMRI Lateralization Patterns of the ROIs. The aim of the main experiment in this study was to investigate whether areas that are involved in WM processes show a bilateral or unilateral activation pattern in younger and older adults when they work on subjectively very demanding tasks. To answer this question, (i) we first searched for potential task-relevant brain areas by means of a second level contrast in SPM. (ii) We next determined a left and a right hemispheric counterpart in each of these ROIs. (iii) Then, we assessed for all participants their individual peak coordinates within the two hemispheric counterparts of all predefined ROIs (for further details, see below) to extract event-related time courses (ERTs) and estimates of percentage of BOLD-signal change (derived from the respective beta weights of our GLMs) from these individually assessed coordinates. We decided for this subject-based ROI approach due to the fact that the brains of elderly adults typically exhibit structural changes (16, 47). Consequently, we could not be sure—even after spatial normalization of the brains—that the same group-based coordinates would occupy the same functional locations in different age groups (and perhaps also not in different individuals of the same age group). (iv) We illustrated the results by means of ERTs and (v) finally conducted our statistical analyses on the acquired individual beta weights. Below, we describe all steps in more detail.

i) To reveal potential task-relevant brain areas that might play a role in the maintenance phases of the experiment, we established a full-factorial model on the second level with the factors age (two levels: young vs. old) and load (five levels: 1–5), separately for every WM domain, by entering the appropriate first-level contrast images in SPM [set 1 in *Materials and Methods, First-Level Analysis*]. Then, we applied an “effects of interest” (EOI) contrast with a minimal cluster-size criterion of $k \geq 10$ voxels and a statistical threshold of $P < 0.05$ that was corrected for multiple comparisons using the familywise error (FWE) correction. This *F* contrast investigated which voxels show significantly different activation strengths from baseline in any of the 10 factor combinations (2 age groups \times 5 relative load levels) during the maintenance period. Areas that were displayed by the EOI contrast (Table S1 and Fig. S1) were considered candidates for potential task-relevant areas and/or for areas showing age-related differences because the

BOLD signal was modulated by the memory tasks and/or by the age of the subjects in these regions. Areas that exhibited stronger activation during baseline than during the maintenance period were not considered, because we have no biologically plausible reason supporting the assumption that a negative BOLD response during the maintenance phase could reflect a neural correlate of WM maintenance.

- ii) In a next step, we defined the voxels with the highest *F* values within left and right counterparts of the ROIs as their representative group coordinates (Table S1). Because we wanted to find out whether ROIs show bilateral activation patterns in young and old subjects, it was crucial to compare the activation strengths of spots that are cross-hemispheric functional counterparts of each other. We frequently found significant voxels in the left and right counterparts of these ROIs across all three WM domains by means of the described EOI approach. In case of identifying significant voxels within a ROI in only one hemisphere, we mirrored the representative group coordinate of this hemisphere to the other hemisphere. Then, we searched for significant spots within a 20 mm sphere around the mirrored coordinate while changing the statistical threshold ($P < 0.05$, FWE correction on cluster-level at $P < 0.001$, $k \geq 10$). If we succeeded in finding significant voxels according to this latter small-volume approach, we chose the voxel with the highest *F* value that anatomically matched its equivalent in the other hemisphere as the representative group coordinate (underlined voxels in Table S1). If we did not succeed, we accepted the mirrored coordinate as the representative group coordinate (empty field in one of the two hemispheric counterparts in Table S1). Because, only for the spatial domain, we did not find significant voxels in one of the ROIs, namely the calcarine sulcus, we used the representative group coordinates of this ROI of the verbal domain in the spatial domain for further analyses.
- iii) Then, we applied the contrast that represented the maintenance phase independent of load level (set 2 in *Materials and Methods, First-Level Analysis*) in all subjects ($P < 0.001$, uncorrected, $k \geq 10$ voxels). We placed a 20 mm sphere separately for each hemispheric counterpart of all ROIs around the representative group coordinate and determined the voxel with the highest *t* value that anatomically matched the respective ROI. Whenever we were not able to find any matching voxel in a subject, we assigned the representative group coordinate to this person. For instance, for DLPFC and aPFC we only assigned the representative group coordinate in up to one case per age group and hemispheric counterpart, with the exception of aPFC in the object domain. Here, the group coordinate was assigned twice in each hemispheric counterpart in the young group, whereas it was assigned to one old subject in the left hemispheric counterpart. Also, in almost all other ROIs, we found individual coordinates in the majority of our subjects of both age groups except for calcarine sulcus, PMv, and SMA. On a group level, we did not find representative group coordinates in calcarine sulcus in the spatial domain, so we instead used the ones of the verbal domain for further analyses (compare Table S1). It is thus not surprising that we had to assign the group coordinate in ~50% of the cases in this ROI but we did so for both age groups and for both hemispheres. Importantly, across ROIs, there was no systematic difference in how often we assigned group coordinates to a specific age group or to a specific hemisphere, with two exceptions: In case of PMv, we assigned the group coordinate in ~50% of young and old subjects to the right hemispheric counterpart in the spatial and object domain. Also, we did so in ~50% of the young participants for the left counterpart, whereas we found an individual coordinate for left PMv in each subject of the old group and in both WM domains. Moreover, in case of SMA, the group coordinates were frequently assigned to the right counterpart of young subjects in both the verbal (five times) and the object domain (seven times), whereas we did not have to do such assignment in old subjects and in the left counterparts of both age groups. Despite these differences in the assignment of group coordinates, we did not reveal any differences in PMv and SMA lateralization between both age groups in our ROI-based analyses of percentage of BOLD-signal change.

Separately for every subject, ROI, and WM domain, we then extracted ERTs of signal intensities and estimates of the percentage of BOLD-signal change for each of the five regressors (load levels 1–5) of the maintenance period and averaged them across a sphere with a radius of 3 mm (and 9 mm) around the individually determined voxel.

- iv) The ERTs of signal intensities illustrate how the BOLD-signal developed across a trial and were extracted by means of scripts that were adapted from the Nod Lab ERT for SPM toolbox (NERT4SPM; by Axel Lindner and Christoph Budziszewski; <https://svn.discfish.de/MATLAB/spmtoolbox/NERT4SPM>). We generated ERTs from every individual subject across load levels and trials, aligned them to the onset of the maintenance phase and

filtered (high pass filter: cutoff period, 128 ms) and normalized them by an estimate of overall baseline activity across all conditions. This baseline activity represented the mean image intensity at the very end of the baseline period (between -5 and -2 s relative to the onset of the encoding period). In the end, we averaged ERTs across subjects within each age group.

- v) We extracted the GLM-based estimates of percentage of BOLD-signal change during the maintenance period for all conditions and all subjects by means of self-written scripts in MATLAB R2007b (The MathWorks). We calculated three-way repeated measures ANOVAs separately for each WM domain with the factors hemisphere (two levels: left vs. right), age (two levels: young vs. old), and load (five relative load levels: 1–5) for each of our ROIs and used the extracted estimates of percentage of BOLD-signal change as dependent variables. As previously mentioned, we were mainly interested in investigating whether our ROIs were bilaterally or unilaterally involved in the memory tasks. When an ANOVA revealed a significant main effect of hemisphere in an area, we interpreted this region to be more unilaterally involved in the task because one hemisphere showed stronger activation than the other one. Note that—with the exception of DLPFC and aPFC—we only report main effects of hemisphere and interactions between hemisphere and age for all ROIs because these statistical effects provide information about the lateralization pattern and about putative differences of the pattern between young and old subjects (but see Table S2 for an overview about all effects).

We additionally calculated Bayes factors (B) for every ROI on the acquired estimates of percentage of BOLD-signal change independently for young and old subjects according to Dienes (24). These factors quantified how probable the alternative hypothesis (there are differences in ROI activity between the hemispheres) is versus the null hypothesis (there are no

differences in ROI activity between the hemispheres). We modeled the prediction of our alternative hypothesis as a uniform distribution. In every ROI, we determined which of the two hemispheric counterparts showed the higher estimate of percentage of BOLD-signal change and used this as an upper limit of the model and we chose a value representing 5% of this value as the lower limit. We decided to use varying lower and upper limits depending on the ROIs to take into account the individual activation strengths in different brain areas. When the resulting Bayes factor B turned out to be above 1 for a given ROI, the experimental data supported the alternative hypothesis; on the contrary, when B was below 1, the experimental data spoke in favor of the null hypothesis and when B equaled 1, the experimental data were not sensitive enough to say which of the two hypotheses was more likely.

The procedure of analyzing lateralization patterns of our ROIs in the control experiment was identical to the previously described approach. We used the representative group coordinates of the main experiment (see *ii* above) to determine individual peak voxels within our ROIs (see *iii* above). However, for the latter step, we used, separately for the verbal and spatial domain, the statistical *t*-contrast images representing the maintenance period of the difficult condition of the control experiment.

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