Diminished alpha lateralization during Working Memory but not during attentional cueing in older adults

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Abstract

Aging has been associated with declined performance in tasks that rely on working memory (WM). Because attention and WM are tightly coupled, declined performance on a WM task in older adults could be due to deficits in attention, memory capacity, or both. We used alpha (8-14 Hz) power modulations as an index to assess how changes in attention and memory capacity contribute to decreased WM performance in older adults. We recorded the magnetoencephalogram in healthy older (60–76 years) and younger adults (18–28 years) while they performed a lateralized WM task. At matched difficulty, older adults showed significantly lower memory-spans than younger adults. Alpha lateralization during retention was nearly absent in older adults due to a bilateral reduction of alpha power. By contrast, in younger adults alpha power was reduced only contralateral to the attended hemifield. Surprisingly, during the cue interval, both groups showed equal alpha lateralization. The preserved alpha lateralization during attentional cueing, and lack thereof during retention, suggests that reduced WM performance in older adults is due to deficits in WM-related processes, not deficits in attentional orienting, and that a compensatory mechanism in aging that permits significant residual WM performance in the absence of alpha lateralization.

Keywords: Attention, Healthy aging, MEG, Oscillations

Growing old is characterized by general cognitive slowing and decline (for a review, see e.g. Hedden and Gabrieli, 2004), which often involves working memory (WM) deficits (Cabeza et al. 2002; Park et al. 2002; Bopp and Verhaeghen 2005; Sander et al. 2011; Murre et al. 2013). WM refers to the ability to briefly store information for later use (D'Esposito 2007), and is crucial for many types of cognition. WM includes encoding, retention, and recollection or recognition phases. It has limited capacity, and most individuals can only store three to four items (Luck and Vogel 1997, 2013; Cowan 2000; Vogel et al. 2001). This limited capacity requires efficient use of resources, and thus WM benefits from an attentional filter that prevents encoding of irrelevant stimuli, thereby limiting encoding to the relevant stimuli. As a result, attention and WM are closely interrelated, and declined WM performance in older adults has indeed frequently been linked to deficits in selective attention (Vogel et al. 2005; Gazzaley et al. 2008; Jost et al. 2011; Sander et al. 2011; McNab et al. 2015).

A striking finding when using tasks that require lateralized covert attention, such as the Delayed Match-to-Sample (DMS) task in Vogel and Machizawa (2004), is that alpha power (8 – 14 Hz) in the hemisphere contralateral to a relevant stimulus is lower than in the hemisphere contralateral to an irrelevant stimulus (Worden et al. 2000; Thut 2006; Sauseng et al. 2009; Händel et al. 2011). This observation gave rise to the current understanding of alpha oscillations as reflecting the active suppression of both encoding and maintenance of irrelevant stimuli in WM.

These experiments have thus far been performed almost exclusively in younger adults and it remains unclear to what extent these findings can be generalized to older adults, and to what extent attention and WM deficits associated with aging may be reflected by changes in the bilateral distribution of alpha. To our knowledge, there have been only three earlier studies that investigated aging and alpha lateralization during a WM task. Using EEG, Sander

et al. (2012b) found that older adults showed lateralized alpha power during a 1000 ms retention interval for medium loads, but not for high memory loads. Younger adults on the other hand showed lateralized alpha power under both high and medium loads. In another EEG study using a cued target discrimination paradigm, Hong et al. (2015) found that unlike younger adults, older adults did not show lateralized alpha oscillations during spatial attention in a 1000 ms interval following a 200 ms directional cue. Recently, measuring MEG in older adults, Mok et al. (2016) found that older adults retain the ability to orient attention within WM, as evidenced by alpha lateralization in response to a so called 'retro-cue', a cue that turned on after bilateral stimulus presentation. Taken together, these results point to age related changes in alpha lateralization. However, it is as yet unclear to what extent these observations generalise to other tasks, and moreover whether they are specific to either spatial attention or WM-related processes.

Here we combine a lateralized DMS task with MEG to investigate the differences in alpha lateralization between younger and older adults. We recorded alpha power during a prolonged cueing interval and a subsequent retention interval of equal length. This paradigm allowed us to investigate whether age related differences in alpha modulation were specific to either attentional cueing or WM retention, or were a general feature of both processes. A key element of our study was that the directional cue remained visible throughout each trial, eliminating the need to keep the directional cue in memory. The cueing interval in our study thus represented a period of spatial attention without WM contribution, and any changes in alpha modulation in this interval could be interpreted in terms of spatial attention. The WM retention interval combines attentional processes with maintenance of WM content. It is thus difficult to separate WM from its associated attentional processes (Gazzaley and Nobre 2012). However, our design offers a step forward in permitting the separate probing of attention

91 during the spatial cueing interval and of WM and its associated processes during the retention
92 interval.

Materials and Methods

Participants

Forty-six older adults were recruited via advertising at an on-campus education center for older adults, by advertisement in the Donders Institute's participant waiting room, and via the first author's network of colleagues. Of these forty-six adults, three participants did not pass an initial screening on performance (less than 60% accuracy on the lowest load) and/or MRI/MEG compatibility (due to metal implants). Four more participants were excluded from the experiment after the MRI measurement due to claustrophobic complaints and the discovery of implants that had not been reported to the researchers. Five more participants were excluded after the MEG session, due to MEG (DSQ) electronics errors, excessive head motion and muscle artifacts.

Data for the remaining thirty-four participants (21 men, 13 women), 60-76 years old (M = 65.8 years), was fully analyzed. All participants reported to be right-handed and had normal or corrected-to-normal vision, as assessed with a Landolt C chart. Participants with glasses were given MEG compatible lenses, such that they were able to read the Landolt C chart equally well with the MEG compatible lenses as with their prescription glasses. We did not test visual acuity in participants who used contact lenses or who did not wear glasses or lenses. All participants were screened with a Dutch test resembling the Mini-Mental State Examination, known as the *"Cognitieve Screening Test"* (De Graaf and Deelman 1991). All participants scored normally on the screening test, indicating the absence of any major neuropsychiatric disorders.

We compared task performance and MEG data from the group of older adults to parallel data acquired in younger adults during an earlier experiment with the same task (Lozano-Soldevilla et al. 2014). In that experiment, the influence of GABA on visual gamma and alpha oscillations was investigated by exposing participants to an experimental and a

placebo session. For the current experiment, we used the placebo sessions of 25 participants (12 men, 13 women), aged 18-28 years (M = 22.4 years) as a control, after eliminating 7 of 32 recruited participants according to the same criteria used for the older participants (for details, see the supplementary material of Lozano-Soldevilla et al., 2014).

---------- Figure 1 near here ----------

Task and stimuli

For the behavioral tests, stimuli were presented on a 24" BenQ LED TFT-monitor (1920x1080 px, 120 Hz refresh rate). For the MEG recordings we used an EIKI LCD projector (60 Hz) projecting stimuli onto the back of a translucent screen via two mirrors.

We used an adapted version of a classic lateralized delayed match-to-sample task (cf. Vogel and Machizawa, 2004). Participants have to decide whether an array of stimuli presented in an attended hemifield is identical to a remembered array, while ignoring stimuli in the other hemifield. In our version of the task, participants had to merely report the presence or absence of a color change in one of the stimuli in the attended hemifield (Figure 1).

Each trial started with a fixation cross, followed by a 1500 millisecond cue period, during which participants received an arrow cue that pointed towards the hemifield in which the relevant parts of the stimulus arrays would be presented. This cue remained visible throughout the trial. After an initial attentional cue period, a bilateral sample array of colored squares was presented for 100 milliseconds, and participants had to memorize the colors of the squares in the cued hemifield. The other (distractor) squares were irrelevant to the task. After a retention period of 1500 ms in which only the cue was visible, a memory probe array appeared and was presented until participants responded, up to a maximum response time of

2000 ms. In the attended hemifield, the probe stimuli either matched those in the sample array (50% of trials), or differed by the color of one square. Independent of the attended hemifield, the irrelevant side of the probe array also differed from the sample array by one square in half of the trials. Participants were instructed to ignore changes on the irrelevant side and only report changes in color on the relevant side. Responses were made by pressing either a button indicating 'no change in colors', or another button indicating 'change in colors', using the right index and middle finger. The mapping of the two response buttons to change or no-change responses was randomized across participants.

Experimental procedure

The older participants were invited to two sessions. In the first session the procedure was explained to the participant, and they could then opt out of the experiment or consent to participate. After giving informed consent, a screening took place which consisted of the CST, and a final check on MEG and MRI eligibility. Similar to the procedure in Lozano-Soldevilla et al. (2014), the experimenter then explained the task and participants completed 8-16 practice trials on a computer in a private cubicle with dimmed lights, in order to familiarize themselves with the task. Head position was not restrained, although participants were placed roughly 60 cm from the screen. These practice trials were presented with only one square in each hemifield ('load 1'). After participants confirmed that they understood and were able to perform the task, they completed 144 trials with loads of 2, 3, and 4 squares per hemifield (48 trials per load). This procedure both trained the participant and allowed us to adjust the difficulty level for each participant individually before MEG acquisition. The load-condition in which a participant performed with accuracy closest to 75% was selected as the load-condition that would be presented during the MEG session. Thus the difficulty of the task was matched for all participants. In the first session, participants also underwent a structural

MRI scan (T1 weighted imaging, see next section). The total duration of the first session was 1.5 h.

In the second session, which was always separated from the first by at least 5 days, participants returned for MEG acquisition. After arriving, participants were asked whether they still wanted to participate in the experiment. If so, they were again given 8-16 practice trials (load 1) to refresh their memory of the task. After that, they were prepared for MEG measurement. Participants with glasses received MEG compatible glasses following the procedure for vision correction outlined above. EOG and ECG electrodes were placed, and the participant was guided to the MEG system. Participants then completed 4 blocks of 100 trials of the task with the load that was selected for them based on session 1. Preparation took 1 hour, and the MEG acquisition was limited to 1 hour.

Younger adults completed the MEG acquisition session three times with at least 4 days in between, where in each session a different dosage of drug was administered, 1.5 mg, 0.5 mg and placebo control (for details, see Lozano-Soldevilla et al., 2014). Here we used the recordings from the placebo control condition.

MRI acquisition

T1-weighted images were acquired on a 1.5T Siemens Magnetom Avanto MRI system (Siemens Healthcare, Erlangen, Germany). TR, TE, and TI were set to 2300 ms, 2.95 ms, and 850 ms, respectively. A flip angle of 15° was used, and 192 saggital slices were taken. The purpose of these MRI scans was to screen for any brain abnormalities, and to retain the possibility of conducting source analysis for future work.

MEG acquisition

Brain activity was measured using a 275 axial gradiometer MEG system (VSM MedTech/CTF MEG, Coquitlam, Canada), with a sampling rate of 1200 Hz and a built-in low-pass anti-aliasing filter with a cutoff at 300 Hz. Eye movements and blinks were monitored using bipolar electrodes, applied above and below the left eye (vertical EOG), and between the bilateral temples and outer canthi (horizontal EOG). To measure the heartbeat, bilateral electrodes were applied above the right clavicle and below the left side ribs. Impedance was kept below 10 kΩ for all applied electrodes.

Once inside the MEG helmet, participants were instructed to rest their head against the back of the MEG helmet, to alleviate tension on the neck muscles and to gain optimal signal from posterior brain sites. To track the position of the head inside the MEG helmet, we used three head coils placed at anatomical landmarks (nasion and both ear canals). Using a real-time head localizer (Stolk et al. 2013), we could track the position of the head relative to the MEG helmet. The position of a participant in the first few trials was saved as a template for the rest of the recording. If a participant's head position deviated from the template beyond a threshold of 5 mm in any direction, the measurement was paused and the participant was guided back into his or her original position.

Data analysis

Behavior analysis

Task performance was assessed by computing accuracy (correct responses divided by total responses). Response bias (c) and d' were also computed, using the formulas below (cf. Hautus, 1995):

$$d' = \varphi^{-1}(h + 0.5) - \varphi^{-1}(f + 1)$$

$$c = \frac{-\left(\varphi^{-1}(h + 0.5) - \varphi^{-1}(f + 1)\right)}{2}$$

With h being the hit rate, f the false alarm rate, and φ^{-1} converting probabilities into z-scores. K_{span} is a classic measure of memory span, we calculated it using Pashler's formula (Pashler 1988).

$$K_{span} = N\left(\frac{h-f}{1-f}\right)$$

This formula takes into account the memory load by multiplying the ratio with load factor N.

MEG analysis

The MEG data was analyzed using FieldTrip, an open-source toolbox (Oostenveld et al. 2011). All recordings were down-sampled to 600 Hz, and low-pass filtered at 200 Hz. The continuous data was segmented into trials that started 2 s before array onset, and ended 3 s after array onset (total trial length: 5 seconds). Line noise was eliminated by fitting sine and cosine functions at 50, 100, and 150 Hz and subsequently subtracting these estimated components. Trial offset was compensated by subtracting the mean.

Trials were visually inspected for artifacts caused by, among other sources, muscle contractions, head movement, and saccades. If such artifacts were present in a trial, the entire trial was excluded from analysis. Trials without any behavioral response and trials with eye-blinks near array onset and probe onset (±500 ms) were also removed, to ensure that participants actually saw the to-be-encoded array. Eye-blink artifacts at other time-points in each trial were identified by visually inspecting the results of an independent component analysis (ICA; Jung et al., 2000). The same method was applied to identify fields detected by the MEG sensors as a result of the electric activity of the heart. The MEG signal was subsequently reconstructed from all components excluding the blink- and heart-related field components, thus removing those from the signal.

For easier interpretation of power measurements, we created synthetic planar gradients by comparing field gradients between horizontally and vertically adjacent axial gradiometers

238 separately, yielding two vectors per gradiometer (Bastiaansen and Knösche 2000). A time-
239 frequency analysis was conducted on these vectors, before combining them by vector
240 summation. Time-frequency representations (TFR) of power were calculated by sliding a
241 time window over each trial in steps of 5 ms. Time window length was set per frequency to
242 fit 6 cycles ($\Delta t = 6/f$). Frequencies were assessed from 2 to 40 Hz in 1 Hz steps. TFRs were
243 then averaged across correct trials for each participant.
244 From the resulting average TFRs for correct trials the power modulation index (PMI)
245 was computed, using the following formula:

$$PMI = \frac{(P_{left} - P_{right})}{(P_{left} + P_{right})}$$

246 where P_{left} is the power of a given frequency band in the 'attend left' condition and P_{right} the
247 power of that band in the 'attend right' condition. Positive PMI values indicated that power
248 was higher when attending left of the fixation compared to attending right, whereas negative
249 values indicate the opposite. Thus, according to the hypothesis that higher alpha power
250 occurs contralateral to a to-be-ignored hemifield, positive PMI values should appear in the
251 left hemisphere ($P_{left} > P_{right}$), and negative PMI values should appear in the right hemisphere
252 ($P_{right} > P_{left}$).
253
254 Statistical Analysis
255 In the behavioral data, group effects were tested using a two-sided independent samples
256 t-test, with age-group as the between-group factor and a behavioral parameter (e.g. accuracy)
257 as dependent variable. To assess functional brain differences in alpha power between the two
258 age groups, the analysis was constrained to those sensors that were sensitive to the
259 experimental manipulation of attention ('attend left' versus 'attend right'). To select these
260 sensors of interest, a cluster-based nonparametric permutation test was used (Maris and
261 Oostenveld 2007), which controls for multiple comparisons over sensors. TFRs of all 'attend

left' correct trials were pooled together (ignoring Age-group labels), as were the TFRs of all 'attend right' correct trials. To identify the sensors that most reliably distinguished between the two attention conditions, without any contribution from WM-related processes, we used a time-window from the cue interval (-1 – -0.1 s before array onset). First, a test statistic was calculated for each sensor, based on a paired samples t-test with attention condition (attend left versus attend right) as independent variable, and alpha power (8 – 14 Hz) as the dependent variable. Sensors that were significant with $p < 0.025$ (two-sided t-test) were clustered according to spatial adjacency. To be considered a cluster, at least three significant adjacent sensors were required. For each cluster, t-statistics were summed. The cluster with the largest summed value was the cluster-based test statistic.

To test the statistical significance of the identified cluster, we applied a permutation test. We obtained a cluster-based test statistic distribution by permuting the independent variable labels and recalculated the power differences 20000 times. At each permutation, we applied the clustering algorithm, and the cluster with the largest sum of t-statistics entered the test statistic distribution. The actual cluster-based t-statistic determined from empirical (non-permuted) data was then compared to the distribution of permuted cluster-based t-statistics. A p-value was estimated by calculating the proportion of t-statistics higher than the empirical t-statistic, and that p-value was then compared to the critical alpha-level of 0.05. In other words, if the empirical cluster-based t-statistic fell outside of the 95% confidence interval, the null hypothesis that the two labels were interchangeable was rejected.

The resulting significant clusters of sensors were used to compare the PMI for the two age groups. To summarize the positive and negative modulations in the left and right hemisphere, a combined PMI (cPMI) measure was created by considering the average PMI of the right hemisphere and subtracting it from the average PMI of the left hemisphere. Positive values of the resulting cPMI indicate effective modulation in the hypothesized direction. The

two age groups were compared using a Repeated Measures ANOVA, with Interval (cue interval vs. retention interval) as a within-subject factor, Age group (young adults vs. older adults) as a between-subjects factor, and cPMI value as the dependent variable.

Results

Behavioral results

Memory load adjustment

In the first behavioral session, we performed an experiment aimed at selecting a WM load that allowed older participants to reach the same accuracy as the younger adult control group. For each older participant, we aimed to find a load setting at which accuracy was near 75%. To this end, we followed the same procedure as Lozano-Soldevilla et al. (2014), which is outlined in the Method section. Behavioral results of the first session are summarized in *Table 1*. Note that younger adults were tested up to load 6. Older adults were only tested up to load 4, as we did not expect high performance at load 5 and 6 and wished to avoid frustrating the participants. There was a significant difference in accuracy between the two age groups for load 3 ($t(56)=2.43$, $p=0.019$) and load 4 ($t(56)=2.86$, $p=0.006$). At load 2, no significant difference in accuracy was found ($t(34,97) = 0.09$, $p = 0.93$). The load that was selected for each individual differed significantly between groups ($t(30.35)=4.05$, $p = 0.000$), with younger adults able to perform near 75% accuracy with higher loads ($M = 4.12$, $SD = 1.30$) than older adults ($M = 3.00$, $SD = 0.55$).

Accuracy and reaction times

In the second session, participants completed the same DMS task with the individually adjusted load. Accuracies of younger adults ($M = 76\%$, $SD = 8.2$) and older adults ($M = 80\%$, $SD = 8.3$) did not differ significantly ($t(57) = -1.69$, $p = 0.097$). The memory span scores (Pashler's K) differed significantly between the two groups ($t(39.05) = 2.71$, $p = 0.01$), with younger adults ($M = 2.38$, $SD = 0.62$) having higher K_{spans} than older adults ($M = 2.00$, $SD = 0.41$), reflecting successful performance under a higher load in younger adults. Older adults ($M = 0.97$ s, $SD = 0.13$ s) had significantly slower reaction times ($t(57) = 5.32$, p

315 = 0.000) than younger adults (M = 0.76 s, SD = 0.16 s). However, a test of Spearman's rank
316 correlation between reaction times and alpha lateralization revealed no significant
317 correlations in the cue or retention intervals, in either younger or older adults (four tests, all r
318 < 0.16, all p > 0.4). There were no significant differences in d' ($t(56) = 1.873$, $p = 0.066$) or
319 criterion ($t(56) = -0.551$, $p = 0.584$), indicating no age differences in sensitivity or response
320 bias (note that one younger participant could not be included in this analysis, because the
321 data-file was corrupted and single-trial performance was lost).
322
323 *Suppression of distractors*
324 We were interested in testing whether older adults correctly oriented attention in this
325 task. Therefore we tested whether they were specifically more prone to respond to stimuli
326 from the uncued hemifield. We coded trials according to whether there was a change in the
327 attended side (A^C) or whether there was no change (A^{NC}), and according to whether a change
328 occurred in the unattended side or not (U^C or U^{NC}). To test whether older adults were
329 encoding both hemifields of the array, we compared participant's rate of reporting a change
330 when one occurred solely on the unattended side (A^{NC}/U^C) with the response rate when no
331 change occurred in either hemifield (A^{NC}/U^{NC}). We found no significant difference (paired t-
332 test, $t(33) = 1.30$, $p = 0.20$) in older adults between A^{NC}/U^C trials (M = 14.8%, SD = 14.0%
333 reported change) and A^{NC}/U^{NC} trials (M = 12.6%, SD = 9.9% reported change). There was
334 however a significant difference (paired t-test, $t(23) = 2.60$, $p = 0.02$) in younger adults
335 between A^{NC}/U^C trials (M = 16.9%, SD = 10.9% reported change) and A^{NC}/U^{NC} trials (M =
336 14.2% , SD = 8.8% reported change). From this, one might conclude that younger adults were
337 more likely to respond to uncued stimuli. However when we calculated the distraction cost as
338 the contrast between those two rates for each individual (A^{NC}/U^C - A^{NC}/U^{NC}) there was no
339 significant difference (independent sample t-test, $p = 0.79$) between the older adults (M =

2.1%, *SD* = 9.5%) and the younger adults (*M* = 2.7%, *SD* = 5.1%). We also tested for distractor benefit in trials where a change occurred in both sides compared to trials in which a change occurred only on the attended side (A^C/U^C - A^C/U^{NC}). Response rate for A^C/U^C was significantly higher than for A^C/U^{NC} in both young adults ($t(23) = 4.96$, $p = 0.000$) and older adults ($t(33) = 2.93$, $p = 0.006$), with older adults reporting a change 3.8% (*SD* = 12.9%) more often, and young adults 5.5% (*SD* = 5.5%) more often. As before, when we tested for differences in the individual subjects' contrast there was no significant difference between age groups (independent sample t-test, $p = 0.33$).

Finally, we tested for the effect of distraction on reaction times. Although older adults were slower than younger adults, they were not significantly slower (paired t-test, $p = 0.72$) for U^C trials (*M* = 0.96 s, *SD* = 0.14 s) than for U^{NC} trials (*M* = 0.97 s, *SD* = 0.13s). For younger adults, there was no significant difference either (paired t-test, $p = 0.35$). Taken together, these findings do not support the possibility that the reduced alpha lateralization in older adults during WM is due to a failure to orient attention or greater interference from the distractors in older adults.

---------- Figure 2 near here ----------

MEG results

Sensor selection

Figure 2A shows the results of the sensor selection. Positive values (red) indicate that alpha power was greater in the 'attend left' condition than in the 'attend right' condition, while negative values (blue) indicate the opposite. The cluster-based permutation test on the grand average (all subjects combined) of normalized alpha power in the cue interval revealed two clusters that differed significantly between the 'attend left' and 'attend right' conditions.

A significant (p = 0.004) positive cluster of 68 sensors was found over the left posterior hemisphere, and a significant (p = 0.02) negative cluster of 37 sensors was found over the right posterior hemisphere (Figure 2A, bold dots). In order to prevent a bias in sensitivity between hemispheres due to differing amounts of sensors, we selected only those sensors that were symmetrically significant in both clusters, resulting in 35 sensors per hemisphere (Figure 2A, bold black dots).

Alpha modulation and lateralization

Average TFRs belonging to the respective clusters during correct trials are shown in Figure 2B (young adults) and 2C (older adults). It was apparent from the TFRs that alpha power modulation within the clusters was roughly similar for younger and older adults in the cue interval (-1.5 s – 0 s). However, in the retention interval there was a striking difference between the age groups; in younger adults alpha modulation was higher than during the cue interval, whereas in older adults modulation was nearly absent. Figure 2D shows the same data in another format, to emphasize the strong alpha power modulation during the retention interval in both hemispheres in younger adults, and the absence of such modulations in the older group. In contrast, in the preceding cue interval there appeared to be no difference between the age groups.

---------- Figure 3 near here ----------

To quantitatively investigate these observations, we calculated combined PMI (cPMI) values by subtracting values of the negative cluster from values of the positive cluster. The cPMI values are shown in Figure 3, averaged per age group and interval. The data show similar cPMI values between younger and older adults in the cue interval, while in the

retention interval cPMI was clearly higher for younger adults. These observations were tested by conducting a Repeated Measures (RM) ANOVA, which revealed a significant main effect of Interval ($F(1,57) = 6.523$, $p = 0.013$), with the cue interval cPMI being lower ($M = 0.04$, $SD = 0.05$) than the retention interval cPMI ($M = 0.06$, $SD = 0.08$). The main effect of Age group was also significant ($F(1,57) = 16.943$, $p = 0.000$), with younger adults showing higher cPMI ($M = 0.076$, $SD = 0.069$) than older adults ($M = 0.026$, $SD = 0.045$). The cPMI similarity in the cue interval and the cPMI difference in the retention interval resulted in a significant interaction between Interval and Age group ($F(1,57) = 21.15$, $p = 0.000$). Post-hoc t-tests confirmed that there was no significant difference ($t(57) = 0.684$, $p = 0.497$) between the age groups during the cue interval. However, there was a highly significant difference ($t(31.50) = 4.641$, $p = 0.000$) between younger adults ($M = 0.110$, $SD = 0.094$) and older adults ($M = 0.016$, $SD = 0.043$) during the retention interval.

To exclude the possibility that the diminished alpha lateralization was due to older adults making more eye-movements, we compared the rectified horizontal EOG traces during the retention interval between young and older adults. There was no significant difference (independent samples t-test, $t(54) = -0.65$, $p = 0.519$) between the traces, although on visual inspection of the traces, older adults did seem to move their eyes slightly farther. In order to confidently exclude eye-movements as the cause of diminished lateralization, we analyzed the cPMI again after applying a strict procedure to exclude trails in which small eye movements were present, based on visual inspection of the EOG traces of each trial. The results on alpha lateralization remained, as we still found a significant effect for Interval ($F(1,54) = 11.838$, $p = 0.001$), Interval X Age-group ($F(1,54) = 25.399$, $p = 0.000$), and Age-group ($F(1,54) = 18.327$, $p = 0.000$). Thus, eye-movements could not explain the diminished lateralization during the retention interval in older adults.

Raw and baselined alpha power

The modulation index does not provide any information on whether the lack of modulation in older adults was due to alpha power being equally high or equally low in both conditions. To tease apart the mechanisms underlying the modulation we first investigated the absolute levels of alpha power. After log-transforming the time-frequency data, cue and retention interval values were combined and averaged per individual, and averaged over both sensor clusters (Figure 4C). An independent samples t-test on the resulting average (log-transformed) alpha power values revealed that older adults (M = -27.03, SD = 0.32) showed significantly lower alpha power ($t(57) = 3.04$, $p = 0.004$) than younger adults (M = -26.77, SD = 0.33). Furthermore, we were able to replicate (Figure 4C) recent findings by Voytek et al. (2015), who found that older adults have significantly flatter 1/f-noise spectra ($t(57) = -3.97$, $p = 0.000$). This could indicate more spontaneous (and thus less synchronized) high frequency activity, pointing at deficiencies in the regulation of high frequency activity by lower frequency oscillations such as alpha (Canolty et al. 2006; Jensen and Colgin 2007; Bastos et al. 2015; Voytek et al. 2015; Lowet et al. 2016).

Next we investigated the development of alpha power from a baseline through the cue and retention intervals. Because alpha power developed differently depending on the attention condition and hemisphere, those parameters were combined by labeling, per trial, each hemisphere as ipsilateral or contralateral relative to the target hemifield. The log-transformed data were then sorted and averaged according to their laterality, age group, and interval. Then, from each signal a baseline (-1.75 s – -1.5 s) was subtracted, so that Figure 4A and 4B show changes from baseline as a function of time. The resulting traces show that, in both younger and older adults, alpha power decreased in the cue interval compared to baseline. In both groups, alpha power decreased more over the hemisphere contralateral to the relevant side of the array than over the ipsilateral hemisphere, leading to alpha

lateralization. In the WM retention interval, younger adults showed an initial alpha suppression caused by the onset of the sample array, followed by an ipsilateral alpha power increase to baseline levels. Alpha power contralateral to the relevant side of the array continued to be suppressed compared to the ipsilateral hemisphere. Strikingly, in older adults there was an even larger decrease in both ipsilateral and contralateral alpha power in the retention interval, during which, ipsilateral and contralateral alpha power levels were both reduced to a similar level. Thus, the absence of modulation in older adults during the retention interval was paired with an overall bilateral decrease in alpha power.

These observations were tested with an RM-ANOVA, with Laterality (ipsilateral vs. contralateral) and Interval (cue interval vs. retention interval) as within-subject factors, and Age-group as a between subject factor (Figure 4D). There were significant interactions between Laterality and Age-group ($F(1,57) = 18.189$, $p = 0.000$), Laterality and Interval ($F(1,57) = 5.139$, $p = 0.027$), and Laterality, Interval, and Age ($F(1,57) = 23.728$, $p = 0.000$), underlining the fact that ipsilateral and contralateral alpha power were affected differently by the cue and retention intervals, and age. Paired sample t-tests confirmed that in the cue interval, both younger adults ($t(24) = 5.261$, $p = 0.000$) and older adults ($t(33) = 3.522$, $p = 0.001$) had higher alpha power in the ipsilateral hemisphere than in the contralateral hemisphere. In the retention interval this was the case for younger adults ($t(24) = 5.675$, $p = 0.000$), but not for older adults ($t(33) = 1.159$, $p = 0.255$). Interestingly, there was no significant difference in ipsilateral alpha power between the cue and retention intervals in younger adults ($t(24) = 0.998$, $p = 0.328$), whereas in older adults ipsilateral alpha power was significantly lower in the retention than in the cue ($t(33) = 5.238$, $p = 0.000$). Contralateral alpha power decreased significantly from cue to retention in both younger adults ($t(24) = 2.444$, $p = 0.022$) and older adults ($t(33) = 4.883$, $p = 0.000$). The lack of alpha lateralization

observed in older adults during the retention interval was hence due mostly to a reduction in alpha power contralateral to the irrelevant side of the array.

---------- Figure 4 near here ----------

Control analyses

The younger group was part of a pharmacological study consisting of two drug sessions and one placebo session. In the current study only data from the placebo session was used. However, due to the counterbalancing of drug conditions, in the younger group the placebo session was not always the second session (first MEG session after the initial training and MRI acquisition session). Therefore, some of the younger adults could be more experienced with the task than participants in the older group. To test whether practice effects contributed to our findings, the main analysis on cPMI was repeated including as controls only those younger adults (N=9) who received a placebo in their second session (Figure 5A). Again, an RM-ANOVA, with cPMI as the dependent variable, Age-group (younger adults vs. older adults) as between-subject factor, and Interval (cue interval vs. retention interval) as a within-subject factor, revealed similar effects to the main analysis summarized in Figure 3, including roughly equal modulation of alpha lateralization in the cue interval for both age groups, and different modulation in the retention interval. The analysis confirmed a significant effect for Interval ($F(1,41) = 4.084$, $p = 0.050$). Post-hoc tests revealed higher cPMI in the cue interval ($M = 0.034$, $SD = 0.039$) than in the retention ($M = 0.031$, $SD = 0.055$) interval. Age-group also had a significant effect ($F(1,41) = 47.04$, $p = 0.007$), with younger adults ($M = 0.060$, $SD = 0.046$) having higher cPMI than older adults ($M = 0.025$, $SD = 0.029$). Furthermore, the interaction Age-group X Interval was significant as well ($F(1,41) = 15.307$, $p = 0.000$). Independent sample t-tests within each interval revealed a significant effect for Age-group in

the retention interval ($t(9.55) = 3.25$, $p = 0.009$), but not in the cue interval ($t(41) = -0.30$, $p = 0.763$). Figure 5A and the associated analysis (Figure 5B) showed stronger modulation in the retention interval among younger adults than among older adults. Practice effects thus cannot explain the difference in modulation between younger and older adults.

Another possible confound was that there were on average more items on the screen for younger adults than for older adults, due to the individual adjustment in load. To exclude the possibility that the amount of squares in the array caused the different modulation patterns, the main analysis was repeated once more, selecting only younger (N=5) and older adults (N=24) in the memory load condition most commonly presented to older people: 3 squares per hemifield (Figure 5C). Again, the main observation was replicated (Figure 5D), with a significant effect of Age-group ($F(1,27) = 9.809$, $p = 0.004$) and a significant interaction between Interval and Age-group ($F(1,27) = 5.084$, $p = 0.032$). In this analysis, independent sample t-tests only revealed a trending effect for Age-group in the retention interval ($t(4.457) = 2.358$, $p = 0.071$), which is most likely due to the low number of younger adults in this group. In the cue interval there were no significant or trending differences ($t(27) = 0.761$, $p = 0.453$). Thus, younger and older adults exhibited similar modulations during the cue, whereas during the retention interval modulation was stronger in younger adults and nearly absent in older adults.

---------- Figure 5 near here ----------

Finally, the male to female ratio was higher in the older group. We tested whether the effects we found could be caused by gender differences in the sample, and found that both males and females exhibited the same effect; no age-differences in cue interval lateralization and larger age-differences during the retention interval. This was summarized by the

514 significant Age-group X Interval interactions for the male ($F(1,31) = 38.555$, $p = 0.000$) and
515 female ($F(1,24) = 5.083$, $p = 0.034$) participants. The three-way interaction Age-group X
516 Interval X Gender was also significant however ($F(1,55) = 6.110$, $p = 0.017$), reflecting that
517 the effect of Age-group on Interval was stronger in males than in females. This may reflect an
518 interesting gender difference which could be explored in future research. Taken together
519 these control analyses suggest that the differences in experimental procedures and gender
520 ratio between the two groups do not underlie our central findings.

Discussion

Many studies have shown that tasks which require attention to be allocated to one hemifield lead to lateralized alpha power over posterior sites (e.g. Worden et al., 2000; Thut, 2006; Händel et al., 2011). Recent studies have demonstrated that this idea can be extended into the domain of WM (Sauseng et al. 2009). In addition, current data and theories suggest that increased alpha power suppresses processing, while decreased alpha power facilitates processing (Hanslmayer et al. 2005; Kelly et al. 2006; Rihs et al. 2007; Jensen and Mazaheri 2010; Händel et al. 2011). We therefore used MEG to test whether a decline in this mechanism may underlie decreased WM performance during aging. One of the benefits of MEG over most common EEG systems is that the superior number of sensors allows for greater spatial precision at the scalp level. More importantly, our experimental design allowed us to separate the processes involved in cue-related attentional orienting from the processes involved in WM retention and WM-related attention.

We used a lateralized DMS task in which difficulty was individually adjusted so that all participants were equally challenged and engaged. In the cue interval, the two hemispheres showed the typical pattern of alpha power lateralization in both age-groups, namely that alpha power was higher when target stimuli were expected in the ipsilateral hemifield, compared to when they were expected in the contralateral hemifield. In the retention interval, however, the expected alpha lateralization effect was strongly present only in the younger adults, but nearly absent in the older adults. Additional analyses of the absolute power in the two hemispheres showed that this lack of modulation in older adults was paired with a bilateral reduction in alpha power to the same level. Furthermore, alpha power was lower in the retention interval than in the cue interval for older adults, whereas in younger adults ipsilateral alpha power remained at the same level in both intervals. These results suggest that the main difference between younger and older adults during the retention interval lies in a

546 deficiency to recover alpha power after an initial stimulus related drop in power in older
547 adults, in the hemisphere processing irrelevant stimuli.
548 The fact that alpha power was modulated by the same relative amount in response to a
549 directional cue in both younger and older adults, suggests that the brain relies on the same
550 mechanism to distribute attentional resources in both age groups, in line with Mok et al.
551 (2016). But what then could cause the difference in hemispheric alpha lateralization between
552 the two groups during the retention interval? One possible explanation is that there was
553 insufficient top-down drive to inhibit encoding of irrelevant stimuli at the onset of the arrays.
554 The exogenous onset of the sample array may have caused a redistribution of attention over
555 the two hemifields, overriding the endogenous drive that directs attention to the target
556 location. In line with reduced top down control, we and others (Dustman et al. 1999; Voytek
557 et al. 2015) observed lower overall alpha power in older adults. Feedforward input may thus
558 be more dominant in older adults. Furthermore, Sander et al. (2012b) found that the alpha
559 phase immediately after stimulus onset was more coherent across trials in older adults,
560 indicating that alpha processes in this age-group were more strongly affected by feedforward
561 input. A deficit in top down drive fits with several theories in the literature, such as the early
562 inhibition deficit found in older adults by Gazzaley et al. (2008), as well as the two-
563 component framework proposed by Sander et al. (2012a), which states that WM may rely on
564 the interplay of low-level feature binding processes and top-down control processes. In terms
565 of these theories, the deficits during retention may reflect a weakening of top-down control
566 processes, and increased dominance of feedforward processing. However, arguing against the
567 interpretation that healthy aging coincides with a shift towards feedforward processing, we
568 found no difference in sensitivity and response bias between the age groups, as evidenced by
569 *d'* and criterion measures. Moreover, we found that older adults were not more likely to
570 report changes in stimuli when one occurred in the uncued array than when no change

occurred in either hemifield, as might be expected had they encoded the uncued stimuli. This suggests attentional control remained intact in healthy older adults. One reason for the lack of evidence for the inhibition deficit theory in the current study could be that most studies investigating inhibition deficit featured serially presented stimuli of varying relevance. In such non-concurrent presentations there may be no opportunity for older adults to prioritize one set of stimuli over another set. Another explanation was presented by Vaden et al. (2012), who also found no evidence for suppression deficits in older adults. They propose that there may be a difference in task demands between the Sternberg tasks with realistic pictures and the relatively simple displays employed in lateralization studies, which allows the older adults to suppress the irrelevant information. Furthermore, older adults did maintain a reasonable level of WM performance, despite weak alpha lateralization in the retention interval. Hence, alpha lateralization deficits in older adults no longer seemed to be an accurate electrophysiological index of WM performance deficits.

Despite the reduced alpha lateralization during retention, there was significant residual WM performance. Interestingly, the reduction of alpha lateralization was paired with an overall reduction in alpha power in both hemispheres. This finding could be seen as part of the deficit in the older adults, but it could also be a correlate of a compensatory mechanism. Specifically, we suggest that both hemispheres were recruited to maintain the relevant part of the array in WM. A number of fMRI studies have shown that tasks which evoke lateralized activity in younger adults evoke bilateral activity in high-functioning older adults (but lateralized activity in low-performing older adults), indicating that a shift towards bilateral activity could be a compensatory strategy (Reuter-Lorenz et al. 2000; Cabeza et al. 2002; Reuter-Lorenz and Cappell 2008). In line with these findings, the increase in bilateral processing in our data (as reflected by the bilateral alpha power decrease) could be interpreted as reflecting compensatory mechanisms. In this explanation, older adults rely on a

reconfigured retention mechanism in which alpha operates in a non-lateralized manner. The fact that this compensatory mechanism operates during retention and not during cueing (where alpha lateralization was intact) is perhaps due to different but spatially overlapping neural networks being involved in alpha lateralization when allocating attention (cueing) and WM (retention). A possible separation of mechanisms of alpha lateralization during cueing and WM may underlie the observation that a compensatory strategy during aging comes into existence for WM, leaving mechanisms for attentional orienting unaffected. However, it is also possible that older adults switch from a lateralized to a bilateral mechanism in a task dependent manner, without a need for different alpha generating networks for attentional orienting and WM. It is as yet unclear how the reconfigured retention mechanism operates in older adults. Irrespective of how this reconfiguration is achieved it is noteworthy that, although fairly effective, it is less effective than the processes in young adults as WM capacity (K_{span}) was reduced.

Our findings differ from those of Hong et al. (2015), who concluded that only younger adults showed alpha power lateralization in anticipation of a cued stimulus. This contrasts with our data, which show a comparable alpha lateralization in younger and older age groups during the cue interval, and a reduction of alpha power and lateralization during retention in the older age group specifically. Thus, we suggest that the reduction in alpha lateralization related to normal aging is more selective than previously thought, being only apparent during the retention interval in our task. The difference in results between the Hong et al. (2015) study and our own may be due to differences in experimental design. In this regard, it is noteworthy that in Hong et al. (2015) the target was always known to the participants, whereas in our task the target was unknown to the participants during the cue interval. Therefore, what they termed a cue interval in their study perhaps is more comparable to the retention interval in our study, rather than to our cue interval. In this light both investigations

find that in older adults alpha power was not lateralized during WM retention. Importantly, our experimental design, which separates processes related to attentional cueing from WM-related processes, allowed the identification of a decline in alpha lateralization and alpha power in older adults specific to WM-related operations and not to attentional spatial cueing.

One limitation in the current study was that because difficulty was individually adjusted, we could not compare electrophysiological processes at play during high and low loads, as in Sander et al. (2012b). We were also unable to demonstrate correlations between individual performance and the amount of alpha power modulation as demonstrated by e.g. Sauseng (2009). These analyses would have furthered our understanding of the performance deficits and compensatory strategies of older adults, and crucially of their underlying neuronal mechanisms. However, the current design was also one of the study's strengths, as we ensured that the task was equally difficult and engaging for younger and older adults. This was especially important considering that in some studies differences in experienced task difficulty alone explained differences in brain activation (Schneider-Garces et al. 2009).

In conclusion, our analysis of alpha power in older and younger adults revealed different mechanisms during retention in a WM task, but no differences were found in response to attentional cueing without WM. In older adults, we found bilateral alpha power reductions and lack of alpha lateralization during retention, which may either reflect a failure to suppress distractors, or be part of a compensatory mechanism. We found that older adults did not respond more to irrelevant items than younger adults, and that both younger and older adults showed lateralized alpha oscillations during attentional orienting. This supports our tentative conclusion that mechanisms involved in attentional orienting and encoding remain relatively intact during healthy aging, and that declined WM performance in our task is specifically due to a reconfigured retention mechanism that is not as effective as in the young adults.

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773 **Tables**

774

Table 1 Accuracy in session 1

Load	Sig	Younger adults	Older adults
2		90 (±9.8) %	90 (±6.0) %
3	*	82 (±8.6) %	76 (±9.0) %
4	*	73 (±8.7) %	67 (±8.0) %
(5)		68 (±6.5) %	N/A
(6)		65 (±7.8) %	N/A

775 Note: Load indicates number of squares in each hemifield. Asterisks indicate significant
776 differences in mean accuracy between younger adults and older adults. Standard deviations in
777 brackets.

778

Captions to figures

Figure 1 The delayed match-to-sample task. Participants always fixated on the center symbol. After an inter-trial period of 2 seconds, in which participants were free to blink, the fixation cross changed into a directional cue ('<' or '>'). This cue indicated which hemifield should be remembered and compared to the probe array, and which hemifield should be ignored. The cue remained visible for the remainder of the trial. After the 1500 ms cue interval a sample array was shown for 100 ms, consisting of multiple colored squares. Participants had to retain information about the color of squares in the cued hemifield during a 1500 ms retention interval. Finally, a probe array was shown, in which one square per hemifield could have changed color. No duplicate colors were possible. The positions of squares never changed within a trial, but varied between trials. The number of squares per hemifield was the memory load and was specific for each participant (titrated to ~75% accuracy). The memory load was fixed for the entire MEG experiment. Loads ranged from 2 to 6 squares across younger adults, and from 2 to 4 squares across older adults (see Results). Participants had to report within 2 seconds whether the probed squares in the cued hemifield were identical or different from the sample array. The correct response in this example would be 'different'.

Figure 2 A) Grand average alpha Power Modulation Index (PMI) topographical plot. Sensors are marked as dots, and sensors that significantly differed between attend left and attend right conditions are marked as bold dots. Significant sensors indicated by white dots were left out of the final analysis because there were no significant sensors that mirrored them in the opposite hemisphere. The positive and negative sensor clusters were found by employing a cluster-based permutation test on the grand-average cue-interval (not shown). **B)** Topographical plots and time frequency representations belonging to the positive cluster

(left) and negative cluster (right) in younger adults, showing the average PMI. Topographical plots show activity during the retention interval. Dashed boxes indicate the range of frequencies and latencies that were averaged and included in statistical analysis. **C)** Identical to B, but showing data from older adults. **D)** Average alpha PMI for both age groups. Dashed vertical lines indicate different epochs within a trial. Shaded areas represent standard error of the mean.

Figure 3 The combined Power Modulation Index (cPMI) in the alpha band (8-14 Hz), for younger and older adults per interval, calculated by subtracting right hemisphere alpha PMI from left hemisphere alpha PMI. There was no difference between older and younger adults in cue interval cPMI, but in the retention interval there was a significant difference. The effect of age is also different in the two intervals, indicated by a significant interaction between age and interval. Asterisks indicate significance (*** $p = 0.000$; n.s. = not significant).

Figure 4 A) Log-ratio between alpha power and baseline (in dB), averaged over younger adults. Darker colors indicate ipsilateral alpha power, lighter colors indicate contralateral alpha power. **B)** Like A, but averaged over older adults. **C)** Log-transformed power spectrum for younger (blue) and older (red) adults, averaged over cue and retention intervals. Dashed lines represent linear fits of 1/f noise (see Voytek et al., 2015). The shaded area indicates the alpha band. **D)** Log-transformed alpha power, relative to baseline, averaged separately over the cue and retention intervals. Significance of paired t-tests is indicated by asterisks (*** $p = 0.000$).

828 **Figure 5** Mean alpha Power Modulation Index (PMI) comparisons between older adults and
829 younger adults. **A)** Mean alpha PMI for older adults and younger adults that were recorded in
830 the second session (rather than session 3 or 4), in the same format as Figure 2D. Shaded areas
831 show standard error of the mean. **B)** Mean alpha combined PMI for young and old adults
832 from data recorded in the second session, in the same format as Figure 3. **C)** Mean alpha PMI
833 for older adults and younger adults in conditions where there were always 3 squares per
834 hemifield on the screen. **D)** Mean alpha combined PMI for young and old adults from data
835 recorded when there were 3 squares per hemifield on the screen. Note that there are still only
836 small differences between age groups in the cue interval (-1.5 s – 0 s) and large differences in
837 the retention interval (0.1 s – 1.6 s).
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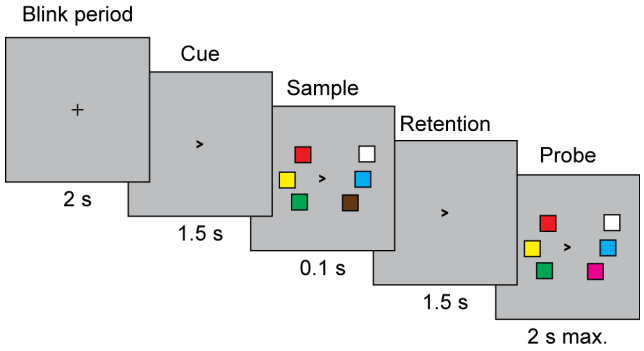

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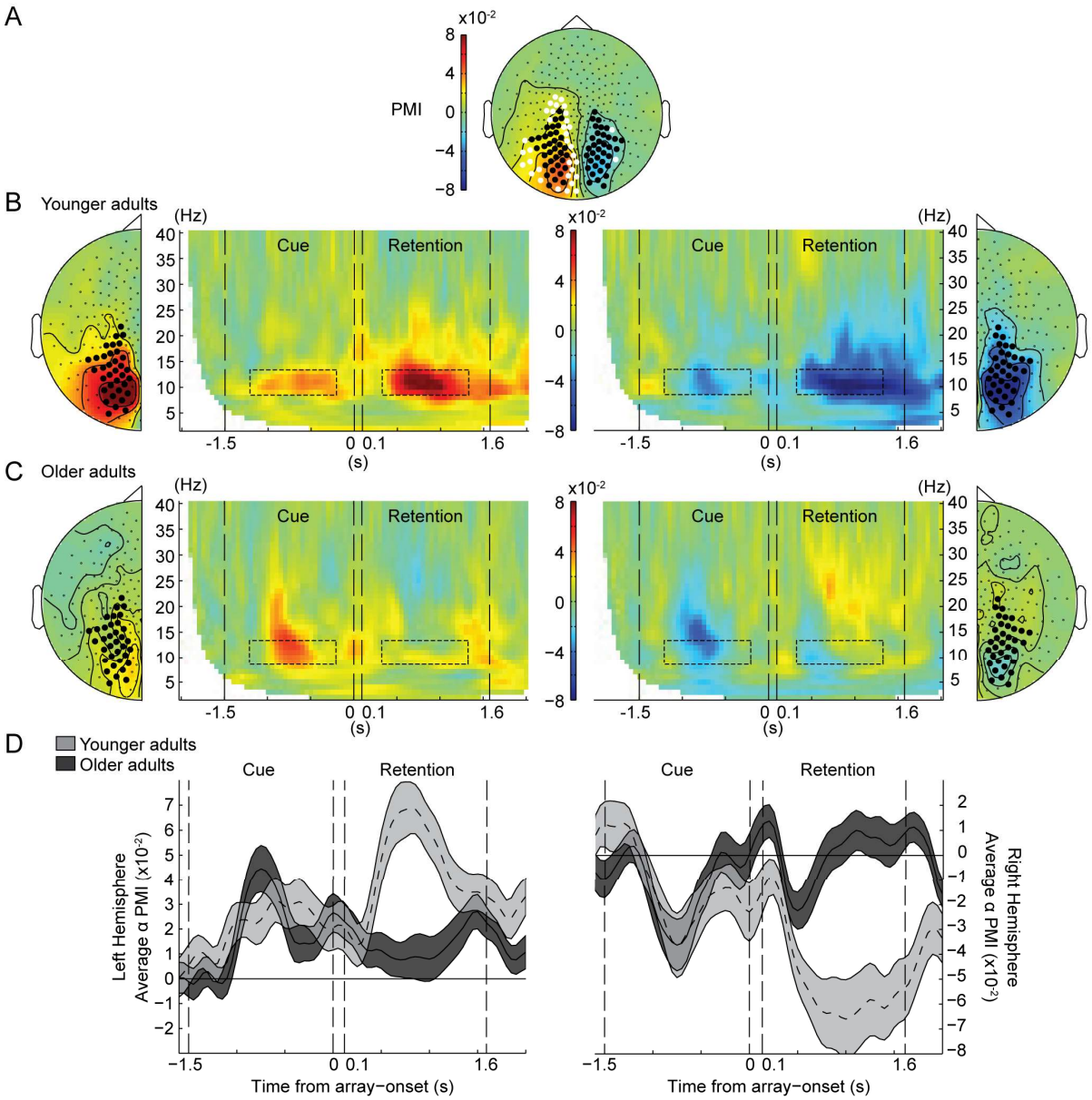

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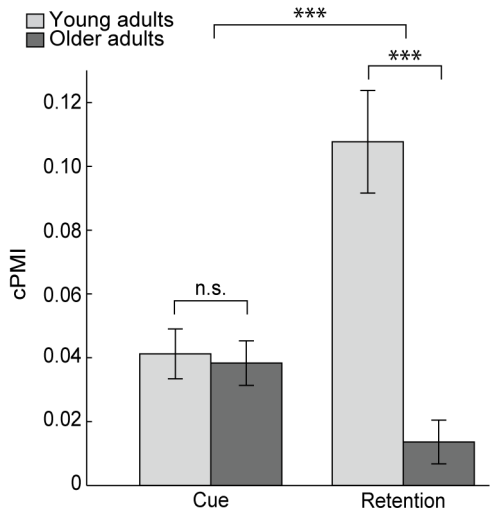

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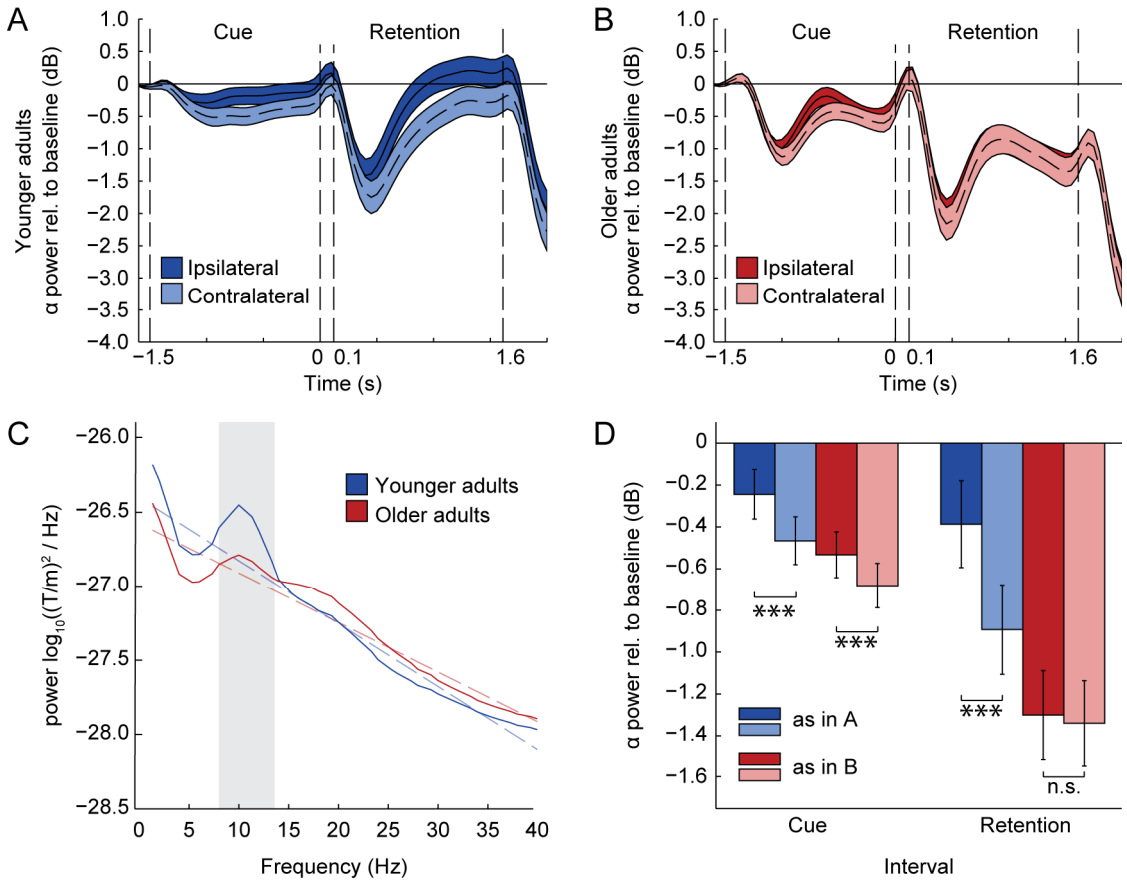

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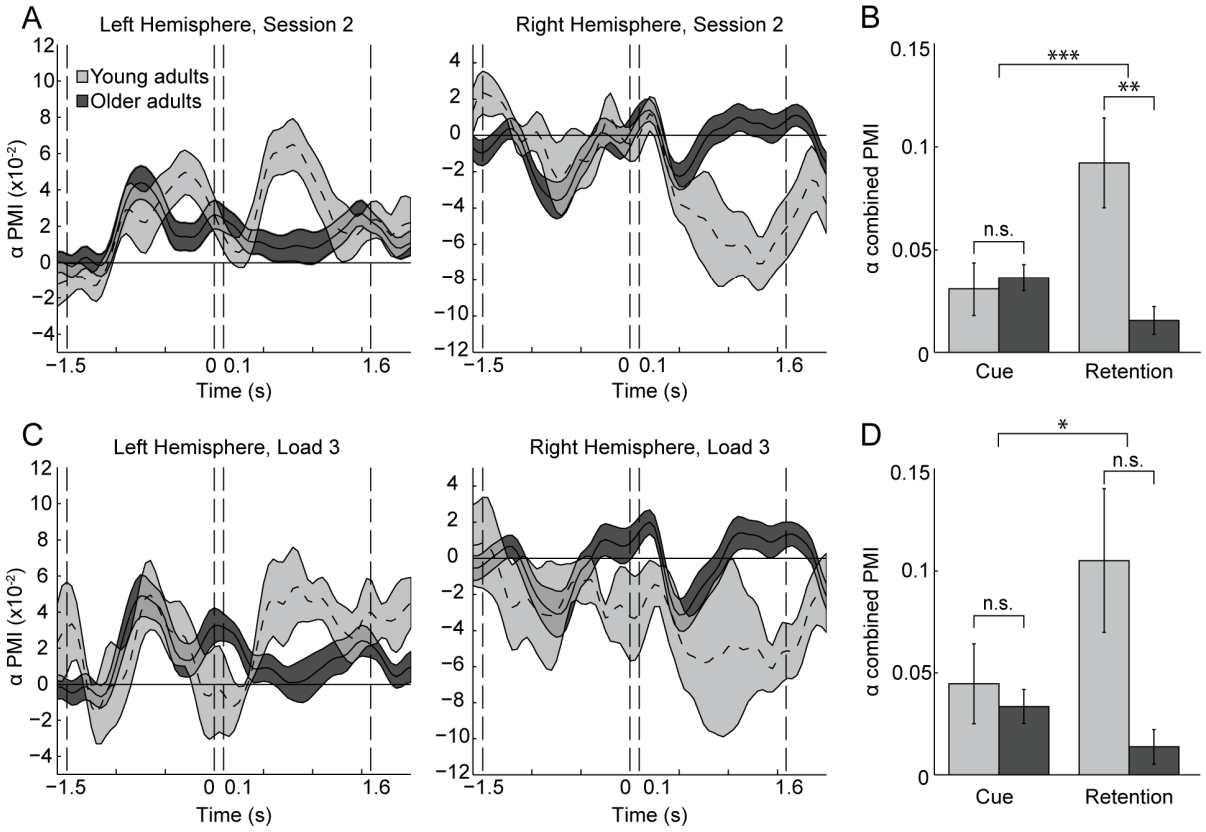
A
Left Hemisphere, Session 2
Young adults
Older adults
α PMI (x10-2)
Time (s)
Right Hemisphere, Session 2
B
α combined PMI
***
**
n.s.
Cue
Retention
C
Left Hemisphere, Load 3
Right Hemisphere, Load 3
D
*
n.s.

861