Alpha Phase Dynamics Predict Age-Related Visual Working Memory Decline

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Abstract

Alpha oscillations (7-14 Hz) are modulated in response to visual temporal and spatial cues. However, the neural response to alerting cues is less explored, as is how this response is affected by healthy aging. Using scalp EEG, we examined how visual cortical alpha activity relates to working memory performance. Younger (20-30 years) and older (60-70 years) participants were presented with a visual alerting cue uninformative of the position or size of a lateralized working memory array. Older adults showed longer response times overall and reduced accuracy when memory load was high. Older adults had less consistent cue-evoked alpha phase resetting than younger adults, which predicted worse performance. Alpha phase prior to memory array presentation predicted response time, but the relationship between phase and response time was weaker in older adults. These results suggest that changes in alpha phase dynamics, especially prior to presentation of task-relevant stimuli, potentially contribute to age-related cognitive decline.

Keywords

Oscillations, alpha, aging, working memory, attention, alerting cue

Introduction

In order to achieve high behavioral performance, limited attentional resources must be efficiently directed towards task-relevant information. Such information could include the timing or spatial position of upcoming visual stimuli. Knowledge of when (Nobre et al., 2007) or where (Posner, 1980) a target will appear enhances detection and shortens response times. Likewise, presentation of neutral warning cues improves response times by heightening alertness or preparedness for upcoming stimuli. The effects of informative temporal and spatial cues are strongly related to the dynamics of 7-14-Hz alpha oscillations, as observed in anticipatory changes in alpha amplitude (Thut et al., 2006; van Diepen et al., 2015; Worden et al., 2000; Zanto et al., 2011) and phase (Samaha et al., 2015). How alpha dynamics are modulated in response to warning or alerting cues is less understood.

Neurologically healthy aging is associated with declines in attention and working memory. Behaviorally, the benefits of spatial cuing are relatively resistant to healthy aging (Hartley et al., 1992; Madden, 1990), but older adults derive less benefit from the presence of temporal (Zanto et al., 2011) and alerting cues (Gamboz et al., 2010; Jennings et al., 2007). Physiologically, older adults show reduced alpha modulation in response to temporal (Zanto et al., 2011) and spatial cues (Hong et al., 2015), though a recent study found no age-related differences in neural response to alerting cues (Williams et al., 2016). However, because alpha activity was not examined in that study, it is unclear whether older adults' reduced use of alerting cues can be predicted by concomitant changes in alpha oscillatory dynamics.

To investigate alpha response to alerting cues and how this response is affected by healthy aging, we recorded EEG from younger and older adults performing a unilateral visual working memory task. Each trial of the task included an alerting cue signaling the upcoming presentation of a lateralized memory array. This cue allowed us

89   to probe participants' preparedness for upcoming stimuli independent of motor
90   preparation. The alerting cue was uninformative of the size and location of the upcoming
91   memory array, but was perfectly predictive of its timing. To favor bottom-up, reflexive
92   alerting over voluntary orienting or temporal expectation, the foreperiod between the cue
93   and memory array was kept relatively short (Weinbach and Henik, 2012). We
94   hypothesized that age-related changes in neural activity would manifest themselves in
95   the alpha amplitude and phase response to presentations of the alerting cue. We also
96   hypothesized that the extent to which neural response to the alerting cue was altered
97   would also predict declines in working memory performance.
98
99   **Materials and Methods**
100 **Behavioral Task.** Healthy right-handed younger (20-30 year olds, $n = 17$, eight female)
101 and older (60-70 year olds, $n = 14$, seven female) adults with normal or corrected-to-
102 normal vision participated in a visual working memory paradigm. All participants gave
103 informed consent approved by the UC Berkeley Committee on Human Research. In
104 each trial, participants were instructed to maintain central fixation, and at the beginning
105 of each trial, the central fixation cross flashed from gray to pink for 50 ms, alerting
106 participants to the start of the upcoming trial (Fig. 1A). This alerting cue offered no
107 information on either the size or location of upcoming visual stimuli. Three hundred ms
108 after the end of the alerting cue, participants were presented with one, two, or three
109 colored squares for 180 ms in only one visual hemifield. After a 900 ms delay period,
110 during which time no stimuli other than the fixation cross were present, a test array of
111 the same number of squares in the same spatial locations appeared. Participants would
112 manually respond with their right thumb to indicate whether or not the test array had the
113 same color squares as the initial memory array.
114   Behavioral accuracy was assessed using d', a sensitivity measure that takes
115 false alarm and miss rates into account to correct for response bias. To avoid
116 mathematical constraints in the calculation of d', we applied a standard correction
117 procedure in the case of 100% hit rate or 0% false alarm rate. Specifically, hit rate was
118 decreased to $1 - 1/(2N)$ when necessary, with N being the total number of trials.
119 Similarly, false alarm rate was increased to $1/(2N)$ when necessary (Macmillan and
120 Creelman, 2004).
121
122 **Data Acquisition.** We recorded 64-channel scalp electroencephalography (EEG) from
123 each participant. Participants were tested in a sound-attenuated EEG recording room
124 using a 64+8 channel BioSemi ActiveTwo amplifier (Amsterdam, Netherlands). EEG
125 was amplified (-3 dB at ~819 Hz low-pass, DC coupled), digitized (512 Hz), and stored
126 for offline analysis. Horizontal eye movements (HEOG) were recorded with electrodes at
127 both external canthi. Vertical eye movements (VEOG) were monitored with a left inferior
128 eye electrode and either a superior eye or a fronto-polar electrode. All data was
129 referenced offline to the average potential of two mastoid electrodes and analyzed in
130 MATLAB[®] (R2015A, Natick, MA) using custom scripts and the EEGLAB toolbox
131 (Delorme and Makeig, 2004).
132

Data Preprocessing. EEG data was downsampled to 256 Hz and had DC offset removed. EEG data was then highpass filtered above 0.1 Hz using a two-way, fourth-order Butterworth infinite impulse response filter. Any channel whose standard deviation was ±2.5 standard deviations away from the mean standard deviation of all channels was spherically interpolated (on average, 2 channels per participant). Independent component analysis (ICA) was performed using the EEGLAB toolbox, and to remove blink artifacts, ICA components most correlated with the difference between the frontopolar and left inferior eye electrodes were removed.

For event-related potential (ERP) analyses and to detect trials with artifacts, continuous EEG data was lowpass filtered below 30 Hz using a two-way, fourth-order Butterworth infinite impulse response filter. Data was epoched around the onset of the memory array using a pre-stimulus baseline of -500 ms to -400 ms. For scalp topographic visualization, and to normalize electrode locations, electrode potentials were swapped right to left across the midline as though stimuli were always presented in the right visual hemifield, making left and right hemisphere channels contralateral and ipsilateral to the stimulus, respectively. Lateralized potentials were analyzed in this ipsilateral-contralateral fashion. Trials where the standard deviation of a scalp electrode exceeded three times the standard deviation of that electrode across all trials were excluded. For saccade trials, trials where the standard deviation of the difference between the HEOG channels exceeded three times the mean of the HEOG channels across all trials were excluded. On average, 69.6% of total trials or 165 trials were kept per participant. For younger adults, an average of 151 trials (minimum 21, maximum 364) per memory-load condition were included, and for older adults, an average of 182 trials (minimum 27, maximum 324) per memory-load condition were included. The number of trials did not differ between younger and older adults ($p = 0.23$, Cohen's $d = -0.44$). No participants were excluded.

Data Analysis. P1 amplitudes were calculated as the average amplitude in a 50-ms window centered on participants' most positive local peak amplitude 80-180 ms after stimulus onset. Peak alpha frequency (PAF), the frequency of maximum power between 7 and 14 Hz, varies in a trait-like manner (Grandy et al., 2013) and predicts visual performance (Samaha and Postle, 2015). To estimate PAF for each participant, we constructed power spectral densities (PSDs) using Welch's method. In order to account for individual differences in $1/f$ electrophysiological background, which changes with age (Voytek et al., 2015a), we used robust linear regression to estimate and remove the slope and offset of log-log space PSDs prior to identification of PAF.

Continuous, non-lowpass-filtered EEG data was bandpass filtered with a 4-Hz passband centered on each participant's PAF. Filters were designed as two-way finite impulse response filters with filter length equal to three cycles of the low cutoff frequency. For each channel, bandpass-filtered time series were converted to z-scores using the mean and standard deviation of artifact-free alpha-band data across all trials and conditions. After normalization, the absolute value and angle of the Hilbert transform of the continuous EEG data was used to extract alpha analytic amplitudes and instantaneous phases, respectively. The phase time series yields cosine phase

177 values of (-π, π] radians, with π radians corresponding to the trough and zero radians to
178 the peak of the oscillation. This method yields results equivalent to sliding-window fast
179 Fourier transform and wavelet approaches (Bruns, 2004).
180   After epoching and removal of marked artifact trials, alpha analytic amplitude
181 time series were subjected to event-related analyses, including the subtraction of
182 baseline activity from -500 ms to -400 ms. To assess trial-to-trial phase consistency
183 (also called intertrial coherence, ITC), event-related phase time series were extracted,
184 and for each time point, the mean vector length of the timepoint's phase distribution was
185 calculated across trials (*circ_r.m* function in the CircStats toolbox (Berens, 2009)). This
186 mean vector length represents the degree of ITC, with ITC of unity reflecting a single
187 adopted phase across trials and a value of zero reflecting uniformly distributed phases
188 across trials.
189
190 **Statistical Analyses.** All analyses were performed on data from EEG channels O1/2,
191 PO3/4, and PO7/8, with channels O1, PO3, and PO7 considered contralateral to the
192 memory array. Multiple-factor statistical analyses were assessed via ANOVAs, with age
193 as a between-group factor and memory load and hemisphere as within-group factors.
194 Where sphericity assumptions were violated, degrees of freedom (and hence *p*-values)
195 were adjusted using Greenhouse-Geisser corrections. All single-factor comparisons
196 were analyzed via paired-samples or between-samples *t*-tests. For all alpha ITC
197 analyses, ITC values were log_{10}-transformed and baseline subtracted. To test for
198 increases in ITC, each trial's phase time series was randomly scrambled, and null
199 values of ITC were calculated using the scrambled trials. This procedure was repeated
200 1000 times per memory load per participant, and a significant increase in ITC was
201 considered as a true ITC value higher than the 97.5% percentile of the null ITC
202 distributions. Peak cue- and array-related ITC were assessed using the maximum ITC
203 peak after cue and memory array presentation, respectively. To correlate circular
204 variables like alpha phase with linear variables like response time, a circular-linear
205 correlation was used (*circ_corrcl.m* function in the CircStats toolbox).
206
207 **Results**
208 **Behavior**
209 **Response Time.** We compared younger and older adults' response times (RTs) on a
210 lateralized visual working memory task (Fig. 1a, see Methods). RTs showed main
211 effects of age (Fig. 1b, $F_{1,29} = 13.32$, $p = 0.0010$, generalized $\eta^2 = 0.31$) and memory
212 load ($F_{2,58} = 67.20$, Greenhouse-Geisser (GG) $\varepsilon = 0.88$, $p_{GG} < 10^{-13}$, $\eta^2 = 0.089$) and an
213 interaction between age and memory load ($F_{2,58} = 3.75$, $\varepsilon = 0.88$, $p_{GG} = 0.029$, $\eta^2 =$
214 0.0054). Between groups, younger adults had faster RTs than older adults in each load
215 condition. This included load-one (541 ms vs. 643 ms, mean difference 95% confidence
216 interval [-166 ms, -39 ms], $t_{28.91} = -3.29$, $p = 0.0027$, Cohen's $d = -1.17$), load-two (565
217 ms vs. 670 ms, [-166 ms, -44 ms], $t_{29} = -3.51$, $p = 0.0015$, Cohen's $d = -1.24$), and load-
218 three conditions (591 ms vs. 721 ms, [-195 ms, -65 ms], $t_{29} = -4.09$, $p < 10^{-3}$, Cohen's d
219 = -1.45).
220

Accuracy. As assessed using the sensitivity measure d', accuracy showed an effect of memory load (Fig. 1c, $F_{2,58} = 51.04$, $\varepsilon = 0.92$, $p_{GG} < 10^{-11}$, $\eta^2 = 0.16$) and an interaction between age and memory load ($F_{2,58} = 5.78$, $\varepsilon = 0.83$, $p_{GG} = 0.0065$, $\eta^2 = 0.021$). Accuracy was comparable between younger and older adults in load-one ($p = 0.73$, Cohen's $d = 0.13$) and load-two conditions ($p = 0.22$, Cohen's $d = 0.45$). However, younger adults outperformed older adults in load-three conditions (3.32 vs. 2.58, [0.042, 1.45], $t_{29.00} = 2.17$, $p = 0.039$, Cohen's $d = 0.77$). In summary, older adults showed slower RTs overall and reduced working memory accuracy specifically during high-load trials.

a
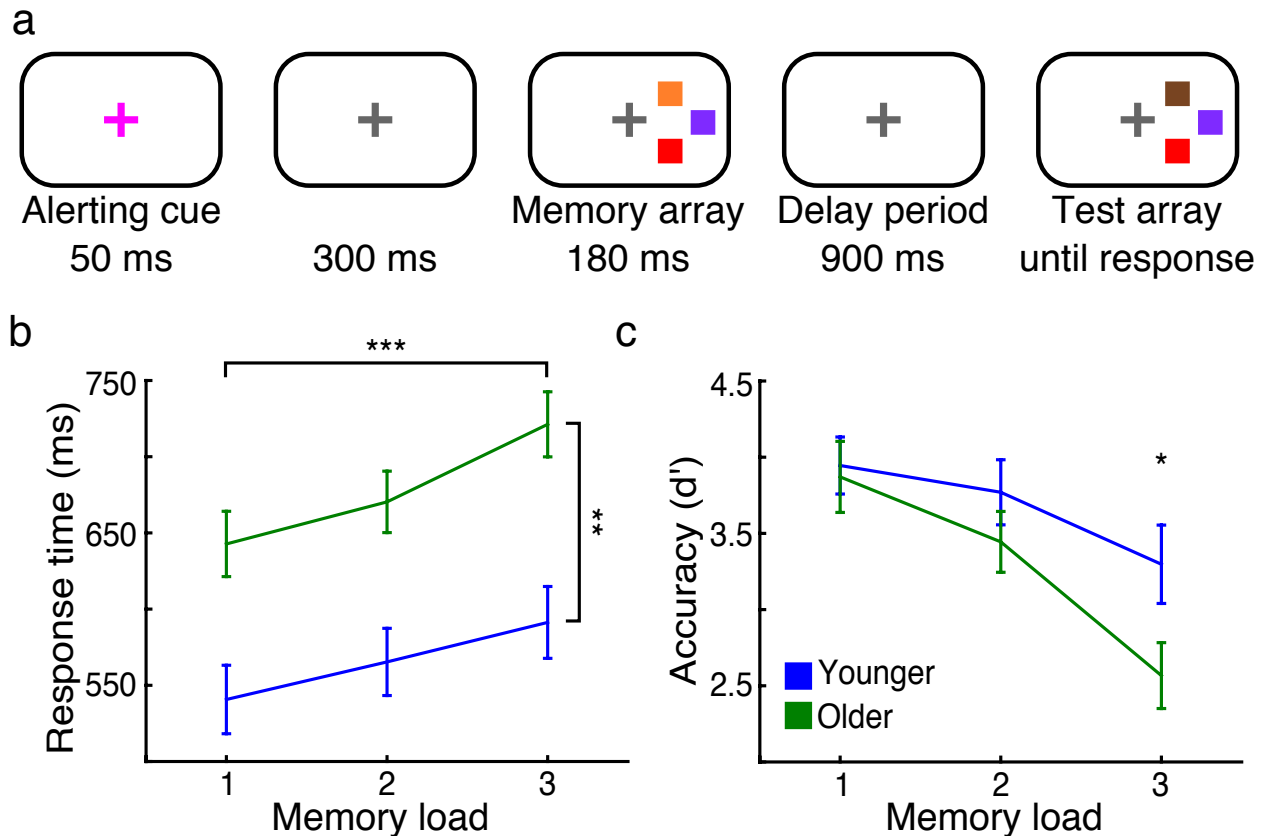
Figure 1. Paradigm and behavioral performance. (*a*) Diagram of the task design, in this example showing a non-matching test array. (*b*) Response times increased with increasing memory load, with younger adults (blue) faster than older adults (green, ***p* < 0.01, ****p* < 0.001; error bars, SEM). (*c*) Accuracy decreased with increasing memory load, with younger adults more accurate than older adults during load-three trials (**p* < 0.05; age by memory load interaction: *p* < 0.01; error bars, SEM).

EEG
Alerting Cue Activity. To investigate neurophysiological measures potentially underlying decreased behavioral performance in older adults, we first examined younger and older adults' neural response to presentations of the alerting cue. During task performance, younger and older adults exhibited 7-14 Hz oscillatory alpha activity

244 in visual parietal-occipital regions (Fig. 2a). Based on participants' peak alpha
245 frequency, previously shown to be lower in older adults[14], we determined individualized
246 alpha bands and compared participants' normalized alpha analytic amplitude and
247 instantaneous phase activity during the task. To also examine the consistency in alpha
248 phase activity across trials, we computed alpha intertrial coherence (ITC) per
249 participant.
250 　　　　Parietal-occipital visual regions showed alpha amplitude and ITC response to
251 presentations of the alerting cue (Fig. 2b, 2c). Alpha amplitude modulation in response
252 to the alerting cue (-350 to 0 ms) showed no effects of age ($F_{1,29} = 2.82$, $p = 0.10$, $\eta^2 =$
253 0.074), hemisphere ($F_{1,29} < 1.0$), or memory load ($F_{2,58} < 1.0$). This lack of hemisphere
254 and memory load effect is consistent with the alerting cue being uninformative of the
255 lateral position or number of upcoming stimuli.
256 　　　　Compared to baseline (-500 to -350 ms), average alpha ITC increased in
257 response to the alerting cue in younger adults (Fig. 2c, [-0.56, -0.29], $t_{16} = -6.73$, $p < 10^{-5}$
258 , Cohen's $d = -1.63$) and weakly in older adults ([-0.14, 0.011], $t_{13} = -1.83$, $p = 0.090$,
259 Cohen's $d = -0.49$). As compared to ITC values calculated using phase-scrambled trials,
260 true average cue-evoked (-350 to 0 ms) ITC was higher in 17 of 17 younger adults as
261 well as 11 of 14 older adults. Peak cue-evoked ITC occurred on average 207 and 185
262 ms after alerting cue onset in younger and older adults, respectively, with peak ITC
263 latency comparable between younger and older adults ($p = 0.39$, Cohen's $d = 0.34$).
264 These increases in ITC suggest the presence of stimulus-evoked alpha phase resets in
265 both younger and older adults. As with alpha amplitude, peak cue-evoked ITC did not
266 show an effect of hemisphere ($F_{1,29} < 1.0$) or memory load ($F_{2,58} < 1.0$), again consistent
267 with the noninformative nature of the alerting cue. However, younger adults had higher
268 peak cue-evoked ITC than did older adults (Fig. 3a, 3b, 0.63 vs. 0.23, [0.24, 0.56], $F_{1,29}$
269 $= 23.64$, $p < 10^{-4}$, $\eta^2 = 0.32$). There was also no age-related difference in cue-evoked P1
270 amplitude ($p = 0.24$, Cohen's $d = 0.40$).
271
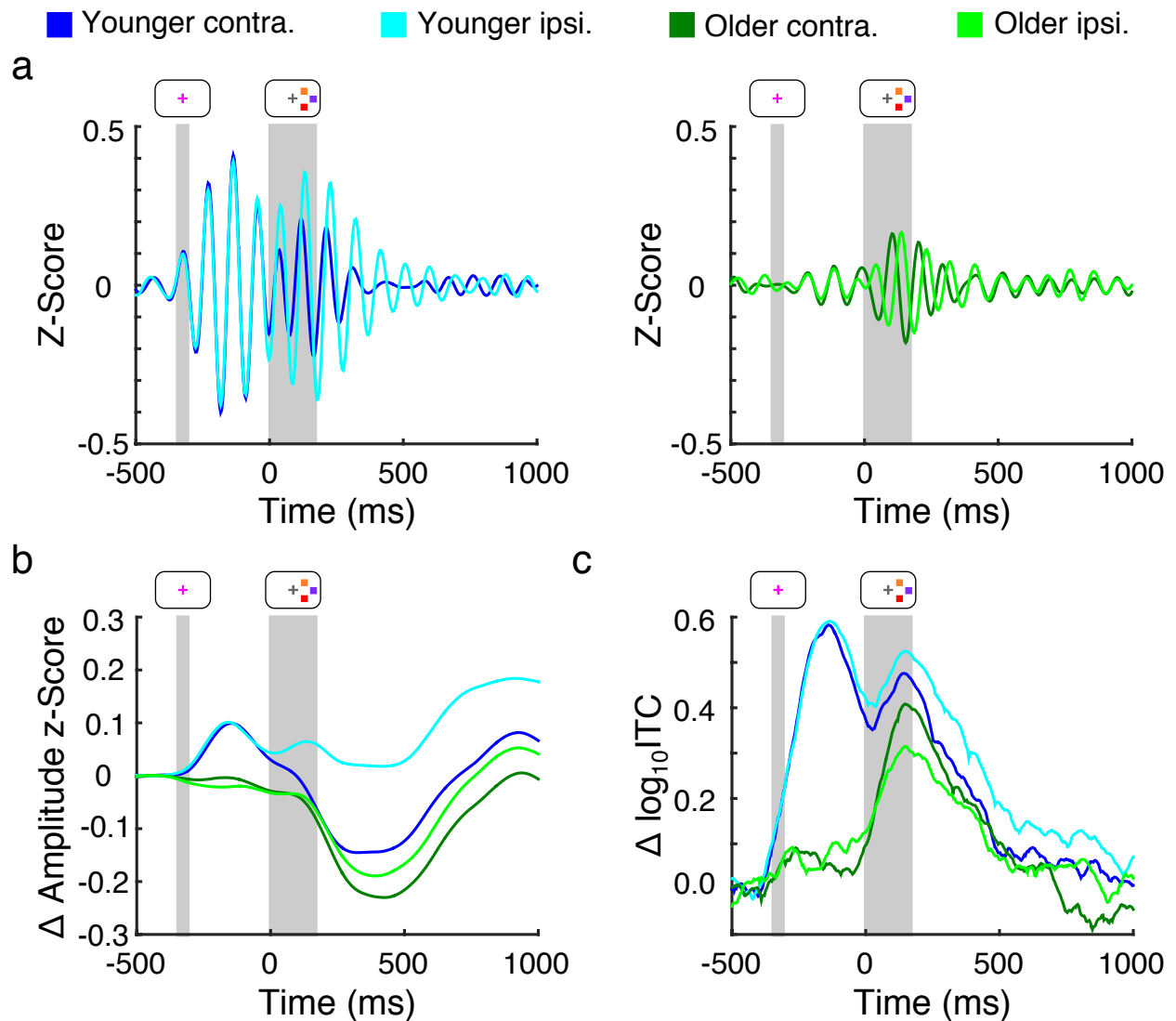
Figure 2. Alpha amplitude and phase activity. (a) Grand average visual-area alpha activity contralateral (darker) and ipsilateral (lighter) to the memory array in younger (blue, left panel) and older adults (green, right panel). Gray regions indicate presence and duration of the alerting cue and memory array. Note the hemispheric amplitude differences and strong phase consistency in younger compared to older adults. (*b*) Grand average of changes in normalized visual-area alpha amplitude and (*c*) intertrial coherence relative to baseline, emphasizing the effects observable in (*a*).
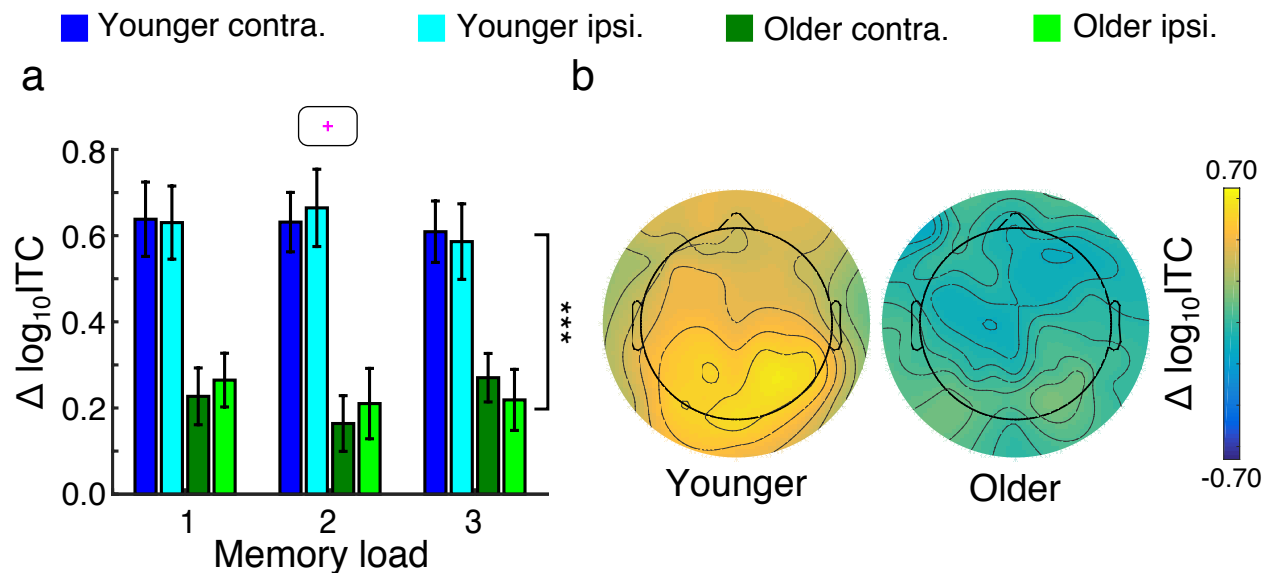
Figure 3. Alerting cue activity. (*a*) Peak alpha intertrial coherence (ITC) in response to the alerting cue. Younger adults (blue) had higher peak cue-evoked ITC than older adults (green; ***$p < 0.001$; error bars, SEM). (*b*) Topographies of cue-evoked ITC response in younger (left) and older adults (right) during load-three trials.

Memory Array Activity. Younger and older adults also showed alpha response to presentation of the memory array. After memory array onset, alpha amplitude diverged between hemispheres in younger and older adults (Fig. 2b). Mean alpha amplitude (0 to 400 ms) showed main effects of memory load (Fig. 4a, 4b, $F_{2,58} = 4.29$, $\varepsilon = 0.87$, $p_{GG} = 0.024$, $\eta^2 = 0.011$) and hemisphere ($F_{1,29} = 18.15$, $p < 10^{-3}$, $\eta^2 = 0.034$) and an interaction between age and hemisphere ($F_{1,29} = 9.10$, $p = 0.0053$, $\eta^2 = 0.017$). Post hoc analysis revealed that alpha amplitude decreased from load-one to load-two ([0.0053, 0.056], $t_{30} = 2.47$, $p = 0.019$, Cohen's $d = 0.44$), but not from load-two to load-three conditions ($p = 0.37$, Cohen's $d = 0.17$). In addition, alpha lateralization, or the difference in alpha amplitude between hemispheres, was greater in younger than older adults (0.11 vs. 0.019, [0.034, 0.15], $t_{23.21} = 3.22$, $p = 0.0038$, Cohen's $d = 1.09$).

As with alerting cue presentation, memory array presentation also caused alpha phase resets (Fig. 2c). Overall, both younger ([-0.43, -0.18], $t_{16} = -5.27$, $p < 10^{-4}$, Cohen's $d = -1.28$) and older adults ([-0.30, -0.099], $t_{13} = -4.25$, $p < 10^{-4}$, Cohen's $d = -1.14$) showed increased average alpha ITC in response to the memory array. Compared to phase-scrambled ITC values, true average array-evoked (0 to 600 ms) ITC was higher in all 17 younger adults and all 14 older adults. Unlike with cue-evoked ITC, peak array-evoked ITC showed no effects of memory load ($F_{2,58} < 1.0$), age ($F_{1,29} = 1.60$, $p = 0.22$, $\eta^2 = 0.028$), or hemisphere ($F_{1,29} < 1.0$).
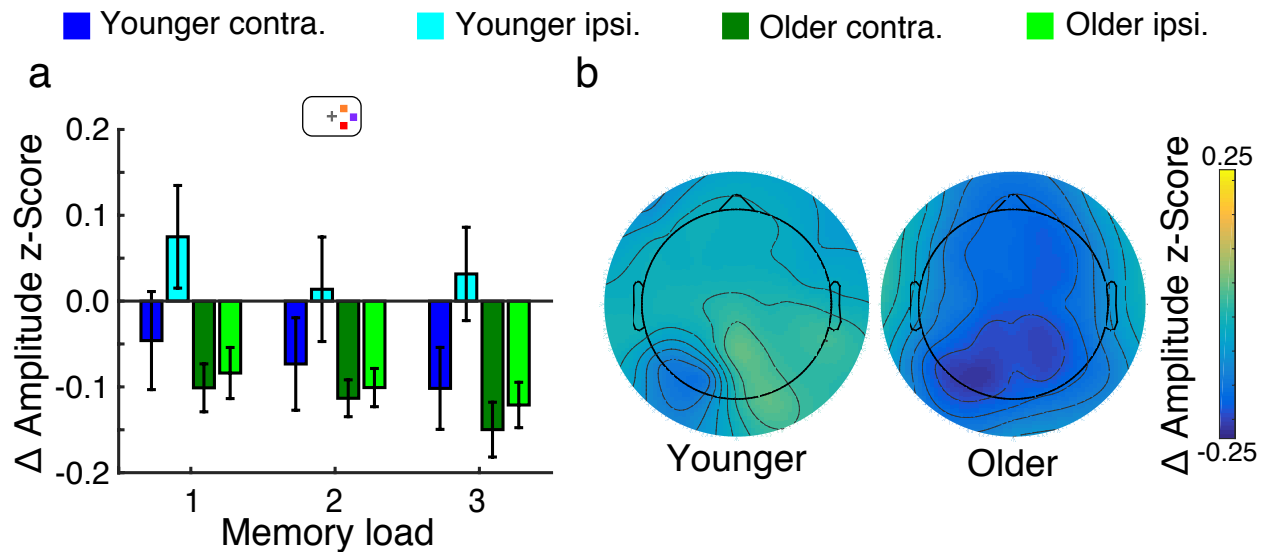
Figure 4. Memory array activity. (*a*) Average change relative to baseline in normalized alpha amplitude 0 to 400 ms after memory array presentation. Amplitude decreased from load one to two ($p < 0.05$), and older adults (green) showed decreased alpha lateralization ($p < 0.01$; error bars, SEM). (*b*) Topographies of delay-period alpha amplitude in younger (left) and older adults (right) during load-three trials.

Contralateral Delay Activity. We also investigated participants' contralateral delay activity (CDA), an event-related potential measure indicative of working memory capacity (McCollough et al., 2007; Vogel and Machizawa, 2004) and top-down attentional processes (Drew and Vogel, 2008; Eimer and Kiss, 2010; Fukuda and Vogel, 2009; Woodman and Vogel, 2008). We observed sustained delay-period (300 to 900 ms) negativity in the hemisphere contralateral to the memory array (Fig. 5a). This negativity or CDA showed a main effect of memory load (Fig. 5b, $F_{2,58} = 14.88$, $\varepsilon = 0.96$, $p_{GG} < 10^{-5}$, $\eta^2 = 0.080$) wherein CDA increased in magnitude from load-one to load-two conditions ([0.34 μV, 0.86 μV], $t_{30} = 4.66$, $p < 10^{-4}$, Cohen's $d = 0.84$). CDA was comparable between load-two and load-three conditions ($p = 0.47$, Cohen's $d = 0.13$). However, CDA did not differ between younger and older adults ($F_{1,29} = 1.05$, $p = 0.31$, $\eta^2 = 0.029$), nor did we observe an interaction between age and memory load ($F_{2,58} < 1.0$).
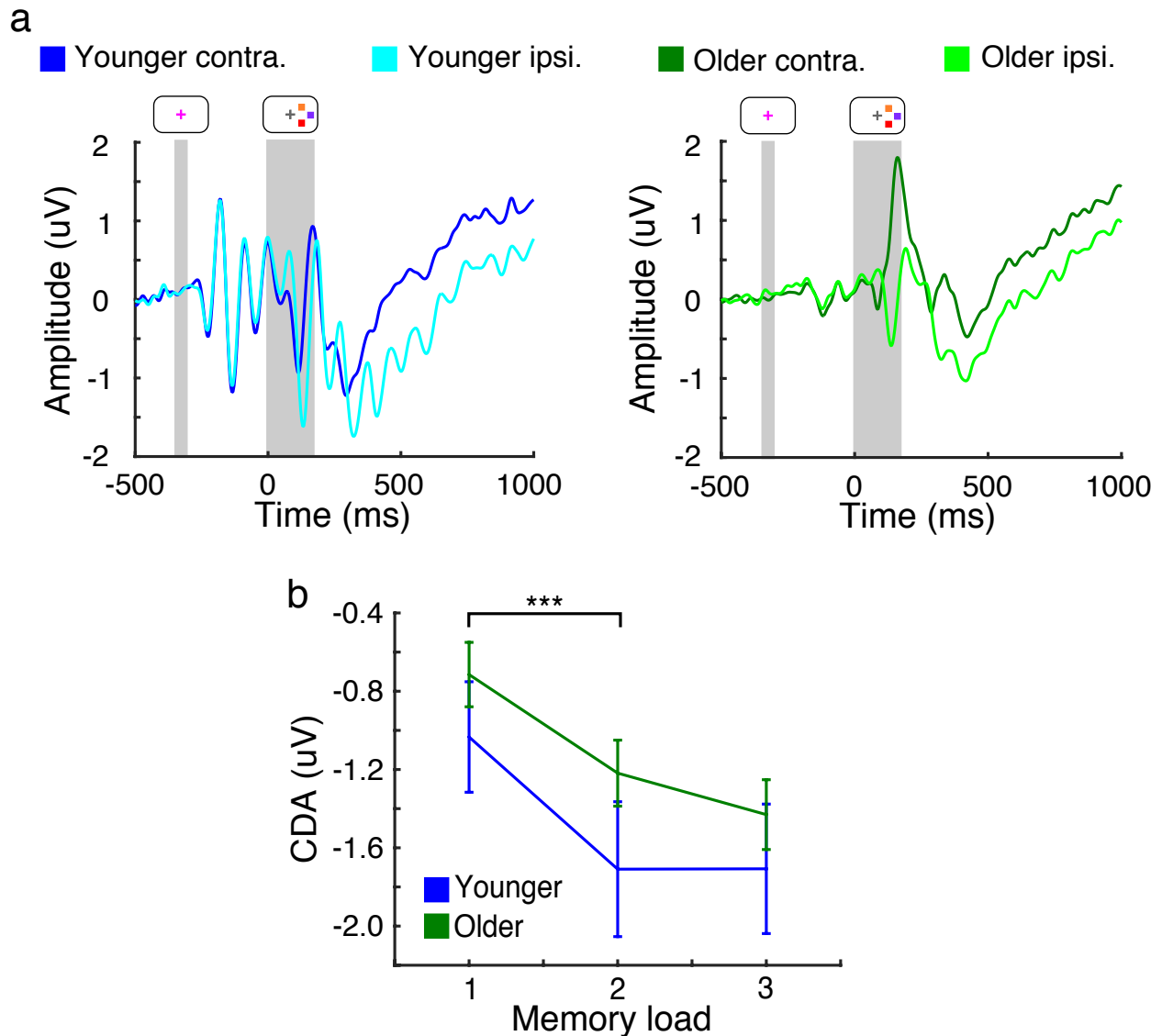
Figure 5. Event-related potential and delay period activity. (*a*) Grand average visual-area activity contralateral (darker) and ipsilateral (lighter) to the memory array in younger (left panel) and older adults (right panel). Gray regions indicate presence and duration of the alerting cue and memory array. Note the sustained negativity in the contralateral hemisphere in both younger and older adults. (*b*) Contralateral delay activity (CDA) increased in magnitude from load-one to load-two conditions, but did not differ between younger and older adults (***$p < 0.001$; error bars, SEM)

Alpha Phase Activity Predicts Behavior. Given the age-related changes in neural activity that we observed, we examined how these changes related to behavioral performance. As noted, older adults performed as well as younger adults on the easiest (load-one and load-two) trials, but performed worse for more difficult load-three trials. To examine the neurophysiological basis for this aging effect, we focused our analyses on measures of cue-evoked alpha ITC, array-evoked alpha amplitude modulation, and

343   delay-period CDA. Peak cue-evoked ITC was averaged across visual hemispheres, and
344   the differences in alpha lateralization and CDA between load-two and load-three
345   conditions were used. Importantly, these physiological measures were indexed during
346   times *prior to* the actual memory challenge and thus are related to trial-by-trial changes
347   in alertness, encoding, or memory maintenance, rather than memory retrieval or
348   response.
349   Across all participants, between-load differences in alpha lateralization were not
350   predictive of load-three accuracy ($N = 31$, $p = 0.45$), nor were between-load differences
351   in alpha lateralization and CDA correlated with one another ($N = 31$, $p = 0.85$). Similar to
352   previous results (Vogel and Machizawa, 2004), between-load differences in CDA were
353   predictive of load-three accuracy ($N = 31$, $r = -0.41$, $p = 0.022$). This effect was driven by
354   a correlation across younger adults alone ($N = 17$, Spearman's $r = -0.65$, $p = 0.0048$),
355   with no such correlation among older adults ($p = 0.42$). Peak cue-evoked ITC was also
356   correlated with load-three accuracy across all participants (Fig. 6a; $N = 31$, Spearman's
357    $r = 0.47$, $p = 0.0071$). As with CDA effects, this was driven by a correlation across
358   younger adults alone ($N = 17$, Spearman's $r = 0.49$, $p = 0.044$), with no such correlation
359   among older adults ($p = 0.62$).
360   Next, to examine the relative contribution of each neurophysiological measure to
361   behavioral accuracy, we modeled load-three d' as a linear combination of load-three
362   peak cue-evoked alpha ITC and the between-load differences in array-evoked alpha
363   lateralization and delay-period CDA. This model explained 18.5% of the variance in
364   accuracy ($p = 0.036$). Examining the relative contribution of each predictor, we found
365   that after accounting for between-load differences in alpha lateralization and CDA, peak
366   cue-evoked ITC remained predictive of load-three accuracy ($p = 0.025$). Between-load
367   differences in alpha lateralization and CDA, on the other hand, did not remain predictive
368   of load-three accuracy after accounting for other physiological measures ($p = 0.70$ and p
369    $= 0.22$, respectively). Thus, peak cue-evoked ITC prior to the presentation of to-be-
370   remembered stimuli was a strong predictor of behavioral accuracy, even after adjusting
371   for array-related alpha amplitude and delay-period CDA effects.
372   To further investigate how cue-evoked alpha ITC is associated with behavioral
373   performance, we examined how alpha phase at peak ITC related to subsequent working
374   memory performance. To do so, we determined the timepoint of each participant's peak
375   cue-evoked ITC, and we pooled all participants' corresponding alpha phases at peak
376   cue-evoked ITC and RTs across trials. During load-three trials in younger adults, alpha
377   phase at peak cue-evoked ITC predicted RTs on a trial-by-trial basis (Fig. 6b, blue; $N =$
378   2499, $r = 0.13$, $p < 10^{-3}$). Alpha phase at peak cue-evoked ITC also predicted RTs in
379   older adults (Fig. 6B, green; $N = 2090$, $r = 0.080$, $p = 0.0013$). Specifically, in both
380   younger and older adults, longer response times were predicted by peak cue-evoked
381   ITC occurring at the peak of the alpha cycle. Thus, despite older adults' relatively
382   inconsistent cue-evoked phase response, prestimulus alpha phase was still predictive of
383   load-three RTs. However, the relationship between alpha phase at peak cue-evoked
384   ITC and RT was weaker in older than younger adults ($z = 1.79$, $p = 0.036$), indicating a
385   weaker prestimulus alpha phase effect among older adults.
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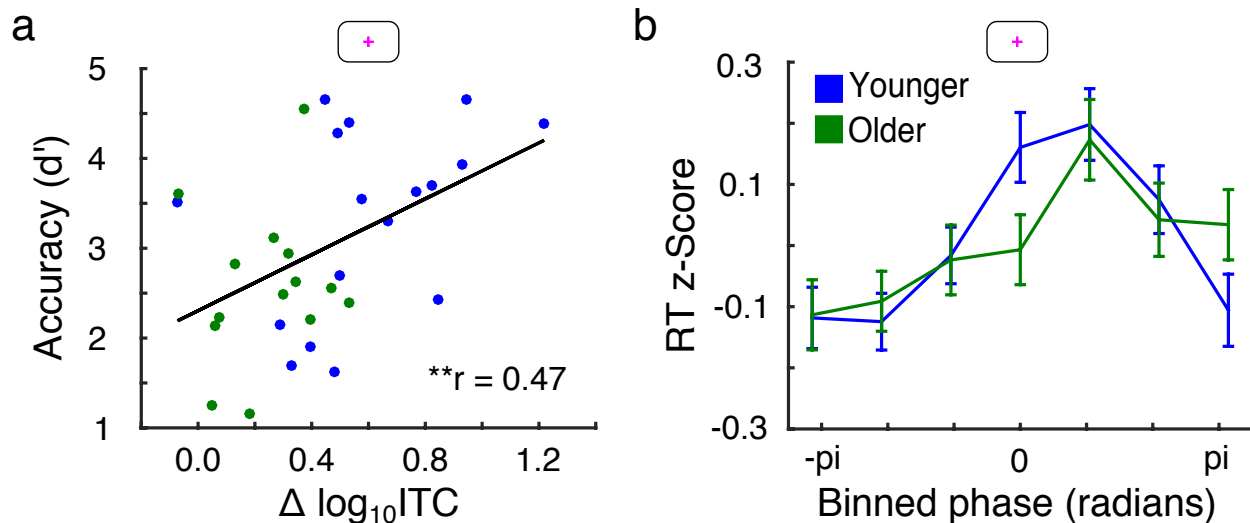
Figure 6. Alpha phase predicts working memory performance. (*A*) Peak cue-evoked alpha intertrial coherence (ITC) versus accuracy during load-three trials across younger (blue) and older adults (green). Peak cue-evoked ITC was predictive of load-three accuracy (**$p < 0.01$). (*B*) Average response time (RT) binned by alpha phase at peak cue-evoked ITC. Phase of zero and ±pi correspond to the peaks and troughs of alpha, respectively. Trial-by-trial alpha phase predicted RTs ($p < 10^{-3}$; error bars, SEM).

Discussion

In this study, we used a combined visual attention and working memory task to investigate how age-related changes in alertness and spatial attention affect later working memory performance. Using scalp EEG, we found that alpha activity showed age-related alterations during the task, including in older adults' reduced alpha amplitude lateralization during working memory maintenance. In addition, prior to working memory encoding, older participants showed less consistent phase response to a spatially noninformative alerting cue. The consistency of cue-evoked alpha phase reset predicted working memory performance, as did prestimulus alpha phase prior to memory array presentation. Our results provide evidence that alerting cue presentation is accompanied by alpha activity modulation, that neural response to alerting cues is altered during healthy aging, and that the degree of alteration could influence behavioral outcomes.

Previous research has found that contralateral delay activity (CDA) is related to reduced working memory performance in older frontal and basal ganglia lesion patient populations (Voytek et al., 2010; Voytek and Knight, 2010). In this study, we observed that between-load modulation of CDA predicted working memory performance, which is consistent with previous findings (Vogel and Machizawa, 2004). We observed no difference in the amplitude or load-dependent modulation of CDA between younger and older adults. A previous study has reported alterations in CDA modulation in older adults (Sander et al., 2011), but differences between that study and our present study are likely due to our study only presenting stimuli in one visual hemifield at a time. Thus, any

417   age-related differences in the suppression of distractor processing were not tested,
418   likely altering patterns of CDA modulation in older adults.
419   After memory array presentation, alpha amplitude in younger adults diverged
420   between hemispheres, with ipsilateral amplitude higher than contralateral amplitude.
421   Consistent with previous studies (Thut et al., 2006; Worden et al., 2000), this alpha
422   lateralization is suggestive of differential processing of the two visual hemifields and the
423   deployment of selective spatial attention in anticipation of the test array, which
424   participants knew would appear in the same visual hemifield as the memory array. This
425   interpretation is also consistent with the lack of alpha lateralization in response to the
426   spatially uninformative alerting cue. Compared to younger adults, older adults showed
427   reduced alpha lateralization, as previously reported in studies with spatial cuing (Hong
428   et al., 2015; Sander et al., 2012). However, between-load modulation of alpha
429   lateralization did not predict older adults' lower accuracy during load-three trials.
430   Instead, cue-evoked alpha phase resetting was less consistent in older adults
431   and was predictive of behavioral performance even after adjusting for array-evoked
432   alpha lateralization and delay-period CDA. Because the alerting cue appeared prior to
433   any stimulus to be encoded in working memory, this result supports findings of reduced
434   alertness in older adults (Gamboz et al., 2010; Jennings et al., 2007), with participants'
435   general attentional state being the single best predictor of accuracy more than a second
436   later in the trial. Because the alerting cue was also temporally predictive and preceded
437   memory array onset by 300 ms each trial, these results are similar to those of Zanto *et*
438   *al.* (2011), which showed that older adults had reduced pre-target alpha activity
439   modulation during a 600 ms foreperiod. Our results extend these previous findings
440   because of our use of a shorter foreperiod designed to test alerting over orienting
441   response (Weinbach and Henik, 2012). Thus, while Zanto *et al.* (2011) demonstrated
442   age-related reductions in neural measures of temporal expectation, our results highlight
443   older adults' reduced reflexive response instead.
444   Although the observed age-related differences in cue-evoked ITC are consistent
445   with previous reports of reduced alertness in older adults (Gamboz et al., 2010;
446   Jennings et al., 2007), age-related changes in early perceptual processing could also
447   have contributed to the observed effects, especially given the briefness of alerting cue
448   presentation (50 ms). However, younger and older adults had comparable cue-evoked
449   P1 amplitudes, suggesting that both groups visually processed the cue in a similar
450   manner. If this were not the case, lower performance in older adults would potentially be
451   more attributable to changes in visual processing than to changes in alerting response.
452   Nevertheless, although we did not observe any changes in cue-evoked P1 amplitude,
453   differences in perceptual processing cannot be ruled out as a potential factor
454   contributing to age-related changes in working memory performance.
455   While the age-related inconsistency in cue-evoked alpha phase resetting is
456   opposite that in a previous study (Sander et al., 2012), this discrepancy could be due to
457   the lack of distractor stimuli and the briefness with which we presented the alerting cue
458   (50 ms). This briefness potentially exacerbated any age-related alterations in cue
459   response, which has not been observed in other studies (Williams et al., 2016; Zanto et
460   al., 2011). Interestingly, we also found that array-evoked ITC was similar between

461 younger and older adults, despite previous reports showing increased ITC among older
462 adults (Sander et al., 2012). However, the large, asymmetric cue-evoked ITC
463 differences between younger and older adults may have shifted the ITC baseline,
464 artificially driving up younger-adult ITC. That is, the peak-to-peak difference between
465 cue- and array-evoked ITC is much larger among older, compared to younger, adults.
466 Nevertheless, that cue-evoked alpha phase consistency was predictive of behavioral
467 performance is consistent with previous studies examining alpha phase resetting in
468 response to task-relevant stimuli (Klimesch et al., 2004; Werkle-Bergner et al., 2012;
469 Yamagishi et al., 2008). Our results extend these findings by demonstrating that alpha
470 phase resetting in response to alerting cues, even prior to presentation of to-be-
471 remembered stimuli, can predict subsequent working memory performance.
472   Alpha phase prior to memory array presentation also predicted response time in
473 high-load trials. This result provides further evidence for the effects of alpha phase on
474 visual working memory (Myers et al., 2014). These effects have also been
475 demonstrated in visual detection paradigms (Busch and VanRullen, 2010; Mathewson
476 et al., 2009). Due to the consistent time interval between cue and memory array
477 presentation in our study, it is possible that cue-evoked alpha phase resets led to
478 subsequent memory array presentation at phases facilitative of or detrimental to
479 perception or encoding of the memory array. Older adults' inconsistency in phase
480 response could have led to a greater number of instances in which memory array
481 presentation occurred at suboptimal alpha phases, potentially explaining part of the age-
482 related reductions in performance we observed during high-load trials. However, older
483 adults' weaker relationship between alpha phase and response time also suggests age-
484 related reductions in the influence of alpha phase on visual cognition. Physiologically,
485 this reduced influence, as well as older adults' inconsistent cue-evoked phase
486 responses, may relate to age-related increases in neural noise (Voytek and Knight,
487 2015; Voytek et al., 2015b).
488
489 **Conclusions**
490   Overall, we find that oscillatory alpha dynamics may underlie age-related
491 alterations in attention. Our analysis of alpha phase highlights reductions in older adults'
492 response and attentiveness to alerting cues, with such responsiveness being the
493 strongest predictor of working memory performance. In addition, prestimulus alpha
494 phase predicted performance on a trial-by-trial basis, but less reliably so in older adults.
495 Given that lower performance in older adults can be explained by altered response to
496 alerting cues prior to the task, age-related working memory decline is likely multifaceted
497 and includes alterations in anticipatory attentional allocation as well as in stimulus
498 encoding and maintenance. These findings suggest that changes in neural response,
499 especially in older adults, can occur at multiple timepoints both before and after
500 presentation of task-relevant stimuli, and such alterations likely all have an impact on
501 later cognitive performance.
502
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