

Title:

Noradrenergic responsiveness supports selective attention across the adult lifespan

Abbreviated title: Noradrenergic responsiveness supports attention

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1 **Abstract**

2 Selectively attending to relevant information while blocking out distractors is crucial for
3 goal-directed behavior, yet with advancing age, deficits emerge in attentional selectivity.
4 Decrements in attention have been associated with altered noradrenergic activity in
5 animals. However, research linking noradrenergic functioning to attention in aging
6 humans is scarce, likely reflecting long-standing methodological challenges in non-
7 invasive assessments. We studied whether age-related differences in the noradrenergic
8 system predict differences in attention. We measured pupil dilation, a non-invasive
9 marker of phasic norepinephrine (NE) release, while concurrently recording the
10 electroencephalogram (EEG), of male younger (N=39; 25.2±3.2 years) and older adults
11 (N=38; 70.6±2.7 years). Arousal was triggered on a trial-by-trial basis using fear-
12 conditioned (CS+) stimuli. During conditioning, pupil and EEG markers related to
13 heightened NE activity were identified. Afterwards, in a dichotic listening task,
14 participants were cued to direct attention to either the left or right ear while highly
15 similar syllable pairs were presented simultaneously to both ears.
16 During the dichotic listening task, presentation of fear-conditioned stimuli reinstated the
17 acquired fear response, as reflected in pupil and EEG alpha–beta-band responses.
18 Critically, pupil dilation to CS+ was correlated with stronger EEG alpha–beta
19 desynchronization, suggesting a common dependence on NE release. On a behavioral
20 level, stronger arousal reactions were associated with better attention. In particular,
21 structural equation modeling revealed that the responsiveness of the NE system is
22 associated with attention on a latent construct level, measured by several indicator tasks.
23 Overall, our results suggest that the responsiveness of the NE system supports attention
24 across the lifespan.

25 *Keywords:*

26 cognitive aging, norepinephrine, locus coeruleus, rhythmic neural activity, selective
27 attention

28 **Significance statement**

29 In old age the ability to selectively process relevant aspects of the environment
30 fades. Animal research suggests that the neuromodulator norepinephrine helps to
31 maintain selective attention. We tested younger and older adults across a variety of
32 attention tasks. In addition, we used arousing stimuli to experimentally activate
33 participants' noradrenergic system while recording pupillometry and
34 electroencephalography (EEG) to infer its functional capacity. Older adults showed
35 compromised attention and reduced noradrenergic responsiveness as indicated by
36 interrelated pupil and EEG markers. Crucially, in both age groups a more responsive
37 noradrenergic system was strongly associated to attention. Our findings link animal and
38 human studies on the neural underpinning of attention in aging and underscore the
39 importance of the noradrenergic system in late life cognition.

40 **Introduction**

41 Daily situations confront us with a plethora of competing sensory inputs that far
42 exceed neural processing capacities, thus prioritization and selection is essential for
43 adaptive behavior (e.g., Desimone & Duncan, 1995). Impaired attentional selection in
44 aging (for reviews see Kennedy & Mather, 2019; Plude, Enns, & Brodeur, 1994) has been
45 linked to deficient neuromodulation (Li et al., 2001; Bäckman et al., 2006). The
46 neuromodulator norepinephrine (NE) is strongly implicated in attentional processes
47 that facilitate the processing of relevant information (Berridge & Waterhouse, 2003).
48 First, increased NE release is associated with the transition to and the maintenance of an
49 activated cortical and behavioral state – as evident in a desynchronized (high frequency,
50 low amplitude) electroencephalogram (EEG) and alert waking (sometimes termed
51 arousal; Carter et al., 2010; McGinley et al., 2015; Neves et al., 2018). In the waking state,
52 fast, burst-like (phasic) and slow, rhythmic (tonic) firing patterns of the locus coeruleus
53 (LC), the primary cortical NE source, have been tied to focused attention and
54 distractibility, respectively (Aston-Jones and Cohen, 2005). Further, a series of
55 pharmacological and lesion studies demonstrated that, via actions at α_{2A} -adrenoceptors
56 in the prefrontal cortex, NE facilitates top-down selective attention (Arnsten & Li, 2005).
57 In the sensory cortices, phasic NE release interacts with local glutamate levels to allow
58 the selective processing of currently relevant representations, mediated via α_{2A} - and β -
59 adrenoceptors (Mather et al., 2016; Gelbard-Sagiv et al., 2018). Finally, NE has been
60 linked to the reorienting and switching of attention via disruption of the dorsal- and
61 activation of the ventral attention network (Bouret & Sara, 2005; Corbetta, Patel, &
62 Shulman, 2008). In line with these links between NE and attention, recent theories of
63 both healthy (Mather and Harley, 2016) and pathological (Weinshenker, 2018; Satoh and
64 Iijima, 2019) cognitive aging have proposed a prominent role of the LC-NE system in late

65 life cognition. However, LC's anatomical location in the brainstem, adjacent to the
66 ventricular system and its widespread, unmyelinated axons expose it to blood- and
67 cerebrospinal-fluid bound toxins, making it vulnerable to neurodegeneration (Mather
68 and Harley, 2016; Liu et al., 2019) with potentially wide-ranging consequences. For
69 instance, Wilson and colleagues (2013) reported an association between LC's structural
70 integrity, as assessed post-mortem via autopsy, and longitudinal cognitive decline in
71 aging (cf. Hämmerer et al., 2018; Betts et al., 2019; Dahl et al., 2019b). However, the
72 question of how LC's functional characteristics, i.e., its capacity to respond to
73 behaviorally relevant information, are linked to attention in aging humans is still
74 unresolved. Long-standing technical challenges in the non-invasive assessment of LC-NE
75 activity in vivo (e.g., Astafiev, Snyder, Shulman, & Corbetta, 2010) have contributed to
76 this lack of information. However, recently, multiple independent studies (Joshi et al.,
77 2016; Reimer et al., 2016; Breton-Provencher and Sur, 2019; Zerbi et al., 2019)
78 demonstrated that pupil dilation in the absence of interfering visual input serves as valid,
79 non-invasive proxy for LC activity. In addition, use of optogenetics established a causal
80 link between phasic LC activity and event-related EEG responses (i.e., P300 ERP; Vazey,
81 Moorman, & Aston-Jones, 2018). Moreover, EEG reveals fluctuations in cortical states
82 (i.e., global EEG de/activation as reflected in a de/synchronized EEG) that have been
83 associated with LC activity (McCormick et al., 1991).

84 In this study we thus used a multimodal assessment to evaluate individual
85 differences in selective attention among younger and older adults and their dependence
86 on functional characteristics of the LC-NE system. In order to experimentally induce LC
87 activity, we made use of LC-NE's well-established role in fear processing (cf. Lee et al.,
88 2018; Szabadi, 2012; Uematsu et al., 2017). We hypothesized that the functional capacity
89 of the LC-NE system as assessed by simultaneous, interrelated pupil and EEG responses

90 would be closely associated with individual differences in selective attention. In sum, the
91 overall goal of this study was to extend our knowledge about the role of the LC-NE
92 system in human cognitive aging by generating a multimodal, non-invasive index of LC
93 functioning and linking it to attention abilities in younger and older adults.

94

95 **Methods**

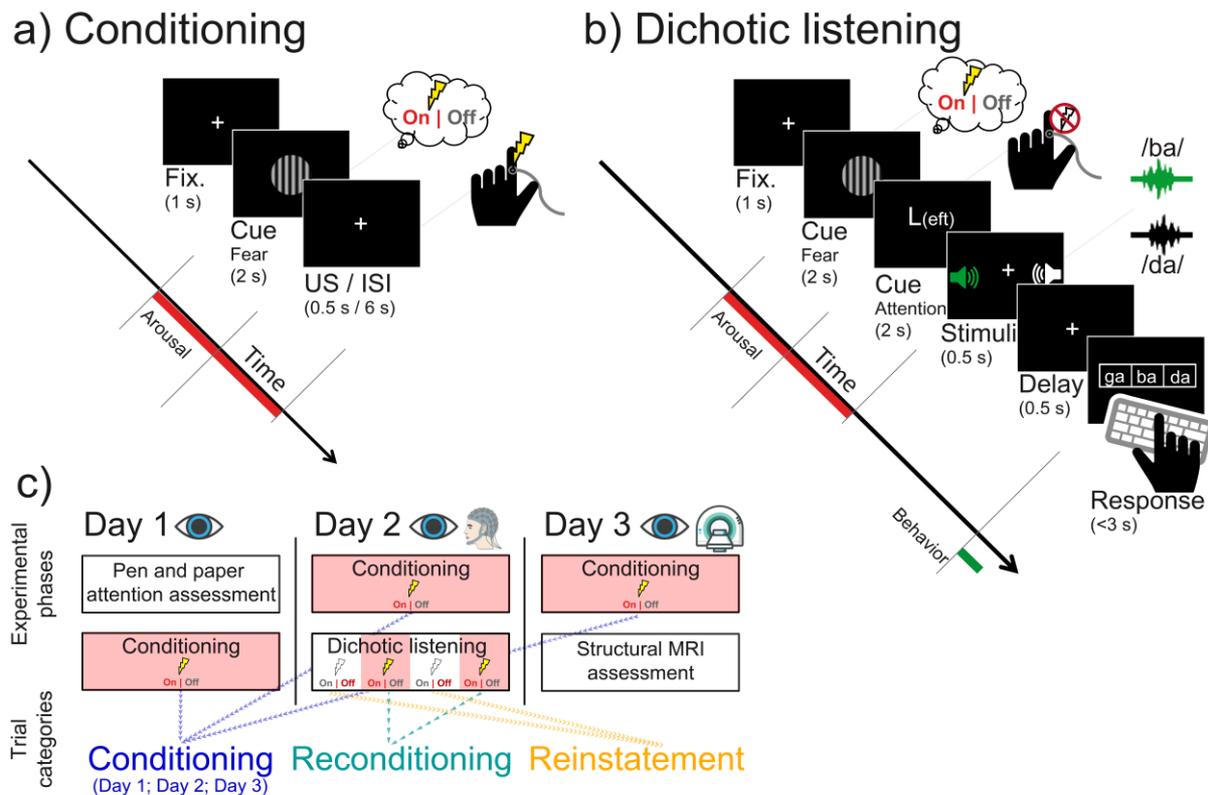
96 **Study design**

97 Data was collected within the framework of a larger study investigating the
98 interplay of neurophysiological indices of LC-NE activity and their association to
99 selective attention in younger and older adults (YA; OA, respectively). Only aspects of the
100 study that are relevant to the current analyses are introduced in detail below.

101 Participants were invited on three successive days (Day 1–Day 3) for individual
102 assessments that spanned approximately 4 hours on Day 1 and Day 2 and 2 hours on
103 Day 3. Time of assessment (morning, afternoon, evening) was kept constant across
104 sessions within participants.

105 In short, on the first day, participants completed a neuropsychological selective
106 attention battery as well as an assessment of fear conditionability (see Figure 1 a and c)
107 while pupil dilation was recorded. To adapt auditory stimuli during later attention
108 assessments for hearing thresholds, we assessed hearing acuity (on Day 1 for younger
109 adults and on a separate occasion preceding Day 1 for older adults). On the second day,
110 we concurrently recorded pupil dilation and EEG while participants underwent another
111 fear conditioning session and an in-depth evaluation of their auditory selective attention
112 performance (see Figure 1b). The last day comprised a final fear conditioning session
113 while recording pupil dilation (see Figure 1c) and an MRI assessment which is reported
114 in more detail here: <https://doi.org/10.17605/OSF.IO/G9FQI> . The study was approved

115 by the ethics committee of the German Psychological Association (DGPs) and was
 116 conducted in accordance with relevant guidelines and regulations.



117

118 *Figure 1.* Experimental procedure of the (a) fear conditioning session and (b) dichotic listening
 119 task as well as (c) resulting trial categories. (a) Each conditioning trial began with a 1 s baseline
 120 interval during which a white fixation cross was presented. Then, either the conditioned (CS+) or perceptually matched control stimulus (CS-; horizontal or vertical Gabor patch) was
 121 displayed for 2 s. In CS+ trials, upon offset of the Gabor patch, a mild electric shock was applied
 122 to participant's finger. After 6 s of fix cross presentation (inter-trial-interval), the next trial
 123 started. (b) Importantly, the beginning of trials in the dichotic listening task was identical to the
 124 fear conditioning session. Upon offset of the CS, an attention cue (2 s) indicated which ear
 125 participants should focus on. Tightly synchronized syllable-pairs were then presented
 126 simultaneously to the left and right ear (0.5 s) and participants indicated by button press which
 127 syllable they heard on the cued ear (up to 3 s). (c) Participants underwent fear conditioning
 128 sessions (cf. a) on each day of the experiment while pupil dilation was recorded (Conditioning;
 129 blue). The arousal manipulated dichotic listening task (cf. b) was completed once on the second
 130 day while both pupil dilation and EEG was recorded. Interleaved after each break of the dichotic
 131 listening task participants were reconditioned (cf. a) to prevent extinction of the fear response
 132 (Reconditioning; teal). During re/conditioning participants received electrical stimulation (US)
 133 and thus the observed responses may represent a mixture of fear and somatosensory responses.
 134 In contrast, during the dichotic listening task no shocks were applied and thus observed
 135 responses to the arousal manipulation (CS+ vs CS-) indicate the reinstatement of the fear
 136 response (Reinstatement; orange). On the first day of the experiment, participants additionally
 137 completed a pen and paper attention assessment while on the last day structural magnetic
 138 resonance imaging (MRI) data was recorded. Fix.: Fixation; US: Unconditioned stimulus; ISI:
 139 Inter stimulus interval. Numbers in brackets indicate presentation times in seconds (s).
 140

141 **Participants**

142 Forty-one younger adults participated in the study. Two of these (4.88%; aged:
143 24.59 and 29.02 years) were not re-invited after Day 1 due to low quality eye tracking
144 data, reducing the final sample to 39 younger adults (mean (*M*) age: 25.23 ± 3.23 years
145 (standard deviation; *SD*); range: 20.17–31 years; 100% male). In addition, thirty-eight
146 older adults took part in the experiments (*M* age: 70.61 ± 2.71 years (*SD*); range: 65.50–
147 75.92 years; 100 % male). All participants were healthy, MRI-compatible, right-handed,
148 fluent German speakers with normal or corrected-to-normal vision who provided
149 written informed consent and were reimbursed for participation. Intake of centrally
150 active drugs and in particular medication directly influencing the LC-NE system (e.g.,
151 beta blockers) precluded participation. Please note that the current study only tested
152 male subjects due to our pilot data demonstrating reliable sex differences in the
153 stimulation intensity participants selected for the fear conditioning sessions. Previous
154 research indicates sex differences in the capability to learn and maintain fear responses during
155 conditioning (Merz et al., 2018; but also see Gruene et al., 2015 and Voulo and Parsons, 2017,
156 for evidence for sex-specific expressions of fear learning). Some of these differences in fear
157 learning may be associated with sex differences in the LC-NE system (Bangasser et al., 2016;
158 Mulvey et al., 2018). To limit the number of control variables, we decided to test male
159 participants; however, we would like to underscore the need to follow up on the reported
160 findings including both sexes. Descriptive characteristics of the two age groups are
161 provided in Table 1. Both groups showed comparable educational levels and did not
162 differ reliably on a brief dementia screening (Mini Mental State Examination (MMSE);
163 Folstein, Folstein, & McHugh, 1975). All participants scored above the commonly used
164 MMSE cut-off of 26 points. In line with previous reports (e.g., Passow et al., 2012, 2014),
165 older adults demonstrated higher scores on a test of verbal knowledge (Spot a Word;
166 Lehl, 1977) and increased age-related hearing loss. On average, older adults selected

167 higher intensities as unpleasant unconditioned stimulus for the fear conditioning
168 procedure, presumably reflecting age related differences in skin conductivity
169 (Chamberlin et al., 2011).

170 Table 1

171 Descriptive statistics for younger and older adults

Measure	Younger adults (n = 39)	Older adults (n = 38)	<i>U</i>	<i>Z</i>	<i>p</i>
Age (years)	25.231 ± 0.516	70.614 ± 0.440	780	-7.546	<0.001
Education (years)	16.171 ± 0.406	17.263 ± 0.560	1320	-1.487	0.137
Hearing level (dB)	8.027 ± 0.758	19.626 ± 1.075	907	-6.251	<0.001
Shock intensity (mA)	0.3 ± 0.026	0.4 ± 0.024	1211	-3.227	0.001
Spot-A-Word (correct rows)	21.487 ± 0.551	29.158 ± 0.382	834	-7.021	<0.001
Mini Mental State (points)	29.410 ± 0.120	29.053 ± 0.181	1631	1.216	0.224

172 Note: For younger and older adults, group means ± 1 standard error of the mean are reported. Age group
173 comparisons are based on non-parametric Mann-Whitney U-tests. Hearing level is averaged across
174 frequencies (250–3000 Hz) and ears. Shock intensity denotes the intensity participants individually
175 defined as uncomfortable yet not painful on Day 2.

176

177 **Experimental procedures and stimuli**

178 *Neuropsychological attention assessment*

179 On the first day of the experiment, participants completed a multimodal,
180 standardized neuropsychological attention assessment comprising the D2 test of
181 attention (Brickenkamp and Zillmer, 1998), Digit-Symbol-Substitution Test (Wechsler,
182 1981) and auditory digit sorting task (cf. Kray & Lindenberger, 2000).

183 The D2 test is a paper and pencil cancellation task asking participants to cross
184 out any letter *d* with two marks (") around, above or below it from a stream of highly
185 similar surrounding distractors (e.g., *p* with two marks or *d* with only one mark).
186 Participants were granted 20 s to complete each of a total of 12 lists of items. The
187 difference between processed items and committed errors (errors of omission and
188 errors of commission) across lists was taken as a measure of attention.

189 During the Digit-Symbol-Substitution Test participants were presented with a list
190 of digit-symbol pairs (e.g., 1: – ; 2: ⊥; [...] 9: =) along with a list of digits. Participants
191 were asked to write down the corresponding symbol under each digit as quickly and

192 accurately as possible. The number of correctly copied symbols within 90 s was taken as
193 an index of attention.

194 In the auditory digit sorting task we auditorily presented participants with a
195 stream of numbers (e.g., 2-7-5) ranging from three to eight digits. Participants then had
196 to write down the numbers sorted according to numerosity (e.g., 2-5-7). The sum of
197 correctly reported answers across all trials was taken as a measure of attention.

198

199 *Fear conditioning*

200 To experimentally activate the LC-NE system (cf. Rasmussen & Jacobs, 1986;
201 Szabadi, 2012; Uematsu et al., 2017) on each assessment day (Day 1-3), participants
202 completed a brief fear conditioning session in which they learned the association
203 between a visual stimulus and an aversive electrical shock (cf. Lee et al., 2018; see Figure
204 1a). During this phase, either a horizontal or vertical sinusoidal luminance pattern (i.e.,
205 Gabor patch; CS+) was paired with an unconditioned stimulus (US; shock). The other
206 pattern was never paired with the US and served as perceptually matched control
207 stimulus (CS-); the association between pattern orientation (horizontal/vertical) and
208 shock was kept constant within subject across days and was counterbalanced within age
209 groups (YA: 21:18; OA: 20:18). Note that this design guaranteed a matched luminance of
210 CS+ and CS- while the former acquired the behavioral relevance to stimulate LC-NE
211 activity (Szabadi, 2012). Each conditioning session comprised 40 trials which started
212 with a central white fixation cross on a black background (baseline; 1 s), followed by the
213 visual stimulus (2 s; CS+ or CS-; see Figure 1a). After offset of the visual stimulus the
214 shock was applied in CS+ trials for 0.5 s with a 80% reinforcement schedule (i.e., 0 s
215 trace conditioning) using a ring electrode connected to a bipolar current stimulator
216 (DS5; Digimeter; Welwyn Garden City, United Kingdom) that was taped either to

217 participant's left or right index finger (hand assignment was constant within subject
218 across days and counterbalanced within age groups: YA: 19:20; OA: 19:19). The inter-
219 trial-interval (ITI; white fixation cross) was set to 6 s to allow sufficient time for the
220 pupil to return to baseline in CS+ trials (cf. Lee et al., 2018). The conditioning phase
221 consisted of 20 CS+ and 20 CS- trials that were presented in pseudorandomized order.
222 After half of the trials, participants had a self-paced break during which they were asked
223 to indicate which of the two visual stimuli (horizontal; vertical) was paired with the
224 shock and how many shocks were delivered (i.e., manipulation check). On each day, prior
225 to the experiment participants individually selected an intensity for the US which they
226 perceived as unpleasant but not painful (cf. Lee et al., 2018; see Table 1). During all
227 conditioning sessions, gaze position and pupil dilation was recorded, interfering sensory
228 input was minimized and central fixation was enforced (see below).

229 During data collection, for one older adult, assignment of Gabor patch orientation
230 (horizontal/vertical) to CS condition (CS-/CS+) was switched between the first and
231 second day of assessment. Since this error worked against finding a reliable difference in
232 responses to CS- and CS+, we decided not to exclude this subject.

233

234 *Dichotic listening task*

235 On the second assessment day, we probed selective auditory attention by cueing
236 participants to focus attention to either the left (focus left condition; FL) or right (focus
237 right condition, FR) ear while highly similar consonant-vowel (CV) syllable pairs were
238 presented dichotically (i.e., simultaneously one stimulus to the left and one to the right
239 ear). Only syllables played to the cued ear should be reported while distractor stimuli
240 should be ignored. To indicate their response, after a brief delay participants selected the

241 target syllable from three visually displayed response options (including the target,
242 distractor and one highly similar novel, i.e., not presented, syllable; see Figure 1b).

243 Within attentional conditions (FL and FR) we manipulated participant's arousal
244 level on a trial-by-trial basis. In particular, each trial started with a central white fixation
245 cross on a black background (baseline; 1 s), followed by one of the conditioned stimuli (2
246 s; CS+ or CS-). After offset of the CS, a letter was centrally displayed cuing participants to
247 adapt their attentional focus (2 s; *L* for FL; *R* for FR). Next, a syllable pair was presented
248 dichotically for 0.5 s. After a delay of 0.5 s a recognition matrix (containing the target,
249 distractor and one novel syllable) was visually displayed for up to 3 s and participants
250 indicated by button press which syllable they heard in the cued ear. Response hand
251 assignment was counterbalanced within age groups (YA: 20:19; OA: 19:19; shocks were
252 never applied to the response hand). The ITI was set to 0.5 s and consisted of a white
253 fixation cross. Matched trial timing between fear conditioning and dichotic listening
254 tasks (1 s baseline; 2 s CS; ~6 s until next trial) allows a comparison of arousal responses
255 across both tasks (see Figure 1).

256 Twelve consonant-vowel syllable pairs consisting of syllables of voiced (/b/, /d/,
257 /g/) or unvoiced (/p/, /t/, /k/) consonants combined with the vowel /a/ served as
258 auditory stimuli in the dichotic listening task. Each pair contained two syllables with the
259 same voicing that were matched for onset times (cf. Hugdahl et al., 2009; Westerhausen
260 et al., 2009). To account for age-related hearing loss, syllable pairs were presented at an
261 individually adjusted volume (i.e., 65 dB above participant's average hearing threshold
262 between 250 and 3000 Hz as assessed by means of pure-tone audiometry; cf. Passow et
263 al., 2014). All twelve dichotic syllable pairs were presented six times in each of the
264 attention and arousal conditions, summing to 288 trials in total (i.e., 12 syllable pairs × 6
265 presentations × 2 attentional focus × 2 arousal conditions) that were split in blocks of 48

266 trials. In 8.33% of the trials, no conditioned stimulus (CS+; CS-) was displayed (no-CS
267 trials; $n = 24$), with a fixation cross instead occurring at that time point to obtain an
268 index of auditory attention irrespective of CS presentation. In another 8.33% of the trials,
269 the CS+ was followed by an electrical shock (booster trials; cf. fear conditioning phase; n
270 = 24; cf. Lee et al., 2018) to prevent extinction of the conditioned response. No-CS and
271 booster trials were excluded from analyses. After each block, participants had a self-
272 paced break during which their average accuracy was displayed graphically. Breaks were
273 followed by a brief reconditioning period of 20 trials that resembled one half of the fear
274 conditioning phase (presented in pseudorandomized order) to maintain the fear
275 response throughout the experiment (see Figure 1c).

276 To thoroughly familiarize participants with both the auditory material and the
277 instructions prior to testing, on the first assessment day we presented the six syllables
278 first diotically (i.e., the same syllable at the same time to the left and right ear; 24 trials)
279 followed by a presentation to only one ear (6 left and 6 right ear trials). Participants
280 indicated by button press which syllable they heard / on which ear (mean accuracy:
281 94.801 ± 0.983 (SEM) %). In addition, participants completed a dichotic listening task
282 without arousal manipulation (96 trials; mean accuracy: 46.749 ± 0.010 (SEM)%; please
283 note that chance performance in this task is 33.3%, i.e., one of three possible choices).

284 All stimuli were presented using Psychtoolbox ([Psychophysics Toolbox](#),
285 RRID:SCR_002881) for Matlab ([MATLAB](#), RRID:SCR_001622; The MathWorks Inc., Natick,
286 MA, USA) and insert earphones (ER 3A; Etymotic Research, Inc. Elk Grove Village, IL,
287 USA). During the fear conditioning and dichotic listening task, gaze position, pupil
288 dilation and the EEG (Day 2 only) were continuously recorded (see below). To minimize
289 the influence of sensory input on pupil dilation, testing took place in a dark, sound-
290 attenuated and electro-magnetically shielded room (cf. Hong, Walz, & Sajda, 2014).

291 Further, to minimize the influence of eye movements on pupil dilation (Gagl et al., 2011)
292 at the beginning of each trial (baseline period) participant's gaze position was sampled
293 online and the trial only started if central fixation was either maintained (> 75% of the
294 time) or restored upon presentation of a re-fixation target.

295

296 **Behavioral analyses**

297 *Dichotic listening task*

298 To evaluate age differences in selective attention, we calculated the auditory
299 laterality index (LI; Marshall, Caplan, & Holmes, 1975), for each Attentional focus
300 condition (FL, FR), collapsing across arousal conditions. This index expresses the
301 amount of right relative to left ear responses (i.e., $LI = (Right - Left) / (Right + Left)$). The
302 LI ranges from -1 to 1 whereby negative values indicate more left ear responses and
303 positive values index a tendency towards selecting the right ear syllable. Younger and
304 older adults' laterality indexes were analyzed in a two-factorial (Age group \times Attentional
305 focus (FL, FR)) mixed measures analysis of variance (ANOVA) that was followed-up by
306 post-hoc tests within age groups. To judge the influence of age-related hearing loss on
307 auditory selective attention, in a second ANOVA (Age group \times Attentional focus) we
308 included participants' average hearing loss as a covariate. For further analyses, the
309 difference between laterality indexes for the FL and FR condition was calculated to
310 provide an overall measure of participant's auditory selective attention ability.

311

312 *General attention*

313 To obtain a single measure for general attention performance, i.e., independent of
314 the specific task used, we made use of the comprehensive cognitive battery available for
315 this data set. In particular, we integrated performance across multiple visual and

316 auditory attention tasks (i.e., dichotic listening task; D2 test of attention; digit-symbol-
317 substitution task; auditory digit sorting task) by means of a structural equation
318 modeling approach (SEM; see Figure 2, lower part) using the Ω nyx 1.0-1013 software
319 package (von Oertzen et al., 2015) with full information maximum likelihood estimation
320 (FIML). SEM offers a multivariate approach in which observed (manifest) variables can
321 be used to examine hypotheses about unobserved (latent) variables. Latent variables
322 have the benefit of accounting for measurement error in observed scores and thereby
323 increasing statistical power (Curran et al., 2010; Kievit et al., 2018).

324 In particular, in each age group standardized performance in the dichotic
325 listening task, D2 test of attention, digit-symbol-substitution and digit sorting tasks
326 served as manifest variables and loaded on a single latent selective attention factor (i.e.,
327 a multiple-group model). Factor loadings (other than the first, which was fixed to one)
328 were estimated freely but were constrained to be equal across groups. The model
329 demonstrated metric factorial invariance (i.e., it required variant manifest intercepts and
330 variances across groups) and thus precluded an interpretation of age group differences
331 in the means of the latent factor (Meredith and Teresi, 2006; Schwab and Helm, 2015).
332 We assessed the adequacy of the proposed selective attention model by testing for
333 differences between the model-implied and empirically observed covariance matrices
334 (Eid et al., 2015). The χ^2 -test formally tests for equity of the covariance matrices.
335 However, since it is particularly sensitive to sample size it should be interpreted with
336 caution in large samples (Brown, 2006; Eid et al., 2015). We thus additionally examined
337 two frequently reported fit indices: First, the root mean square error of approximation
338 (RMSEA) that is a closeness of fit coefficient expressing how much the postulated model
339 approaches the true model. Second, the comparative fit index (CFI), an incremental fit
340 index which compares the goodness of fit of the proposed model with a more restrictive

341 nested baseline model (Brown, 2006; Curran et al., 2010; Eid et al., 2015). In contrast to
342 the χ^2 -test, the RMSEA and CFI are not influenced by sample size. RMSEA values close to
343 or below 0.06 and CFI values of close to 0.95 or greater indicate good model fit (Brown,
344 2006). After establishing model fit, differences in parameters of interest were tested by
345 fixing parameters to zero and comparing model fit to a model in which parameters were
346 freely estimated using a likelihood ratio difference test (Curran et al., 2010; Eid et al.,
347 2015).

348

349 **Physiological data recording and preprocessing**

350 *Pupil dilation*

351 We recorded participant's pupil dilation as a proxy for central LC-NE activity
352 (Reimer et al., 2014; Costa and Rudebeck, 2016; Joshi et al., 2016; Breton-Provencher
353 and Sur, 2019; Deitcher et al., 2019; Zerbi et al., 2019) along with gaze position using an
354 infrared video-based eye tracker (EyeLink 1000 desktop mount; monocular setup; SR
355 Research Ltd.; Ottawa, Canada) with a spatial resolution of up to 0.25° and a sampling
356 rate of 1000 Hz. A forehead- and chin rest 53.5 cm from the computer screen was used to
357 minimize participants' head movements during measurements. Participants were
358 instructed to maintain central fixation throughout all experiments and compliance with
359 this instruction was enforced at the beginning of every trial. Each experiment started
360 with a (re)calibration of the eye tracking system using a standard 5-point grid. During
361 (re)calibration, fixation errors were kept < 0.5°.

362 For synchronous, integrated analysis of eye tracking and EEG data we used the
363 Eye-EEG toolbox ([Eye-EEG](#); Dimigen, Sommer, Hohlfeld, Jacobs, & Kliegl, 2011), an
364 extension for the open-source Matlab toolbox EEGLab ([EEGLAB](#), RRID:SCR_007292;
365 Delorme & Makeig, 2004) as well as the FieldTrip toolbox ([FieldTrip](#), RRID:SCR_004849;

366 Oostenveld, Fries, Maris, & Schoffelen, 2011). Eye tracking data of the re/conditioning
367 and dichotic listening sessions was resampled to 500 Hz and segmented in bins of 8.5 s
368 (i.e., -1.5–7 s with respect to CS onset). Time segments contaminated by blinks or
369 excessive eye movements were automatically detected and imputed using custom-
370 written Matlab code. In particular, segments falling more than three standard deviations
371 below a participant's median pupil dilation (calculated across the whole experiment)
372 were considered as blink or partly occluded pupil. Further, periods with excessive eye
373 movements as indicated by z-scored vertical gaze channel values > 3 (computed across
374 the whole experiment) were considered as artifacts. All artifacts were padded by ± 50
375 samples to account for biased pupil estimates shortly before/after artifacts (cf. de Gee,
376 Knapen, & Donner, 2014).

377 Excluding detected artifacts, we computed the average event-related pupil
378 response for each trial category (i.e., CS+; CS-; separately for fear re/conditioning and
379 dichotic listening data; see Figure 1c). In all trials, artifact containing segments were
380 then replaced by the corresponding time segments of the demeaned average response
381 centered at the given trial. Due to technical issues, no pupil data was available for one
382 younger adult for fear conditioning on Day 2 and one older adult for fear conditioning on
383 Day 3 and the dichotic listening task (Day 2).

384 Notably, we performed a set of control analyses that included a linear
385 interpolation of missing pupil samples instead of the mean imputation approach
386 described above. Importantly, irrespective of the preprocessing pipeline qualitatively
387 similar results are obtained on the group level (see
388 <https://doi.org/10.17605/OSF.IO/G9FQJ>).

389

390 *Electroencephalography*

391 To evaluate neural responses during re/conditioning and dichotic listening (cf.
392 Figure 1c), we recorded the EEG. Data was continuously sampled from 61 Ag/AgCl
393 electrodes embedded in an elastic cap that were placed according to the 10-10 system
394 using BrainVision Recorder (BrainAmp DC amplifiers, Brain Products GmbH, Gilching,
395 Germany; Braincap, BrainVision, respectively). An electrode above the forehead (AFz)
396 served as ground. Three additional electrodes were placed next to each eye and below
397 the left eye to acquire horizontal and vertical electrooculograms. Data was sampled at
398 1000 Hz in a bandwidth between 0.1–250 Hz and online-referenced to the right mastoid
399 while the left mastoid was recorded as additional channel. During EEG-preparation,
400 electrode impedances were kept <5 k Ω .

401 EEG data processing was performed by means of the Eye-EEG (Dimigen et al.,
402 2011), EEGLab (Delorme and Makeig, 2004) and FieldTrip (Oostenveld et al., 2011)
403 toolboxes in addition to custom-written Matlab code. For analyses, data was demeaned,
404 re-referenced to mathematically linked mastoids, down-sampled to 500 Hz and band-
405 pass filtered (0.2–125 Hz; fourth order Butterworth). A multi-step procedure was
406 applied to purge data of artifacts: First, data was visually screened for periods of
407 excessive muscle activity and subsequently independent component analysis (ICA) was
408 used to identify and remove components related to eye, muscle and cardiac activity (e.g.,
409 Jung et al., 2000). Next, data was segmented in 8.5 s epochs (– 1.5 s and + 7 s with
410 respect to stimulus onset) and submitted to a fully automatic thresholding approach for
411 artifact rejection (cf. Nolan, Whelan, & Reilly, 2010). Excluded channels were
412 interpolated with spherical splines (Perrin et al., 1989). Finally, remaining trials were
413 again visually screened to determine successful cleaning.

414 Time-varying power information for each trial and electrode was then extracted
415 by convolution of the cleaned time domain signal with a series of Morlet wavelets with a
416 length of seven cycles (cf. Herrmann, Grigutsch, & Busch, 2005; Werkle-Bergner, Shing,
417 Müller, Li, & Lindenberger, 2009). Time-varying power estimates were computed for
418 frequencies between 1–40 Hz (in steps of 1 Hz) in a time window between –1.5 s to 7 s
419 with respect to stimulus onset (time bins of 4 ms), separately for CS+ and CS– trials of
420 the reconditioning and dichotic listening phases (see Figure 1c).

421

422 **Physiological data analyses**

423 *Within modality within-subject statistics (first level)*

424 Within younger and older subjects, we contrasted arousing (CS+) and neutral
425 control trials (CS–) by means of independent-samples *t*-tests to isolate arousal-
426 associated response patterns. Contrasts were computed for time domain pupil data (i.e.,
427 Event-Related Pupil Response; ERPR), time domain EEG data (i.e., Event-Related
428 Potential; ERP) and time-frequency domain EEG data (i.e., Event-Related
429 Desynchronization; ERD). To counteract potential unequal distribution of CS+ and CS–
430 trials (e.g., more artifacts in arousing trials), we iteratively selected random, equally
431 sized subsets of the available trials using a bootstrapping procedure ($n_{\text{bootstraps}} = 50$
432 iterations; $n_{\text{SelectedTrials}} = \text{lowest trial number across conditions} - 1$). The mean *t*-value
433 over the 50 bootstraps served as final first level test statistic that was passed on to the
434 second level (see below). First level statistics were computed within subjects for
435 conditioning (separately for each day (Day 1–3); see Figure 1c), reconditioning and
436 dichotic listening trials. While the contrast (CS+ vs. CS–) remained the same across these
437 analyses, please note that during re/conditioning participants received electrical
438 stimulation (US) and thus the observed responses may represent a mixture of fear and

439 somatosensory responses. In contrast, during the dichotic listening task no shocks were
440 applied and thus observed responses (CS+ vs CSin-) indicate the reinstatement of the
441 fear response (cf. Figure 1c).

442 Notably, the CS+ vs. CS- first level *t*-maps express the difference in pupil and EEG
443 responses to arousing and non-arousing stimuli. That is, in the strict sense of the word
444 they do not constitute an ERPR / ERP /ERD, but rather the standardized difference
445 between two pupil / EEG responses. However, to ease readability, we use the terms
446 ERPR, ERP and ERD also for these contrasts.

447

448 *Within-modality group statistics (second level)*

449 For analyses on the group level, we contrasted first level *t*-maps (i.e., CS+ vs CS-)
450 against zero to identify neural correlates associated with the arousal manipulation in
451 conditioning and reconditioning trials (cf. Figure 1c) that were shared across subjects in
452 each group. Analyses were run separately for each day, first across all subjects (YA and
453 OA) and then within YA and OA for all modalities (ERPR, ERP and ERD data). In
454 particular, we calculated non-parametric, cluster-based, random permutation tests as
455 implemented in the FieldTrip toolbox that effectively control the false alarm rate in case
456 of multiple testing (Maris and Oostenveld, 2007; Oostenveld et al., 2011). Please note
457 that the same statistical procedure was applied to two-dimensional (i.e., channel × time)
458 and three-dimensional (i.e., channel × frequency × time) data. That is, ERPR, ERP and
459 ERD were analyzed in the same manner. Here, however, only the approach for three-
460 dimensional data (ERD) is described to ease readability. In short, first a two-sided,
461 dependent samples *t*-test was calculated for each spatio-spectral-temporal (channel ×
462 frequency × time) sample. Neighboring samples with a *p*-value below 0.05 were grouped
463 with spatially, spectrally and temporally adjacent samples to form a cluster. The sum of

464 all t -values within a cluster formed the respective test-statistic (t_{sum}). A reference
465 distribution for the summed cluster-level t -values was computed via the Monte Carlo
466 method. Specifically, in each of 1000 repetitions, group membership was randomly
467 assigned, a t -test computed and the t -value summed for each cluster. Observed clusters
468 whose test-statistic exceeded the 97.5th percentile for its respective reference probability
469 distribution were considered significant.

470 On a group level, cluster statistics revealed reliable arousal effects during
471 conditioning and reconditioning within all modalities (ERPR, ERP, and ERD). To evaluate
472 a potential reinstatement of these fear responses also during the dichotic listening task
473 (in which no shocks were applied anymore; cf. Figure 1c), each subjects' first level (CS+
474 vs. CS-) dichotic listening data was averaged across spatio-spectral-temporal samples
475 that reached significance on a group level during the reconditioning period. That is, we
476 applied the observed reconditioning fear response (i.e., significant cluster) as a search
477 space to evaluate its reinstatement within the dichotic listening data. This approach
478 yielded a single reinstatement value for each subject for each modality (i.e., ERPR, ERP
479 and ERD data). Within modalities, the reliability of the reinstatement was then
480 determined by means of non-parametric Wilcoxon signed rank (W) tests (across and
481 within age groups).

482 To judge the temporal stability of fear conditioned pupil responses (ERPR) over
483 assessment days (Day 1–3; cf. Figure 1c), in addition each subjects' first level (CS+ vs.
484 CS-) conditioning and reconditioning ERPR data was averaged across time points that
485 reached significance on a group level (i.e., second level statistic for the respective day).
486 This yielded a single ERPR value for each subject for each conditioning session (Day 1–3)
487 and the reconditioning phase (Day 2). We then used intra-class-correlations (ICC; two-

488 way mixed; consistency) to evaluate the temporal stability of participants' fear
489 conditioned pupil dilation.

490

491 *Cross-modality group statistics*

492 To determine whether EEG correlates of the arousal manipulation (i.e., ERP, ERD)
493 were linked to the LC-NE system, we correlated participants' EEG responses with their
494 pupil dilation, a proxy of noradrenergic activity, across age groups. We assessed this
495 association within the dichotic listening data, since this provides an estimate of the
496 reinstatement of the fear response irrespective of potential somatosensory artifacts
497 related to the reinforcement (US; see Figure 1). In particular, participants' first level EEG
498 *t*-maps (CS+ vs. CS-) were correlated with participants' average pupil reinstatement (see
499 within modality group statistics) in a non-parametric, cluster-based, random
500 permutation framework as implemented in the FieldTrip toolbox. Analyses were run
501 separately for ERP and ERD data, however, here only the approach for time-frequency
502 data (ERD) is described to ease readability. For each spatio-spectral-temporal sample a
503 two-sided Pearson's correlation between the EEG and the pupil reinstatement data was
504 calculated. As done for the within-modality statistics, neighboring samples with a *p*-
505 value below 0.05 were grouped with spatially, spectrally and temporally adjacent
506 samples to form a cluster. The sum of all *rho*-values within a cluster formed the
507 respective test-statistic. A reference distribution for the summed cluster-level *rho*-values
508 was computed via the Monte Carlo method. In particular, the null hypothesis of
509 statistical independence between EEG and pupil data was tested by randomly permuting
510 pupil estimates between subjects over 1000 repetitions. For each repetition, a
511 correlation was computed and *rho*-values were summed for each cluster. Observed
512 clusters whose test-statistic exceeded the 97.5th percentile for its respective reference

513 probability distribution were considered significant. To specifically target reinstatement
514 responses, we restricted the cross-modality analyses to EEG samples that showed a
515 reliable arousal effect (i.e., were part of significant clusters in the second level
516 reconditioning analyses). Note however, that analyses were performed solely on
517 reinstatement data (i.e., dichotic listening ERPR, ERP and ERD data; cf. Figure 1).

518

519 *Cross-modality structural equation model*

520 Cluster-correlation analyses revealed reliable associations between EEG and
521 pupil reinstatement for both ERP and ERD data, suggesting a common underlying pupil-
522 EEG factor. For each subject, we thus extracted and averaged those samples of the EEG
523 reinstatement response that showed a reliable link to pupil reinstatement. This returned
524 a single pupil-associated reinstatement estimate for ERP and ERD data, respectively. As
525 for the behavioral data, we then used a structural equation modeling approach to
526 integrate over the interrelated indicators of the arousal response (see Figure 2, upper
527 part). In particular, in younger and older adults, standardized pupil reinstatement and
528 pupil-associated EEG reinstatement estimates served as manifest variables and loaded
529 on a single, latent NE responsiveness factor (i.e., a multiple-group model). Factor
530 loadings (other than the first, which was fixed to one) were estimated freely but were
531 constrained to be equal across groups. The model demonstrated strict factorial
532 invariance (i.e., showed invariant manifest intercepts and variances across groups) and
533 thus allowed an interpretation of age group differences in the means of the latent factor
534 (Meredith and Teresi, 2006; Schwab and Helm, 2015). We evaluated age differences in
535 latent NE responsiveness by means of Spearman correlations (across age groups).
536 Adequacy of the proposed model was assessed using a χ^2 -test as well as two additional
537 fit indices (RMSEA, CFI; see above).

538

539 **Analyses of associations between physiological and behavioral data**

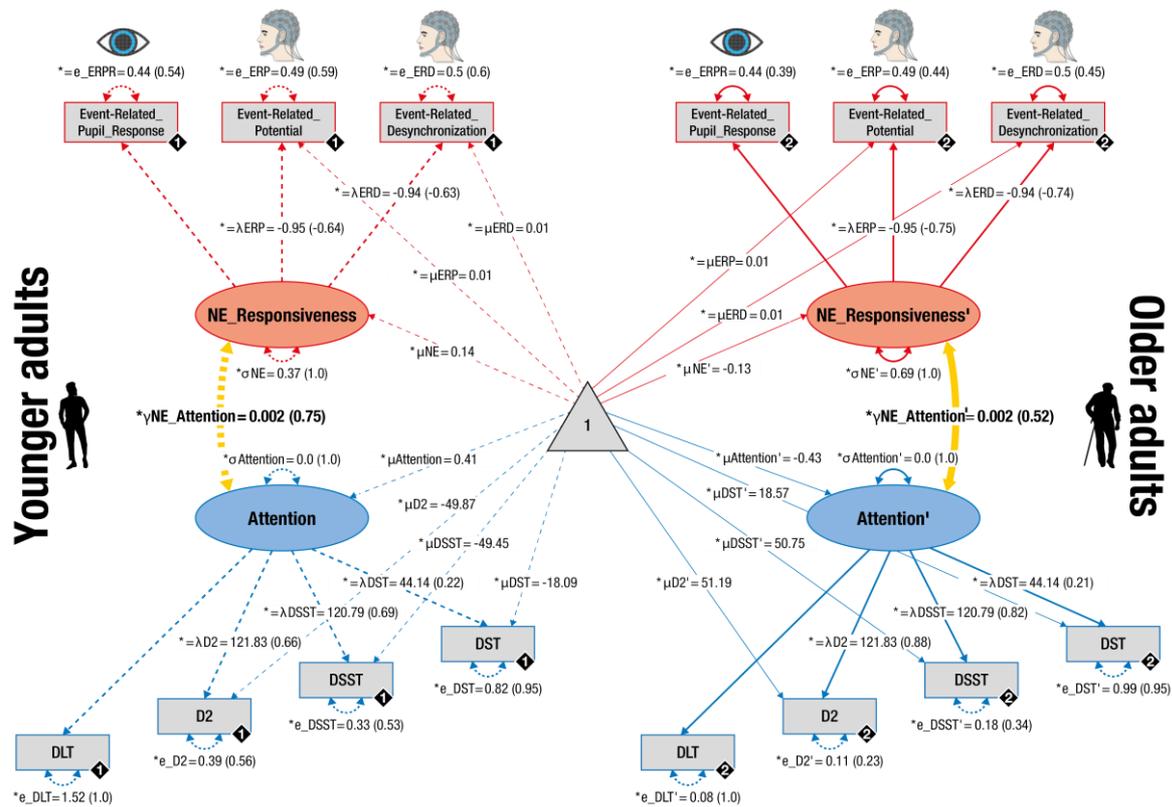
540 After generating structural equation models for our cognitive and physiological
541 measures, respectively, we set out to link both modalities. That is, we were interested in
542 assessing the relation between interindividual differences in attention and
543 interindividual differences in NE responsiveness. For this, we first built a unified model
544 merging the attention and responsiveness models described above (see Figure 2). We
545 then investigated associations between cognitive and physiological factors by allowing
546 for freely estimated covariances on a latent level (shown in yellow, Figure 2). As before,
547 model fit for all described models was determined using a χ^2 -test in combination with
548 two additional fit indices (RMSEA, CFI).

549

550 **Code and data availability**

551 The custom code and (anonymized) data used for these analyses is available from
552 the corresponding authors upon request.

553



554

555 *Figure 2.* Pictorial rendition of the structural equation model that probes associations (yellow
 556 lines) between noradrenergic responsiveness (NE_Responsiveness; red) and attention
 557 performance (blue) in younger and older adults on a latent level. Rectangles and ellipses
 558 indicate manifest (observed) and latent variables, respectively. The constant is depicted by a
 559 triangle. Cognitive manifest variables represent attention performance assessed in a dichotic
 560 listening task (DLT; cf. Figure 1 and 3), D2 task of attention (D2; cf. Table 2), digit-symbol-
 561 substitution task (DSST) and digit sorting task (DST). Physiological manifest variables represent
 562 the reinstatement of fear conditioned Event-related Pupil Responses (ERPR; cf. Figure 4a, 5a),
 563 Event-related Potentials (ERP; cf. Figure 4a) and Event-related Desynchronization (ERD; cf.
 564 Figure 5a). Black diamonds on manifest variables indicate the age group (younger adults = 1,
 565 broken lines; older adults = 2, solid lines). (Co)Variances (γ , σ) and loadings (λ) in brackets
 566 indicate standardized estimates. Loadings that are freely estimated (*) but constrained to be
 567 equal across age groups (=) are indicated by both asterisk and equal signs (*=). Note that the
 568 cognitive sub-model demonstrated metric factorial invariance (invariant manifest means and
 569 errors across age groups) whereas the physiological sub-model showed strict factorial
 570 invariance (manifest means and errors are constrained across groups).

571 **Results**

572 **Impaired selective attention in older adults**

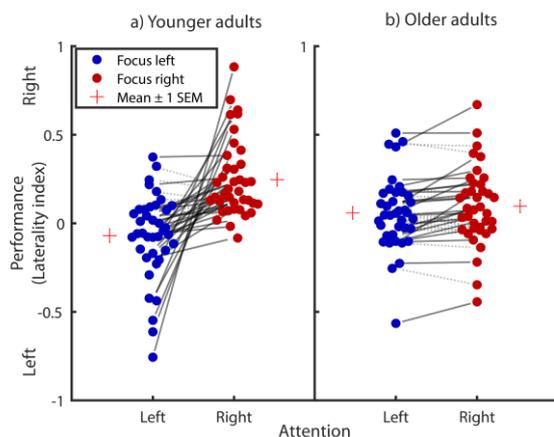
573 Participants demonstrated successful auditory selective attention in the dichotic
574 listening task as indicated by a two-factorial mixed measures ANOVA (Age group ×
575 Attentional Focus; main effect of attentional focus: $F(1, 75) = 26.413, p < 0.001, \eta^2 =$
576 0.260). Post-hoc analyses within younger and older adults demonstrated that both
577 groups were able to exert auditory selective attention (one-factorial repeated measures
578 ANOVA; main effect of attentional focus: For YA $F(1, 38) = 22.803, p < 0.001, \eta^2 = 0.375$;
579 For OA $F(1, 37) = 5.702, p = 0.022, \eta^2 = 0.134$).

580 Younger and older adults, however, differed reliably in their ability to modulate
581 their attentional focus. While the Age group main effect was not significant ($F(1, 75) =$
582 $0.087, p = 0.769, \eta^2 = 0.001$); we observed a reliable Age group × Attentional focus
583 interaction ($F(1, 75) = 16.318, p < 0.001, \eta^2 = 0.179$; see Figure 3) indicating impaired
584 selective attention in old age. Please note, that here a main effect of Age (e.g., lower LI in
585 older compared to younger adults) would indicate better performance in one
586 Attentional focus condition (e.g., FL) and worse performance in the other (e.g., FR; cf.
587 Figure 3). The observed Age group × Attentional focus interaction in contrast reveals
588 worse performance in older adults in both conditions (i.e., lower LI values in the FR
589 condition; higher LI values in the FL condition).

590 Post-hoc analyses indicated that age differences in auditory selective attention
591 were not explained by age related differences in hearing loss (i.e., Age group ×
592 Attentional Focus mixed measures ANOVA including hearing loss as covariate: Age group
593 × Attentional focus: $F(1, 74) = 4.862, p = 0.031, \eta^2 = 0.062$; Hearing loss × Attentional
594 focus: $F(1, 74) = 0.740, p = 0.393, \eta^2 = 0.010$). Similarly, control analyses indicated that

595 age differences in auditory selective attention persisted after including interaural
596 threshold differences in the model (see: <https://doi.org/10.17605/OSF.IO/G9FQJ>).

597 We replicated this finding of impaired selective attention in aging across multiple
598 visual and auditory attention tasks using non-parametric Mann-Whitney U-tests (all p s <
599 0.05; see Table 2). In order to later reliably relate attention performance to physiological
600 indices of the LC-NE system (see below), we integrated performance over tasks to derive
601 a single measure reflecting general attention performance (see Figure 2, lower part). The
602 proposed model fit the data well ($\chi^2 = 9.827$, $df = 23$; RMSEA = 0.0; CFI = 1.594; Brown,
603 2006). The variances of the attention factors differed reliably from zero in both age
604 group (all $\Delta\chi^2 \geq 11.225$, $\Delta df = 1$, all $p < 0.001$) indicating interindividual differences in
605 attention.



606

607 *Figure 3.* Selective auditory attention performance of younger (a) and older adults (b) in a
608 dichotic listening task. Negative and positive laterality index values indicate a tendency
609 for left and right ear responses, respectively. Circles connected by solid lines show
610 participants who demonstrate a behavioral selective attention effect (i.e., more
611 responses of the cued ear relative to the not cued ear), with the slope of the lines
612 reflecting the degrees of attentional modulation. Circles connected by grey dotted lines
613 indicate a reversed effect. While the amount of selective attention is markedly decreased
614 in older adults, both younger and older participants demonstrate reliable selective
615 attention on a group level. SD = Standard Deviation; Laterality index = (Focus Right -
616 Focus Left) / (Focus Right + Focus Left).

617

618 Table 2

619 Overview of age differences in attention

Task	N (YA/OA)	PerformanceYA (z±SEM)	Performance OA (z±SEM)	Z	p
DLT	77 (39/38)	0.415 (0.200)	-0.425 (0.048)	3.790	<0.001
D2	77 (39/38)	0.634 (0.133)	-0.651 (0.113)	6.109	<0.001
DSST	77 (39/38)	0.629 (0.129)	-0.645 (0.120)	5.689	<0.001
DST	77 (39/38)	0.206 (0.153)	-0.212 (0.164)	2.066	0.039

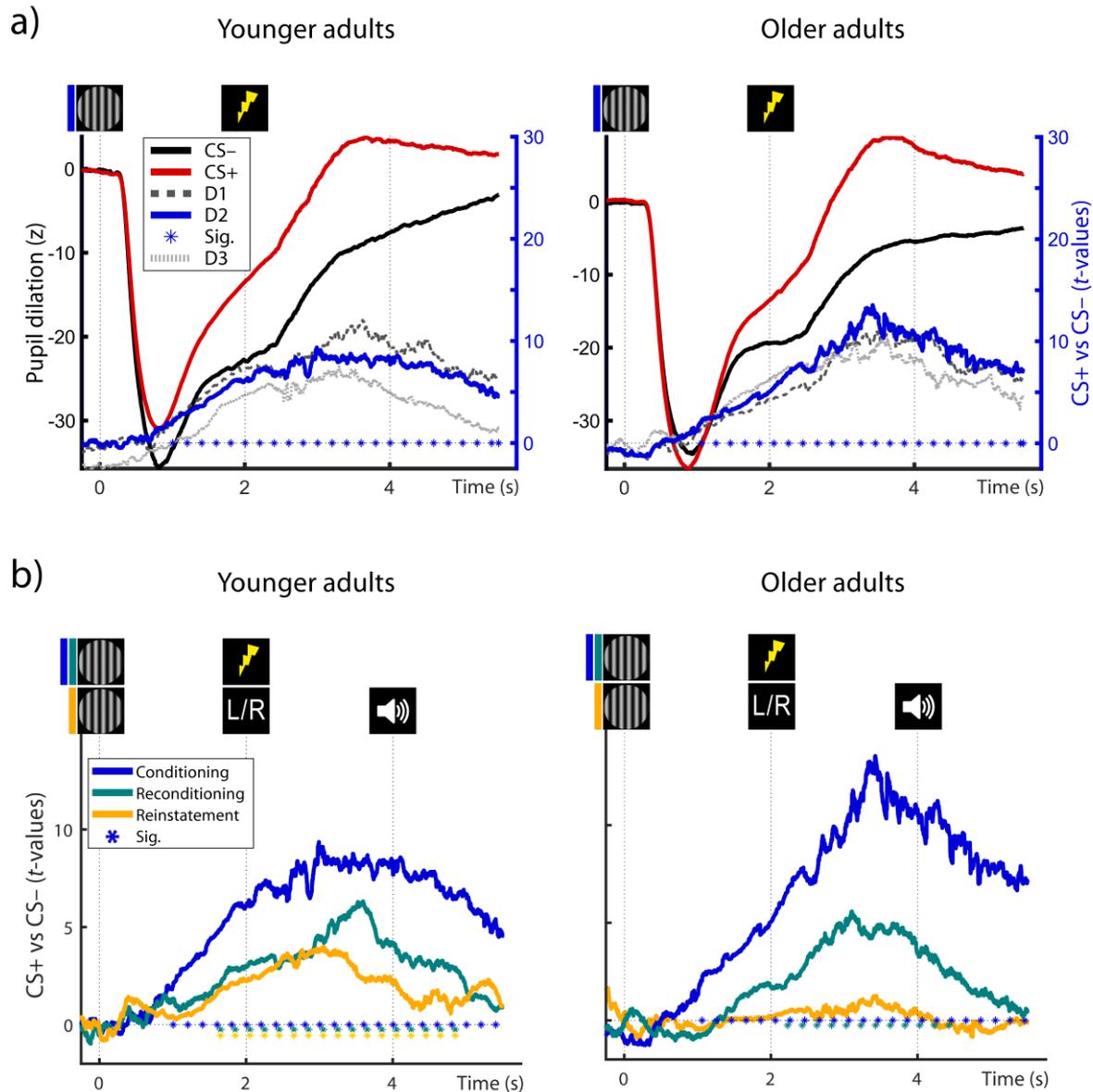
620 Note: For each age group for all cognitive tasks mean performance is provided as z-value ± the standard
621 error of the mean. DLT: Dichotic listening task; D2: D2 test of attention; DSST: Digit-Symbol-Substitution
622 Task; DST: Digit-Sorting Task; YA: Younger adults; OA: Older adults; All comparisons are evaluated using
623 non-parametric Mann-Whitney U-tests (YA vs. OA).

624 **Stable fear conditioned pupil dilation in younger and older adults**

625 In the conditioning and reconditioning phases of the assessment (see Figure 1c),
626 younger and older adults demonstrated a reliable, multimodal response to the arousal
627 manipulation. In the following, first modality-specific results are reported (i.e., pupil
628 dilation and EEG) before detailing their interrelation.

629 During fear conditioning and reconditioning, conditioned stimuli (CS+ vs. CS-)
630 reliably elicited pupil dilation over prolonged time windows as revealed by cluster
631 permutation analyses (both across and within age groups all $p_{s_{corr}} < 0.01$; see Figure 4
632 and also <https://doi.org/10.17605/OSF.IO/G9FQJ>).

633 Fear conditioned pupil responses demonstrated a moderate to high stability
634 across assessments (Day 1–3) as indicated by intra-class-correlations (two-way mixed;
635 consistency; ICC (95%CI) = 0.652 (0.502–0.766); $p < 0.001$). In line with pupil dilation as
636 a non-invasive marker of LC activity, this points to a stable phasic activation of the NE
637 system by fear conditioned stimuli (and US) across age groups.



638

639 *Figure 4.* Average pupil dilation of younger and older adults in response to the presentation of
 640 fear conditioned (CS+; red) and neutral control stimuli (CS-; black) during fear conditioning (a;
 641 Day 2) and during the dichotic listening task (b; i.e., reconditioning and reinstatement). Group
 642 statistics depict the consistency of the CS+ vs CS- contrast on the second level. **a.** Statistics are
 643 presented for conditioning data for the first (D1; light grey, dashed), second (D2; solid, blue) and
 644 third (D3; dark grey, dotted) day of conditioning assessments (see right y-axis). **b.** Pupil
 645 responses during conditioning (blue), reconditioning (teal) and dichotic listening trials
 646 (reinstatement; orange) on day 2. Horizontal lines of asterisks indicate significant time windows
 647 (blue *, Sig.). Reinstatement of the fear conditioned pupil response during the dichotic listening
 648 task (see Figure 1c) is evaluated statistically using Wilcoxon tests (YA: $W(39) = 586$; $Z = 2.735$; p
 649 $= 0.006$; OA: $W(37) = 364$; $Z = 0.189$; $p = 0.850$).

650

651 **Reinstatement of pupil dilation in younger adults**

652 In the absence of reinforcements (US), fear conditioned stimuli maintained their
653 arousing nature and led to a marginally significant reinstatement of pupil dilation across
654 groups ($W(76) = 1839$; $Z = 1.948$; $p = 0.052$). While younger adults demonstrated a
655 robust reinstatement effect, in older adults reinstatement did not reach statistical
656 significance on a group level (see Figure 4; YA: $W(39) = 586$; $Z = 2.735$; $p = 0.006$; OA:
657 $W(37) = 364$; $Z = 0.189$; $p = 0.850$). The lack of pupil reinstatement in older adults
658 presumably reflects age-related difficulties in triggering and maintaining self-initiated
659 processing (i.e., reinstatement; Lindenberger and Mayr, 2014) in line with previous
660 reports (van Gerven et al., 2004). By contrast, age differences are known to be reduced
661 or even disappear when older adults can rely on external information (e.g., reminders),
662 like the reinforcements (US) during re/conditioning. The age difference in the
663 reinstatement of pupil dilation approached statistical significance (YA vs. OA: $U(76) =$
664 1671 ; $Z = 1.756$; $p = 0.079$). Since the reinstatement of pupil dilation occurs in the
665 absence of somatosensory stimulation and associated artifacts, it is attributed to the
666 arousal response following the reactivation of the fear memory. We thus interpret the
667 reinstatement of the fear-induced pupil response as indicator of the effectiveness of the
668 LC-NE system in modulating memory, which trends to be reduced in aging.

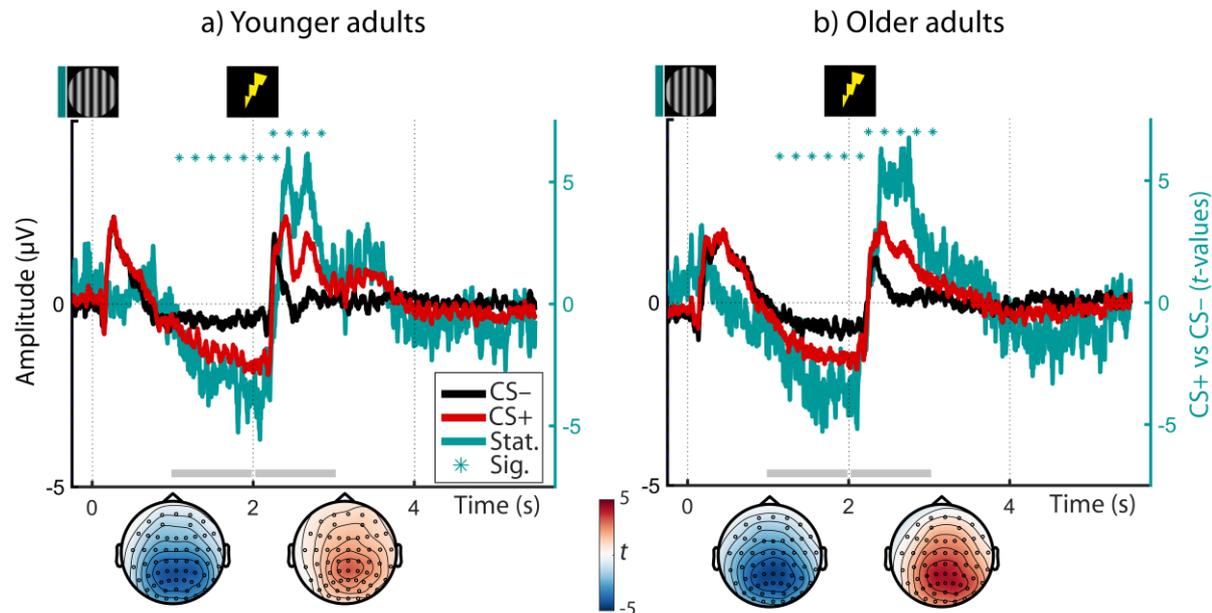
669

670 **Fear conditioned parietal event-related potentials in younger and older adults**

671 During fear reconditioning, conditioned stimuli also reliably elicited event-related
672 EEG responses (ERP) both across and within age groups as revealed by cluster
673 permutation analyses (all $p_{\text{corr}} < 0.01$; see Figure 5 and
674 <https://doi.org/10.17605/OSF.IO/G9FQJ>). In particular, we observed that after an
675 initially similar ERP (< 1 s) to CS+ and CS-, conditioned stimuli (CS+) were associated

676 with an increasingly more negative going slow wave in the delay interval (between CS+
677 (t = 0 s) and US onset (t=2 s)). This was reflected in a sustained negative cluster with
678 strongest polarity at centro-parietal electrodes (i.e., parietal slow wave; see Figure 5).
679 Following the onset of the reinforcement (US), in CS+ trials the ERP rapidly flipped its
680 polarity while maintaining a highly similar parietal topography, thus giving rise to a
681 sustained positive cluster (i.e., late parietal potential; see Figure 5). In line with the
682 established role of anticipatory slow waves and late parietal potentials in arousal and
683 emotion processing (for reviews see Schupp, Flaisch, Stockburger, & Junghöfer, 2006 and
684 van Boxtel & Böcker, 2004; Vazey et al., 2018), this points to increased sustained
685 attention to CS+ during the anticipatory delay interval (0–2 s) and an augmented arousal
686 response following US (> t = 2 s). Both the topography and time course of the ERP
687 responses were highly similar across age groups, indicating a maintained arousal
688 response to conditioned stimuli (CS+; and US) across the lifespan.

689 Notably, as the earlier anticipatory potential emerges before onset of the
690 reinforcement, we can rule out that it constitutes an artifact of the somatosensory
691 stimulation. The latter potential in contrast may be influenced by the reinforcement and
692 should only be considered further if it is reliably reinstated in absence of the stimulation
693 (see below).



694

695 *Figure 5. Averaged Event-Related Potentials (ERP) of younger (a) and older adults (b) in*
696 *response to the presentation of fear conditioned (CS+; red) and neutral control stimuli (CS-;*
697 *black) during reconditioning (left y-axis; on Day 2). Group statistics depict the consistency of the*
698 *CS+ vs CS- contrast on the second level (teal) and are shown on the right y-axis. Horizontal lines*
699 *of asterisks indicate significant time windows (*, Sig.). The topography of the group statistics*
700 *between 1–2 and 2–3 s relative to CS onset is shown below the time courses (gray horizontal*
701 *bars).* For visualization, time courses are averaged across all electrodes.

702

703 **Reinstatement of parietal event-related potentials in younger and older adults**

704 ERP to the arousal manipulation were reinstated in the dichotic listening task in

705 the absence of reinforcements (US). Across younger and older adults, both the earlier,

706 anticipatory negative potential as well as the later, positive potential reached

707 significance (Negative: $W(77) = 861$; $Z = -3.252$; $p = 0.001$; Positive: $W(77) = 2028$; $Z =$

708 2.673 ; $p = 0.008$). While in younger adults, only the anticipatory response was reliably

709 reinstated (Negative: $W(39) = 214$; $Z = -2.456$; $p = 0.014$; Positive: $W(39) = 456$; $Z =$

710 0.921 ; $p = 0.357$; see Figure 6), in older adults both reached statistical significance

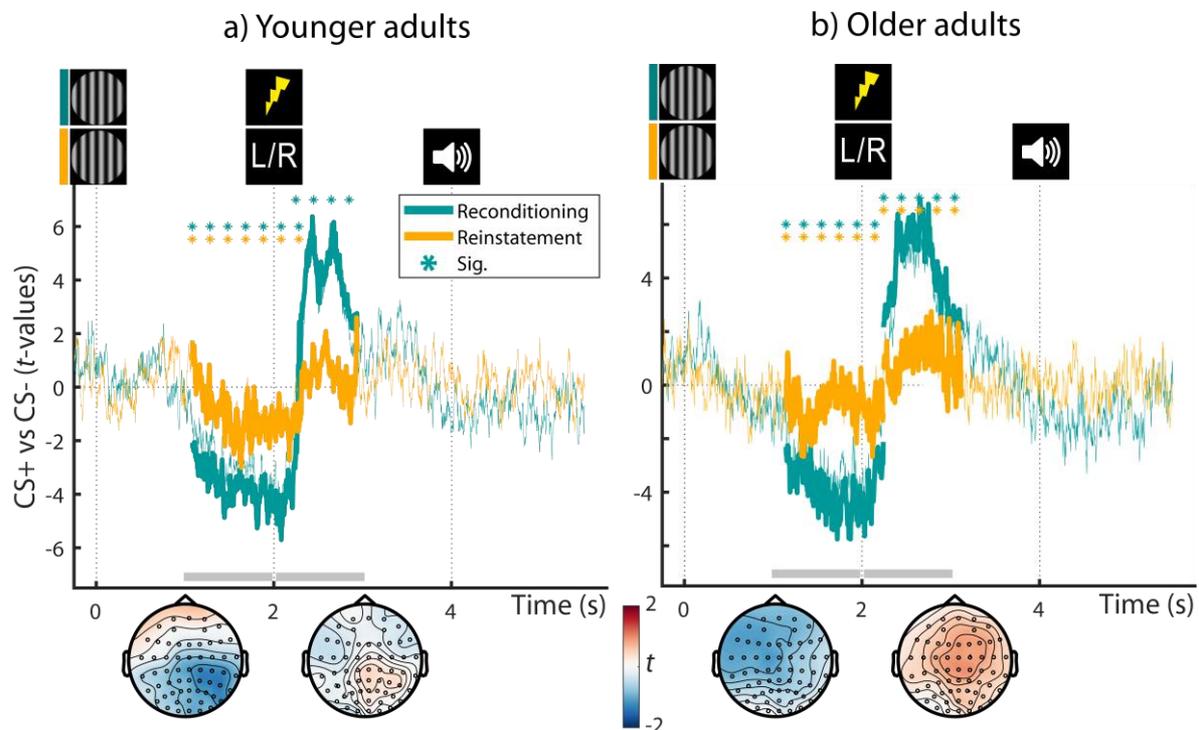
711 (Negative: $W(38) = 214$; $Z = -2.270$; $p = 0.023$; Positive: $W(38) = 582$; $Z = 3.067$; $p =$

712 0.002 ; see Figure 6). The age difference in the latter, positive response was marginally

713 significant (YA vs. OA: $U(77) = 1335$; $Z = -1.890$; $p = 0.059$). In the absence of

714 somatosensory stimulation and associated artifacts, the reinstatement of the parietal

715 reconditioning ERPs is attributed to the arousal response following the reactivation of
716 the fear memory (van Boxtel and Böcker, 2004; Schupp et al., 2006).



717

718 *Figure 6.* Group statistics for younger (a; YA) and older adults' (b; OA) Event-Related Potentials
719 (ERP) during reconditioning (teal; cf. Figure 5), and dichotic listening trials (orange;
720 reinstatement) on day 2. All statistics depict the consistency of the CS+ vs CS- contrast on the
721 second level. Teal horizontal lines of asterisks (*; Sig.) indicate the extent of the significant
722 reconditioning clusters. Reinstatement of the earlier, negative and later, positive ERP clusters
723 during the dichotic listening task is evaluated statistically using Wilcoxon tests (see orange lines
724 of asterisks; YA: Negative: $W(39) = 214$; $Z = -2.456$; $p = 0.014$; Positive: $W(39) = 456$; $Z = 0.921$; $p =$
725 0.357 ; OA: Negative: $W(38) = 214$; $Z = -2.270$; $p = 0.023$; Positive: $W(38) = 582$; $Z = 3.067$; $p =$
726 0.002). The topography of the reinstatement group statistics between 1–2 and 2–3 s relative to
727 CS onset is shown below the time courses (gray horizontal bars). CS+ = fear conditioned
728 stimulus; CS- = perceptually matched, neutral control stimulus. For visualization, time courses
729 are averaged across all electrodes.

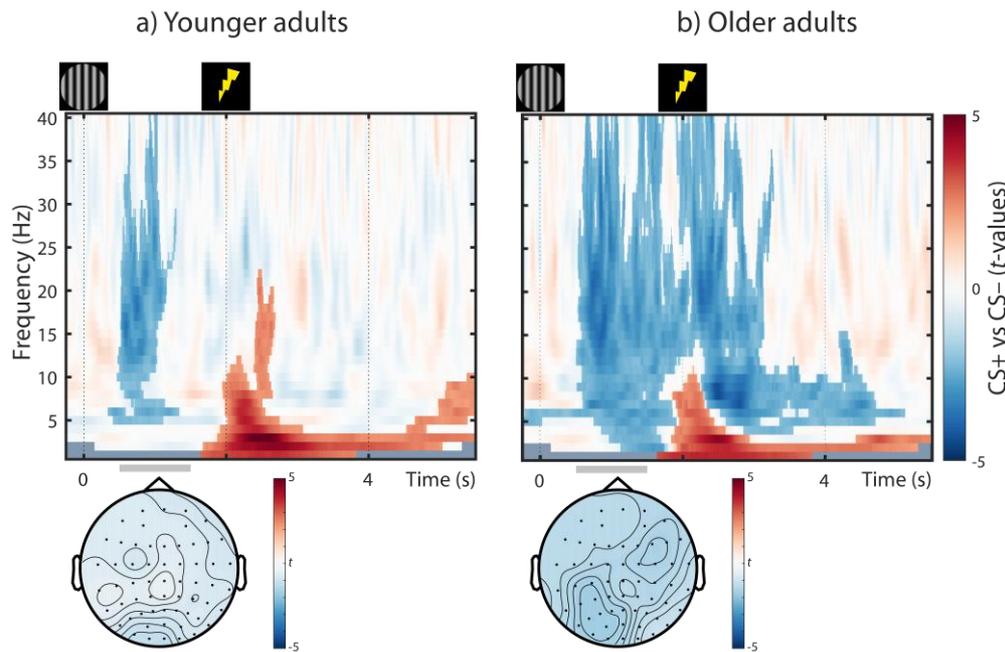
730

731 **Fear conditioned posterior desynchronization in younger and older adults**

732 Across age groups, fear conditioned stimuli were also associated with a sustained
733 ($t = -0.248$ – 4.956 s) decrease in low EEG frequencies (4–40 Hz). The observed cluster
734 was most pronounced in the theta to beta frequency bands (~ 5 – 25 Hz) and showed its
735 strongest polarity at parieto-occipital electrodes (cf. van Boxtel & Böcker, 2004; YA and
736 OA: $p_{\text{corr}} = 0.002$). Analyses within younger and older adults revealed reliable

737 desynchronization effects in both age groups with strongest extent at posterior
738 electrodes (YA: $p_{\text{corr}} = 0.024$; OA: $p_{\text{corr}} = 0.002$; see Figure 7). However, in younger adults
739 desynchronization was restricted to the anticipatory delay phase (i.e., before US onset; t
740 = 0.352–1.360 s; 5–40 Hz) whereas in older adults a more persistent desynchronization
741 was observed ($t = -0.248$ –5.144 s; 2–40 Hz). In addition, coinciding with onset of the
742 reinforcement (US), a positive low frequency cluster emerged across and within age
743 groups (see Figure 7). However, this positive cluster most likely reflects an artifact of the
744 electric stimulation (2 Hz pulse at $T = 2$ s) and consequently was not evident in absence
745 of the US (see Figure 8, below).

746 Desynchronization in low frequencies has been associated with NE-associated
747 changes in cortical and behavioral state (McCormick et al., 1991; Harris and Thiele,
748 2011; Marzo et al., 2014; Safaai et al., 2015; Neves et al., 2018). In particular, in humans
749 desynchronization in the alpha–beta band was linked to facilitated information
750 processing resulting from a decrease in cortical inhibition (for reviews, see Hanslmayr,
751 Staudigl, & Fellner, 2012; Jensen & Mazaheri, 2010; Klimesch, Sauseng, & Hanslmayr,
752 2007). Accordingly, the pronounced low frequency desynchronization in response to
753 conditioned stimuli (CS+; and US) suggests an anticipatory transition towards a more
754 activated cortical state, including increased cortical excitability and attention
755 deployment. For spectral responses to the arousal manipulation split by frequency band,
756 please see : <https://doi.org/10.17605/OSF.IO/G9FQI>



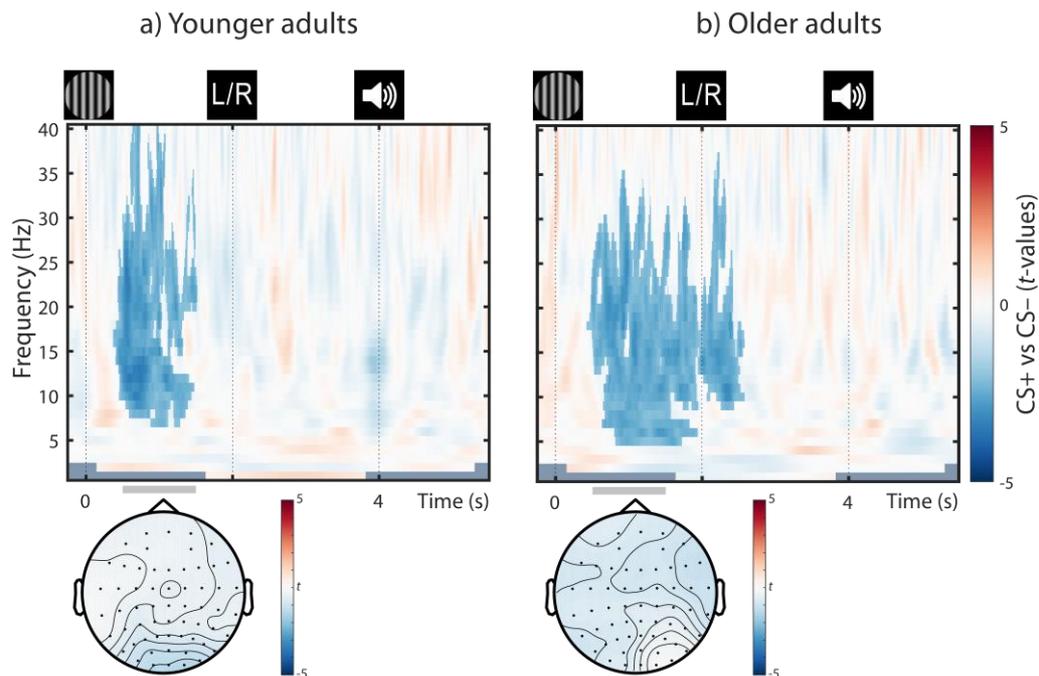
757

758 *Figure 7.* Group statistics for younger (a) and older adults' (b) time-frequency EEG responses
759 during reconditioning trials on day 2 (i.e., Event-Related Desynchronization). Statistics depict
760 the consistency of the CS+ vs. CS- contrast on the second level. Non-significant samples are
761 displayed with 50% transparency, while significant clusters are overlaid without transparency.
762 The topography between 0.5–1.5 s relative to CS onset is shown below the time courses (gray
763 horizontal bars). For topographies, data is averaged across all frequencies.

764

765 **Reinstatement of posterior desynchronization in younger and older adults**

766 Presentation of fear conditioned stimuli (CS+) during the dichotic listening task
767 (i.e., without reinforcements; US) reinstated a pronounced decrease in low frequencies
768 across age groups (YA and OA: $W(77) = 900$; $Z = -3.054$; $p = 0.002$). Similarly, within
769 younger adults we observed a reliable reinstatement with a mostly posterior topography
770 (YA: $W(39) = 161$; $Z = -3.196$; $p = 0.001$), whereas older adults showed a marginally
771 significant reinstatement with a more wide-spread extent (OA: $W(38) = 239$; $Z = -1.907$;
772 $p = 0.057$; see Figure 8). As for the pupillary and parietal ERP reinstatement, the
773 reinstatement of the low frequency desynchronization is considered as arousal response
774 to the reactivated fear memory.



775

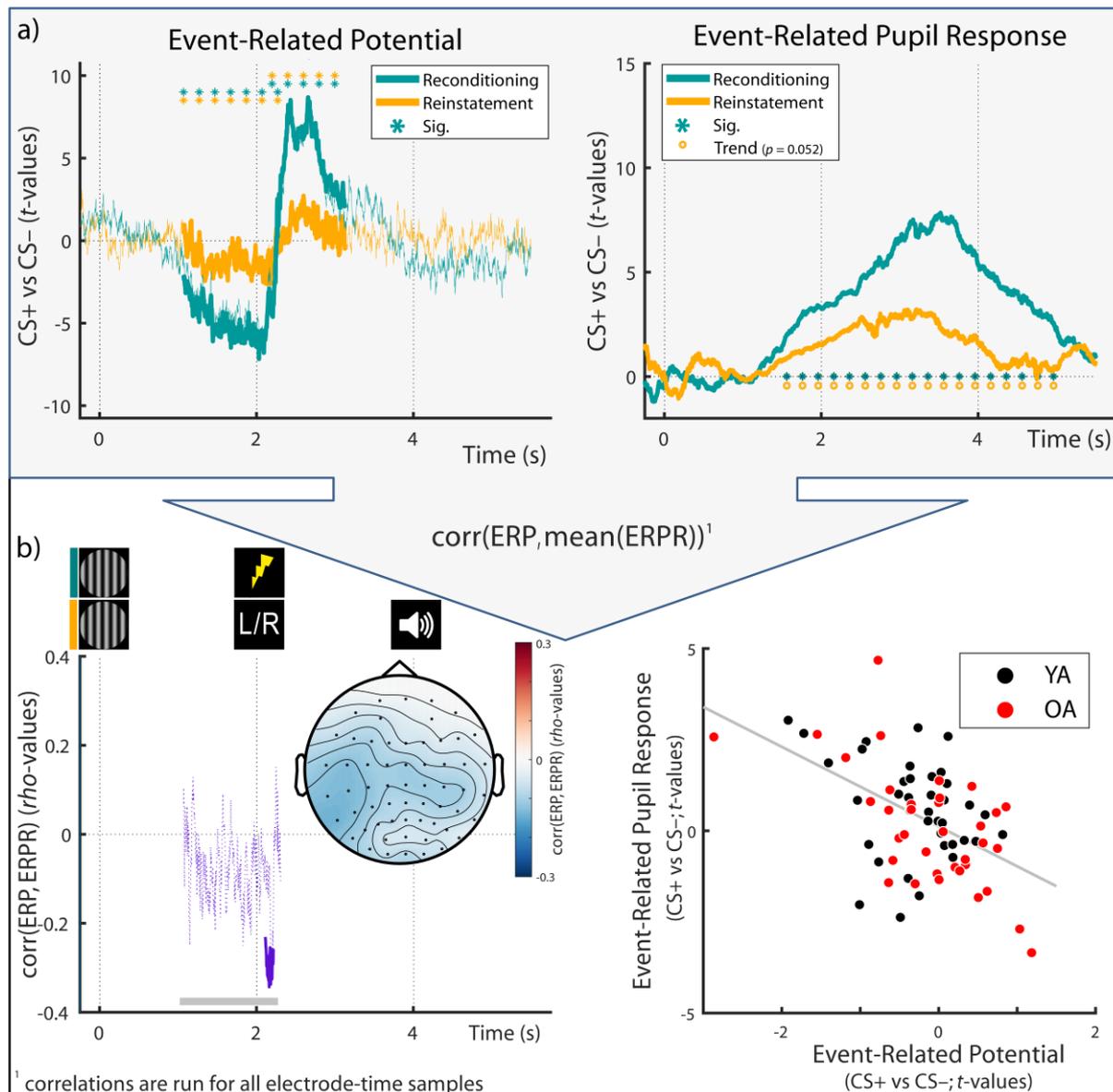
776 *Figure 8.* Group statistics for younger (a) and older adults' (b) time-frequency EEG responses
777 during dichotic listening trials on day 2 (i.e., reinstatement of the Event-Related
778 Desynchronization). Statistics depict the consistency of the CS+ vs CS- contrast on the second
779 level. For visualization purposes, non-significant samples are displayed with 50% transparency,
780 while significant clusters are overlaid without transparency (YA: $p_{\text{corr}} = 0.044$; OA: $p_{\text{corr}} = 0.004$).
781 The topography between 0.5–1.5 s relative to CS onset is shown below the time courses (gray
782 horizontal bars). For topographies, data is averaged across all frequencies.

783

784 **Reinstatement of EEG arousal responses is associated with pupil dilation**

785 To briefly summarize the modality-specific findings, across groups we observed a
786 negative, anticipatory slow wave and a late, positive parietal potential (ERP; see Figure
787 5; van Boxtel and Böcker, 2004; Schupp et al., 2006), a low frequency desynchronization
788 (ERD; see Figure 7; McCormick et al., 1991; Harris and Thiele, 2011; Marzo et al., 2014),
789 as well as pupil dilation (ERPR; see Figure 4; Joshi et al., 2016; Reimer et al., 2016;
790 Breton-Provencher and Sur, 2019; Deitcher et al., 2019; Zerbi et al., 2019). Within the
791 dichotic listening task (i.e., in the absence of reinforcements; US; see Figure 1) we largely
792 witnessed a reliable reinstatement of the arousal response across modalities (i.e., ERP,
793 ERD, ERPR; see Figures 4, 6, and 8). We interpret the reinstatement of the arousal
794 response as reflecting a phasic activation of the LC-NE system by the reactivated fear

795 memory. To support this claim, electrophysiological reinstatement marker (ERP, ERD)
796 should be linked to pupil reinstatement, a non-invasive index of locus coeruleus activity.
797 Accordingly, cluster permutation correlations revealed a reliable association
798 between the reinstatement of the anticipatory, parietal slow wave and pupillary
799 reinstatement ($p_{\text{corr}} = 0.028$). The cluster reached significance in the time window
800 previously filled by the reinforcement (during (re)conditioning; $t = 2.108\text{--}2.212$ s; see
801 Figure 1 and 9) and showed its strongest polarity at left lateralized centro-parietal
802 electrodes. Spearman correlation coefficients are reported in Table 3 for analyses across
803 and within groups (for this, EEG data was averaged across the cluster). No reliable link
804 was observed between the second, positive ERP cluster (late parietal potential) and
805 pupil dilation ($t > 2$ s; $p_{\text{corr}} > 0.1$). This indicates that the late parietal potential was not
806 reliably linked to our LC-NE activity index and we thus dropped it from further analyses.



807

¹ correlations are run for all electrode-time samples

808 *Figure .9* (a) Across age groups, fear conditioned Event-Related Potentials (ERP) and Event-
 809 Related Pupil Responses (ERPR) to the arousal manipulation learned during re/conditioning
 810 (teal lines) were reinstated in the dichotic listening task (orange lines in the left and right panel,
 811 respectively). For ERPR and ERP analyses within age-groups, see Fig. 4 and 5–6, respectively. (b;
 812 left panel) Within electrode and time ranges that demonstrated a reliable arousal effect during
 813 reconditioning, ERP and ERPR reinstatement data were correlated. A significant negative
 814 association was observed between $t = 2.108$ – 2.212 s (solid purple line). The topography
 815 between 1–2.3 s relative to CS onset (see gray horizontal bars) is shown below the time course.
 816 (b; right panel) For visualization purposes only, an additional scatter plot is provided depicting
 817 the same association between ERP and ERPR reinstatement data (here ERP data is averaged
 818 over those samples [time, electrodes] that formed the reliable cluster [see left panel for cluster
 819 extend]). Corr: Correlation; YA: Younger adults; OA: Older adults; CS+: Conditioned stimulus; CS-
 820 : Neutral control stimulus, perceptually matched to the CS+

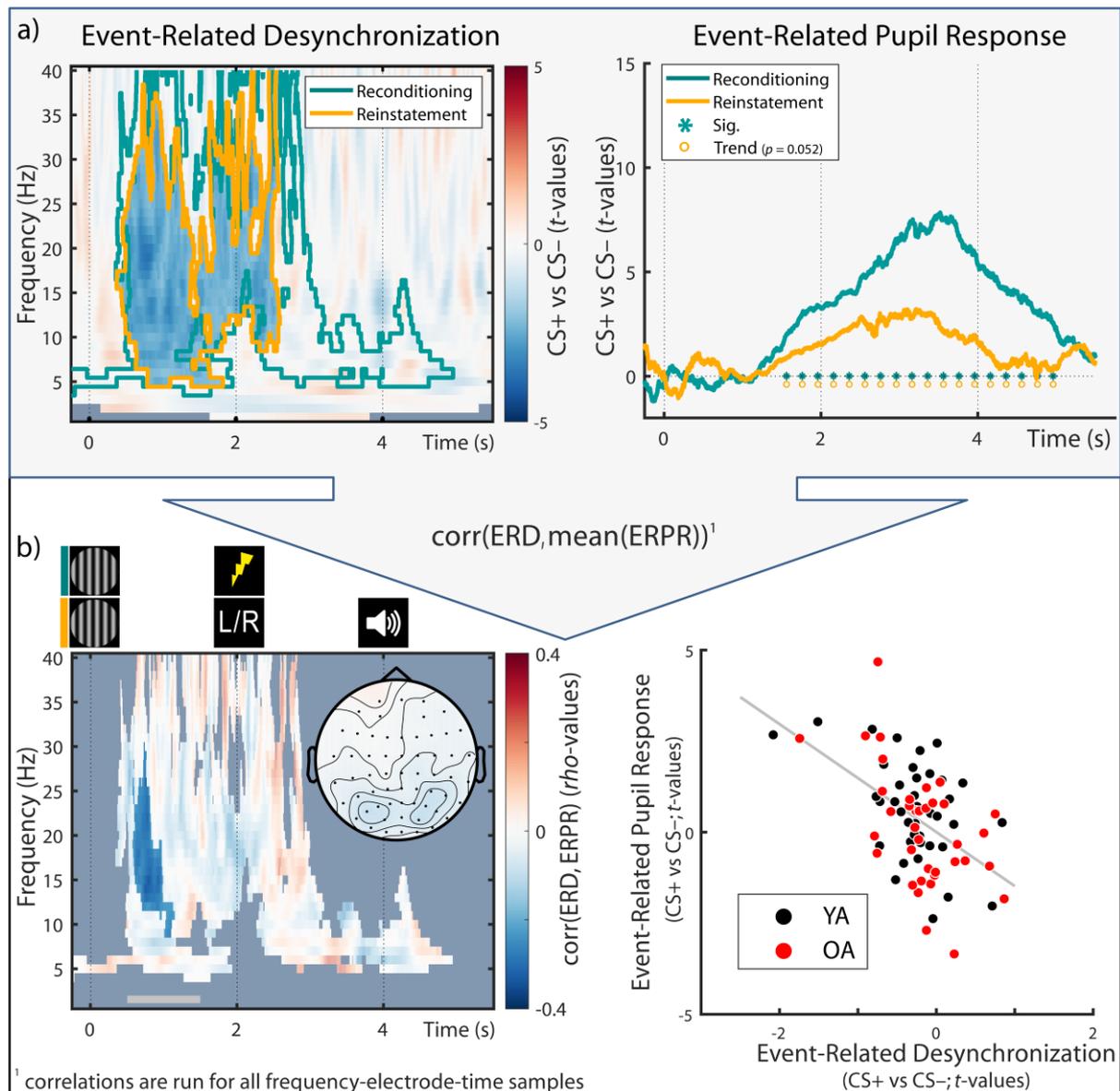
821

822 Moreover, a stronger reinstatement of low EEG frequency desynchronization in

823 response to conditioned stimuli (CS+ vs. CS-) was associated with a larger reinstatement

824 of pupil dilation ($p_{\text{corr}} = 0.022$; see Figure 5b). The cluster reached significance in the
825 anticipatory delay phase (i.e., before US onset during (re)conditioning; $t = 0.588\text{--}1.160$
826 s) in the alpha–beta frequency band (9–30 Hz) and was most pronounced at parieto-
827 occipital electrodes (see Figure 10). Spearman correlation coefficients (based on EEG
828 data averaged across the cluster) are provided in Table 3.

829 In sum, in line with our interpretation cluster correlations indicated that both
830 ERP and ERD responses to the arousal manipulation were linked to pupil dilation, a
831 proxy for LC-NE activity. To further corroborate this conclusion, we repeated our
832 analyses, this time using reconditioning instead of reinstatement pupil and EEG data (cf.
833 Figure 1c). We again observed a reliable, qualitatively similar, association between EEG
834 responses and pupil dilation, suggesting a common dependence on LC-NE activity (ERP:
835 $p = 0.026$ and $p = 0.044$ (two reliable clusters), $t = 1.12\text{--}1.218$ s and $t = 1.706\text{--}1.832$ s;
836 ERD: $p = 0.03$, $t = 0.648\text{--}1.112$ s, frequency range = 13–37 Hz). Crucially, we additionally
837 repeated these analyses on the single-trial level. That is, we tested whether we could
838 predict a given trial’s phasic pupil dilation based on its ERP and ERD data. We obtained
839 findings qualitatively similar to the here reported between-subject analyses, see:
840 <https://doi.org/10.17605/OSF.IO/G9FQJ>.



841 ¹ correlations are run for all frequency-electrode-time samples

842 **Figure 10.** (a) Across age-groups, fear conditioned Event-Related Desynchronization (ERD) and
 843 Event-Related Pupil Responses (ERPR) to the arousal manipulation learned during
 844 re/conditioning (teal (out)lines) were reinstated in the dichotic listening task (orange (out)lines
 845 in the left and right panel, respectively). For ERPR and ERD analyses within age-groups, see Fig.
 846 4 and 7–8, respectively. (b; left panel) Within electrode, time and frequency-ranges that
 847 demonstrated a reliable arousal effect during reconditioning, ERD and ERPR reinstatement data
 848 were correlated. A significant negative association was observed between $t = 0.558-1.160$ s
 849 (non-transparent cluster). The topography between 0.5–1.5 s relative to CS onset (see gray
 850 horizontal bar) is shown below the time course. (b; right panel) For visualization purposes only,
 851 an additional scatter plot is provided depicting the same association between ERD and ERPR
 852 reinstatement data (here ERD data is averaged over those samples [time, electrodes,
 853 frequencies] that formed the reliable cluster [see left panel for cluster extend]). Corr:
 854 Correlation; YA: Younger adults; OA: Older adults; CS+: Conditioned stimulus; CS-: Neutral
 855 control stimulus, perceptually matched to the CS+

856 Table 3

857 Overview of associations between pupillary and EEG reinstatement components

Measure	Group	(N)	<i>rho</i>	<i>p</i>
Parietal slow wave	YA + OA	(N = 76)	-0.424	<0.001
Alpha-beta desynchronization	YA + OA	(N = 76)	-0.424	<0.001
Parietal slow wave	YA	(N = 39)	-0.255	0.116
Alpha-beta desynchronization	YA	(N = 39)	-0.401	0.011
Parietal slow wave	OA	(N = 37)	-0.567	<0.001
Alpha-beta desynchronization	OA	(N = 37)	-0.411	0.011

858 *Note:* Pupil and EEG reinstatement was assessed in the dichotic listening task (cf. Figure 1c). The first row
859 within age groups reports Spearman's correlations of pupil dilation and the anticipatory time domain EEG
860 cluster while the second row reports the time-frequency domain EEG cluster. YA: Younger adults; OA:
861 Older adults.
862

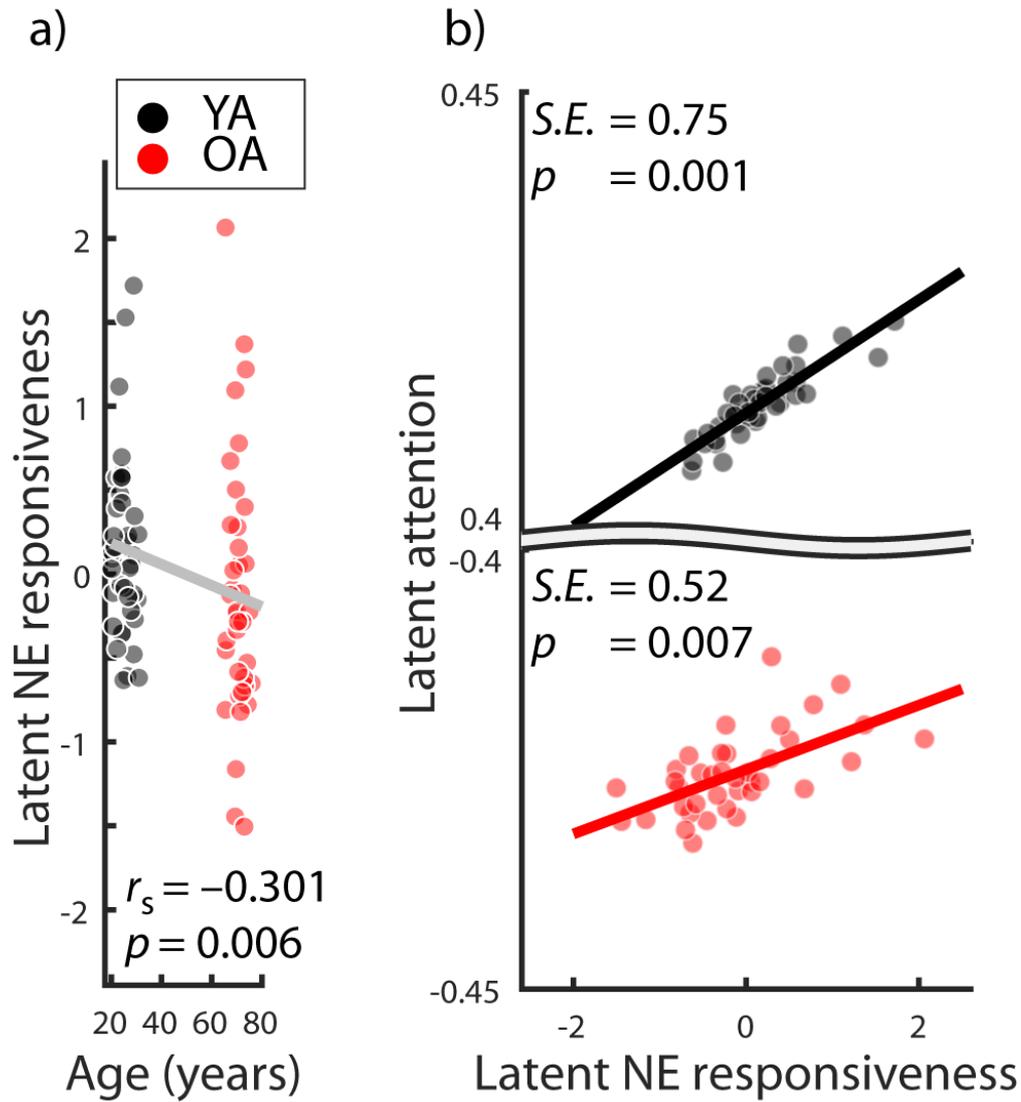
863 **Multimodal assessment of noradrenergic responsiveness is linked to selective**
864 **attention in younger and older adults**

865 We integrated over (pupil-associated) EEG and pupil dilation markers to derive a
866 single, latent multimodal measure reflecting LC-NE responsiveness (see Figure 2, upper
867 part). The proposed model fit the data well ($\chi^2 = 6.935$, $df = 16$; RMSEA = 0.0; CFI =
868 1.205; Brown, 2006). The variances of the latent factors differed reliably from zero in
869 each age group (all $\Delta\chi^2 \geq 23.845$, $\Delta df = 1$, all $p < 0.001$), indicating interindividual
870 differences in NE responsiveness. Older age was associated with lower NE
871 responsiveness scores ($rho = -0.301$; $p = 0.006$; see Figure 11 a).

872 To evaluate the behavioral relevance of interindividual differences in NE
873 responsiveness in younger and older adults, we merged our general attention (see
874 above) and NE responsiveness SEM in a unified neurocognitive model that
875 demonstrated good fit to the data ($\chi^2 = 45.624$, $df = 85$; RMSEA = 0.0; CFI = 1.625; Brown,
876 2006).

877 Importantly, general attention was positively associated with latent NE
878 responsiveness scores in both younger and older adults (YA: $\Delta\chi^2 = 10.323$, $\Delta df = 1$, $p =$
879 0.001, standardized estimate = 0.75; OA: $\Delta\chi^2 = 7.262$, $\Delta df = 1$, $p = 0.007$, standardized

880 estimate = 0.52; see Figure 6b). The strength of the NE–attention association did not
881 differ reliably between age groups ($\Delta\chi^2 = 0.003$, $\Delta df = 1$, $p = 0.954$). This indicates that, in
882 face of declining selective attention in aging, a responsive NE system was linked to
883 preserved cognitive abilities (Nyberg et al., 2012). Notably, qualitatively similar results
884 were obtained when we analyzing composite scores of noradrenergic responsiveness
885 and selective attention (i.e., without relying on a structural equation model; see:
886 <https://doi.org/10.17605/OSF.IO/G9FQI>).
887



888

889 *Figure 11.* Associations between (a) age and latent norepinephrine (NE) responsiveness,
890 evaluated using Spearman's correlation, as well as (b) latent NE responsiveness and latent
891 attention in younger adults (YA; black) and older adults (OA; red). Note the broken y-axis in
892 panel (b). S.E. = standardized estimate.

893 **Discussion**

894 Animal studies suggest that attention deficits in aging are linked to altered central
895 noradrenergic activity (Arnsten and Goldman-Rakic, 1985; Ramos et al., 2006). In vivo
896 research in aging humans, however, was long hampered by methodological challenges in
897 the reliable assessment of LC-NE activity (Astafiev et al., 2010). Here we build on recent
898 reports that pupil dilation (Joshi et al., 2016; Reimer et al., 2016; Breton-Provencher and
899 Sur, 2019; Deitcher et al., 2019; Zerbi et al., 2019) and certain event-related EEG
900 components (Harris and Thiele, 2011; Marzo et al., 2014; Neves et al., 2018; Vazey et al.,
901 2018) are valid, non-invasive proxies for noradrenergic activity. In particular, we made
902 use of LC-NE's well-established role in fear processing (Rasmussen and Jacobs, 1986;
903 Szabadi, 2012; Uematsu et al., 2017) to experimentally test the responsiveness of the
904 central noradrenergic system while recording pupil dilation and the EEG. In addition, we
905 applied a multimodal assessment to probe general attention performance in samples of
906 healthy younger and older adults. Our findings demonstrate impaired attention in aging
907 across multiple tasks. Moreover, older age was associated with a reduced NE
908 responsiveness as indexed by pupil dilation and EEG. Crucially, within both younger and
909 older adults individual differences in attention were positively related to the
910 responsiveness of the noradrenergic system.

911 On the behavioral level, both younger and older adults demonstrated successful
912 auditory selective attention in a dichotic listening task (Hugdahl et al., 2009). That is,
913 participants in both age groups were able to adapt their attentional focus according to
914 changing demands. However, in line with earlier reports (Passow et al., 2012, 2014; Dahl
915 et al., 2019a), older adults showed impaired attention performance in the dichotic
916 listening task and beyond that, across a variety of alternative attention tasks (Kennedy &
917 Mather, 2019).

918 On the physiological level, we observed a multimodal response to the arousal
919 manipulation during fear (re)conditioning in younger and older adults. In particular,
920 compared to perceptually matched control stimuli (CS-), conditioned stimuli (CS+)
921 elicited a sustained dilation of the pupil, as previously reported (e.g., Lee et al., 2018). In
922 line with recent animal work linking LC activity to pupil dilation, we thus conclude that
923 our manipulation successfully activated the LC-NE system in younger and older adults
924 (Rasmussen and Jacobs, 1986; Szabadi, 2012; Uematsu et al., 2017; Deitcher et al., 2019).

925 However, using non-invasive measures we cannot rule out that other arousal-
926 related neuromodulatory systems also influenced pupil diameter ((Reimer et al., 2016).

927 Conditioned stimuli (CS+) further gave rise to two sustained centro-parietal
928 event-related EEG components: First, an anticipatory slow wave and second, a late
929 parietal potential that occurred before and after onset of the reinforcement (US),
930 respectively. A comparable slow wave (Stimulus-Preceding Negativity; SPN), has been
931 observed in response to cues (S1) that prepared participants for the occurrence of
932 following arousing or behaviorally relevant stimuli (S2; cf. Breska and Deouell, 2017; for
933 a review see van Boxtel and Böcker, 2004). Concerning its functional relevance, the SPN
934 has been suggested as marker of anticipatory processes that adjust the excitability of
935 cortical networks to facilitate subsequent processing (of S2; Birbaumer, Elbert, Canavan,
936 & Rockstroh, 1990). Similarly, Brunia (Brunia, 1993) proposed the SPN as index of
937 regionally-targeted changes in cortical excitability that are produced via cortico-
938 thalamic interactions. Interestingly, various peripheral correlates of noradrenergic
939 activation (e.g., skin conductance, heart rate, cf. Szabadi, 2013) have been observed
940 concomitant with the SPN (van Boxtel and Böcker, 2004; Poli et al., 2007). Taken
941 together, larger SPN following fear conditioned stimuli (CS+ vs. CS-) point to a
942 heightened anticipatory attention deployment in arousing situations in younger and

943 older adults. After presentation of the reinforcement (US), conditioned stimuli (CS+)
944 were associated with a second sustained parietal event-related component (Late Parietal
945 Potential; LPP). Previous studies have observed the LPP during fear conditioning
946 (Bacigalupo and Luck, 2018) and suggested it as index of facilitated attention allocation
947 to arousing stimuli (for review, see Schupp et al., 2006). Furthermore, the LPP has been
948 linked with peripheral markers of noradrenergic activity (e.g., skin conductance
949 response; cf. Szabadi, 2013) and subjective arousal ratings. In line with previous work,
950 we interpret the LPP as reflecting elevated selective attention during arousing
951 conditions in younger and older adults.

952 In addition to ERP, fear conditioned stimuli (CS+) produced pronounced changes
953 in rhythmic neural activity within younger and older adults. We observed an anticipatory,
954 long-lasting desynchronization in low EEG frequencies (ERD) with strongest magnitude
955 at parieto-occipital electrodes (van Boxtel & Böcker, 2004). Increased activity in
956 neuromodulatory nuclei like the LC causes global cortical desynchronization (i.e.,
957 cortical state changes; McCormick et al., 1991; Marzo et al., 2014; Neves et al., 2018). Of
958 note, the neural patterns associated with cortical state changes and selective attention
959 are highly similar (Harris and Thiele, 2011; Thiele and Bellgrove, 2018). In particular,
960 the global, LC-NE mediated cortical desynchronization may achieve the spatial precision
961 necessary to selectively process attended stimuli in interaction with glutamate (Harris
962 and Thiele, 2011; Mather et al., 2016). A wide range of human EEG studies established
963 desynchronization in the alpha–beta range as marker of decreased cortical inhibition
964 that allows for facilitated information processing (Hanslmayr, Staudigl, & Fellner, 2012;
965 Jensen & Mazaheri, 2010; Klimesch, Sauseng, & Hanslmayr, 2007). Employing a similar
966 fear conditioning procedure in rats, Headley and Weinberger (2013) demonstrated that
967 the CS+ induced decrease in low frequencies is accompanied by a strong increase in high

968 frequency multiunit activity (gamma; 40–120 Hz), indicating facilitated feed-forward
969 processing (Fries, 2005, 2015). In line with earlier work, the pronounced low frequency
970 desynchronization in response to conditioned stimuli (and US) suggests a transition
971 towards a more activated cortical state, including increased cortical excitability and
972 attention deployment.

973 Most of the arousal responses observed during (re)conditioning (i.e., ERPR, ERP;
974 ERD) persisted in both age groups and were reinstated during the dichotic listening task
975 in the absence of reinforcements (US). As a notable exception, in older adults, pupil
976 reinstatement did not reach significance on a group level, potentially reflecting age-
977 related difficulties in triggering and maintaining self-initiated processing (Lindenberger
978 and Mayr, 2014). That is, during re/conditioning repeated external reminders (i.e., US)
979 may have supported older adults and thus obscured age differences in pupil responses.
980 In contrast, the lack of this external support during the dichotic listening task may have
981 specifically affected older adults and revealed underlying age-related differences in fear
982 conditionability (LaBar et al., 2004) and the central noradrenergic system (Betts et al.,
983 2017; Dahl et al., 2019b; Liu et al., 2019). In line with this notion, older adults
984 demonstrated reliable modulation of pupil dilation during phases of high external
985 support (i.e., encoding of series of visually presented digits) but no significant
986 modulation during phases requiring more self-initiated processing (i.e., cued recall; see
987 Figure 1 and 3 in Van Gerven et al., 2004).

988 Crucially, however, in both age groups, individual differences in pupil
989 reinstatement were linked to EEG correlates of the arousal response (i.e. SPN-ERP, ERD),
990 suggesting a common underlying factor. The association between pupil dilation, i.e. our
991 index of LC activity, and EEG responses is in line with optogenetic and pharmacological
992 animal studies (Berridge and Waterhouse, 2003; Vazey et al., 2018). In particular, Vazey

993 and colleagues (2018) demonstrated that LC photoactivation produced a positive
994 cortical ERP ~140–400 ms after LC stimulation in the absence of sensory input (cf.
995 Nieuwenhuis et al., 2005). Both the parietal topography as well the time course of the
996 observed pupil-associated ERP cluster overlap with such a LC-induced parietal positivity
997 (i.e., 108–214 ms after $t = 2$; [i.e., the onset of the reinforcement during
998 (re)conditioning]). Further, pharmacological animal studies causally implicate LC
999 activity in the modulation of cortical and behavioral states (for a review see Berridge
1000 and Waterhouse, 2003). This effect is presumably mediated via NE's action in the
1001 thalamus and an activation of the basal forebrain (Buzsáki et al., 1988, 1991; McCormick,
1002 1989; McCormick et al., 1991). Behaviorally significant environmental stimuli elicit a
1003 reflexive (re)orienting of attention (orienting response) that is tightly linked to LC
1004 activity (Bouret and Sara, 2005; Sara and Bouret, 2012). Remarkably, the orienting
1005 response is always accompanied by EEG desynchronization and pupil dilation (Sara and
1006 Bouret, 2012), supporting a common dependency on LC activity.

1007 We thus integrated over (pupil-associated) EEG and pupil dilation markers to
1008 derive a single, multimodal measure reflecting LC-NE responsiveness. We observed a
1009 lower NE responsiveness with older age which complements previous reports of
1010 structural age differences in the LC(see: <https://doi.org/10.17605/OSF.IO/G9FQJ> and:
1011 Betts et al., 2017; Dahl et al., 2019b; Liu et al., 2019) and age differences in LC functional
1012 connectivity (Lee et al., 2018). Crucially, within both younger and older adults, a higher
1013 noradrenergic responsiveness was associated with better selective attention
1014 performance (cf. Arnsten & Goldman-Rakic, 1985). That is, in the face of declining
1015 selective attention in aging, a responsive NE system was linked to preserved cognitive
1016 abilities (Nyberg et al., 2012).

1017 Notably, however, as our study reports correlational data, we cannot exclude that
1018 better attentional abilities may have facilitated a preferential processing of conditioned
1019 stimuli which in turn may have led to increased noradrenergic drive. In addition, while
1020 previous research demonstrated a link between LC activity and pupil dilation (LC →
1021 pupil), increases in dilation do not necessarily imply that (only) changes in LC-NE activity
1022 have occurred. In this study we applied an experimental manipulation, fear conditioning, that
1023 reliably drives LC-NE activity, as indicated by markers of neuronal activity in animals (e.g.,
1024 LC spiking activity: Rasmussen and Jacobs, 1986, Ca²⁺ responses in LC axons: Deitcher et
1025 al., 2019, and c-Fos: Uematsu et al., 2017; cf. Szabadi, 2012). Combining a manipulation that
1026 elicits LC activation (fear conditioning) with a non-invasive marker sensitive to LC activation
1027 (pupil dilation), we believe that our findings are at least partly attributable to the effects of NE.
1028 This argument is supported by our finding that pupil dilation was associated with
1029 electrophysiological indices that have also been linked to NE activity in invasive animal
1030 studies (i.e., the P300 ERP: Nieuwenhuis et al., 2005; Vazey and Aston-Jones, 2014; and low
1031 frequency desynchronization: McCormick et al., 1991; Marzo et al., 2014; Neves et al., 2018).
1032 Targeting the noradrenergic system from multiple angles we hope to narrow down our
1033 conclusions. Finally, using LC-MRI recordings (see <https://doi.org/10.17605/OSF.IO/G9FQJ>),
1034 we observed a reliable association between our NE responsiveness factor and peak LC-MRI
1035 contrast.

1036 To conclude, we used non-invasive in-vivo markers of noradrenergic activity
1037 (Joshi et al., 2016; Reimer et al., 2016; Neves et al., 2018; Vazey et al., 2018) to uncover
1038 age differences in NE responsiveness. Importantly, structural equation modeling
1039 revealed reliable positive associations between NE responsiveness and attention in both
1040 younger and older adults. Our findings link animal and human studies on the neural
1041 underpinning of selective attention in aging (Arnsten & Li, 2005) and underscore the

1042 importance of the LC-NE system in late life cognition (Wilson et al., 2013; Mather and
1043 Harley, 2016).

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