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Spaced learning enhances episodic memory by increasing neural pattern similarity across repetitions

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1 **Abstract**

2 Spaced learning has been consistently shown to benefit memory as compared
3 to massed learning, yet the neural representations and processes underlying
4 the spacing effect are still poorly understood. In particular, two influential
5 models (i.e, the encoding-variability hypothesis and the study-phase retrieval
6 hypothesis) could both model behavioral performance very well, but they make
7 opposite hypotheses regarding the spacing effect's neural mechanisms. The
8 present study attempted to provide empirical neural evidence to adjudicate
9 these competing hypotheses. Using spatiotemporal pattern similarity (STPS)
10 analysis of EEG data, this study examined whether and how repetition lags
11 (massed / short-spaced / long-spaced) modulated the STPS's contribution to
12 episodic memory encoding in male and female human participants. The results
13 revealed that greater item-specific STPS in the right frontal electrodes at
14 543-727ms after stimulus onset was associated with better memory
15 performance. More importantly, this STPS was larger under the spaced
16 learning condition than massed learning condition and partially mediated the
17 spacing effect on memory performance. In addition, we found that massed
18 learning was associated with stronger repetition suppression in the N400
19 component that reflected momentary retrieval strength, but reduced activity in
20 the late positive component (LPC) which was associated with memory retrieval.
21 These results suggest that spaced learning improves long-term memory by
22 increasing retrieval effort and enhancing the pattern reinstatement of prior

23 neural representations, which may be achieved by reducing the momentary
24 retrieval strength as the extended repetition lags might help to eliminate the
25 residual representation in working memory.

26 **Significance statement**

27 As one of the most ubiquitous and fundamental phenomena in the history of
28 memory research, the spacing effect provides an important window to
29 understanding how enduring memory is formed in the brain and how different
30 practice strategies could modulate these mechanisms to affect memory
31 performance. By leveraging the neural representational analysis on scalp EEG
32 data, the current study provides the first empirical data to show that spaced
33 learning enhances memory by improving the spatiotemporal similarity that
34 occurs at a late time window. Our results support the study-phase retrieval
35 hypothesis but not the encoding-variability hypothesis and emphasize the role
36 of neural pattern reinstatement in strengthening memory via repeated study.

37

38 **Introduction**

39 One of the most robust and fundamental phenomena in learning and memory
40 is the spacing effect (Ebbinghaus, 1964; Toppino and Gerbier, 2014).
41 Compared with restudying the material in immediate succession (i.e. massed
42 learning), interleaving repetitions with time or other materials (i.e. spaced
43 learning) benefits memory. The spacing effect has been observed across
44 diverse learning tasks and various learning materials in human and nonhuman
45 species (Cepeda et al., 2006; Gerbier and Toppino, 2015; Smolen et al., 2016).
46 Although many cognitive theories and computational models have been
47 proposed to account for the spacing effect, whether and how the neural
48 representations contribute to it remain unknown.

49

50 Among these models, the encoding-variability hypothesis makes specific
51 predictions regarding the representational mechanisms of the spacing effect.
52 In particular, it assumes that greater variability across learning repetitions
53 provides more routes to effective retrieval (Estes, 1959). Due to contextual drift
54 over time (Glenberg, 1979), longer inter-repetition intervals would lead to
55 greater contextual change and thus more variable encoding, resulting in better
56 memory performance. Consistent with this hypothesis, introducing variations
57 across massed repetitions has been found to improve memory performance
58 (Paivio et al., 1988; Appleton-Knapp et al., 2005). Nevertheless, variations
59 under spaced learning condition are not beneficial and sometimes are even

60 detrimental to memory performance (Verkoeijen et al., 2004; Toppino and
61 Gerbier, 2014).

62

63 To account for such results, the study-phase retrieval hypothesis proposes that
64 each repetition serves as a retrieval cue to reactivate and then strengthen the
65 representation of the prior experience (Thios and D'Agostino, 1976). Spacing
66 could reduce the momentary retrieval strength, thus create greater difficulty in
67 memory retrieval and benefit later memory (Bjork, 1988). Consistently, items
68 that were not recognized at the second presentation were recalled poorly
69 (Madigan, 1969). Still, the introduction of variations in the spaced condition
70 could lead to retrieval failure and impair memory (Johnston and Uhl, 1976;
71 Verkoeijen et al., 2004).

72

73 Studies examining the neural representational mechanisms of memory
74 encoding might help to test these competing hypotheses. The
75 encoding-variability hypothesis predicts that better memory is achieved when
76 the representations were more dissimilar across repetitions, and that spacing
77 the repetitions enhances memory by further increasing the dissimilarity.
78 Contrary to these predictions, however, studies using fMRI and
79 representational similarity analysis have found that greater similarity rather
80 than dissimilarity in neural representations across repetitions was associated
81 with better subsequent memory (Xue et al., 2010; Ward et al., 2013; Hasinski

82 and Sederberg, 2016; Zheng et al., 2018). Other studies have further
83 demonstrated that reactivations of prior representations during subsequent
84 learning contribute to successful memory encoding (Kuhl et al., 2010; Lu et al.,
85 2015; Koen and Rugg, 2016).

86

87 Two questions remain to be addressed. First, because no study has compared
88 the neural representations under the spaced and massed learning conditions,
89 it is still unclear whether spacing could enhance neural pattern reinstatement
90 to improve subsequent memory. Second, although massed learning was
91 associated with larger neural repetition suppression (Wagner et al., 2001;
92 Callan and Schweighofer, 2010; Xue et al., 2011), stronger momentary
93 retrieval strength, and less retrieval processing (Appleton-Knapp et al., 2005;
94 Zhao et al., 2015), the relationships among momentary retrieval strength,
95 retrieval processing, and neural pattern similarity are yet to be established.

96

97 The present study used EEG and spatiotemporal pattern similarity analysis (Lu
98 et al., 2015) to address these questions. We chose EEG instead of fMRI for
99 two main reasons. First, due to the temporal autocorrelation of BOLD response,
100 the neural pattern similarity between two trials is affected by their temporal
101 distance (Mumford et al., 2014), which seriously confounds the spacing effect.
102 Second, EEG provides higher temporal resolution to differentiate 350-450ms
103 component reflecting retrieval strength (Rugg and Curran, 2007; Zhao et al.,

104 2015), and the 500-700ms component containing the neural pattern similarity
105 that supports later memory (Lu et al., 2015). By comparing the neural
106 processes and neural pattern similarity for trials under the massed,
107 short-spaced, and long-spaced conditions, and linking them to memory
108 performance, our results could help to achieve a deeper mechanistic
109 understanding of the spacing effect in learning.

110

111

112 **Materials and Methods**

113 ***Participants***

114 Thirty-three healthy Chinese college students (19 females; mean age = 19.8 ±
115 1.8 years, ranging from 17-25 years) completed the experiment. All
116 participants were right-handed, had a normal or corrected-to-normal vision,
117 and no history of neurological or psychiatric diseases. Six additional subjects
118 were recruited but excluded from final analysis due to their high rate of "no
119 response" trials (1 subject) or noisy EEG data (5 subjects). The study was
120 approved by the Institutional Review Board of the State Key Laboratory of
121 Cognitive Neuroscience and Learning at Beijing Normal University.

122

123 ***Materials***

124 We used 288 pictures of Chinese faces in the learning phase and another 288
125 faces as foils in the recognition memory test. To minimize the primacy and

126 recency effects, 12 additional faces (4 for each run) were added at the
127 beginning and the end of the study lists but were not tested in the recognition
128 task. All faces were unfamiliar to the subjects and were drawn from the
129 CAS-PEAL face database (Gao et al., 2008). They were presented in the same
130 size (180 X 240 pixels) in the center of the computer screen on grey
131 background.

132

133 ***Procedure and design***

134 During the encoding phase, participants were asked to make an age judgment
135 (older or younger than 30 years old) on each presented face by pressing one
136 of two buttons. They were not told about the subsequent memory task. All
137 faces were presented twice within a run, with one third of which under the
138 massed learning (MA) condition, i.e., inter-repetition interval (IRI) was 0-1 trials,
139 one third under the short-spaced learning (SS) condition, i.e., IRI was 4-8 trials,
140 and the rest under the long-spaced learning (LS) condition, i.e., IRI was 94-96
141 trials (Fig.1A). The materials used in the three conditions were fully
142 counterbalanced across participants. Each trial started with a fixation cross
143 lasting 500-800ms (randomly jittered), followed by the presentation of the
144 stimulus for 1000ms, and a blank screen for 2500ms. Participants were
145 allowed to respond within 2000ms after stimulus onset. The encoding phase
146 consisted of three runs, each lasting 10 min.

147

148 A recognition memory test was conducted after a 30 min visual change
149 detection task that was used as a distractor. During the recognition phase,
150 participants were asked to judge whether they had studied each face earlier on
151 a 6-point scale, with 1 indicating “Definitely new” and 6 indicating “Definitely
152 old”. In total, 576 faces (288 old faces and 288 new faces) were
153 pseudorandomly mixed and presented one by one over three runs, with the
154 constraint that the numbers of old and new faces were matched within each
155 run. Each trial started with a fixation cross lasting 500-800ms (randomly
156 jittered), followed by the presentation of the face for up to 3000ms unless a
157 response was made. A blank screen was then presented until the next trial (Fig.
158 1B). We used a fixed inter-trial-interval of 4000ms in the recognition phase so
159 that the total duration of this phase was not affected by participants’ response
160 time, which could help to discourage the participants from making hasty
161 responses.

162

163 ***Behavioral data analysis***

164 For memory performance, the old faces recognized with high confidence
165 (scored 5 or above) were defined as remembered items and those scored 3 or
166 below were defined as forgotten items. These cutoffs were chosen so that
167 there were roughly equal numbers of remembered (42.59%) and forgotten
168 items (40.82%). Both the hit rate and discriminability (d') were analyzed by
169 condition. Response time (RT) and response consistency (i.e. the rate of same

170 response between two repetitions) in the age judgment task during the
171 encoding phase were analyzed by spacing condition (MA, SS, LS),
172 subsequent memory (remembered vs. forgotten), and, for RT only, by
173 repetition (first vs. second presentation). Repeated measures ANOVA and
174 paired-sample *t*-test were conducted to examine the spacing effect in the
175 encoding task and memory performance.

176

177 ***EEG recording and preprocessing***

178 Participants were seated approximately 100 cm away from the computer
179 screen in a soundproof, light adjustable room. Continuous EEG data were
180 recorded with a sampling rate of 1024 Hz using the 64-channel Biosemi
181 ActiveTwo EEG system (Biosemi, Inc). Ag–AgCl electrodes were mounted
182 according to the 10-20 system.

183

184 EEG data preprocessing was implemented using Matlab-based toolbox
185 Fieldtrip (RRID: SCR_004849) (Oostenveld et al., 2011) and in-house
186 MATLAB (RRID: SCR_001622) scripts. EEG data were re-referenced to the
187 average of all electrodes, down-sampled to the rate of 256 Hz and filtered with
188 a band-pass filter of 0.5-40 Hz. Eye movements, blinks, and muscle artifacts
189 were identified and corrected using the independent component analysis (ICA)
190 algorithm. The continuous data were then segmented into epochs from -200 to
191 1000ms with regard to stimulus onset. The pre-stimulus interval (-200 to 0ms)

192 was used as the baseline for baseline removal procedure. Trials contaminated
193 by any remaining eye movement, blink or muscle activity were rejected by
194 visual inspection.

195

196 ***Spatiotemporal pattern similarity analysis (STPS)***

197 We constructed spatiotemporal feature vectors from the single-trial epoch data
198 and conducted the spatiotemporal pattern similarity analysis (Lu et al., 2015).
199 The spatial features were scalp voltages from one of the six regions for better
200 spatial specificity (15 channels per region) (Fig. 2A), and the temporal features
201 were selected using a 100ms sliding window (26-time points) from the epoch
202 data, with a step size of one-time point. The similarity between trials was
203 calculated using Pearson correlation. The correlation coefficients were then
204 converted to Fisher's Z scores for subsequent statistical analysis.

205

206 The within-item (WI) STPS was obtained by calculating the similarity between
207 two repetitions of the same item. To examine whether the within-item similarity
208 reflected item-specific representations or common cognitive processes, we
209 calculated the similarity for between-item (BI) pairs that matched the WI pairs
210 in terms of their memory performance, spacing condition, number of
211 repetitions (1 or 2), and inter-repetition interval. Specifically, for a WI pair, we
212 selected a BI pair in which the two trials were from the same spacing condition
213 and showed the same subsequent memory performance as those in the WI

214 pair. In addition, one trial of the pair was the first repetition of an item and the
215 other trial was the second repetition of another item. Finally, the
216 inter-trial-interval (ITI) between BI pairs and WI pairs were matched as closely
217 as possible, although we did not find a significant effect of ITI on the pattern
218 similarity of BI pairs ($\chi^2_{(1)} = 0.21, p = 0.65$). A greater within-item similarity than
219 between-item similarity should reflect item-specific encoding.

220

221 In the current study, we aimed to examine the neural representational
222 mechanisms underlying the spacing effect in enhancing episodic memory. As a
223 result, we were particularly interested in the neural differences between
224 spaced and massed condition that were associated with subsequent memory
225 effect. In other words, although there could be many neural differences
226 between spaced and massed condition, they might reflect different cognitive
227 functions, such as sensory processing, motor control, etc., but such similarities
228 are not theoretically (directly) related to the condition differences in memory
229 performance. Instead, only the condition differences in neural pattern similarity
230 that are linked to successful memory encoding would explain the spacing
231 effect in memory. As a result, we needed firstly to localize the memory related
232 neural patterns and then tested whether spacing modulated them.

233

234 To achieve this goal, we did the following hypothesis-driven statistical analyses.
235 First, we located the spatiotemporal windows where the item-specific

236 representation was associated with subsequent memory performance. The
237 within-item STPS and between-item STPS were separately grouped and
238 averaged across pairs according to the status of subsequent memory
239 performance and spacing condition, separately for each individual participant.
240 Whole-brain three-way ANOVAs were conducted, with spacing condition (MA,
241 SS, and LS), subsequent memory performance (remembered/forgotten), and
242 item-specificity (within-items/between-items) as within-subject factors. We
243 particularly focused on the contrast of subsequent memory by item-specificity
244 interaction, which should be orthogonal to the spacing effect. In other words,
245 although there were more remembered items in the spaced learning conditions
246 than massed learning condition, the spacing effect should not bias the
247 subsequent memory effect since the remembered and forgotten items were
248 separately averaged within each learning condition before the three-way
249 ANOVA. To make sure that the subsequent memory effect was consistent
250 across spacing conditions, we also examined the subsequent memory by
251 spacing interaction as well as the three-way interaction. Focusing on the time
252 windows showing significant item-specific subsequent memory effects (i.e.,
253 significant item-specificity by subsequent memory interaction, but no
254 three-way interaction or memory by spacing interaction), we conducted
255 post-hoc comparisons to examine whether remembered items showed greater
256 item-specific representations.

257

258 To examine the representational mechanisms of the spacing effect on
259 subsequent memory, we then focused on these windows, where the
260 item-specific pattern similarity predicted subsequent memory performance, to
261 further examined how spacing affected item-specific representations. In this
262 analysis, the remembered items and forgotten items in each learning condition
263 were pooled together and then averaged, which would allow for a better
264 examination of the spacing effect than would separate averages of
265 remembered and forgotten trials, because there were different numbers of
266 remembered items in different spacing conditions. We then conducted
267 item-specificity by spacing ANOVA. Focusing on the clusters showing
268 item-specificity by spacing interactions, we conducted post-hoc comparisons
269 to examine whether spacing could enhance item-specific pattern similarity.

270

271 ***Univariate ERP analysis***

272 To detect the ERP components showing the subsequent memory effect, we
273 averaged the EEG responses according to subsequent memory performance,
274 spacing condition, and repetition, separately for each individual participant.
275 Similar to the STPS analysis, we first conducted a whole-brain three-way
276 ANOVA, with spacing condition (MA, SS, and LS), subsequent memory
277 performance (remembered/forgotten), and repetition (Rep1/Rep2) as
278 within-subject factors. The ERP components associated with subsequent
279 memory performance were defined as those showing a significant main effect

280 of subsequent memory and no significant interaction with other two factors.

281

282 Focusing on these components, we then examined whether spacing would

283 modulate these components. Again, the remembered items and forgotten

284 items in each learning condition were pooled together and then averaged.

285 Since spacing could only modulate the EEG response evoked by the second

286 repetition, we separately compared MA vs. SS, MA vs. LS, and SS vs. LS on

287 the ERP evoked by the second repetition. In an exploratory analysis, we also

288 examined whether spacing could modulate the repetition priming effect by a

289 whole-brain spacing by repetition ANOVA.

290

291 ***The nonparametric cluster-based permutation test***

292 Corrections for multiple comparisons were performed using a nonparametric

293 statistical method based on cluster-level permutation tests implemented in

294 Fieldtrip toolbox. Statistical testing was performed for every time window, and

295 the time windows whose statistical value was larger than a threshold ($p = 0.05$)

296 were selected and clustered into connected sets on the basis of temporal

297 adjacency. The observed cluster-level statistics were calculated by taking the

298 sum of the statistical values within a cluster. Then, condition labels were

299 permuted 10,000 times based on their exchangeability, and the maximum

300 cluster statistic over all six regions in each permutation was chosen to

301 construct a distribution of the cluster-level statistics under the null hypothesis.

302 The nonparametric statistical test was obtained by calculating the proportion of
303 randomized test statistics that exceeded the observed cluster-level statistics.
304 For the spacing effect, the permutation test was conducted within the
305 pre-defined window showing subsequent memory effect. For univariate
306 analyses on ERPs, the procedures were the same except that the cluster was
307 set on the basis of temporal and spatial adjacency. When pair-wise
308 comparisons between the three spacing conditions were conducted, the
309 cluster-level tests were further corrected for multiple comparisons using
310 Bonferroni correction.

311

312 ***Mixed-effects model***

313 Mixed-effects model is useful for modeling the influence of predictors at
314 multiple levels of variables simultaneously and for jointly modeling both
315 discrete and continuous variables (Gelman and Hill, 2006). It has been used in
316 sophisticated fMRI designs (Ward et al., 2013; Xiao et al., 2017) and
317 single-trial ERP analyses (Valente et al., 2014; Payne et al., 2015). In this
318 study, the mixed-effects model was implemented with lme4 (Bates et al., 2012)
319 in R (RRID: SCR_001905). Participants were included as a random effect. We
320 used the likelihood ratio test to compare the models (with vs without the
321 predictor) to determine the effect of the predictor.

322

323 ***Controlling the effect of univariate ERP amplitude on STPS***

324 To examine whether our key findings of pattern similarity were due to
325 differences in univariate amplitude, we constructed linear mixed-effects
326 models to examine the subsequent memory effect and spacing effect, by
327 including the amplitude as covariate. In the model for the subsequent memory
328 effect, memory strength (1-6) was used as the dependent variable; the
329 within-item pattern similarity in the spatiotemporal clusters showing
330 subsequent memory effect was used as the predictor, and the corresponding
331 mean EEG amplitude was included as the confounding factor. In the model for
332 the spacing effect, the mean within-item pattern similarity was used as the
333 dependent variable, the spacing condition was used as the predictor, and the
334 mean EEG amplitude was included as the confounding factor. Participants
335 were included as a random effect.

336

337 ***Mediation analysis***

338 We performed the mediation effect test to further examine whether the spacing
339 effect on memory was mediated by the within-item pattern similarity, which was
340 related to both spacing condition and subsequent memory performance.

341 Mixed-effects models as implemented by lme4 (Bates et al., 2012) in R (RRID:
342 SCR_001905) were used to test the relationship between (1) spacing and
343 memory strength (1-6 confidence responses were used to index memory
344 strength) ($Y = a_1 + b_1X + \varepsilon_1$); (2) spacing and within-item similarity
345 ($M = a_2 + b_2X + \varepsilon_2$); (3) spacing and memory strength with a mediator

346 ($Y = a_3 + b_3X + bM + \varepsilon_3$). In those equations, Y is the dependent variable,
347 X is the predictor, and M is the mediator. The indirect effect was estimated as
348 $b_2 \times b$. We used distribution-of-the-product method to compute the confidence
349 interval.

350

351

352 **Results**

353 ***Spaced learning was associated with better memory***

354 Consistent with previous observations, the current study revealed a significant
355 spacing effect on subsequent memory performance (Fig. 1C) (Hit rate: $F_{(2,64)} =$
356 $6, p = 0.004$; d' : $F_{(2,64)} = 8.63, p = 0.0005$). The mean hit rate with high
357 confidence (5 or above) for MA, SS, and LS were 40.08%, 42.94%, and
358 44.75%, respectively. Compared to MA, the hit rate was significantly higher
359 under SS ($t_{(32)} = 2.5, p = 0.02$) and LS ($t_{(32)} = 3.39, p = 0.002$). Similarly, the d'
360 was also higher under SS ($0.53, t_{(32)} = 3.96, p = 0.0004$) or LS ($0.55, t_{(32)} = 3.46,$
361 $p = 0.002$) than MA (0.41). No significant difference between SS and LS was
362 found for either hit rate ($t_{(32)} = -1.18, p = 0.25$) or d' ($t_{(32)} = -0.63, p = 0.53$).

363

364 ***Spaced learning reduced repetition priming and response consistency***

365 Three-way (spacing condition, subsequent memory performance, and
366 repetition) repeated-measures ANOVA revealed no significant main effect of
367 subsequent memory (remembered vs. forgotten) on reaction time ($F_{(1,32)} = 0.21,$

368 $p = 0.65$), nor its interactions with other two factors (all $ps > 0.066$) (Fig. 1F).

369 The interaction between repetition (P1 vs. P2) and spacing condition (MA, SS,
370 and LS) was significant ($F_{(2,64)} = 31.69$, $p < 0.0001$). Further analyses showed
371 that the RTs at the first presentation were comparable across the three spacing
372 conditions (MA: 787ms, SS: 790ms, LS: 793ms; $F_{(2,64)} = 0.48$, $p = 0.62$), but
373 the RTs at the second presentation were much shorter under the MA condition
374 (694ms) than under the SS (766ms, $t_{(32)} = -9.83$, $p < 0.0001$) and LS
375 conditions (781ms, $t_{(32)} = -10.16$, $p < 0.0001$), and slightly shorter under the SS
376 condition than the LS condition ($t_{(32)} = -2.19$, $p = 0.04$) (Fig. 1D).

377

378 Two-way (spacing condition by subsequent memory performance)
379 repeated-measures ANOVA were then used to analyze the response
380 consistency between the two presentations. Results revealed a significant
381 main effect of spacing condition ($F_{(2,64)} = 25$, $p < 0.0001$), but no effect of
382 subsequent memory performance ($F_{(1,32)} = 1.64$, $p = 0.21$) or the interaction
383 between spacing condition and subsequence memory performance ($F_{(2,64)} =$
384 1.4 , $p = 0.25$). Further paired sample t -test revealed significantly higher
385 consistency for MA (82.65%) than SS (76.45%) ($t_{(32)} = 4.4$, $p = 0.0001$) and LS
386 (72.41%) ($t_{(32)} = 6.85$, $p < 0.0001$), and for SS than LS ($t_{(32)} = 3.35$, $p = 0.0021$)
387 (Fig. 1E). Those results suggest that spaced learning was associated with
388 weaker repetition priming and lower response consistency during learning, but
389 these factors were not directly associated with subsequent memory

390 performance.

391

392 ***Subsequently remembered items showed greater item-specific STPS***

393 The above analyses revealed a significant spacing effect on subsequent
394 memory performance. To examine the underlying neural mechanism, we
395 tested the hypothesis that spaced learning would enhance memory by
396 increasing item-specific neural pattern similarity that was associated with
397 subsequent memory performance. As the first step, we located the
398 spatiotemporal windows where the item-specific STPS was associated with
399 subsequent memory performance, using the contrast of subsequent memory
400 by item-specificity interaction in the spacing by subsequent memory by
401 item-specificity three-way ANOVA. This analysis revealed a 543-727ms cluster
402 in right frontal region (Region 2) showing a significant subsequent memory by
403 item-specificity interaction ($F_{(1,32)\max} = 12.84$, $F_{\text{clustersum}} = 391.75$, $p_{\text{cluster}} = 0.03$,
404 Fig. 2B & C). No cluster in the whole-brain showed significant spacing by
405 subsequent memory interaction or spacing by subsequent memory by
406 item-specificity interaction. Post hoc tests showed significantly greater
407 within-item STPS for remembered items than forgotten items ($F_{(1,32)} = 10.98$, p
408 $= 0.002$), but no difference in between-item STPS ($F_{(1,32)} = 0.34$, $p = 0.56$). In
409 addition, significantly greater within- than between-item STPS was only found
410 for subsequently remembered items ($F_{(1,32)} = 10.8$, $p = 0.003$), but not for
411 forgotten items ($F_{(1,32)} = 1.81$, $p = 0.19$) (Fig. 2D). The subsequent memory

412 effect in within-item STPS remained significant after controlling the EEG
413 amplitude ($\chi^2_{(1)} = 7.99, p = 0.005$). This finding replicated previous results from
414 a study that used foreign characters as learning stimuli (Lu et al., 2015).

415

416 ***Spaced learning was associated with greater item-specific STPS***

417 Having shown that remembered items were associated with greater
418 item-specific STPS in the late time window, we further tested our core
419 hypothesis that spaced learning improved memory performance by enhancing
420 the item-specific STPS associated with memory performance. Focusing on the
421 right frontal cluster that showed greater item-specific STPS for remembered
422 items than forgotten items, we found a significant item specificity by spacing
423 (MA vs. SS) interaction in the 606-652ms time window ($F_{(1,32)\max} = 13.52$,
424 $F_{\text{clustersum}} = 123.89, p_{\text{cluster}} = 0.016$) (Fig. 2E & F). Post hoc tests revealed that
425 compared to MA, SS showed significantly greater within-item STPS ($t_{(32)} =$
426 $2.43, p = 0.02$), but comparable between-item STPS ($t_{(32)} = 0.46, p = 0.66$) (Fig.
427 2F). The difference in within-item STPS remained significant after controlling
428 the EEG amplitude ($\chi^2_{(1)} = 4.83, p = 0.028$). We also found a 676-710ms
429 time-window that showed a spacing (SS vs. LS) by item-specificity interaction
430 ($F_{(1,32)\max} = 9.54, F_{\text{clustersum}} = 70.16, p_{\text{cluster}} = 0.036$), but it did not survive
431 Bonferroni correction. There was no time window showing significant
432 difference in item-specificity between MA and LS.

433

434 ***Within-item STPS partially mediated the spacing effect on memory***

435 The above results suggest that spaced learning could enhance the
436 item-specific STPS's contribution to memory performance by increasing the
437 within-item STPS. We further examined whether the within-item STPS indeed
438 mediated the spacing effect on memory. We focused on the spacing effect
439 between MA and SS since no significant difference between MA and LS in
440 item-specific STPS was found. The within-item STPS in the right frontal region
441 (606-652ms), which was associated with both subsequent memory
442 performance and spacing effect, was averaged and used as the mediator.
443 Mediation analysis showed that the within-item STPS partially mediated the
444 spacing effect on memory (indirect effect = 0.0047, 95% CI was [0.001 0.0093])
445 (Fig. 3).

446

447 ***The late positive component was associated with the spacing effect on***
448 ***memory***

449 The above analysis tested and supported our hypothesis that spaced learning
450 could enhance memory by increasing item-specific STPS. Besides STPS,
451 previous studies have found several ERP components during encoding that
452 were associated with subsequent memory performance and were modulated
453 by repetition lags. To examine whether these ERP components could also
454 support the spacing effect in our study, we first compared remembered items
455 and forgotten items to identify memory-related ERPs and further examined

456 whether those ERPs were modulated by spacing condition. We found that a
457 500-844ms response over the occipito-parietal electrodes (i.e., late positive
458 component, LPC) (Fig. 4A) showed a significant subsequent memory effect
459 ($F_{\text{clustersum}} = 6097.4$, $p_{\text{cluster}} = 0.01$), with remembered items evoking more
460 positive-going waveforms than forgotten items (Fig. 4D & E). We did not find
461 any cluster showing significant spacing by subsequent memory interaction or
462 spacing by subsequent memory by repetition interaction. Focusing on the LPC,
463 we found that on the second presentation, items under the MA condition
464 evoked less positive-going LPC than those under the SS (672-813ms, $t_{\text{clustersum}}$
465 $= -520.49$, $p_{\text{cluster}} = 0.008$) and LS condition (613-766ms, $t_{\text{clustersum}} = -703.71$,
466 $p_{\text{cluster}} = 0.002$) (Fig. 4F & G). No cluster showed significant difference between
467 SS and LS (all p_{clusters} > 0.13). Those results showed that spacing could
468 modulate the LPC amplitudes that were associated with subsequent memory
469 performance.

470

471 ***LPC reflected memory-related cognitive processes***

472 To further probe the nature of neural representation encoded by the LPC,
473 which was associated with the spacing effect, we applied the spatiotemporal
474 pattern similarity analysis on this component, i.e., 672-766ms time-window
475 over the occipito-parietal electrodes (P1, CPz, Pz, POz, and P2). We found
476 that within this component, there was a significant main effect of subsequent
477 memory, i.e., remembered items showed greater pattern similarity than

478 forgotten items ($F_{(1,32)} = 6.26, p = 0.018$), but no significant effect of
479 item-specificity ($F_{(1,32)} = 1.97, p = 0.17$), or subsequent memory by
480 item-specificity interaction ($F_{(1,32)} = 0.002, p = 0.96$) (Fig. 4H). In addition, there
481 was no significant main effect of spacing ($F_{(2,64)} = 2.23, p = 0.12$) or spacing by
482 item-specificity interaction ($F_{(2,64)} = 0.37, p = 0.69$) (Fig. 4I). These results
483 suggest that the LPC might not carry item-specific representations. Instead, it
484 may reflect general memory-related cognitive processes.

485

486 The above results suggest that both the LPC that reflects general cognitive
487 processing and the item-specific STPS in the right frontal region were
488 associated with the spacing effect on memory. Interestingly, they occurred at a
489 similar time-window but with different topographic distributions. Does LPC
490 response contribute to the neural pattern reinstatement? We conducted a
491 mixed-effects model analysis to examine the association between LPC
492 amplitude and the degree of STPS. The result revealed a strong positive
493 association between the LPC response of the second presentation and the
494 within-item STPS ($\chi^2_{(1)} = 128.16, p < 0.0001$). The correlation remained
495 significant ($\chi^2_{(1)} = 74.74, p < 0.0001$) after controlling for the spacing condition,
496 memory strength, and the mean amplitude of right frontal region. These results
497 suggest that the LPC may contribute to the neural pattern reinstatement in the
498 right frontal region. Due to the exploratory nature of the analysis on the
499 relationship between ERP response and neural representation, more

500 investigations are required to replicate these results and to further examine the
501 nature of this correlation.

502

503 ***Spaced learning reduced the repetition effect on N400***

504 In addition to more positive LPC, spaced learning also reduced the repetition
505 effect on N400 in the central region as revealed by a significant interaction
506 between spacing condition and repetition (300-484ms, $F_{\text{clustersum}} = 20845$,
507 $p_{\text{cluster}} = 0.0002$) (Fig. 5A), though this cluster did not show a significant
508 subsequent memory effect. Post hoc t tests revealed a significant repetition
509 effect under the MA condition ($t_{(32)} = 6.79$, $p < 0.0001$), but not under the SS
510 ($t_{(32)} = 0.08$, $p = 0.94$) or LS condition ($t_{(32)} = 0.14$, $p = 0.89$) (Fig. 5D & E).
511 Moreover, mixed effects analysis suggested that the strength of N400
512 repetition suppression could predict the behavioral repetition priming effect
513 under the MA condition ($\chi^2_{(1)} = 14.54$, $p < 0.0001$, $\beta = 0.0047$), but could not
514 predict subsequent memory performance ($\chi^2_{(1)} = 0.2$, $p = 0.66$).

515

516 We also conducted the STPS analyses for this component, i.e., 300-484ms
517 time window over the central electrodes (FC1, FCz, FC2, C1, Cz, C2, CP1,
518 CPz, and CP2). We did not find any significant main effects or interactions (all
519 $ps > 0.17$) (Fig. 5F & G).

520

521

522 **Discussion**

523 The present study used EEG and representational analysis to examine the
524 representational mechanisms underlying the spacing effect. Using novel faces
525 as stimuli, the current study revealed that item-specific STPS that occurred at
526 543-727ms time window over the right frontal scalp was greater for
527 subsequently remembered items than forgotten items. This result replicated
528 previous findings using novel foreign characters (Lu et al., 2015), suggesting
529 the role of STPS in memory is not affected by the choice of learning stimulus.

530 Together with fMRI studies (Xue et al., 2010; Visser et al., 2013; Ward et al.,
531 2013), existing evidence across various stimulus types, experimental tasks,
532 repetition lags, and imaging techniques converges to emphasize the critical
533 role of neural pattern similarity in supporting durable memory (Xue, 2018).

534

535 More importantly, this memory-related STPS was larger under the spaced
536 learning condition than the massed learning condition and it partially mediated
537 the spacing effect on memory. This contradicts the encoding-variability
538 hypothesis that greater dissimilarity benefits memory. Given the temporal
539 contextual drift (Glenberg, 1979), how could spaced learning generate
540 stronger pattern similarity than massed learning? According to the context
541 maintenance and retrieval model (CMR) (Polyn et al., 2009; Siegel and
542 Kahana, 2014), when the first presentation was retrieved, its context could be
543 reinstated (Manning et al., 2011). This context reinstatement could partially

544 counteract the temporal context drift. Moreover, under the massed condition,
545 the neural representation of the first learning experience might be still activated
546 in the short-term memory system when the inter-repetition interval is short
547 (Raaijmakers, 2003; Van Strien et al., 2007). According to the new theory of
548 disuse (NTD) (Bjork and Bjork, 1992; Bjork, 1999), an item in memory can be
549 characterized by two “strengths”: Storage strength reflects how well an item is
550 learned, and retrieval strength represents how accessible an item can be via
551 recall or recognition. Under the massed learning condition, items are readily
552 accessible and the strong momentary retrieval strength would reduce the
553 memory retrieval processes, resulting in less gain in storage strength (Zhao et
554 al., 2015).

555

556 By combining ERP and spatiotemporal pattern analysis, the current study
557 revealed three lines of neural evidence to support the above hypotheses. First,
558 consistent with many previous studies (Van Strien et al., 2007; Zhao et al.,
559 2015; Manuel and Schnider, 2016), we found greater behavioral repetition
560 priming effect and significant N400 repetition suppression under the massed
561 condition than under the short- or long-spaced condition. These results are
562 also in line with the fMRI evidence of stronger neural repetition suppression in
563 the sensory and frontoparietal regions under the massed learning condition
564 (Callan and Schweighofer, 2010; Xue et al., 2010; Xue et al., 2011). Consistent
565 with a previous fMRI study (Ward et al., 2013), we also found that the N400

566 repetition effect could predict the behavioral repetition priming, but not episodic
567 memory performance.

568

569 Second, our results are consistent with previous studies which revealed that
570 the N400 increased with repetitions (Henson et al., 2003; Schweinberger and
571 Neumann, 2016), and reflected the momentary retrieval strength (Zhao et al.,
572 2015). In addition, previous studies also suggested that the N400 supported
573 the familiarity judgment (Curran and Cleary, 2003; Rugg and Curran, 2007;
574 Kutas and Federmeier, 2011). Together, the enhanced N400 response under
575 the massed condition suggested that massed learning was associated with
576 stronger momentary retrieval strength (Van Strien et al., 2007).

577

578 Third, the LPC representation contained no item-specific information but was
579 associated with memory performance. Moreover, the LPC showed reduced
580 response with repetitions and its amplitude was associated with the strength of
581 memory-related STPS. Previous studies have shown that LPC is related to
582 recollection (Rugg and Yonelinas, 2003; Rugg and Curran, 2007; Kappenman
583 and Luck, 2012), in particular, the retrieval of complex information about prior
584 events. Together, these results suggest that the LPC is associated with general
585 memory-retrieval processes that contribute to pattern reinstatement. Due to
586 the stronger momentary retrieval strength under the massed condition, the
587 requirement for memory retrieval of prior learning and the reactivation of prior

588 memory trace are impaired.

589

590 These results also suggest that the representations in early and late time

591 windows might carry distinct information, and have a differential effect on

592 long-term memory formation. A recent study combining MEG and fMRI

593 suggests that whereas the representation in the early time window

594 corresponded to the representations in the early visual cortex, the

595 representations in the later time window corresponded to the representations

596 in the higher-order visual cortex (Cichy et al., 2014). Notably, item-specific

597 representation in the visual cortex was only found during perception, whereas

598 item-specific representation during memory retrieval was found in the inferior

599 parietal lobule (Xiao et al., 2017; Favila et al., 2018), whose representation

600 was more abstract (Jeong and Xu, 2016; Ye et al., 2016), and more aligned to

601 current goals (Favila et al., 2018). Because perceptual details might decay

602 more rapidly than more abstract information, such as semantics (Craik and

603 Tulving, 1975), the early pattern similarity might reflect more sensory

604 information that did not predict later memory, whereas the later item-specific

605 pattern similarity might reflect more abstract information and contribute to

606 long-term memory. Future studies should further examine the nature of

607 representation and their anatomical origins of the early and late components,

608 which would help to deepen our understanding of the role of cortical

609 representation in memory formation.

610

611 These findings could also well account for the differential effect of encoding
612 variability on memory performance. According to the differentiation model of
613 memory (Kılıç et al., 2017), repeated exposure to an item results in the storage
614 of additional information in the single memory trace established during the first
615 exposure. As the memory trace is updated, its similarity to other items
616 decreases and becomes more distinguishable during retrieval. Introducing
617 variance in the massed repetitions could reduce the momentary retrieval
618 strength, and enhance the retrieval of later abstract representations and
619 improve memory. However, introducing variance under the spaced condition
620 could increase the chance of retrieval failure (Verkoeijen et al., 2005; Cepeda
621 et al., 2006), in which case a new trace might be formed. When the
622 study-phase retrieval failed, the probability of retrieving the old trace at the final
623 test would be even lower. Therefore, the probability of recalling the item mostly
624 depended on the new trace, and the performance is thus impaired
625 (Raaijmakers, 2003). This mechanism could also account for the inverted
626 U-shaped relationship between lag and memory (Verkoeijen et al., 2005;
627 Cepeda et al., 2006), as too long a lag could also result in retrieval failure.
628 Finally, it could also account for the superadditivity effect, i.e. observed benefit
629 of repetition on memory strength is higher than that predicted by the
630 encoding-variability hypothesis, since the representations for the two study
631 events should not be considered as independent (Benjamin and Tullis, 2010).

632

633 The present study failed to replicate the detrimental effect of long
634 inter-repetition interval. Some behavioral studies found that the spacing effect
635 could be effective in terms of days or months (Cepeda et al., 2008). Besides,
636 the optimal interval also varied in different learning tasks, different retention
637 intervals, and different retention lags (Cepeda et al., 2006; Pashler et al., 2009;
638 Toppino and Gerbier, 2014). In the current study, we tried the longest possible
639 IRI with the constraint that trials from each condition were all within one
640 session (to avoid any cross-session differences). It seems that this
641 long-spaced interval might not be long enough to bend the curve. In addition,
642 this design unavoidably results in an imbalance in the temporal distributions of
643 repetitions under different spacing conditions, which might have some effect
644 on memory performance. Indeed, we found a significant spacing (MA vs. SS)
645 by serial position interaction ($F_{(3,96)} = 2.74, p = 0.048$). There were significant
646 primacy and recency effects under the massed learning condition, i.e., trials
647 studied in the first and last quartiles of a run were remembered better than
648 those studied in the middle ($t_{(32)} = 2.33, p = 0.026$). No such effect, however,
649 was found in the short spaced condition ($t_{(32)} = 0.86, p = 0.4$). This suggests
650 that the serial position and spacing might interact to affect memory
651 performance, which could potentially confound the result. Future studies could
652 use a multi-day design to examine whether pattern similarity plays a role in the
653 inverted U-shaped relationship of spacing and memory.

654

655 Although our results suggest that repetition priming might be a result of
656 residual working memory representation, which might hinder later pattern
657 reinstatement and impair memory, either behavioral repetition priming or N400
658 repetition suppression could not quantitatively predict memory performance. In
659 fact, many existing studies examining this issue have found mixed results (see
660 (Zhao et al., 2015)). Due to the fact that the repetition priming is affected by the
661 initial processing strength and the repetition lag, and in turn, would affect the
662 retrieval of prior representation and further encoding, it would be difficult to
663 establish a direct association between repetition priming and memory
664 performance (Xue et al., 2011). Future studies should further examine the
665 relationship between repetition priming, neural repetition suppression, pattern
666 reinstatement, and episodic memory performance.

667

668 In conclusion, our study provides several lines of novel neural evidence to
669 advance our understanding of the mechanisms of repeated studies in
670 enhancing memory. Contrary to the encoding-variability hypothesis, better
671 memory was associated with greater STPS that occurred at a late time window,
672 and spacing enhanced memory by increasing the STPS. This pattern similarity
673 in the late window might reflect the reinstatement of more abstract
674 representation, which was reduced under the massed condition due to the
675 strong momentary retrieval strength. These results highlight the complex

676 interactions of multiple memory processes and representations in determining
677 memory performance.
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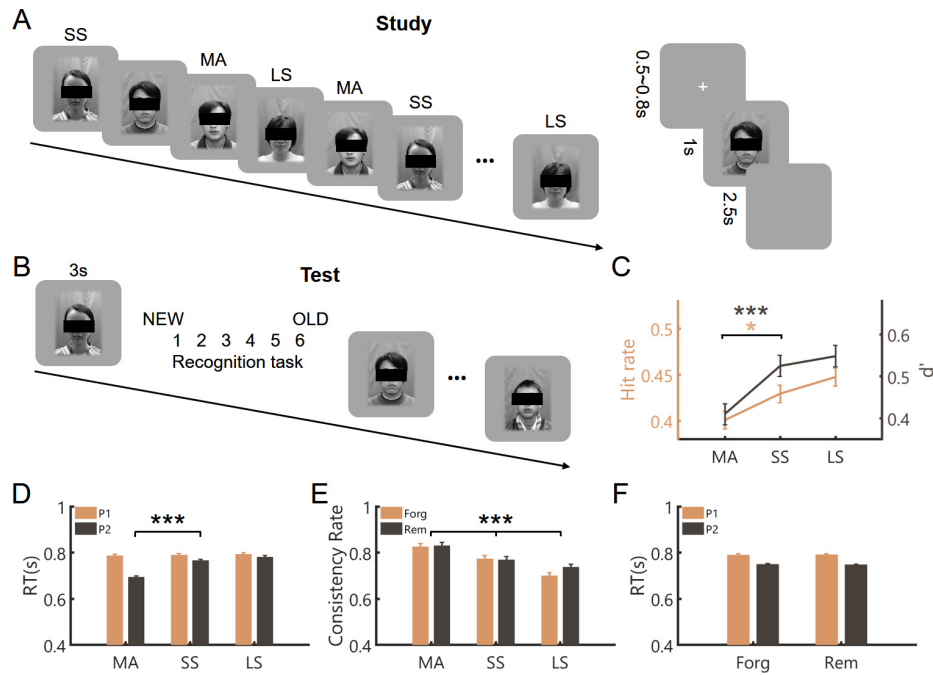
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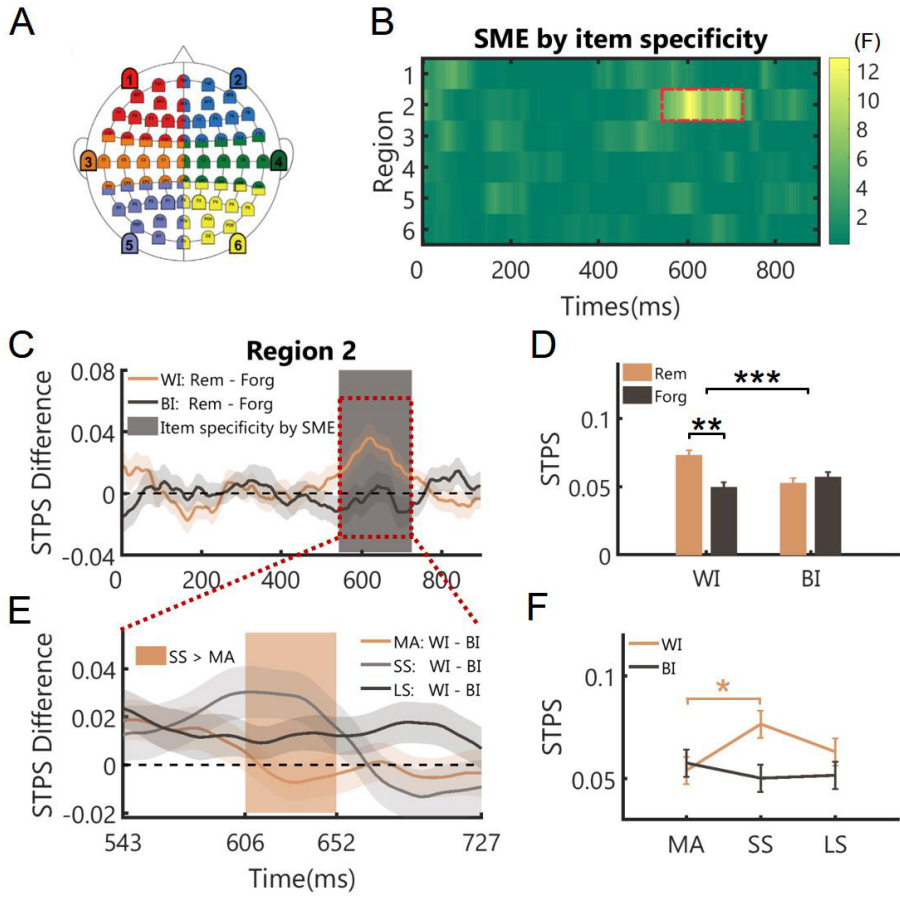
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Figure 1. Experimental paradigm and behavioral results. **A.** Each novel Chinese face was presented twice under one of the three inter-repetition interval (IRI) conditions, i.e., MA (0-1 trials), SS (4-8 trials), and LS (94-96 trials). Participants were asked to perform an age judgment task during learning. **B.** A surprising recognition task was conducted 30 minutes after the encoding task. Participants were asked to decide whether they recognized each face on a 6-point scale, with 1 indicating “definitely new” and 6 indicating “definitely old”. Spaced learning enhanced memory performance as measured by both high confidence (scored 5 or above) hit rate and d' (**C**), reduced repetition priming effect as measured by RT (**D**), and lower response consistency between the two presentations (**E**). **F.** Reaction time was not associated with subsequent memory effect. Error bars represent within-subject SE. * $p < 0.05$; *** $p < 0.001$.

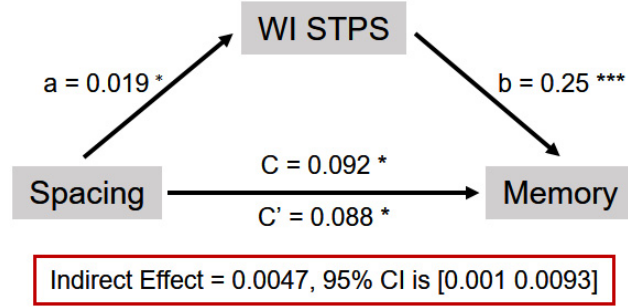
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864 **Figure 2.** Spaced learning was associated with greater item-specific STPS,
 865 which predicted better subsequent memory performance. **A.** The 64 electrodes
 866 were grouped into six regions for better spatial specificity. **B.** The statistics (F
 867 value) of subsequent memory by item-specificity (within-item (WI) vs.
 868 between-item (BI)) interaction, which were obtained under the framework of
 869 memory by item-specificity by spacing three-way ANNOVA. The x-axis
 870 represents time, and Y-axis represents the spatial regions. **C.** Plots of STPS
 871 differences between remembered and forgotten items as a function of WI and

872 BI. The gray shaded area indicates the temporal cluster showing a significant
873 subsequent memory by item-specificity interaction. The cluster remained
874 significant after correcting for multiple comparisons using the cluster-based
875 permutation test. **D.** Bar graph of the mean STPS in the corresponding
876 temporal cluster in Region 2, as a function of subsequent memory, separately
877 for within-item and between-item STPS. **E.** The plot of item-specific
878 representation (WI - BI) across three spacing conditions, within the cluster
879 showing subsequent memory effect. The orange shaded area marks the
880 temporal cluster showing a significant spacing (MA vs. SS) by item-specificity
881 interaction after correcting for multiple comparisons using a cluster-based
882 permutation test. **F.** The plot of the mean STPS in the shaded temporal cluster
883 in (**E**), as a function of item specificity, separately for spacing conditions, with
884 SS being associated with better item-specific representations than MA. Error
885 bars represent within-subject SE. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$
886

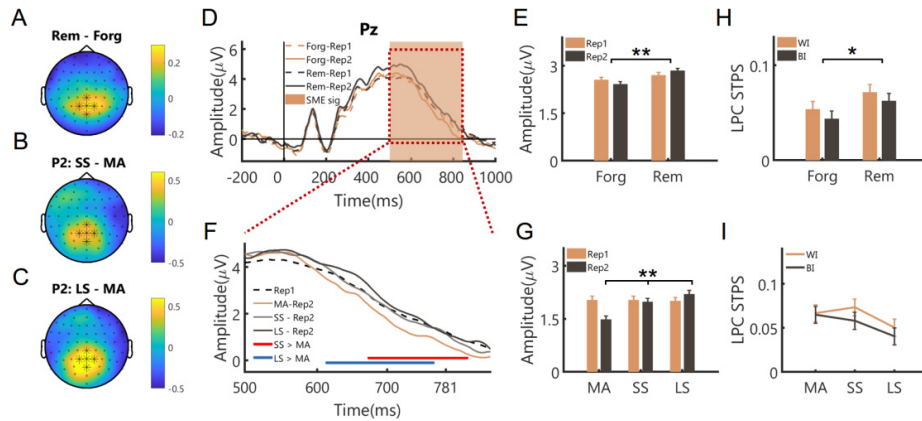


887

888 **Figure 3.** Within-item STPS partially mediated the spacing effect on memory.

889 $*p < 0.05$; $***p < 0.001$

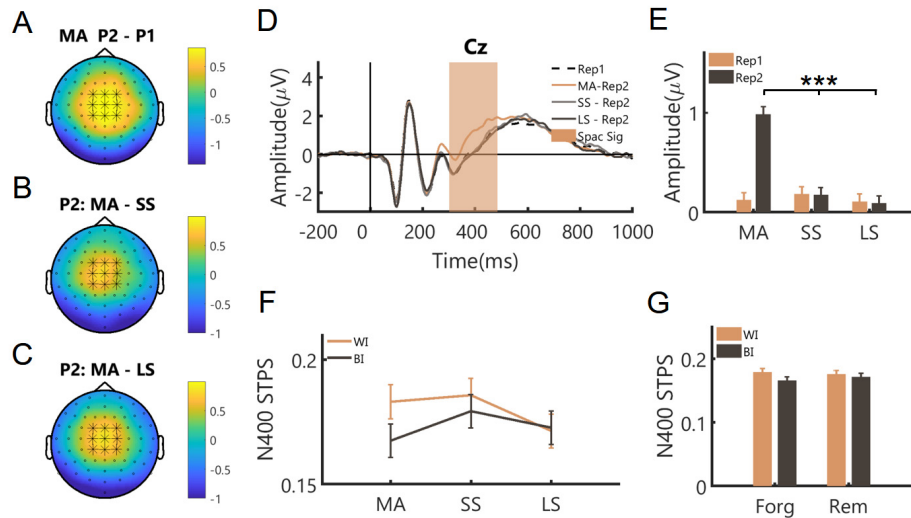
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891

892 **Figure 4.** Spacing enhanced late positive component responses. **A.** The
 893 topographic map of mean ERP differences between subsequently
 894 remembered items and forgotten items during 500-844ms. **B-C.** The
 895 topographic maps of mean ERP differences between SS and MA (**B**), LS and
 896 MA (**C**) on the second presentation during 672-766ms. The asterisks (*) mark
 897 the channels that were used in the STPS analyses. **D.** The plot of ERP at Pz
 898 electrode as a function of memory and repetition. The orange shaded area
 899 marks the temporal cluster showing the subsequent memory effect, with
 900 subsequently remembered items evoking more-positive going LPC than
 901 forgotten items. **E.** The mean amplitudes of ERP response in the cluster
 902 showing the subsequent memory effect. **F.** The plot of ERP at PZ electrode as
 903 a function of repetition and spacing condition. The red line and blue line
 904 represent the temporal clusters showing larger amplitude for SS than MA, and
 905 LS than MA, respectively. **G.** Bar graph of the mean ERP amplitudes in the
 906 cluster showing the spacing effect. **H.** Bar graph of the LPC STPS as a
 907 function of item-specificity and subsequent memory. The LPC did not carry

908 item-specific representation. I. The plot of the LPC STPS as a function of
909 item-specificity and spacing condition. Error bars represent within-subject SE.
910 * $p < 0.05$; ** $p < 0.01$
911



912

913 **Figure 5.** Spacing reduced the repetition effect on N400. **A.** The topographic
 914 map of mean ERP differences between P2 and P1 under MA during
 915 300-484ms. **B-C.** The topographic maps of mean ERP differences between
 916 SS and MA (**B**), LS and MA (**C**) on the second presentation. The asterisks (*)
 917 mark the channels that were used in the STPS analyses. **D.** The plot of ERP at
 918 Cz electrode as a function of spacing condition and repetition. The orange
 919 shaded area marks the temporal cluster showing a significant interaction
 920 between spacing condition and repetition. **E.** The mean amplitudes of N400
 921 response as a function of repetition and spacing condition. **F.** The plot of
 922 within- (WI) and between-item (BI) STPS in N400. **G.** STPS for remembered
 923 (Rem) and forgotten (Forg) items in the N400, which did not show any
 924 subsequent memory effect. Error bars represent within-subject SE. *** $p <$
 925 0.001