

1 **Title: Effect of Fornix Stimulation on Acute Memory Encoding**
2

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41 **Abstract:**

42 The reported memory-related effects of stimulating different nodes within the classical Circuit of
43 Papez have been inconsistent, though the possibility of immediate or chronic memory benefit
44 remains. We undertook memory experiments during deep brain stimulation (DBS) in human
45 subjects with mild, early Alzheimer's Disease (2 males, 3 females; n=5) to rigorously investigate
46 the effects of fornix stimulation on acute memory function. We sought to assess whether some of
47 the reported variability may be attributed to the stimulation protocol, and to determine whether
48 stimulation alters memory formation per se, rather than influencing a process required for but not
49 directly related to memory encoding. We tested fornix stimulation during both awake DBS
50 surgery and post-operatively, in subjects participating in a broader clinical trial (ADvance II). In
51 both settings, using a parametric episodic memory task with distinct encoding, attention, and
52 delayed recall phases, we found that fornix stimulation generally impaired memory, with higher
53 frequencies producing the greatest detriments on memory performance. Furthermore, stimulation
54 specifically interacted with trial-by-trial memory encoding, rather than with other functions such
55 as visual-spatial processing, attention, or short-term working memory. Therefore, in both
56 contexts and across a wide range of stimulation frequencies, open-loop fornix stimulation
57 directly impaired acute, item-specific memory encoding, though the effects of more chronic
58 stimulation on memory and cognitive function are yet to be determined.

59

60 **New and Noteworthy:** Electrical stimulation of different nodes within the Circuit of Papez has
61 been assessed in a variety of human studies with conflicting or indeterminate results. Our goal
62 was to combine a precise psychophysical paradigm with varying stimulation protocols across
63 two experimental settings (intra-op, post-op) to more robustly identify and characterize the

64 interaction between fornix stimulation and memory, and to isolate whether those effects are
65 specific to memory encoding, rather than related to distinct, supporting cognitive functions.

66

67 **Introduction**

68 Electrical brain stimulation is a complex intervention that has been shown to produce variable
69 effects on neural circuit function depending on its timing, frequency, and pulse parameters^{1,2}.
70 Open-loop high-frequency stimulation in the form of deep brain stimulation (DBS) has
71 successfully been applied to treat disorders such as Parkinson's Disease, Essential Tremor, and
72 epilepsy, and, thus, whether it can also successfully be applied to cognitive and behavioral
73 disorders is a critical open question³⁻⁷.

74

75 Prior work applying stimulation to areas within the medial temporal lobe and within the
76 traditional Circuit of Papez—the hippocampal-thalamocortical circuit known to be critical for
77 encoding and storage of episodic memories—to achieve therapeutic improvement in patients
78 with memory deficits has yielded inconsistent results⁸⁻¹². For example, there is controversy about
79 whether stimulation of the entorhinal cortex and hippocampus leads to impairment or
80 improvement in spatial memory^{8,13-16}. Meanwhile, some initial results suggest that DBS of the
81 fornix (DBS-f) may improve memory in patients with epilepsy^{17,18} but definitive evaluation was
82 limited by small sample sizes and potential practice effects. Relatedly, DBS-f in patients with
83 Alzheimer's Disease has been shown to improve cerebral glucose metabolism, the trajectory of
84 regional brain atrophy, and performance on clinical assessments of function¹⁹⁻²¹. None of this
85 previous work, however, undertook a precise, direct examination of the effect of stimulation on
86 acute memory encoding and recall performance in a rigorous, quantitative psychophysical task
87 paradigm. Different stimulation frequencies can also have distinct effects on neuronal
88 activation¹², yet prior DBS-f studies have not conducted a precise examination of the effect of
89 different stimulation protocols¹⁹⁻²¹. High frequency stimulation may cause somatic inhibition

90 whereas lower frequencies may cause excitation. Theta burst stimulation, meanwhile, may
91 promote plasticity and potentially memory enhancement^{22,23}. Therefore, we tested four distinct
92 stimulation frequencies to assess which protocol, if any, had the greatest impact on memory
93 performance.

94

95 Prior work has also suggested that stimulation of white matter tracts (vs. grey matter) may
96 provide greater regulatory control of networks that underlie cognitive processes such as memory,
97 further motivating the present exploration of fornix stimulation¹². Here, we studied DBS-f in
98 humans to understand its effects on memory function over an acute timescale, to assess the
99 impact of different stimulation protocols, and to determine whether stimulation alters memory
100 encoding specifically.

101

102 Stimulation may exert an effect on memory through various mechanisms, including immediate
103 stimulation-driven circuit effects, subacute plasticity-mediated effects over hours to weeks, and
104 long-term (potentially metabolic) effects over months to years^{19,21}. This experiment focused
105 specifically on the question of whether DBS-f has acute effects on event-level memory,
106 independent of other task requirements. Importantly, stimulation may influence other aspects of
107 cognition necessary for, but not directly mediating, encoding or recall. These additional
108 cognitive requirements for successful memory formation include factors such as intact
109 visuospatial perception and sufficiently deep attentive processing of the memorandum. Prior
110 studies did not directly control for non-mnemonic cognitive factors of these sorts^{8,13-16,19-21}. As a
111 result, strictly speaking, the effects of stimulation may not have been specifically linked to
112 memory encoding, *per se*. Using a parametric memory task design with separate stimulus

113 encoding, attention, and recall phases, we sought to rigorously determine whether DBS-f altered
114 memory encoding apart from related functions, such as attention or online, short-term working
115 memory.

116 **Materials and Methods**

117 *Study Population*

118 Patients enrolled in the Phase 3 double-blind trial of deep brain stimulation of the fornix (DBS-f)
119 in mild AD (the AAdvance II trial) at Rhode Island Hospital from 2021-2023 were invited to
120 participate in the present study. The inclusion criteria for the AAdvance II trial have been
121 previously described elsewhere¹; findings presented here may not be entirely representative of
122 the general population. 5 patients (2 males, 3 females) elected to enroll in the study, and these
123 patients had a mean age of 73.8 (*range* = 67-81) and an average ADAS-Cog14 score of 31.6
124 (*range* = 24-37) and CDR-total score of 0.7 (*range* = 0.5-1; Table 1). A total of 152 sets (here, a
125 “set” refers to encoding, immediate report—“attention”—and delayed recall components for a
126 given movie-dot pair) of the memory task across patients were completed intraoperatively, and
127 214 sets were completed postoperatively. There was no attrition from the study; all 5 patients
128 participated in intraoperative and postoperative testing. 4 out of the 5 patients performed
129 preoperative testing. All research activities were performed prior to randomization into the trial.
130 The trial was overseen by the Food and Drug Administration and Health Canada under
131 Investigational Device Exemption G110220 and is registered at clinicaltrials.gov
132 (NCT03622905). This study was undertaken independently from activities related to that clinical
133 trial, with separate regulatory approvals, and assessed phenomena were not directly related to the
134 end-points of that trial. The experimental study protocols for the primary study and for this add-

135 on experiment were approved by the Institutional Review Board at Rhode Island Hospital. All
136 participants and their caregivers signed informed consents in-person.

137

138 *General Surgical and Clinical Methods*

139 Each participant underwent awake, bilateral implantation of Boston Scientific DBS leads (DB-
140 2202-45 Vercise Cartesia 45cm 8 contact DBS Directional Leads) positioned approximately
141 2mm anterior-lateral and parallel to the descending columns of the fornix. Brief, light IV
142 sedation was typically administered at the start of the procedure (Propofol or Dexmedetomidine),
143 but the majority of the procedure, until closing, was performed with the patient fully awake and
144 alert. Subsequently, a Boston Scientific Vercise PC pulse generator was implanted in the chest
145 wall, below the clavicle. Lead and electrode contact locations were verified by co-registration of
146 each patient's pre-operative MRI with their intraoperative and postoperative CT. Due to the
147 proximity of electrode trajectories to the hypothalamus, intra-operative safety testing was
148 performed to determine amplitude tolerance during stimulation. Contacts that elicited autonomic
149 side effects, including diaphoresis and elevations in blood pressure or heart rate (typically more
150 ventral contacts), were avoided for intraoperative and postoperative experiments. All
151 experiments included in the present report occurred prior to patients' randomization into a
152 stimulation group (off, low frequency, or high frequency) for the chronic phase of the AAdvance
153 II trial. To assess the impact of acute stimulation on memory encoding and recall, each
154 participant performed a visual-spatial memory task (described below) pre-operatively, intra-
155 operatively, and 4-weeks post-operatively.

156

157 *Memory Task*

158 To assess episodic visual memory, we asked subjects to learn and remember paired associations
159 between visual cues (5-second, trial-unique movie clips) and the location of memoranda (small
160 white dots). Each association was presented in an “encoding phase” and tested in a separate
161 “recall phase.” Specifically, at the beginning of each trial a short (5 second) movie clip was
162 displayed within a circular aperture and presented alone (Figure 1). The same clip was then
163 immediately replayed concurrent with the presentation of the memorandum: a white dot at a
164 randomly selected location from 0 to 2π around the circular movie window, giving the subject
165 full opportunity to attend to both the movie and memorandum. The movie and white dot were
166 extinguished and then, in the “attention” (immediate report) phase, we asked subjects to indicate
167 the former location of the white dot using a joystick-controlled cursor and button press (to lock-
168 in the selected location). This immediate report provided an opportunity to confirm that subjects
169 had indeed attended to the cue presentation, processed the dot location to a depth at least
170 sufficient for working memory, and were able to perform the required visual-motor response.
171 Participants had unlimited time to make their selection (average reaction time: 8761 +/- 6181
172 ms). Once they made their choice, an inter-trial interval of 1000 ms ensued, followed by the next
173 encoding trial. Patients performed 4 of these “Encoding” trials consecutively. These ensuing
174 encoding trials served as distractors to prevent ongoing mental rehearsal (i.e., persistent working
175 memory) before delayed recall trials were presented. In the delayed “Recall” phase, patients
176 were shown the same 4 movie clips again, but without the white dot. Importantly, the movie in
177 the last trial of the encoding phase was never the first of the recall phase. The objective of the
178 “Recall” trials was to remember the location of the white dot that was previously associated with
179 that movie during “Encoding”. Patients indicated their choice of location using the same
180 joystick-controlled response (Figure 1). Across the experiments, each subject performed up to 96

181 sets of encoding and recall trials (Table 2). Stimuli were presented on a 27-inch LED monitor
182 (resolution 1920 x 1080 pixels, refresh rate 60 Hz).

183

184 *Stimulation Conditions*

185 To assess the effect of acute fornix stimulation on memory encoding and recall, we tested four
186 different stimulation conditions: LOW frequency (40 Hz), HIGH frequency (130 Hz), THETA
187 (intraoperative: theta burst; postoperative: 6 Hz), and no stimulation, (OFF). Low and high
188 frequency stimulation pulses were biphasic, charge-balanced, square-waves (full pulse width: 90
189 µs). Based on prior work²⁴, theta burst stimulation during the intraoperative phase was delivered
190 as bursts of 4 bilateral, charge-balanced biphasic symmetric pulses (phase width = 200 µs, inter-
191 phase interval = 100 µs; Figure S1A) at 130 Hz. Bursts were delivered at 5 Hz (inter-burst
192 interval = 200 ms; Figure S1B). All stimulation was delivered bilaterally using a monopolar
193 configuration on each side via DBS leads implanted adjacent to the fornix (Figure 2, Table 3).
194 We performed amplitude testing to identify the highest tolerated amplitude for stimulation and
195 selected the contact with the fewest side effects on each side (contact 8 bilaterally for all
196 patients).

197

198 During the intraoperative experiment, bilateral stimulation was delivered during concurrent
199 presentation of the dot and movie in the encoding phase for 5 seconds and the stimulation
200 condition varied by trial (Figure 1). During the post-operative experiment, stimulation was
201 delivered block-wise due to the different technical capabilities of the externalized intra-operative
202 vs. fully implanted stimulation systems. Specifically, the 4 stimulation conditions were pseudo-
203 randomized, without replacement, across the 4 trials, such that each condition appeared once in

204 each cycle of 4 trials. No stimulation was delivered during the subsequent recall trials. As
205 mentioned previously, the first recall trial was selected such as to not contain the same movie-dot
206 stimuli as the last encoding trial immediately preceding. The behavioral task was run through a
207 control computer using the NIMH MonkeyLogic toolbox for MATLAB^{25,26}, which was also used
208 to coordinate the programmatic delivery of stimulation by FDA-approved Alpha Omega
209 neurophysiology systems (Alpha Omega, Inc). More specifically, we used the C++ Neuro
210 Omega software development kit compiled into a custom python library that communicated with
211 the Neuro Omega systems. Coordination with the MonkeyLogic behavioral control system was
212 implemented through task-specific python code. The Alpha Omega systems were connected to
213 the leads secured to microdrives resting on patient-specific, 3D-printed stereotactic platforms
214 (StarFix micro-targeting system, FHC Inc)^{27,28}, allowing for precise, controlled delivery of
215 stimulation from the most superior contact (#8).

216

217 During the postoperative experiment, we wirelessly connected to the patient's implanted DBS
218 pulse generator using the designated ADvance II trial study tablet. Due to the technical
219 limitations of this system, stimulation parameters were set manually. Thus, for a set of 4
220 encoding trials, stimulation (in the ON conditions) was delivered continuously at a constant
221 frequency for the entire duration of those 4 encoding phase trials. Stimulation ceased
222 immediately prior to the ensuing recall phase trials. The stimulation condition was assigned
223 pseudo-randomly immediately prior to each block of encoding trials. All other parameters
224 (amplitude, pulse width) were replicated based on the intraoperative conditions. In addition,
225 because the implanted pulse generator was not capable of true "theta burst" stimulation patterns,

226 for the theta frequency condition, stimulation was delivered at a constant 6 Hz without the
227 overlaid higher frequency burst.

228

229 *Statistical Analysis*

230 Statistical analysis of memory task data was conducted using open-source MATLAB toolboxes²⁹
231 and custom MATLAB scripts (Mathworks, Version R2023a, Natick, MA) and R (Posit Software,
232 RStudio, Version 2023.12.1, Boston, MA). Subjects were assigned anonymous codes to remove
233 identifiers for analysis. Performance on both encoding and recall blocks was quantified as the
234 smallest difference between the chosen and true (instructed) locations of the white dot in radians
235 from π to $-\pi$ (Figure 1). Errors during the immediate report phase of the encoding trials were
236 used to identify instances where potential working memory or attentional lapses may have
237 occurred. The rates of such errors were compared across stimulation conditions to assess whether
238 stimulation might have had a non-specific effect on cognitive functions more broadly supporting
239 memory. Then, those encoding trials which had immediate report errors of more than $\pi/4$
240 radians from the true location were discarded along with the corresponding recall trials, allowing
241 assessment of potential effects of stimulation on memory encoding *per se*, in the absence of such
242 non-specific lapses. In total across preoperative, intraoperative, and postoperative sessions, 37
243 out of 922 recall trials were removed from the analysis of delayed recall errors.

244

245 *Bayesian Multivariate Linear Regression*

246 We used R³⁰ and the brms package³¹ to conduct a Bayesian regression for the primary analysis.
247 We used the equation *Position Error* ~ 1 + *Stimulation Condition* + (1 + *Stimulation*
248 *Condition|Patient*) to regress position error, in radians, on each of the four stimulation conditions

249 as categorical variables with the control condition as an intercept. The regression used absolute
250 recall errors in order to treat clockwise and counter-clockwise errors equivalently. Additionally,
251 the regression incorporated patient codes as a random variable to account for individual
252 differences across subjects. We specified uninformative (null) priors for the Bayesian analysis,
253 which were flat distributions and represented little prior expectation of how the data might be
254 distributed. Because the resulting posteriors of Bayesian analyses are a combination of prior
255 distributions and empirical data, an uninformative prior will have minimal impact on the
256 posterior estimates. Bayesian regressions for intraoperative and postoperative data were run
257 separately due to differences in experimental setup between sessions.

258

259 The resulting parameter and posterior of OFF-stimulation represents the average recall error
260 associated with control. Because of the categorical nature of the regression, the parameters and
261 posterior distributions of low, high, theta, and theta burst estimate the offset (i.e., relative values)
262 of errors compared to those of control as opposed to representing a direct estimate of error
263 associated with a condition. In these relative offset posteriors, estimates greater than 0 indicate
264 average errors greater than OFF-stimulation and therefore poorer recall performance. The
265 posteriors of stimulation were further analyzed by quantifying the percentage of estimates that
266 were above 0.

267

268 We then performed an additional analysis based on the assumption that a participant's
269 performance on the delayed recall phase could only be as high as their accuracy during encoding.
270 We subtracted the position error of immediate report trials from the position error of the

271 corresponding delayed recall trial and then used the same Bayesian model as above to analyze
272 this adjusted set of recall errors.

273

274 *Linear Mixed Effects Model*

275 To further address variability in responses among subjects, we employed a linear mixed-effects
276 (LME) model as a secondary analysis, with stimulation frequency (OFF, THETA/THETA
277 BURST, LOW, HIGH) as a categorical fixed effect and intersubject variability as a random
278 effect using the following equation: *Absolute Recall error ~ stimulation + (stimulation|subject)*.

279 The OFF-stimulation condition was set as the reference level. We performed a separate analysis
280 using this model for each session (intraoperative vs. postoperative). Statistical significance was
281 set at p<0.05.

282

283 *Bootstrap Analysis*

284 As a supplementary analysis, we used bootstrap statistics to compare two measures of circular
285 spread of empirical errors between conditions: 1) the standard deviation of a fitted von Mises
286 distribution, and 2) mean resultant length, further detailed below. Within each condition, recall
287 error values from all patients were pooled together and sampled randomly with replacement
288 across 10,000 iterations. Descriptive statistics were subsequently computed for each of the
289 10,000 bootstrapped samples in a condition. Thus, an extensive set of descriptive statistical
290 values were obtained for each condition, allowing us to conduct hypothesis testing and quantify
291 differences in task performance between stimulation frequencies.

292

293 Specifically, we generated 10,000 bootstrapped distributions for each stimulation condition by
294 randomly shuffling our empirical recall error values with replacement. We assessed variance
295 around the correct response location (defined as 0 radians) by extracting either the standard
296 deviation or vector length from each bootstrapped distribution, yielding 10,000 values of
297 variance associated with each stimulation condition. As noted, to quantify the variance
298 distribution, we employed two distinct measures of circular concentration: 1) the standard
299 deviation of a fitted von Mises distribution, and 2) mean resultant length.

300

301 *1. Standard Deviation of von Mises Distribution*

302 We fit a von Mises distribution with a mean of 0 and variable standard deviation for every
303 stimulation condition and session using Maximum Likelihood Estimation (MLE). We chose
304 to fit these distributions specifically centered at 0 radians of error, which represents the
305 spread centered on the correct location. From each fitted von Mises distribution, we
306 calculated the standard deviation by estimating the concentration parameter in the Bays' lab
307 toolbox k2sd³². The von Mises distribution is the circular equivalent of a Gaussian, and
308 therefore a von Mises curve with a lower standard deviation reflects better performance.

309

310 *2. Mean Resultant Length*

311 Because fitting a von Mises distribution using MLE would at times yield convergence errors
312 due to the random shuffling of bootstrapping, we elected to employ an additional measure of
313 variance. Our second method of measuring variance was taking the mean resultant length of
314 each sample, a value that represents the spread of values on a circular plane from 0 to 1, with

315 0 indicating a completely uniform spread, and 1 indicating all data points being concentrated
316 at a single value.

317

318 We compared variance (SD of von Mises distribution or mean resultant length) values in a
319 pairwise fashion between the OFF-stimulation condition and the LOW, HIGH, and
320 THETA/THETA BURST conditions. We compared variances between conditions as opposed to
321 a means because a mean closer to 0 could represent the presence of large errors balanced around
322 0. To make pairwise comparisons, we performed permutation testing by subtracting the
323 bootstrapped values of the OFF condition from those of one of the stimulation conditions,
324 resulting in a single distribution of 10,000 difference values for each set of comparisons. We
325 then determined if the mean of this distribution of differences was significant by centering this
326 distribution, bootstrapping the means of this distribution, then calculating the proportion of
327 values more extreme than the original mean of differences. To supplement these pairwise
328 comparisons, our second method of hypothesis testing used a two-sample t-test to compare the
329 original two sets of circular dispersion measures. In each method, we corrected for multiple
330 comparisons using Benjamini-Hochberg procedure with a q-value of 0.1. We considered a value
331 of $p < 0.05$ to be statistically significant.

332

333

334 **Results**

335 To assess the effects of acute DBS-f on visuo-spatial memory, we asked participants to perform
336 an automated, computer-based memory encoding and recall task while trial- or block-
337 randomized stimulation (intra-operatively vs. post-operatively, respectively) was delivered.

338 Specifically, we tested the effect of four DBS-f conditions on memory performance (see *Methods*
339 – *Stimulation Conditions*).

340

341 *Fornix stimulation did not impair immediate report*

342 First, to assess the possible impact of acute stimulation on attention and/or working memory, we
343 assessed performance on the immediate report (“attention”) phase of the task. Performance
344 accuracy was quantified as the mean absolute error in radians between the chosen location and
345 the correct dot location. Comparison of immediate report performance by stimulation condition
346 revealed that subjects were highly accurate across all intraoperative conditions (OFF: absolute
347 mean error 0.346 radians +/- 1.041 radians; LOW: absolute mean error 0.409 radians +/- 1.152
348 radians; HIGH: absolute mean error 0.169 radians +/- 0.262 radians; THETA BURST: mean
349 absolute error 0.228 +/- 0.616 radians; Figure 3A) and postoperative conditions (OFF: 0.130 +/-
350 0.135 radians; LOW: 0.632 +/- 1.382 radians; HIGH: 0.652 +/- 1.360 radians; THETA: 0.752 +/-
351 1.54 radians; Figure 3B), and no significant differences in mean error were observed between
352 conditions (ANOVA: intraoperative: $p = 0.458$; postoperative: $p = 0.828$). This suggests that
353 stimulation did not negatively impact attentional deployment, working memory, or visual-motor
354 abilities required to successfully encode and subsequently report the dot location.

355

356 *Descriptive statistics for overall memory performance*

357 To understand the effect of fornix stimulation on delayed recall, we excluded trials where
358 immediate report suggested inattention or other potential non-mnemonic influences (see
359 Methods: intraop: 10 of 152, 6.6%, of trials excluded; postop: 16 of 214, 7.5%, of trials
360 excluded; Table 2). As before, we calculated recall error (chosen location – true location) to

361 assess memory performance by stimulation condition (Table 4, Figure 3, Figure S2-3). Recall
362 memory performance had the lowest absolute radial error for the intraoperative OFF conditions
363 (Table 4, Figure 3A) and postoperative OFF conditions (Figure 3B). Individual patient
364 performance demonstrated the same trends for both the intraoperative and postoperative sessions
365 (Figure S2-S3). On average, the amount of time between an encoding trial and its corresponding
366 delayed recall trial was 98.9 +/- 93.2 seconds for intraoperative testing and 58.4 +/- 28.6 seconds
367 for post-operative testing (Figure S4). In the intraoperative sessions, the high variability in time
368 between immediate recall and corresponding delayed recall trials was due to extreme outliers in
369 response time (Figure S4). Notably, there was no significant difference between intraoperative
370 OFF recall compared to preoperative recall performance (intraoperative OFF: mean absolute
371 error: 1.22 +/- 0.93 radians; Preoperative OFF: 1.55 +/- 1.00 radians, p=0.826; Figure S5),
372 suggesting the intraoperative environment itself did not adversely affect performance.
373 Additionally, performance on the intraoperative and postoperative OFF conditions were
374 significantly greater than chance for each subject (p<0.001 for all sessions and subjects; Figure
375 S6) and when individual OFF data was pooled across subjects within a session (p<0.001 for
376 grouped intraoperative OFF, p<0.001 for grouped postoperative OFF; Figure S6). Furthermore, a
377 swap analysis comparing the chosen location for a given incorrect trial to the true locations of
378 other trials within the same block demonstrated relatively large differences, suggesting that
379 erroneous choices were not simply because the subjects mistakenly swapped the dot position
380 between two memoranda (Figure S7).

381

382 *Bayesian analysis of memory performance during DBS-f*

383 To more formally assess performance across stimulation and no-stimulation conditions and to
384 quantify the magnitude and robustness of stimulation effects on recall performance, we
385 performed a Bayesian mixed-effects hierarchical linear regression that predicted position error
386 (in radians) as a function of stimulation condition. Considering that multiple stimulation
387 conditions were collected from each individual, we added a random effect for subject and then
388 estimated the group-level effects of each stimulation condition on absolute position error while
389 accounting for the nested, within-subject design of the study (see *Methods – Bayesian*
390 *Multivariate Linear Regression*). The resulting group level posteriors suggest moderate
391 impairments in performance (as indexed by the proportion of the posterior distribution > 0) for
392 LOW and THETA BURST stimulation in both intraoperative (LOW: 58.0%, THETA BURST:
393 67.4%; Figure 4A-D) and postoperative sessions (LOW: 62.3% of estimated parameter values lie
394 above 0, THETA: 70.8%; Figure 4A-D). Notably, HIGH frequency stimulation strongly
395 impaired performance in both sessions (Intraoperative: 89.45% of estimated parameter values lie
396 above 0; Figure 4C; Postoperative: 81.40%; Figure 4C), suggesting higher frequency stimulation
397 may particularly impact memory performance.

398

399 To further confirm the effect of stimulation frequency (OFF, THETA/THETA BURST, LOW,
400 HIGH) on recall error using a frequentist approach, we performed a secondary analysis using an
401 LME model. Stimulation frequency was treated as a categorical fixed effect, with OFF as the
402 reference level and random intercepts were included to account for inter-subject variability. The
403 LME model results supported the findings from the Bayesian analysis. Compared to stimulation
404 OFF, all stimulation frequencies demonstrated an increase in recall error for intraoperative
405 (LOW: $\beta = 0.070$, SE = 0.265, $p = 0.792$; THETA BURST; $\beta = 0.127$, SE = 0.233, $p = 0.587$;

406 HIGH: $\beta = 0.391$, SE = 0.237, $p = 0.102$ Figure 5A) and postoperative stimulation conditions
407 (LOW: $\beta = 0.098$, SE = 0.227, $p = 0.668$; THETA: $\beta = 0.144$, SE = 0.226, $p = 0.524$; HIGH: $\beta =$
408 0.265, SE = 0.270, $p = 0.327$; Figure 5B). High frequency stimulation led to the greatest
409 impairment in performance. Random effects were not statistically significant, indicating that
410 individual variability in recall errors within a given stimulation condition and session (e.g.,
411 intraoperative HIGH) had minimal impact ($p > 0.05$ across each condition and testing session;
412 Figure S8).

413

414 *Disruption of memory encoding persisted after accounting for immediate report performance*
415 We reasoned that, in the delayed recall trials, participants could answer only as precisely as what
416 they had encoded, as reflected in the immediate report phase. Therefore, to account for
417 performance in that immediate report phase, we subtracted the position error of immediate report
418 trials from their corresponding delayed recall error. Taking this new set of recall errors (Recall
419 position error – immediate report error), we re-computed the Bayesian analysis. The posterior
420 distributions revealed the same patterns of performance across conditions, with HIGH frequency
421 stimulation strongly impairing recall performance in both intraoperative (HIGH: 91.78%; Figure
422 S9A, S9C) and postoperative sessions (HIGH: 74.92%; Figure S9E, S8G). Low frequency and
423 theta/theta burst stimulation also led to a performance decrease, but to a lesser extent than high
424 frequency stimulation (Intraoperative - LOW: 60.50%, THETA BURST: 60.5; Postoperative -
425 LOW: 55.70%, THETA: 50.52%; Figure S9).

426

427 Further supporting a direct causal effect of DBS-f on memory, we observed that the degree of
428 disruption in recall error due to intraoperative stimulation was anticorrelated with the distance

429 between the stimulating contact and the fornix (Left: $R^2 = 0.17$, slope=-0.30; Right: $R^2 = 0.76$,
430 slope=-0.42; Figure S10A); in other words, we observed greater disruptions in memory
431 performance when the electrode was closer to the fornix. Note, however, this effect was not
432 evident for postoperative stimulation (Left: $R^2 = 0.51$, slope=0.22; Right: $R^2 = 0.12$, slope=0.07;
433 Figure S10B), possibly because the significantly increased duration of stimulation in that context
434 (block-wise, rather than trial-phase-specific) may have overwhelmed any distance-related
435 effects.

436

437 *Acute fornix stimulation disrupted memory encoding in supplementary analyses*

438 In a supplementary analysis, we applied bootstrap statistical methods to generate shuffled
439 distributions for each experimental condition that could be compared against empirical results.
440 Specifically, performance data were shuffled to generate 10,000 separate sample distributions of
441 recall errors for each condition. To compare the empirical and bootstrapped distributions, we
442 employed two distinct measures of circular concentration: 1) von Mises distribution with an
443 estimate of the concentration parameter using Maximum Likelihood Estimation (MLE),
444 converted to standard deviation and 2) mean resultant vector length of each sample, representing
445 the spread of values on a circular plane (further detailed in Methods). To assess statistical
446 significance, we compared the distribution of bootstrapped values between each stimulation
447 condition and OFF stimulation.

448

449 Applying the first measure, the width of the distribution of responses, to the intra-operative
450 experiments where stimulation condition was randomized in a trial-by-trial fashion, we observed
451 degraded recall performance on trials where electrical stimulation was delivered compared to

452 OFF trials (Figure S11A, $p < 0.001$ for both two-sample t-test and bootstrap calculation for LOW
453 vs. OFF, THETA BURST vs. OFF, and HIGH vs. OFF). Likewise, recall performance in the
454 post-operative experiments, where stimulation was varied in a block-wise fashion, was
455 significantly impaired in the stimulation-ON conditions compared to the OFF condition (Figure
456 S11C, $p < 0.001$ for two-sample t-test and bootstrap calculation for LOW vs. OFF, THETA vs.
457 OFF, and HIGH vs. OFF). Thus, regardless of the frequency of the ON condition, electrical
458 stimulation negatively impacted memory performance across both settings.

459
460 Because the relatively sparse data could potentially be consistent with non-normal distributions,
461 we confirmed these results were not specific to that particular statistical model by examining
462 performance in a model-free fashion using resultant vectors derived from the spatial choice
463 distributions. Values for mean resultant length range from 0 to 1, where 0 represents a uniform
464 distribution, and 1 indicates a distribution with all values concentrated at a single point. In both
465 intraoperative and postoperative sessions, we observed that all frequencies of DBS-f produced
466 significantly lower mean resultant lengths compared to the OFF distribution (Figure S11B & D;
467 $p < 0.001$ for all comparisons). These findings reflect a greater spread of recall errors in LOW,
468 HIGH, and THETA conditions compared to OFF, demonstrating that any form of stimulation
469 yielded worse performance relative to no stimulation.

470
471

472 **Discussion**

473 Previous studies testing the effect of hippocampal stimulation on memory in epilepsy patients
474 have produced conflicting results^{8,12,15,33}, and data concerning the possible mnemonic and
475 cognitive effects of DBS-f in humans are relatively sparse^{17,20,21,34}. Here, we aimed to

476 characterize the effect of three fornix stimulation protocols compared to control (no-stimulation)
477 on visuospatial memory in patients with mild AD using a location-recall associative memory
478 task. DBS-f acutely disrupted memory formation while preserving other aspects of cognitive
479 function required to process and report a visual-spatial memorandum. Specifically, based upon
480 successful immediate report performance across conditions, we determined that visual-spatial
481 processing, attention, working memory, and visual-motor responses required for this task were
482 spared by fornix stimulation, in contrast to memory encoding.

483

484 *Acute fornix stimulation during encoding led to specific impairments in delayed recall*
485 Our design allowed us to examine working memory maintenance separately from episodic
486 encoding into long term memory. Here, DBS-f disrupted delayed recall performance compared
487 to the no stimulation control but did not impair the ability to report the memorandum (cue
488 location) shortly after its presentation, a measure of working memory. Because the only
489 differences between the immediate report phase and the delayed recall phase were the longer
490 time delay and intervening distraction of additional encoding and/or recall trials, the observed
491 differences in performance across these phases can be more directly attributed to a specific effect
492 of stimulation on memory encoding. Note, stimulation was never delivered during recall and, in
493 the intraoperative case, was delivered only during part of the encoding trials (during the 5-second
494 co-presentation of the cue and memorandum), so there was unlikely any direct or lingering effect
495 of stimulation on recall processes.

496

497 These results are in line with prior findings that episodic memory formation is critically
498 dependent on hippocampal processes and that damage to the hippocampus results in substantial

499 impairment in the ability to acquire and retrieve new memories³⁵. However, because memory
500 function depends on a variety of neural circuits that may operate in discrete or overlapping ways
501 depending on the precise task paradigm, we should be careful to identify what behavioral
502 features were critical for performance in the current paradigm. Here, we employed an immediate
503 report test that, while following closely after cue-memorandum presentation, likely could not be
504 solved using iconic visual memory mechanisms alone given their relatively rapid decay^{36,37}
505 juxtaposed against typical response times in this task (8761 +/- 6181 ms, Figure 1); in other
506 words, some form of active working memory was likely required even for this initial response, in
507 addition to basic visual attention and other psychomotor functions. Meanwhile, delayed recall
508 was tested after 1-6 intervening, potentially interfering encoding / recall episodes (Intraoperative:
509 98.9 +/- 93.2 seconds between encoding and corresponding delayed recall trials; postop: 58.4 +/-
510 28.6 seconds, Figure S4), making it likely that successful performance required more than simply
511 the active maintenance of information in on-line working memory; in other words, encoding of
512 information into a more durable form would have been required. The differential susceptibility of
513 the immediate report and delayed recall phases to fornix stimulation highlights the distinct neural
514 substrates that are presumed to be in play.

515

516 Meanwhile, working memory is likely a distributed neocortical process coordinated by the
517 prefrontal cortex (PFC)³⁸⁻⁴⁰, consistent with the lack of DBS-f impact on immediate report in the
518 present study. However, the term “working memory” is often employed heterogeneously across
519 studies. Neural mechanisms mediating immediate report performance, here, may not map neatly
520 onto those identified by studies that used longer delays or variable presence of distractors. For
521 example, Daume et al found that theta-gamma phase-amplitude coupling in the hippocampus

522 was related to working memory load and suggested a framework where the PFC provides top-
523 down control of working memory storage in the medial temporal lobe ⁴¹. In the present study,
524 any disruption of hippocampal working memory storage by stimulation may have been mitigated
525 by prefrontal control^{42,43}, resulting in high performance on immediate report trials.

526

527 The disruption of memory encoding by DBS-f may occur through a variety of mechanisms.
528 High frequency stimulation, in particular, may produce a depolarization block of some fibers
529 and/or partial entrainment in others^{41,44}, thereby interrupting or adding noise to medial temporal
530 lobe output signals via the fornix. This hypothesis is in line with findings from DBS for
531 movement disorders, which have suggested that noisy activity from stimulation may disrupt
532 information processing in the cortical-subcortical systems⁴⁵⁻⁴⁷. Here, stimulation may also disrupt
533 oscillations critical to optimal memory function^{33,41,44}. Specifically, phase-locked stimulation
534 may enhance, while phase-randomized stimulation may impair memory^{44,48,49}. Our testing of
535 theta-burst DBS was in part motivated by a preliminary study by Miller and colleagues that
536 suggested possible improvement in visual-spatial memory associated with this pattern of fornix
537 stimulation ¹⁸. Indeed, phase-locked vs. phase-randomized stimulation may produce distinct
538 effects ^{44,50}. One mechanism by which phase-locked stimulation might improve performance is
539 through enhanced theta-gamma coupling in the hippocampal memory circuit⁵¹. Critically,
540 performing phase-locked stimulation requires a closed-loop stimulation system, and recent work
541 has shown that whether stimulation causes behavioral improvement or impairment depends on
542 the state of the stimulation site prior to stimulation⁴⁸. Future human DBS-f studies that probe the
543 effect of delivering closed vs. open-loop stimulation, particularly related to phase-locked vs.
544 phase-randomized stimulation delivery are needed.

545

546 The precise timing of stimulating during a memory task may also account for differing results
547 across studies. For example, prior studies from the transcranial magnetic stimulation literature
548 support the notion that stimulation during performance of a cognitive task yields improved
549 performance compared to stimulation prior to the task^{52,53}. Other invasive stimulation paradigms
550 that yielded improvement in visuospatial memory tasks began delivering stimulation at least 20
551 minutes before the start of the task and continued stimulation throughout the retrieval phase¹⁸. In
552 the present experiment, we delivered stimulation during the encoding phase only, not during
553 recall testing, which may account for some of the observed differences in task performance.
554 These findings also suggest that potential stimulation-induced memory improvements may act on
555 a longer timescale and could perhaps outweigh acute disruptions. Furthermore, findings from
556 clinical studies have demonstrated that benefits from DBS may, in part, arise from improvement
557 in cerebral blood flow, glucose metabolism, and regulation of neuroinflammation on a longer
558 timescale⁵⁴⁻⁵⁶. In the context of memory disorders such as AD, these changes may allow for
559 preservation of remaining neural networks and provide necessary compensatory network drive to
560 recover components of memory function⁵⁵.

561

562 The specific types of memory function tested across studies may in part underlie varying or
563 conflicting effects^{8,14-16}. For example, stimulation of other memory-related regions (e.g.,
564 hippocampus), have shown task-dependent effects on memory strength⁸. Specifically, the same
565 stimulation protocol improved associative but decreased item memory performance. Thus, the
566 impairment in recall performance seen after stimulation in the present study may be specific to
567 visuospatial memory encoding. Furthermore, as above, another possible explanation for

568 differences between the results of previous studies and the present experiment is the duration of
569 stimulation and timing of stimulation delivery with respect to the behavioral assessment. Suthana
570 et al¹⁶ used variable stimulation durations that were dependent on patients' interaction time with
571 each trial, while Jacobs¹⁴ applied a fixed duration of stimulation per trial, most similar to the
572 intraoperative experiment, here. In addition, these previous studies were performed with epilepsy
573 patients with varying levels of memory impairment, not the early AD population; the overall
574 mnemonic effect of stimulation may vary across patient groups.

575

576 *The intraoperative environment did not substantially impair task performance*

577 One potential concern with intra-operative task performance is that patients may be cognitively
578 impacted by the surgical environment, adding a confounding factor to the measure of memory
579 encoding and recall during these trials. Comparison between recall errors from preoperative and
580 intraoperative no-stimulation trials showed no statistical difference between the intraoperative
581 and preoperative OFF stimulation condition (Figure S5), consistent with the proposition that
582 patients were not substantively cognitively impaired in the intraoperative setting while
583 performing the memory task.

584

585 *Limitations*

586 This experiment was performed with AD patients; thus the findings may not be entirely
587 representative of the general population. Our task explicitly tested a visuospatial memorandum
588 but semantic encoding may nonetheless have aided memory performance (e.g., the dot location
589 could be remembered in relation to some semantically-represented feature in the movie clip).
590 Additionally, visuospatial and semantic memory may involve distinct circuits, with dominance in

591 different hemispheres^{35,57}. This task was designed to be primarily visuospatial, but semantic
592 representations may nonetheless have contributed to memory and task performance (e.g., “the
593 dot was located near the hand”). We did not explicitly test semantic memory, separately, in our
594 experiment; it is possible that DBS-f might impact this process differently than visuospatial
595 memory. Because we delivered stimulation bilaterally, we did not perform language-dominance
596 or handedness stratification and were also unable to assess potential lateralized effects of DBS-f.
597 Preoperative memory testing data represent task performance from 4/5 patients, as one individual
598 was unable to perform testing prior to their surgery. Additionally, the extent of generalizability
599 of these findings to patients without mild AD is uncertain. For example, there could be certain
600 aspects of AD pathology that interact with DBS-f to produce functional effects that differ in kind
601 or degree, compared to those effects in individuals without AD. The effects of stimulation on
602 memory circuits may depend on other parameters beyond stimulation frequency, such as
603 stimulation current amplitude or pulse width^{55,58-61}. Due to constraints from trial protocol, we
604 were not able to test these different factors. However, it is possible that greater stimulation
605 amplitudes may confer benefit by increasing the overall energy delivered to the
606 hippocampal circuit. Future work exploring the interplay of current intensity, frequency, and
607 pulse width on memory circuits is warranted. Finally, there is some evidence that implicates
608 changes in cerebral glucose metabolism in sensorimotor cortex, temporal lobe structures
609 including the hippocampus, parietal, occipital, and cerebellar regions²¹. However, it is possible
610 that these changes represent downstream, longer-term effects of DBS-f rather than direct,
611 immediate effects of stimulation. Other work modeling fornix stimulation has also suggested that
612 the Circuit of Papez and stria terminalis were likely recruited in patients with DBS-f⁶². Thus,

613 although identification of precise circuit effects is difficult, this prior evidence provides some
614 confirmation of structures and systems that are likely impacted by DBS-f.

615

616

617 **Conclusion**

618 Understanding how stimulation affects memory-related circuits is necessary for the development
619 of effective stimulation-based interventions to treat memory disorders. We performed a
620 controlled investigation to probe the acute effects of stimulating the fornix, a critical output
621 structure of the hippocampus, in two distinct settings and tested a range of stimulation
622 frequencies. Open-loop fornix stimulation specifically impaired acute, item-specific memory
623 encoding, but not visual-spatial processing, attention, or short-term working memory.
624 Specifically, in a parametric memory paradigm, low frequency, high frequency, and theta (+/-
625 burst) stimulation impaired delayed recall performance but spared attention, short-term memory,
626 and sensory-motor functions required for immediate report. DBS-f did not improve acute, item-
627 specific memory; nonetheless, a positive impact of chronic stimulation on memory function may
628 recruit different mechanisms and so remains possible.

629

630 **Supplemental Material:** <https://doi.org/10.6084/m9.figshare.30223216>

631

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- 806

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812

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821 Images shown in Figure 1 were generated using GPT-4o.

822

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827

828 **Competing Interests:**

829 WFA was supported by Functional Neuromodulation Inc. as site PI for the AAdvance II trial.
830 ARK, MC, BZ, GP, PML, JED, UA, LD declare no competing interests.

831

832 **Author Contributions:**

833 Conceived and Designed Research – ARK, BZ, PML, UA, WFA, JED
834 Analyzed Data – ARK, MC, GP, WFA
835 Performed Experiments – ARK, BZ, PML
836 Interpreted Results of Experiments – ARK, BZ, PML, WFA, LD, GP, JED
837 Prepared Figures – ARK, MC, WFA, GP
838 Writing – original draft – ARK, MC, WFA
839 Writing – review and editing final draft – all authors

840

841 **Data and Code Availability:**

842 Data are considered confidential medical records and are thus not publicly available. All original
843 code is available upon request from the lead author. Any additional information required to
844 reanalyze the data reported in this paper is available from the lead contact upon request.

845

846

847 **Figures**

848 **Figure 1. Memory Task.** During the encoding blocks, participants performed encoding trials in
849 which they were shown a 5-second movie clip alone followed by the same movie clip replayed
850 with a white dot (“*memorandum*”) around the circular movie aperture. The location of the white
851 dot was randomly assigned from π to $-\pi$. Participants were then immediately asked to report the
852 location of the dot they just saw to confirm the memorandum was attended (“*immediate report*”).
853 An encoding block consisted of 4 encoding trials. Next, in the recall block, subjects were shown
854 the same movie clips (in a pseudo-randomized order) and asked to recall the dot location
855 assigned to that movie. Subjects indicated their choices using a joystick-guided cursor and a
856 button-press. Position Errors were defined as the difference between the true location of the
857 memorandum and the selected location. **Intraoperative Stimulation:** During intraoperative
858 encoding blocks, stimulation was delivered during only the 5-second co-presentation of the
859 movie and dot. The 4 stimulation conditions were randomized by trial. **Postoperative**
860 **Stimulation:** In the postoperative sessions, stimulation was delivered continuously throughout
861 the whole encoding block of 4 trials; here, stimulation was randomized per block. Images shown
862 in this figure were generated using GPT-4o.

863

864 **Figure 2. DBS-f lead locations.** Axial T1 MRI co-registered with day 0 post-operative CT
865 showing bilateral DBS leads (red arrows) abutting the fornix (white arrows) for each subject.

866

867

868 **Figure 3. Immediate Report and Delayed Recall Performance during the Intraoperative**
869 **and Postoperative Sessions.** Memory recall accuracy for the location of the memorandum

870 (small white dot) is plotted across subjects (N=5) for each stimulation condition (OFF, LOW,
871 HIGH, and THETA [+BURST]), sorted according to session (**A**, intraoperative; **B**,
872 postoperative). The correct response in each case is defined as 0 degrees. The rows for each
873 subplot (A and B) correspond to either immediate report performance, which was generally very
874 accurate, or delayed recall, where performance varied by stimulation condition.

875

876

877 **Figure 4. Bayesian Estimation of DBS-f Effects on Memory Performance.** The posterior
878 distributions of absolute recall errors are shown for each condition across subjects (N=5). Top
879 row shows results from intraoperative testing. Bottom row shows results from postoperative
880 testing. **(A)** Stimulation OFF average absolute recall error. **(B-D)** Distributions depicting the
881 differences in recall error compared to control (OFF) for each of the stimulation conditions.
882 Values greater than 0 (red vertical line) indicate larger average errors compared to control (OFF)
883 and thus worse relative performance. **(IntraOp)** The proportion of values > 0 were: LOW:
884 58.02%, HIGH: 90.45%, THETA BURST: 67.38%. **(PostOp)** Difference in postoperative recall
885 error compared to postoperative control (OFF). The proportion of values > 0 were: LOW:
886 62.33%, HIGH: 81.40%, THETA: 70.78%.

887

888

889 **Figure 5. Linear Mixed Effects Analyses of DBS-f Effects on Memory Performance.**
890 Predicted relative absolute recall error for each stimulation condition across subjects (N=5). High
891 frequency stimulation had the greatest effect on memory performance across both the
892 intraoperative and postoperative testing environments. No significant differences between any of

893 the conditions. **(A)** Coefficient LME estimates for intraoperative experimental conditions. **(B)**

894 Coefficient LME estimates for postoperative experimental conditions.

895

896

Table 1. Study Population Characteristics

| | Subject ID | 1 | 2 | 3 | 4 | 5 | Mean | Min | Max |
|-------------|------------------|-----|-----|-----|-----|----|-------|-----|-----|
| Descriptive | Age at Procedure | 74 | 68 | 67 | 79 | 81 | 73.8 | 67 | 81 |
| | Sex | F | F | M | M | F | | | |
| Screening | ADAS-Cog14 | 32 | 37 | 30 | 24 | 35 | 31.6 | 24 | 37 |
| | CDR-Total | 0.5 | 0.5 | 0.5 | 1 | 1 | 0.7 | 0.5 | 1 |
| Baseline | ADAS-Cog14 | 27 | 38 | 31 | 27 | 28 | 30.2 | 27 | 38 |
| | CDR-Total | 0.5 | 1 | 0.5 | 0.5 | 1 | 0.7 | 0.5 | 1 |
| 6 month | ADAS-Cog14 | 31 | 43 | 31 | 27 | 36 | 33.6 | 27 | 43 |
| | CDR-Total | 0.5 | 2 | 1 | 0.5 | 1 | 1 | 0.5 | 2 |
| 12 month | ADAS-Cog14 | 34 | 63 | 35 | 31 | | 40.75 | 31 | 63 |
| | CDR-Total | 1 | 2 | 1 | 0.5 | | 1.125 | 0.5 | 2 |

Table 2. Trials by Condition and Testing Session

| Subject | Intraoperative Testing | | | | Postoperative Testing | | | |
|---------|------------------------|-------|------------|-------|-----------------------|-------|-------|-------|
| | OFF | LOW | THETABURST | HIGH | OFF | LOW | THETA | HIGH |
| 1 | 9/9 | 6/9 | 7/9 | 4/9 | 12/12 | 12/12 | 12/12 | 12/12 |
| 2 | 6/6 | 6/6 | 5/6 | 4/6 | 7/8 | 8/8 | 7/8 | 8/8 |
| 3 | 8/8 | 9/9 | 8/8 | 9/9 | 8/8 | 8/8 | 8/8 | 8/8 |
| 4 | 10/10 | 10/10 | 9/10 | 10/10 | 11/12 | 10/12 | 12/12 | 11/12 |
| 5 | 6/6 | 5/6 | 5/6 | 6/6 | 11/12 | 11/12 | 11/12 | 11/12 |

Trials used for analysis/total trials for each subject. To understand the effect of fornix stimulation on delayed recall, we excluded trials where immediate report suggested inattention or other potential non-mnemonic influences, yielding the analysis dataset (trials used for analysis).

Table 3. Euclidean Contact to Fornix Distance

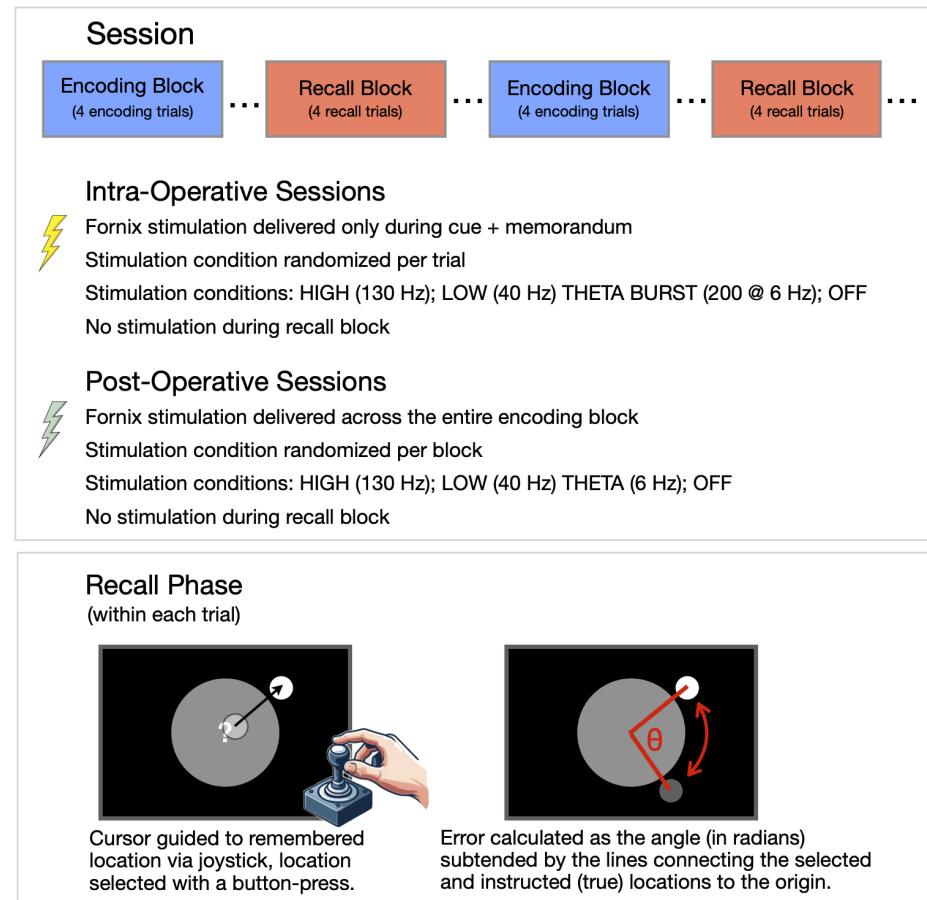
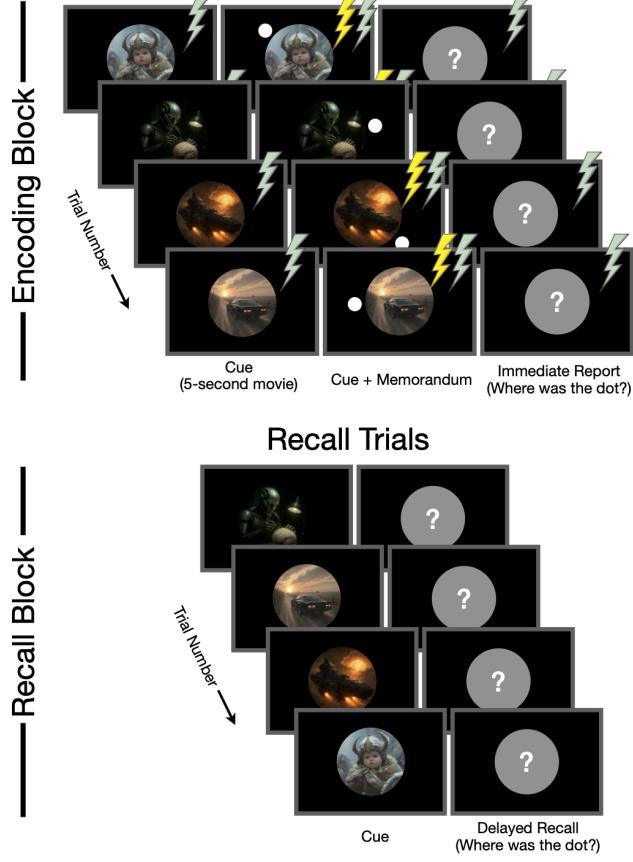
| Subject | Left Contact Edge to Fornix Edge | Right Contact Edge to Fornix Edge | Left Contact Center to Fornix Center (mm) | Right Contact Center to Fornix Center (mm) |
|---------|----------------------------------|-----------------------------------|---|--|
| 1 | 0.5 | 0.3 | 3.3 | 2.8 |
| 2 | 0.6 | 0.3 | 3.4 | 2.2 |
| 3 | 0.7 | 0.5 | 4.0 | 3.5 |
| 4 | 0.5 | 0.4 | 3.2 | 2.7 |
| 5 | 0.9 | 0.7 | 3.6 | 3.0 |

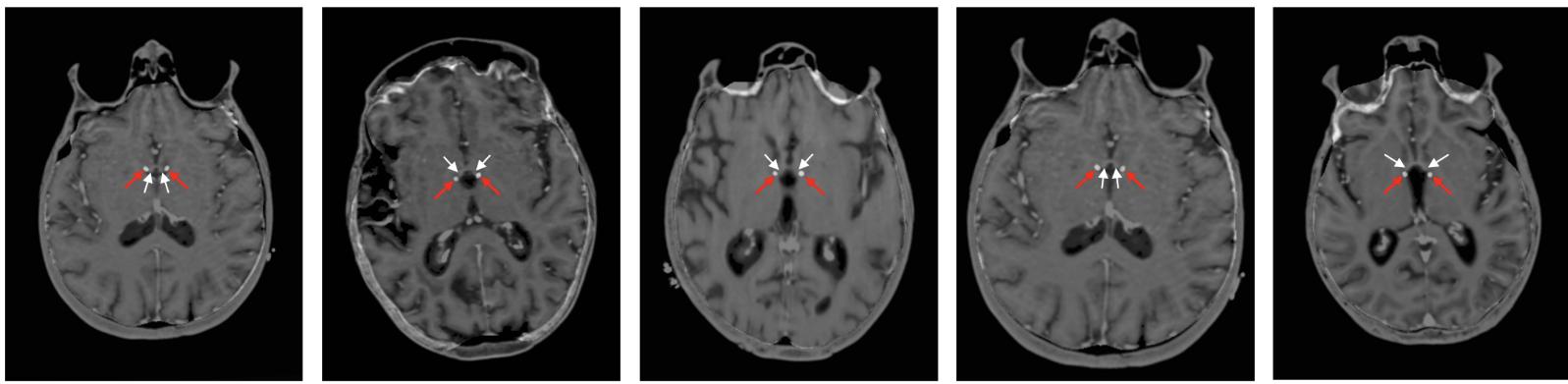
Euclidean contact to fornix distance (stimulation contact 8) bilaterally, by subject. The goal for these DBS-f cases was to place the lead as close as possible to the fornix without damaging the

structure. Thus, the ideal placement would place the DBS lead immediately adjacent to the fornix without an appreciable gap (i.e., 0mm from contact edge to fornix edge). This corresponds approximately to a 1.0-1.5mm contact center-to-fornix center distance.

Table 4. Group Recall Error in Radians By Stimulation Condition

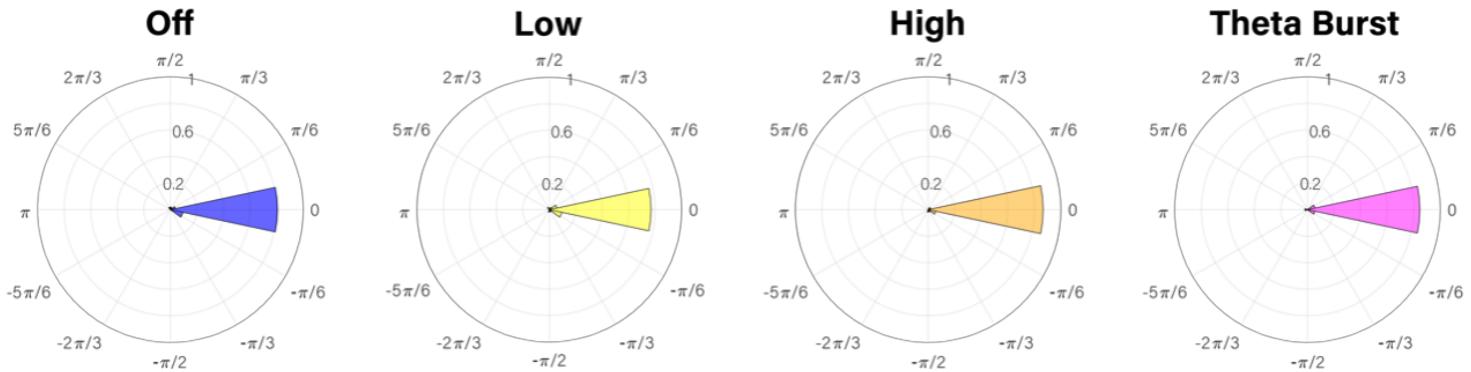
| Session | OFF | LOW | THETA/THETA BURST | HIGH |
|----------------|-------------|-------------|----------------------|-------------|
| Intraoperative | 1.22 ± 0.93 | 1.28 ± 0.94 | 1.33 ± 0.88 | 1.61 ± 1.00 |
| Postoperative | 1.16 ± 1.01 | 1.26 ± 1.05 | 1.30 ± 1.05 | 1.42 ± 1.00 |



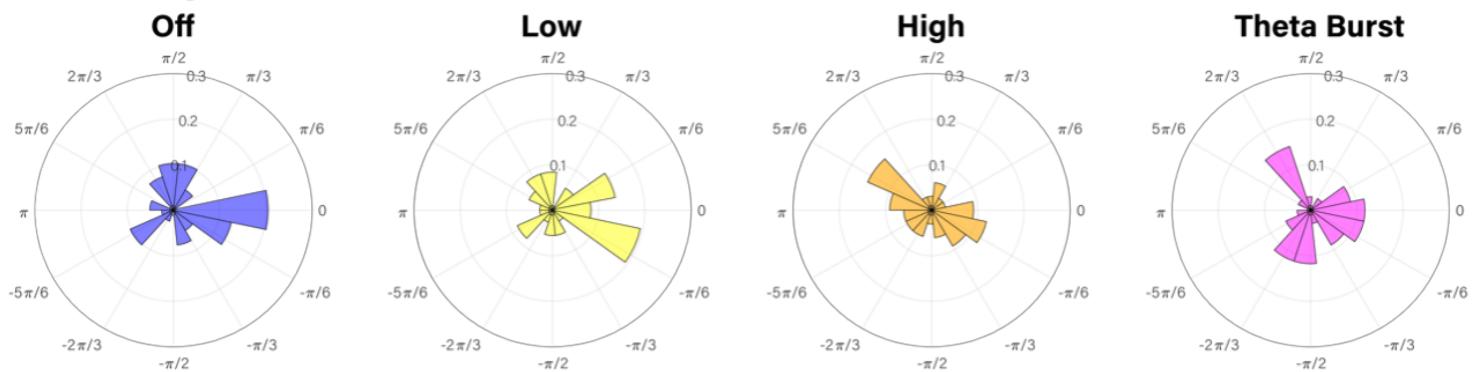


A - IntraOp

Immediate Report

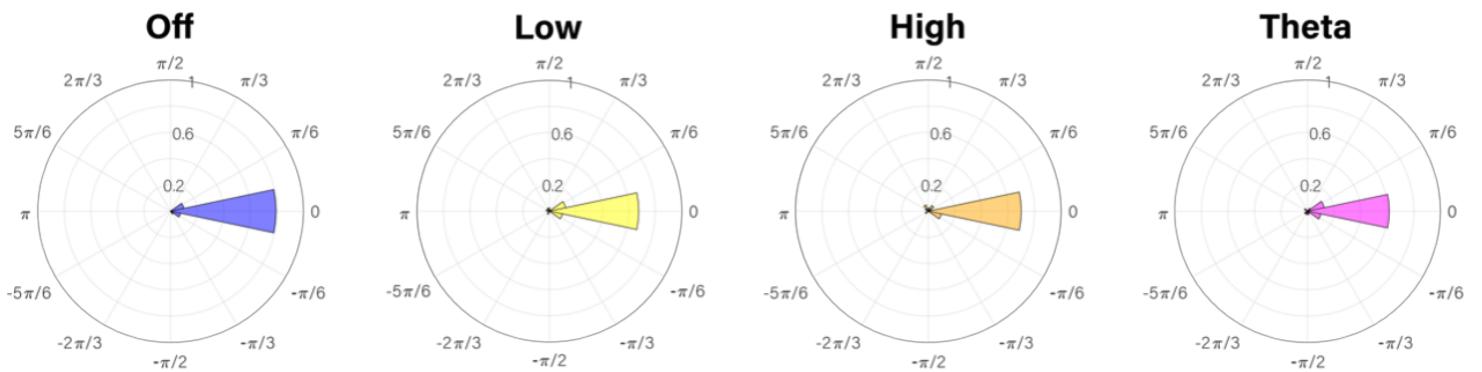


Delayed Recall

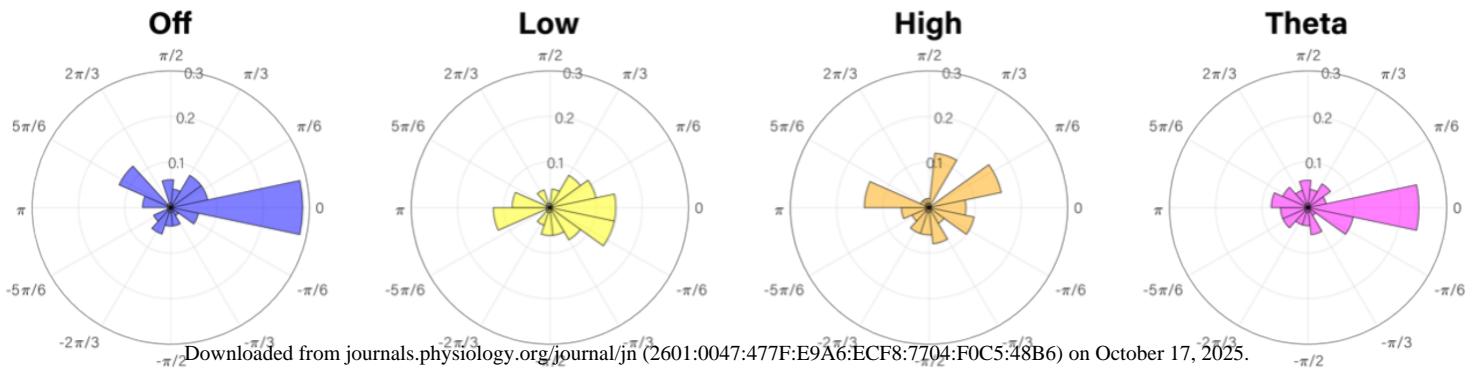


B - PostOp

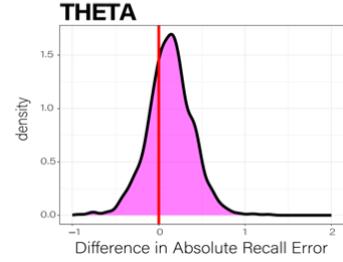
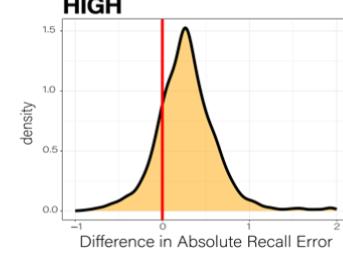
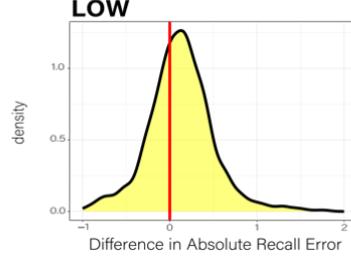
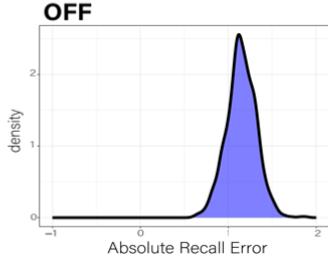
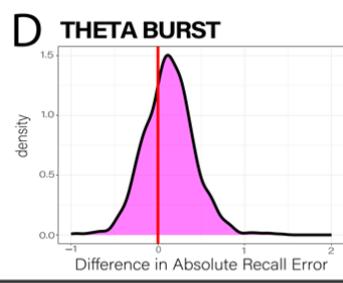
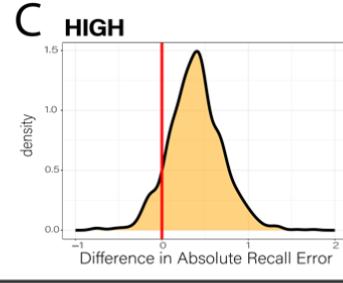
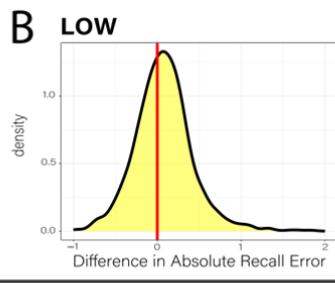
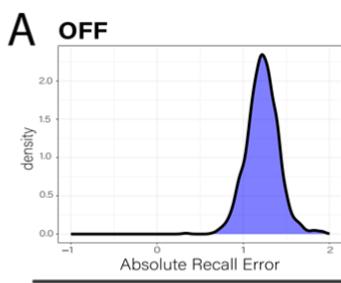
Immediate Report

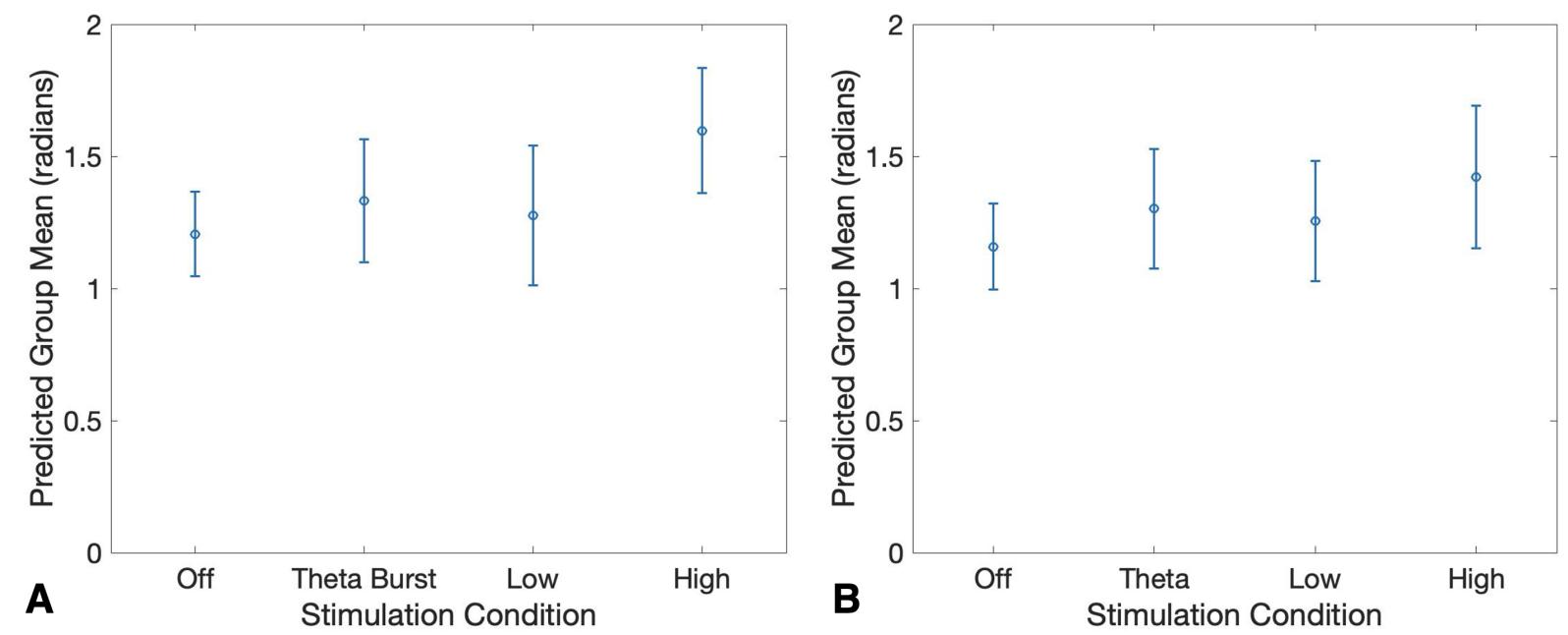


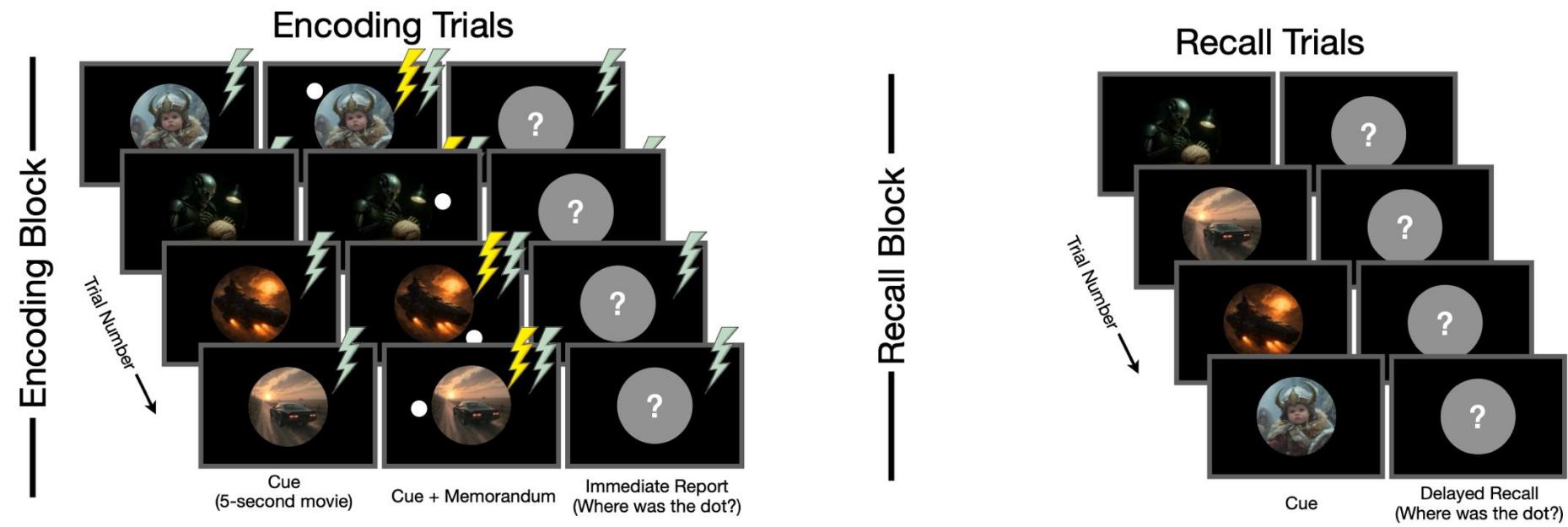
Delayed Recall



IntraOp
PostOp







Acute fornix stimulation disrupted visuo-spatial memory encoding

