Cognitive control of behavior and hippocampal information processing without medial prefrontal cortex

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Abstract

Cognitive control tasks require using one class of information while ignoring competing classes of information. The central role of the medial prefrontal cortex (mPFC) in cognitive control is well established in the primate literature, and largely accepted in the rodent literature because mPFC damage causes deficits in tasks that may require cognitive control, as inferred, typically from the task design. In prior work, we used an active place avoidance task where a rat or mouse on a rotating arena is required to avoid the stationary task-relevant locations of a mild shock and ignore the rotating task-irrelevant locations of those shocks. The task is impaired by hippocampal manipulations, and the discharge of hippocampal place cell populations judiciously alternates between representing stationary locations near the shock zone and rotating locations far from the shock zone, demonstrating cognitive control concurrently in behavior and the hippocampal representation of spatial information. Here we test whether rat mPFC lesion impairs the active place avoidance task to evaluate two competing hypotheses, a “central-computation” hypothesis that the mPFC is essential for the computations required for cognitive control and an alternative “local-computation” hypothesis that other brain areas can perform the computations required for cognitive control, independent of mPFC. Ibotenic acid lesion of the mPFC was effective, damaging the cingulate, prelimbic and infralimbic cortices. The lesion also altered the normal coordination of metabolic activity across remaining structures. The lesion did not impair learning to avoid the initial location of shock or long-term place avoidance memory, but impaired avoidance after the shock was relocated. The lesion also did not impair the alternation between task-relevant and task-irrelevant hippocampal representations of place information. These findings support

the local-computation hypothesis that computations required for cognitive control can occur locally in brain networks independently of the mPFC.

Introduction

Cognitive control is a psychological construct that refers to a set of processes that allow information processing and purposeful behavior to vary and adjust according to the demands of a subject's current goals. Without cognitive control, information processing and behavior would be rigid and inflexible when task demands and goals change [1]. Because cognitive control is not limited to any one task or task domain, and because it engages various processes that include forms of attention, memory processes, behavioral inhibition and the like, it has been a challenge to establish the neuronal basis of cognitive control. What would the neuronal network activity look like in a part of the brain that was implementing cognitive control? From our perspective, until we connect neuronal network function to cognitive control, the construct's value will be limited for understanding brain function and treating the diverse types of dysfunction that manifest as impaired cognitive control. Towards this goal, it has been important to identify regions of the brain that might be crucial for cognitive control. This has largely been approached by investigating brain function while subjects perform tasks designed to require cognitive control because performance depends on the ability to judiciously use task-relevant information while ignoring salient concurrent information that is currently irrelevant for the task.

Studies of human brain function identified subdivisions of the prefrontal cortex (PFC) that are engaged by tasks that are thought to require cognitive control, such as the Wisconsin Card Sort and Stroop tasks. As noted above, it is important to identify the neuronal network activity that the construct of cognitive control assumes must be operating. Recordings of neuronal activity from the PFC of non-human primates as they perform tasks that are thought to require cognitive control has been a particularly important development towards the identification of such neural network activity. Indeed, the consensus view is that PFC is crucial for cognitive control such that PFC activity is central to the underlying computations that operate through prefrontal interactions with

diverse brain areas during cognitive control tasks [2-4]. An influential theory states: “We assume that the PFC serves a specific function in cognitive control: the active maintenance of patterns of activity that represent goals and the means to achieve them. They provide bias signals throughout much of the rest of the brain, affecting not only visual processes but also other sensory modalities, as well as systems responsible for response execution, memory retrieval, emotional evaluation, etc. The aggregate effect of these bias signals is to guide the flow of neural activity along pathways that establish the proper mappings between inputs, internal states, and outputs needed to perform a given task. This is especially important whenever stimuli are ambiguous (i.e. they activate more than one input representation), or when multiple responses are possible and the task-appropriate response must compete with stronger alternatives. From this perspective, the constellation of PFC biases—which resolves competition, guides activity along appropriate pathways, and establishes the mappings needed to perform the task—can be viewed as the neural implementation of attentional templates, rules, or goals, depending on the target of their biasing influence.” [2, page 171]

Like biased competition, in which winner-take-all network representations compete to explain selective visual attention [5-9] the theory is especially valuable and powerful because it predicts what neuronal signals should look like when cognitive control is operating. This enables experimentalists to operationally identify cognitive control using neuronal network behavior so that hypotheses can be rigorously evaluated. Accordingly, cognitive control would be at work when there is sustained neuronal network representations of task-relevant information that suppresses or gates representations of salient task-irrelevant information in accord with purposeful judicious behavior. This is not to say that the control signal itself would have this property, although a so-called “transmissive” type of control signal would include task-relevant context and stimulus information, whereas a “modulatory” type of control signal would only carry the control signal that biases expression of the task-relevant context and stimulus information [10, 11].

The hippocampal role in the cognitive control of spatial and mnemonic information has been investigated using an active place avoidance task [12]. The task conditions rodents to avoid the location of a mild shock and uses continuous rotation of the behavioral arena to dissociate the environment into two spatial frames, one defined by the rotating arena and the other defined by the stationary room [13]. Avoiding shock at a stationary room location requires using the task-relevant spatial information and ignoring spatial information from the other, task-irrelevant arena frame. Dorsal hippocampus dysfunction impairs this avoidance without impairing the place avoidance when the two frames are not dissociated by stopping the rotation or attenuating the arena cues with shallow water [14-17]. During active place avoidance task variants that require cognitive control, place cell discharge in hippocampus subfields, and head-direction cell discharge in the medial entorhinal cortical input to hippocampus demonstrate cognitive control of spatial representations; neural ensemble activity alternates between representing room and arena locations depending on the subject's proximity to the frame-specific location of shock [12, 13, 18-20].

A standard "central-computation" hypothesis centralizes the computations that are necessary for cognitive control to the PFC and predicts that lesion of the PFC will impair active place avoidance [21, 22]. Recent work indicating that the hippocampus [18] and sensory thalamus [23] are also necessary for cognitive control can be reconciled with the central-computation hypothesis by assuming there are necessary interactions between modality-specific information processing in hippocampus or thalamus and the primary, control-specialized processing in the PFC [22, 24, 25]. Alternatively, the role of non-PFC brain structures in cognitive control could be explained by a "local-computation" hypothesis; the computations needed for cognitive control can be performed locally in neural networks specialized for the particular information upon which the task depends and on which cognitive control operates. The local-computation hypothesis predicts that PFC lesion can spare cognitive control. We tested these mutually exclusive hypotheses by making

153 medial prefrontal cortex (mPFC) lesions in rats and evaluating their behavior and hippocampal
154 physiology during active place avoidance (Fig. 1A). We reasoned that if the central-computation
155 hypothesis was valid, active place avoidance behavior would be impaired by mPFC lesion along
156 with discoordination of the alternating dynamics between concurrent hippocampal network
157 representations of task-relevant room-frame and task-irrelevant arena-frame locations of the
158 rotating arena. Alternatively, if the local-computation hypothesis was valid, then mPFC lesions
159 would spare the active place avoidance behavior and the hippocampal place representation
160 dynamics. We used cytochrome oxidase, a metabolic marker of baseline neuronal activity, to
161 confirm the mPFC lesions were effective and that there are non-local network consequences
162 despite the local lesion. We first evaluated cytochrome oxidase activity in regions known to be
163 associated with performance in the active place avoidance task, or regions with known
164 connectivity to the mPFC. We then evaluated covariance of activity amongst the regions in an
165 effort to detect network consequences of the lesion.
166

167 ## Results

168 ***mPFC lesion does not impair cognitive control in the active place avoidance task***

169 Ibotenic acid, but not vehicle, targeted to mPFC caused lesions that included the cingulate cortex,
170 prelimbic and infralimbic areas (Fig. 1B; S2). To assess the effect of mPFC lesion on behavior,
171 we first examined locomotion during the pretraining sessions (Fig. 1C). There is no effect of lesion
172 on the total distance walked across the session (Fig.1D; $F_{1,16} = 0.04$, $p = 0.85$, $\eta^2 = 0.002$). There
173 is a main effect of trial ($F_{1,16} = 15.31$, $p = 0.001$, $\eta^2 = 0.09$) but there is no effect of the group x trial
174 interaction ($F_{1,16} = 0.14$, $p = 0.71$, $\eta^2 = 10^{-3}$). Similarly, locomotion does not differ between the
175 groups or across trials, nor is there a significant group x trial interaction during Initial Training on
176 days 2-3 (df = 3.17/50.77) or during Conflict Training on days 4-5 (df = 4.97/79.58; $F'_S \leqslant 1.96$, p
177 $\geqslant 0.09$, $\eta^2 \leqslant 0.03$).

We then examined the acquisition of active place avoidance memory during Initial Training using the time to first enter the shock zone, the clearest estimate of between-trial memory. Both groups learn to increase the latency to first enter the shock zone (Fig. 1E). There is no effect of group ($F_{1,16}$ = 0.1, p = 0.76, η^2 = 0.001) but clear effects of day ($F_{1,16}$ = 69.61, p = 10^{-7}, η^2 = 0.17) and trial ($F_{5.33, 85.33}$ = 12.15, p = 10^{-9}, η^2 = 0.12). There are also no significant interactions (group x day: $F_{1,16}$ = 0.94; p = 0.35, η^2 = 10^{-3}; group x trial: $F_{5.33, 85.33}$ = 1.83, p = 0.11, η^2 = 0.02; day x trial: $F_{4.78, 76.43}$ = 1.93, p = 0.10, η^2 = 0.03); group x day x trial: $F_{4.78, 76.43}$ = 0.26, p = 0.93, η^2 = 10^{-3}). Neither was there a difference in avoidance learning between the groups measured by the number of entrances into the shock zone (Fig. 1F). The effect of group is not significant ($F_{1,16}$ = 0.002, p = 0.96, η^2 = 10^{-5}) but the effects of day ($F_{1,16}$ = 26.34, p = 10^{-3}, η^2 = 0.19) and trials ($F_{3.22, 51.50}$ = 36.76, p = 10^{-8}, η^2 = 0.1) are significant. There are no significant interactions (group x day: $F_{1,16}$ = 0.003, p = 0.96, η^2 = 10^{-5}; group x trial: $F_{3.22, 11.50}$= 0.74, p = 0.54, η^2= 10^{-3} ; group x day x trial: $F_{4.05, 64.81}$ = 0.35, p = 0.74, η^2 = 10^{-3}). But the interaction between day and trial is significant (day x trial: $F_{2.26, 36.08}$= 13.75, p = 10^{-5}, η^2 = 0.11). The two groups are also indistinguishable on Day 4 during which Retention of 24-h memory is assessed by their times to first enter the shock zone (t_{16}= 1.01, p = 0.3, d = 0.49) and the number of entrances (t_{16}= 0.95, p = 0.4, d = 0.002).

To increase the cognitive challenge, we were motivated by evidence that mPFC manipulation can affect cognitive flexibility as assessed by reversal learning tasks [26, 27]. Accordingly, we trained the rats to avoid the shock zone after relocating it 180° to assess the impact of mPFC lesion on cognitive flexibility with the additional challenge to distinguish between the current and previously learned location of shock, under the cognitive control challenge [28]. Both groups learn the conflict task variant, measured by the number of entrances. There is no effect of group ($F_{1,16}$ = 0.21, p = 0.65, η^2 = 10^{-3}), but the effects of day ($F_{1,16}$ = 8.99, p = 0.01, η^2 = 0.05), and trials ($F_{1.89, 30.12}$ =

203 18.55, $p = 10^{-9}$, $\eta^2 = 0.28$) are significant. The group interactions are not significant (group x day:
204 $F_{1,16} = 0.55$, $p = 0.47$, $\eta^2 = 10^{-3}$; group x trial: $F_{1.88, 30.12} = 1.38$, $p = 0.27$, $\eta^2 = 0.02$; day x trial: $F_{2.30,}$
205 $_{36.87} = 2.13$, $p = 0.11$, $\eta^2 = 0.02$, group x day x trial: $F_{2.30, 36.87} = 1.16$, $p = 0.33$, $\eta^2 = 10^{-3}$). Also, the
206 time to enter the new shock zone, which was low in both groups, consistent with poor between-
207 day memory for the novel location of shock (Fig. 1, Days 4-5 Conflict Training). There is no effect
208 of group ($F_{1,16} = 0.21$, $p = 0.65$, $\eta^2 = 10^{-3}$), but the effects of day ($F_{1,16} = 20.46$, $p = 0.01$, $\eta^2 = 0.04$),
209 and trials ($F_{1.89, 30.12} = 11.52$, $p = 10^{-}$, $\eta^2 = 0.13$) are significant. The group interactions are not
210 significant (group x day: $F_{1,16} = 0.03$, $p = 0.86$, $\eta^2 = 10^{-3}$; group x trial: $F_{1.88, 30.12} = 0.78$, $p = 0.54$,
211 $\eta^2 = 0.01$; group x day x trial: $F_{2.30, 36.87} = 0.47$, $p = 0.76$, $\eta^2 = 10^{-2}$). Also, the interaction between
212 day and trial is not significant (day x trial: $F_{2.30, 36.87} = 1.29$, $p = 0.28$ $\eta^2 = 0.02$). We more closely
213 examined conflict learning by analyzing the initial experience of the new shock zone location when
214 the rats are first confronted with the change in the location of shock. We compared the number of
215 entrances during the first 5 minutes on the first trial of each day to estimate savings, measured
216 as each animal's difference in performance) during initial training (Fig. 1F left inset) and during
217 conflict training (Fig. 1F middle inset). During initial training, both sham (paired $t_7 = 4.5$, $p = 0.003$,
218 $d = 1.2$) and lesion (paired $t_9 = 4.7$, $p = 0.001$, $d = 1.5$) rats improved. During conflict training,
219 sham rats improved across the pair of first conflict trials of each day (Fig. 1F middle inset; paired
220 $t_7 = 3.8$, $p = 0.006$, $d = 1.4$) but not lesion rats (paired $t_9 = 0.87$, $p = 0.4$, $d = 0.27$). Indeed, while
221 all sham rats improved across the first two conflict trials of each day only 6/10 lesion rats improved
222 (test of proportions $z = 2.3$, $p = 0.03$). We also quantified the improvement for each subject during
223 conflict as a savings index (Fig. 1F right inset). The sham rats improved, avoiding more than the
224 lesion rats in the first 5 minutes of the second conflict day compared to the first conflict day ($t_{16} =$
225 2.4, one-tailed $p = 0.03$, $d = 0.85$). This difference on the second day of conflict training was
226 observed despite equivalent performance across eight trials on the first day. We therefore find no
227 evidence that mPFC lesion causes a deficit in active place avoidance learning to avoid the initial

location of shock, nor do we observe a deficit in memory retention up to 24-h for the initial shock location, both of which require cognitive control. However, the lesion is sufficient to impair conflict learning after a 24-h delay.

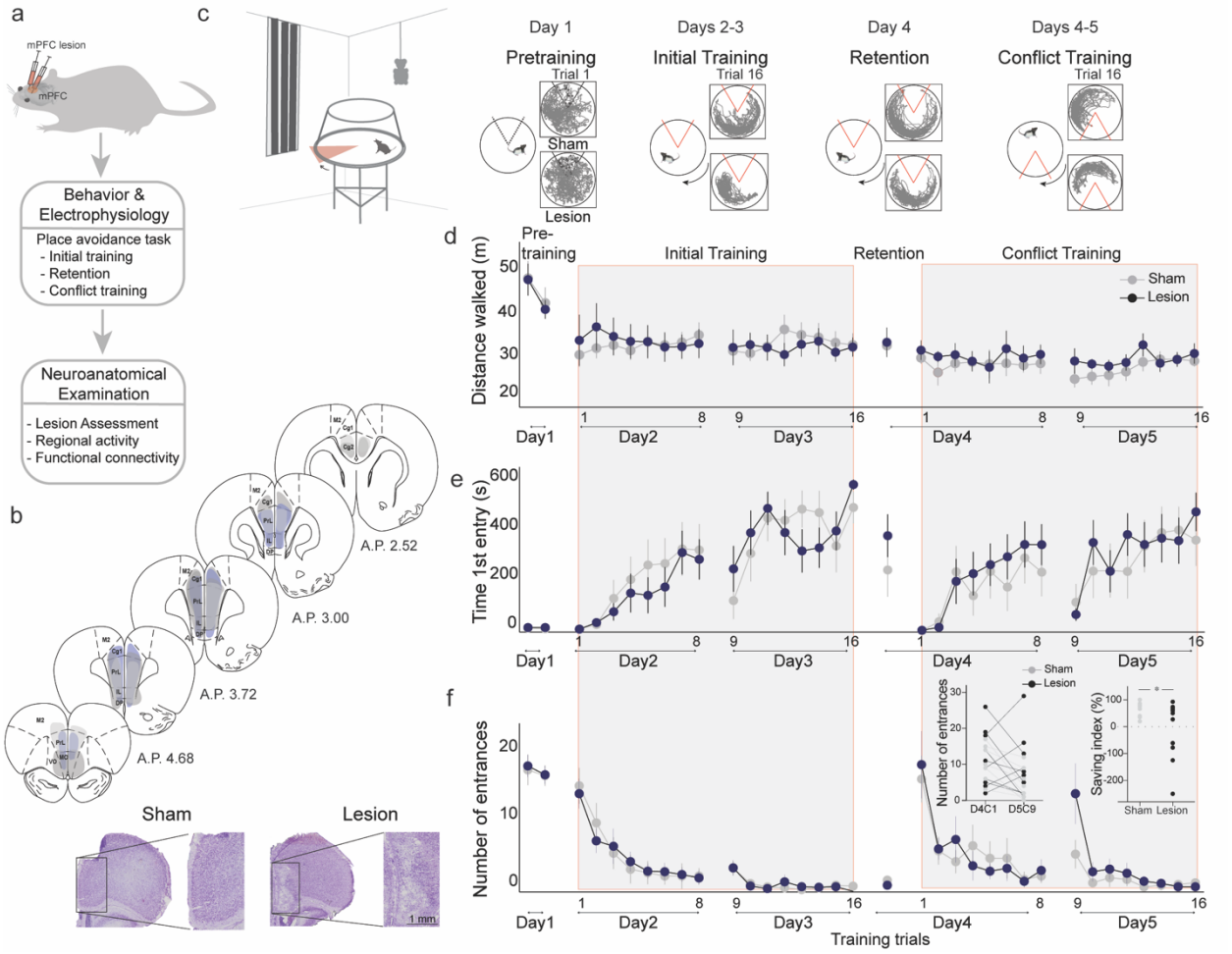

Figure 1. mPFC lesion does not impair initial active place avoidance learning, but impairs cognitive flexibility in the conflict task variant (A) Workflow to assess the impact of mPFC or sham lesions on spatial cognitive control. (**B)** Assessment and impact of the mPFC lesion in three representative subjects (light grey (intermediate with dorsal anterior lesion), dark grey (intermediate with ventral anterior lesion – includes medial orbital cortex), and purple (largest lesion)). The smallest lesion spanned A-P 3.24-2.52. PrL (prelimbic), IL (infralimbic), Cg (cingulate cortex), M2 (secondary motor cortex). Representative mPFC from a sham and a lesion rat

(bottom). **(C)** Tracked room-frame positions from two example rats across active place avoidance training. The shock zone is indicated as a 60° sector, gray (shock off) and red (shock on), and arena rotation by the curved arrow. Day 1 - Pretraining: free exploration with shock off; Days 2&3 - Initial Training: Eight daily trials to avoid the shock zone. Day 4 - Retention: One trial with shock on. Days 4&5 - Conflict Training: Eight daily trials to avoid the shock zone relocated 180° from the initial location. Sham and mPFC lesion rats did not differ in **(D)** locomotor activity, **(E)** avoidance memory, or **(F)** place learning. **(F)** The left inset compares the number of entrances during the first 5 minutes of the first (D2T1) and second days of initial training (D3T9). The right inset compares the first 5 minutes of the first (D4C1) and second (D5C9) days of conflict trials. The percent difference in number of entrances between D5C9 and D4C1 of conflict training was computed as a savings index. Savings was not related to lesion size $r = 0.009$, $p = 0.98$. *$p < 0.05$.

mPFC lesion alters functional relationships amongst related brain areas

Cytochrome oxidase (CO), a sensitive metabolic marker for neuronal function [29], was used to evaluate whether lesion effects were restricted to the mPFC. In a subset of rats (lesion n = 8, sham n = 8), CO activity was evaluated in 14 functionally-related brain regions (Fig. 2A). CO activity in the central amygdala, but not elsewhere, is altered by the lesion, with activity increased in lesion rats (Table S1).

Pair-wise interregional correlations of CO activity were evaluated to assess whether extra-mPFC functional relationships are altered after mPFC lesion. After FDR correction (0.01) 15 of the 91 correlations are significant in the sham sample but only 7 in the lesion sample (Fig. 2B, S3b; test of proportions: $z = 2.26$, $p = 0.03$). The correlations within the ventral hippocampus are preserved after mPFC lesion, but some correlations are lost within the dorsal hippocampal formation (Fig. 2B). Correlations between the nucleus reuniens and both the dorsal and ventral hippocampus are

also lost after mPFC lesion. Correlations between the basolateral amygdala and nucleus reuniens and between the basomedial amygdala and ventral hippocampus are lost after mPFC lesion, and a correlation between dorsal CA1 and the central nucleus of the amygdala appears after mPFC lesion. These data indicate that the mPFC lesion causes functional changes beyond mPFC.

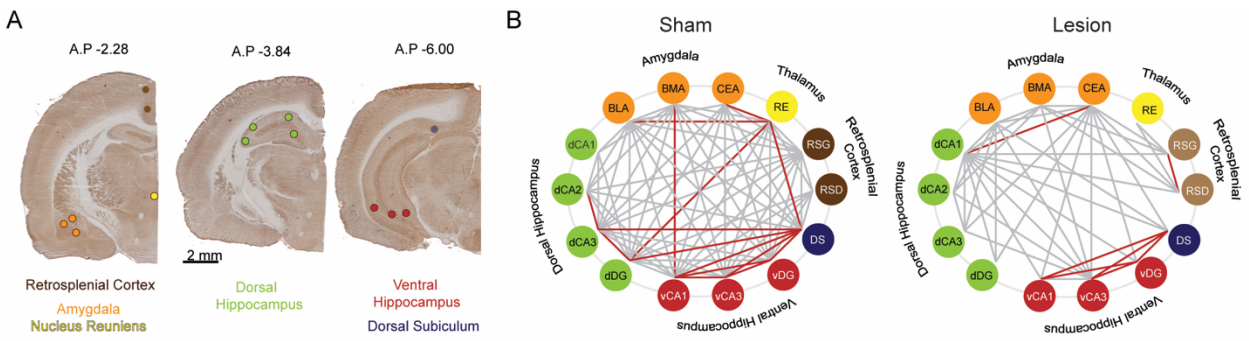

Figure 2. Cytochrome oxidase analysis demonstrates widespread metabolic consequences of mPFC lesion. (A) Representative cytochrome oxidase staining and locations of the optical density readings. Cytochrome oxidase activity was measured in the dysgranular and granular retrosplenial cortices (RSD and RSG, respectively), the nucleus reuniens (RE), the central nucleus of the amygdala (CEA), basomedial and basolateral amygdala (BMA, and BLA, respectively), the dorsal hippocampus CA1, CA2, CA3 and dentate gyrus areas (dCA1, dCA2, dCA3, dDG, respectively) the ventral hippocampus CA1, CA3 and dentate gyrus areas (vCA1, vCA3, vDG, respectively) and the dorsal subiculum (DS) marked as colored circle areas. **(B)** Interarea covariations of CO activity by graph theory analysis. Each line indicates a significant correlation ($p < 0.05$) between the two brain regions ("nodes") it connects; only the red lines survived False Discovery Rate (FDR < 0.01) correction. Sham: n = 8; Lesion: n = 8.

mPFC lesion does not alter cognitive control of hippocampal neural representations

When the discharge of principal cells of the hippocampus is location-specific to so-called place

286 fields, the cells are called place cells. Place fields are disrupted by molecular manipulations that
287 disrupt spatial learning and memory and changes in place cell firing tend to track environmental
288 changes like geometry and other spatial features that often accompany spatial learning and
289 memory challenges [review 30]. In contrast, spatial learning and memory tasks that depend
290 crucially on hippocampus and hippocampal synaptic plasticity, like active place avoidance or task
291 changes, such as those introduced by the conflict task variant, cannot be assessed by simple
292 changes in place fields and their quality [12, 13, 19, 31-36]. This is in part because dynamic
293 cognitive variables, like adjustments of attention and cognitive control, operate during learning
294 and memory tasks. The dynamics of such internal cognitive variables modulate place cell firing,
295 creating extra-positional signals [12, 18, 19, 37-39]. The presence of these extra-positional signals
296 can be detected as momentary discharge deviations from the expectations of firing-field based
297 spatial discharge [40]. On the timescale of the few seconds it takes to walk across a firing field,
298 these noise-like deviations can be measured as overdispersion [41, 42]. We can also measure
299 the momentary positional information in the collective neuronal population discharge dynamics,
300 which during active place avoidance alternates between encoding locations in the room and
301 locations in the arena [18, 43]. The hippocampal and entorhinal cortex neuronal populations, each
302 fluctuate between representing space in these two distinct spatial frames every few seconds [20,
303 31, 44]. These representational dynamics are purposeful and can be summarized as a spatial
304 frame ensemble preference (SFEP) that is biased to room-frame locations near the room-defined
305 shock zone and is biased to arena-frame locations far from the shock zone [12, 13].
306
307 In light of these cognitive dynamics in neuronal activity representations of position, and the ability
308 to decode task information from neuronal population discharge, it is powerful to characterize
309 cognitive control by investigating neuronal population discharge. Cognitive control requires the
310 subject to process and use a class of information purposefully, at the expense of other competing
311 information. Accordingly, we previously demonstrated such a cognitive control signal in the

312 population dynamics of dorsal hippocampus spatial discharge representations of room and arena
313 positions as rats and mice navigate on a rotating arena [12, 13, 18, 39]. Consequently, we
314 examined the SFEP, the representational dynamics of hippocampus CA1 discharge on the
315 rotating arena during pretraining, as well as retention of the conditioned place avoidance of the
316 initial and conflicting shock zone locations (Fig. 3A). Note that the physical conditions were
317 identical in these three trials because the shock was off.
318
319 We first examined basic discharge properties of individual CA1 principal cells, which do not differ
320 between the sham and mPFC lesion groups (Fig 3B, Table S2). Nor does mPFC lesion alter
321 thalamic firing rates, but it reduces the likelihood of bursting activity (Table S3) complementing
322 the CO evidence that the mPFC lesion affected activity in areas beyond the lesion sites.
323
324 We then examined overdispersion of place cell firing, which is known to be reduced by prefrontal
325 inactivation [45]. In contrast, overdispersion is expected to increase with cognitive control and
326 other extra-positional processes that increase discharge non-stationarity [38]. We find that during
327 pretraining, overdispersion of hippocampal discharge is reduced by a factor of two in lesion
328 compared to sham rats, consistent with an effective lesion (Fig. 3C left). Might this also indicate
329 reduced cognitive control in the lesion rats? Remarkably, during conditioned place avoidance the
330 overdispersion in lesion rats increases to the level observed in sham rats, consistent with the
331 increased demand for cognitive control (Fig. 3C middle and right). These findings confirm the
332 effectiveness of the prefrontal lesion and also provide electrophysiological evidence consistent
333 with intact cognitive control in the lesion rats.

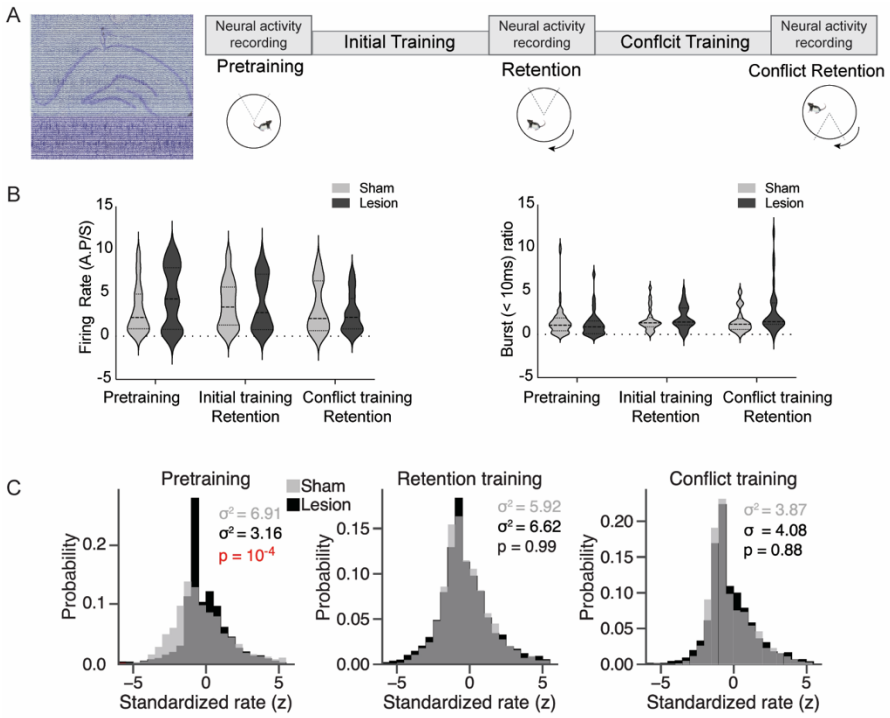

Figure 3. mPFC lesion does not change basic discharge properties, but decreases hippocampus place cell overdispersion only in the absence of the cognitive control challenge. (A) (left) Representative histology with overlaid recording traces from the Neuropixel probe. (right) Recording schedule workflow during the cognitive control task. **(B)** There is no difference between sham and mPFC lesion rats in firing rate (Sham: 3.29 ± 0.27, Lesion: 3.68 ± 0.33, $t_{184} = 0.91$, $p = 0.36$) and burst ratio in hippocampal neurons (Sham: 1.53 ± 0.25, Lesion: 2.02 ± 0.28, $t_{174} = 1.29$, $p = 0.19$). **(C)** Distribution of standardized place cell discharge (z scores) computed during every 5-second episode in which the rat passed through place cell firing fields in the data set. Different numbers of passes qualified for evaluation during the pretraining (Sham = 2777, Lesion = 3398), retention (Sham = 4039, Lesion = 3366), and conflict (Sham = 1748, Lesion = 2336) recordings. The variance of the histograms characterizes overdispersion, statistically evaluated by their ratio as an F-test (pretraining: $F_{2776,3397} = 2.19$, $p = 5.8\times10^{-4}$).

348 We next examined the spatial frame ensemble preference (SFEP), the electrophysiological
349 signature of cognitive control of place representations, during conditioned place avoidance. CA1
350 ensemble discharge alternates between preferentially representing room locations and arena
351 locations (Fig. 4A; runs tests for all recordings were significant; z's $\geqslant$ 12.3, p's $\leqslant$ 10^{-33}). During
352 pretraining, SFEP is equally likely to signal the current room location or alternatively, the current
353 arena location, in both the sham and lesion rats (Fig. 4A). Importantly, during avoidance of the
354 initial shock location, SFEP favors the arena frame because the rat avoids the room frame location
355 of shock (Fig. 4B) and SFEP is room-preferring near the shock zone and arena-preferring far from
356 the shock zone (Fig. 4C,D), as previously demonstrated [12, 13]. Relocating the shock zone 180°
357 for conflict training changes SFEP, but only in the lesion group such that it is equally probable to
358 be room- or arena-preferring, consistent with needing to decide between avoiding the current and
359 previous shock location throughout the environment (Fig. 4B) [46]. The ability to manipulate SFEP
360 of hippocampal representational dynamics by the presence and location of shock directly
361 demonstrates cognitive control at the level of the hippocampus. Despite an influence of mPFC
362 lesion on cognitive control and the non-stationarity of hippocampal representations of space in
363 hippocampal discharge, the lesion does not impair cognitive control of place representations in
364 the place avoidance task.
365

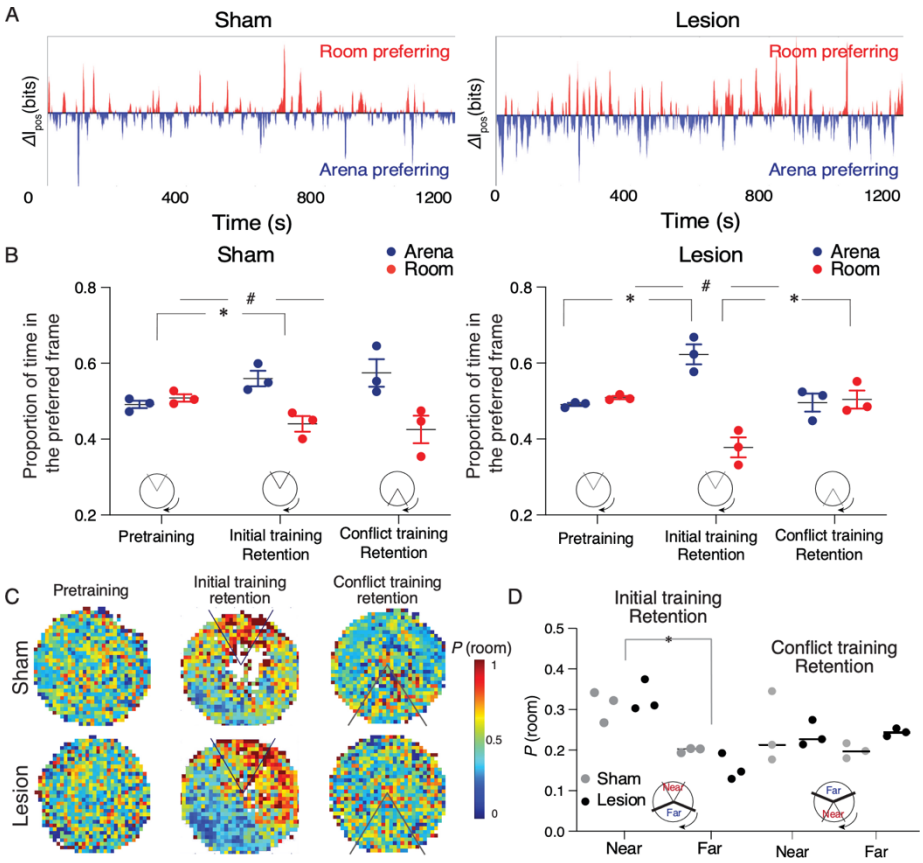

Figure 4. Sham and mPFC lesion rats do not differ in expressing cognitive control of spatial frame-specific representations of location. (**A**) Individual ensemble examples during the Day 4 retention session, and **(B)** group statistics of spatial frame ensemble preference (SFEP), demonstrating cognitive control in both groups. During retention, SFEP is biased to the arena frame in both the sham ($t_4 = 4.16$, $^{\#}p = 0.01$) and lesion rats ($t_4 = 6.62$, $^{\#}p = 0.003$). $^{*}p < 0.05$ post-hoc differences. **(C)** Group spatial probability distribution of SFEP for room frame preference during the pretraining, initial, and conflict retention sessions with no shock. **(D)** Summary of average probability of room-preferring SFEP discharge in half the arena near and far from the shock zone during the initial and conflict retention sessions. Two-way Group x Location ANOVA (Sham: n=3, Lesion: n=3) during retention of the initial shock zone location: Group: $F_{1,4} = 0.17$ $p = 0.68$, $\eta^2 = 10^{-3}$; Location: $F_{1,4} = 54.69$, $p = 0.001$, $\eta^2 = 0.84$; Group x Location $F_{1,4} = 2.04$, $p = 0.2$, $\eta^2 = 10^{-2}$**;** during retention of the conflict shock zone location: Group: $F_{1,4} = 0.71$ $p = 0.45$, $\eta^2 =$

0.05; Location: $F_{1,4} = 0.42$, $p = 0.55$, $\eta^2 = 0.056$; Group x Location $F_{1,4} = 0.67$, $p = 0.45$, $\eta^2 = 0.08$.

Discussion

Although permanent lesion of the mPFC alters baseline metabolic coupling of mPFC- and hippocampus-related brain areas (Fig.2, S3), as well as alters hippocampal representational dynamics during expression of cognitive flexibility in an active place avoidance task (Fig.3), we find no behavioral or electrophysiological evidence that the lesion impairs cognitive control in the basic active place avoidance task (Fig.1, 3, 4), despite the lesion being sufficient to cause a cognitive flexibility deficit when the shock zone was relocated for the conflict training trials (Fig. 1F insets). We observed increased overdispersion in lesion rats but only during pretraining; place cell tuning was not disturbed, only the discharge reliability was reduced in the absence of the place task. We also observed reduced bursting in the discharge of the underlying posterior and lateral posterior thalamus in the lesion group compared to sham (Table S3). Thus, CO imaging and electrophysiological evidence identify changes in the brain beyond the directly damaged mPFC area. In particular, the dorsal hippocampus loses the inhibitory input from mPFC [47, 48] and loses the metabolic correlation with the nucleus reuniens, which is thought to be a relay between the mPFC and the dorsal hippocampus [49, 50].

We have previously demonstrated cognitive control in the active place avoidance task variant we used (Fig. 1) because the rats must ignore local rotating place cues to avoid the stationary shock zone. Even when the arena does not rotate, rats distinctly learn to avoid the location of shock according to distal visual room cues and local olfactory arena cues, such that the distinct place memories can be independently manipulated using probe trials [51, 52]. When the arena rotates, as in the present studies, neural manipulations that impair the place avoidance are no longer impairing when the irrelevant arena cues are hidden by shallow water [16, 17, 53, 54].

404 Furthermore, persistent hippocampal neural circuit changes caused by active place avoidance
405 training are not detected when shallow water hides the irrelevant arena cues to reduce the
406 cognitive control demand [12, 33, 35]. While these findings unequivocally demonstrate the
407 salience of relevant stationary room cues to use for avoiding shock and irrelevant arena cues to
408 ignore during active place avoidance, the most compelling evidence of cognitive control comes
409 from recording hippocampal ensemble discharge. Hippocampal ensemble discharge purposefully
410 represents current position using stationary room information when the subject is close to the
411 stationary shock zone and alternatively represents rotating arena information when the mouse is
412 far from the stationary shock zone [Fig. 4; 12]. Despite this evidence from task design, behavioral
413 observations, and direct electrophysiological representational switching as required to directly
414 demonstrate cognitive control, one might still argue that it is logically possible that the active place
415 avoidance task does not require cognitive control and this is why the mPFC lesion did not impair
416 place avoidance of the initial shock zone. We consider such reasoning to be unproductive
417 because it presumes that only tasks that require an intact mPFC can be cognitive control tasks.
418 We nonetheless acknowledge that, for some, we have not provided sufficient evidence that the
419 active place avoidance requires cognitive control.
420
421 We assert that the evidence presented here is compelling, and that these findings require
422 rejecting the central-computation hypothesis, which states that the mPFC is essential for the
423 neural computations that are necessary for all cognitive control tasks. The present findings do not
424 rule out a role for mPFC and hippocampal interactions in other cognitive processes [3, 55-58].
425 For example, mPFC may be crucial for processes that rely on the ventral hippocampus and
426 perhaps the direct excitatory mPFC-ventral hippocampus and/or the direct mPFC-dorsal
427 hippocampus excitatory [59] and inhibitory connections [47, 48]. Nonetheless, the present data
428 favor the local-computation hypothesis because bilateral and unilateral inactivation, as well as
429 numerous other manipulations of the dorsal hippocampus, impair learning, consolidation, and

430 retrieval of the conditioned active place avoidance [14-16, 60], and optogenetic silencing of
431 dentate gyrus impairs conflict learning. Indeed, we directly confirmed that mPFC lesion does not
432 reduce the goal-directed representational switching of dorsal hippocampus (Fig.4) that is a *sine*
433 *qua non* for cognitive control of spatial information [12, 13, 18, 19, 39, 46], despite detecting other
434 behavioral and electrophysiological effects of the lesion. We emphasize that observed
435 representational switching is neurobiological evidence of cognitive control; it is not itself cognitive
436 control, although it could be part of transmissive control. Rather, the observed representational
437 switching indicates that cognitive control persists after mPFC lesion; indeed, what a control signal
438 itself should resemble is uncertain, even in primates [10, 11]. It is especially important that mPFC
439 lesion impaired conflict avoidance of the relocated shock zone even after eight trials during which
440 both sham and lesion animals learned and performed at a behavioral asymptote (Fig. 1F). We
441 suggest this identifies a key role for the mPFC in cognitive flexibility, specifically the ability to
442 judiciously select between different memories of the location of shock, and that this is
443 demonstrably distinct from judiciously selecting between room- and arena-based classes of
444 spatial information.
445
446 Although muscimol inactivation of mPFC did not impair active place avoidance [61], as observed
447 in the present study, it is possible that acute manipulations of the mPFC, such as optogenetic,
448 chemogenetic or other pharmacological inactivation would lead to different results. In which case,
449 post-lesion reorganization of neural circuits is sufficient to compensate for the loss of the mPFC
450 functions that support cognitive control as required by the active place avoidance task. However,
451 this would not change the conclusion to reject the central-computation hypothesis. It is also
452 possible that the role of the mPFC is best evaluated in tasks that rely on egocentric spatial
453 information [62], rather than the allocentric spatial information upon which the present active place
454 avoidance task variant relies, but this possibility would also require rejecting, or at least severely

455 limiting, the central-computation hypothesis. Finally, we observed impaired performance
456 characterized by cognitive flexibility in the conflict task variant, demonstrating not only that the
457 lesion was effective, but a dissociation of the neural substrates needed for different components
458 of cognitive control, as has been previously reported [63, 64]. The mPFC has a crucial role in
459 judiciously selecting between distinct memories of the room-frame shock location, which arguably
460 is a form of memory-guided cognitive control that also depends on hippocampus [13, 46, 65], but
461 not a form of cognitive control that has been demonstrated in the representational discharge of
462 hippocampal cells [13].
463
464 Taken together, the findings are consistent with the local-computation hypothesis that diverse (but
465 probably not all) brain circuits can perform the computations needed for cognitive control of the
466 information and/or behavior for which that circuit is specialized to process.
467

468 ## Materials and Methods

469 All methods complied with the Public Health and Service Policy on Humane Care and Use of
470 Laboratory Animals and were approved by NYU's University Animal Welfare Committee under
471 protocol 12-1383, which follow National Institutes of Health guidelines.
472
473 *Subjects*
474 Thirty adult, male, Long-Evans rats were purchased from Charles River to arrive at New York
475 University at approximately 40 days old. The rats were given at least one week to acclimate to
476 the facility and were housed two per cage on a 12:12 light:dark cycle with free access to food and
477 water. Fifteen rats were assigned to the lesion group and 14 to the sham group. One animal was
478 used to confirm the coordinates, by injecting fluorogold (Fluorochrome, Denver, CO, 2.5% w/v in

479 distilled water) at the same rate and for the same duration as for the lesions. Three of the sham
480 and three of the mPFC lesions rats were used for the electrophysiology recordings. The behavior
481 of these rats was not included in the behavioral assessment due to the requirement for extended
482 training sessions to record neuronal activity.
483
484 Behavioral analysis followed by cytochrome oxidase activity: One rat in the lesion group was
485 excluded because the lesion was inadequate and one had to be removed from the study due to
486 a skin irritation, resulting in 10 rats in the lesion group. All of these rats underwent behavioral
487 assessment (lesion n=10), eight of which were stained for cytochrome oxidase. The tissue from
488 one lesion and one sham rat could not be used for CO because the tissues were lost to thawing
489 and tissue from one rat from each group was not processed. For the control group, one rat was
490 excluded from performing behavioral experiments because his lesioned cage mate had a skin
491 irritation that resulted in a large skin lesion and required euthanasia. Because the abrupt change
492 to single housing is stressful and can affect cognitive behavior, the control rat was also excluded
493 from behavioral testing; this control brain was still processed for cytochrome oxidase activity. One
494 rat was excluded from the behavioral experiments due to equipment malfunction during training,
495 and one rat had tissue damage during the sham surgery that appeared as a lesion, so this rat
496 was excluded from the study. Thus, the sham group had eight rats for behavioral assessment and
497 eight for cytochrome oxidase assessment. Our final group numbers for the behavioral assessment
498 were therefore sham group n = 8, lesion group n = 10, and our final group numbers for cytochrome
499 oxidase activity were sham group n = 8 and lesion group n = 8.
500
501 *Lesion Surgery*
502 Between the ages of 48-56 days, the rat received prefrontal cortex or sham lesion under sodium
503 pentobarbital (50 mg/kg, i.p.) anesthesia. Bilateral lesion targeted two sites in each hemisphere
504 at the following stereotaxic coordinates: from Bregma, Site 1: A.P +2.5, ML $\pm$0.6, DV - 5.0, relative

505 to the skull surface, Site 2: AP +3.5, ML $\pm$ 0.6, DV - 5.2, relative to skull surface. Ibotenic acid
506 (0.06 M in PBS) was used to create an excitotoxic lesion following published work [66]. A 0.2 µl
507 volume was injected at each site with a micro-infusion pump at a flow rate 0.2 µL/min through a
508 stainless-steel cannula (0.25 mm outer diameter); the cannula was left in place for 4 min (for a
509 total of 5 min per injection site) before being slowly withdrawn. Rats in the sham group underwent
510 the same surgery procedure, but only PBS was injected. The rats were given one week to recover.
511
512 *Active place avoidance task*
513 A commercial rotating arena and tracking software (Tracker, Bio-Signal Group, Acton, MA) was
514 used for the active place avoidance task, which has been described previously [34, 36, 67]. Briefly,
515 the rats were placed on a stainless steel 82-cm diameter arena that could rotate about its center
516 at 1 rpm under computer control. The arena was in the center of a 3m x 3m space that was
517 surrounded by black curtains with a distinctive orienting cue (striped fabric). The arena floor was
518 made of parallel stainless-steel rods organized into 5 electrical poles. A constant current source
519 could be triggered by the software to deliver shock that was scrambled across the 5 poles to
520 ensure it was unlikely that shock could be avoided by a fortuitous posture or by feces shorting the
521 bars. A 50-cm high transparent PETG wall ensured the rats remined on the arena and allowed
522 them to see into the room as the arena rotated. The position of the rat in the spatial frame of the
523 room was tracked 30-times a second at 3.2 mm resolution by analysis of the video image from an
524 overhead camera. An infrared LED that rotated with the arena was tracked similarly from the video
525 image, and the rat's arena-frame position on the arena surface was computed relative to the arena
526 LED [51, 68]. The room-frame and arena-frame position time series along with the delivery of
527 shock were stored in data files for off-line automated software analysis of end-point measures
528 (TrackAnalysis, Bio-Signal Group, Acton, MA). Three end-point measures are reported. i) The
529 distance walked measures how much the rat walked on the arena surface. ii) The time to first
530 enter the shock zone increased with training; it estimates the between-session active place

avoidance memory by estimating how well the rat can remember the previous room-frame locations of shock. iii) The number of entrances into the shock zone decreased with training; it estimates place learning and can decrease due to between-session memory as well as within-session memory of the locations of shock.

Active place avoidance training

After recovery from surgery, the rats were brought to the laboratory in their home cages that were placed to a rack to the side of the experimental room. The rats were each handled for 5 min per day for 5 days. Behavioral training consisted of 10-min trials with an intertrial interval of 10 minutes during which the rat was returned to it's home cage in the experimental room. On the first day of behavior training, animals had a pretraining session that consisted of two trials during which the rats were allowed to explore the stationary arena to habituate to the environment. The following two days, the rats underwent eight training trials per day on the rotating arena, learning to avoid entering a 60° sector shock zone in which the rats received a mild foot shock (500ms, 60Hz, 0.4mA). This shock zone was defined by the stationary cues in the room and was the same for all rats. On the fourth day of the behavioral training, the rats had a single trial with the shock on to test retention of the training. The rats were then trained on days 4 and 5 in a conflict training session in which the rats received eight trials per day with the shock zone located 180° from the initial training position. All trials were 10 min with 10 min intertrial intervals. The total distance walked during the session measured locomotion, the time to first enter the shock zone location measured avoidance memory, and the number of entrances into the shock zone was used to measure place learning. Savings in place learning on the conflict trials when the shock zone was relocated 180° was assessed for each rat by a savings index, which compares the number of entrances during the first 5 minutes of the first and second day of conflict training, Conflict Trials 1 and 9 respectively. The difference is normalized by the number of entrances on the first conflict

trial and reported as a percentage:

$$Savings\ Index = \frac{\left(Number\ of\ Entrances_{conflict1} - Number\ of\ Entrances_{conflict9}\right)}{Number\ of\ Entrances_{conflict1}} X100$$

Electrophysiology procedures

The following procedures have been previously described in detail [20]. Briefly, rats were anesthetized (pentobarbital 50 mg/kg) and received mPFC or sham lesions as described above. The Neuropixel recording system was used [69]. A Neuropixel electrode array was implanted in the brain to traverse Bregma coordinates AP -3.8 mm, ML 2.5 mm for recording dorsal hippocampus and the tip targeted DV 9.3 mm, which allowed recording from the underlying posterior and lateral posterior thalamus. The Neuropixel was stabilized and protected by mounting it in a custom 3-D printed appliance. The appliance and five bone screws were cemented to the skull (Unifast, GC America Inc., IL). The rats were allowed at least 1 week to recover before further manipulation.

The rats received active place avoidance training as described above. In addition, to permit neural ensemble recordings, after the last pretraining, training, and conflict training sessions, shock was turned off and the session was extended for 10 - 20 min during which CA1 neural ensemble discharge was recorded using SpikeGLX. Signals were filtered between 300 Hz and 10 kHz and sampled at 30 kHz for single unit recording. Because of these extended sessions, the behavior from these animals was not included in our behavioral assessment.

Electrophysiology data analysis

Single units were automatically sorted using Kilosort 2 [70]. Units were only studied if the estimated contamination rate was < 20% with spikes from other neurons. This was estimated from refractory period violations relative to expected. Units with non-characteristic or noisy waveforms

were also excluded. We computed a “burst ratio” to characterize burstiness of discharge as: number of spikes with ISI ≤ 30 ms divided by number of spikes with 100 ms ≥ ISI ≤ 130 ms.

Hippocampus single units were classified as complex-spike or theta cells as in prior work [18, 71, 72]. Complex-spike cells appear to be pyramidal cells, having long-duration waveforms (> 250 μs), low discharge rate (< 5 AP/s) and a tendency to fire in bursts. Theta cells are likely local interneurons[73], and had short-duration waveforms (< 250 μs), high discharge rate (> 2 AP/s), and did not tend to fire in bursts. Only hippocampal units classified as pyramidal cells were studied. Thalamic units, recorded from the posterior and lateral posterior thalamic nucleus, which lies directly beneath the hippocampus, fired at high rates and were less likely to discharge in bursts (Table S3).

The representational dynamics of CA1 discharge alternating between preferentially signaling the current location in the stationary room or the current location on the rotating arena was investigated to directly evaluate cognitive control during place avoidance behavior. Spatial-frame-specific momentary positional information (I_{pos}) is used to estimate the location-specific information from the activity of a cell during a brief interval (Δt = 133 ms).

$I_{pos}(t) = p_{i|x} log_2 \left(\frac{p_{i|x}}{p_i}\right)$, $p_{i|x}$ is the probability of observing i activity at location x, and p_i is the overall probability of observing i activity. $I_{pos(room)}$ estimates the information about the current location *x* in the room, whereas $I_{pos(arena)}$ separately estimates the information about current location *x* on the rotating arena[43]. $I_{pos}(t)$ can be positive or negative, but the absolute value is large whenever the cell’s activity at the current location is distinct or ‘‘surprising’’ compared to the location-independent probability of observing the same activity. The value $\left|I_{pos}(t)\right|$ is abbreviated I_{pos}. A unit’s spatial-frame preference is estimated at each Δt moment as the difference:

606 ΔI_{pos} = $I_{pos(room)}$ - $I_{pos(arena)}$, where positive values indicate a momentary preference for signaling
607 the room location, and negative values indicate a preference for signaling the arena location.
608 ΔI_{pos} timeseries were evaluated for significance compared to chance fluctuations around the
609 mean using the z value from a runs test. The spatial frame ensemble preference (SFEP) at each
610 Δt was computed as the average ΔI_{pos} over all cells. This ensemble ΔI_{pos} timeseries (assessed
611 for significance by runs test) was averaged over all times and locations to estimate an overall
612 SFEP as the proportion of time the ensemble activity was room (or arena) preferring [12, 13]. To
613 evaluate if SFEP was purposeful, the arena was divided into approximately two halves based on
614 where individual rats avoided during a retention test with shock off. The "near" half was the largest
615 sector that includes at least 50% of the recording time and surrounds the least visited 20° sector
616 of the room frame (within the shock zone). The "far" half is the remaining sector. The probability
617 of observing room-preferring ΔI_{pos} was computed at each location to make a representational
618 preference map and the average probability in the near and far halves were compared by
619 statistical evaluation.
620 Place cell overdispersion measures discharge non-stationarity by estimating how much neuronal
621 discharge deviates from what is expected if the discharge only signals position [41]. Increased
622 overdispersion indicates an extra-positional signal like attention or cognitive control is modulating
623 discharge up and down in addition to position, whereas decreased overdispersion indicates such
624 modulation is dampened, possibly to sustained attention [38]. Overdispersion of hippocampal
625 discharge was computed as previously described [38]. Briefly, The spike and position timeseries
626 is divided into 5-s episodes and the expected firing (*exp*) is computed assuming an
627 inhomogeneous Poisson process. The standardized rate is computed as the normalized
628 difference between the observed (obs) and expected firing: $z = \frac{obs-exp}{\sqrt{exp}}$. Episodes with *exp* = 0
629 are undefined, and only episodes in which *exp* is greater than the cell's mean firing were analyzed
630 because this criterion selects episodes during which the rat passes through the central region of

631 the firing field. The variance of the distribution of *z* values quantifies overdispersion, which can be
632 compared between conditions using a F test.
633
634 *Tissue processing and histochemistry*
635 Verification of lesion coordinates
636 Immediately following surgery to inject fluorogold, the rat was transcardially perfused with 0.9%
637 saline and 10% formalin, and the brain extracted and postfixed in 10% formalin for 24h at 4°C.
638 The brain was then cryoprotected in 30% sucrose (w/v in 1x phosphate buffered saline) and stored
639 at 4°C until cut on a cryostat (40 μm). The sections were mounted onto gelatin coated slides and
640 scanned using an Olympus VS120 microscope (fluorescence, 10x). The slides were then placed
641 in e-pure water (2 times, 1 min each) before being dehydrated (50, 70, 80, 95, 100, 100% ethanol,
642 1 min each) and defatted in 50:50 chloroform ethanol for 20 min. The slides were then rehydrated
643 (100, 100, 90, 80, 70, 50% ethanol, 1 min each) before being Nissl stained with Cresyl violet (1
644 min), rinsed in e-pure water, and dehydrated (50% ethanol, 1 min, 70% ethanol until the white
645 matter was white, 95% ethanol with acetic acid until desired intensity, 100, 100% ethanol, 2 min
646 each). The tissues were then cleared in xylenes (3 times, 5 min each) before being coverslipped.
647 The slides were then scanned again (light microscope, 10x). Images were manipulated using
648 Adobe Photoshop CS6 to perform auto-contrast on each image and to remove background from
649 the images. The fluorescent images were then all thresholded in a single operation to remove the
650 background and the result was superimposed on the corresponding Nissl-stained sections using
651 Adobe Illustrator.
652
653 Cytochrome oxidase activity and Nissl staining
654 On the day following the completion of behavior training, the rats were anesthetized with
655 isoflurane, immediately decapitated, and the brains were extracted. The brains were rapidly

656 frozen in isopentane on dry ice and stored at -80 °C. Sets of brains consisting of two to four
657 animals per group were cut simultaneously on a cryostat (40 μm), and sorted into the three series,
658 one of which was Nissl stained and one used for cytochrome oxidase histochemistry. The series
659 used for Nissl staining was stored at room temperature and the other two series stored at -80°C
660 until processed for cytochrome oxidase histochemistry. To control for variability across batches
661 of histochemical staining, 20, 40, 60 and 80 μm sections of fresh rat brain tissue homogenate
662 (prepared as in [74]) were included. Cytochrome oxidase staining was performed according to
663 [75]. Stained slides were scanned with an Olympus VS 120 light microscope (2 x) and the optical
664 densities measured from captured images. Images were converted to 8-bit gray scale using
665 ImageJ [76] and optical densities read from the standard slides and 14 brain regions (Figure 1).
666 These brain regions included the dysgranular and granular retrosplenial cortices (RSD and RSG,
667 respectively), the nucleus reuniens (RE), the central nucleus of the amygdala (CEA), basomedial
668 and basolateral amgydala (BMA, and BLA, respectively), the dorsal hippocampal CA1, CA2, CA3
669 and dentate gyrus areas (dCA1, dCA2, dCA3, dDG, respectively) the ventral hippocampal CA1,
670 CA3 and dentate gyrus areas (vCA1,vCA3, vDG, respectively) and the dorsal subiculum (DS).
671 The optical densities were measured using ImageJ (NIH) and cytochrome oxidase activity was
672 normalized as in [67]. Optical densities were measured while blind to the group identity. Three to
673 six optical density readings were taken for each brain region, from both hemispheres and
674 averaged for each individual subject.
675
676 To confirm the lesion site, one series of sections was stained with Cresyl violet. The slides were
677 placed in the e-pure water (2 times, 1 min each) and dehydrated in a series of ethanol baths (50,
678 70, 80, 90, 100, 100%, 1 min each) prior to clearing the fats in a 1:1 mixture of ethanol:chloroform
679 for 20 min. The slides were then rehydrated (100, 100, 90, 80, 70, 50% ethanol, 1 min each),
680 rinsed in e-pure water, and placed in the Cresyl violet for 10 min. The slides were again

681 dehydrated and cleared in xylenes (3 times, 5 min each) before being coverslipped. Images were
682 captured with an Olympus VS120 light microscope at 10x. Contours of the lesion area were drawn
683 using Adobe Illustrator in a layer overlaid on the tissue images. The images were matched to the
684 appropriate section of the Paxinos and Watson rat brain atlas [77]. The filled contours were
685 converted to a .tiff file for quantification of the lesion area (pixels) using ImageJ (see Fig. S2).
686 Rats with verified bilateral lesions that spanned at least 3 sections were included in the data
687 analysis; one rat was excluded from analysis because the lesion was only evident in one
688 hemisphere.
689
690 *Statistical analysis*
691 Cytochrome oxidase activity: Group averages of the optical densities were calculated for each
692 brain regions and expressed as mean ± SEM relative cytochrome oxidase activity/ μm of tissue.
693 Interregional metabolic covariation was examined by calculating Pearson correlations between
694 each brain region. The statistical significance of interregional cytochrome oxidase activity
695 correlations was determined by a 0.01 False Discovery Rate. To determine if the interregional
696 correlations were significantly different between groups, we transformed the r value of the
697 correlation to Fisher's z-scores. Significant correlations ($p < 0.05$) were used to generate graph
698 theoretical networks using the Brain Connectivity Toolbox in MATLAB
699 (https://sites.google.com/site/bctnet/).
700
701 Behavior and electrophysiology: Place avoidance task performance and SFEP electrophysiology
702 measures were compared using multivariate analysis of variance. Repeated measure analyses
703 were performed using the Greenhouse-Geisser correction. One-factor group comparisons were
704 performed by t test. Pairs of binomial proportions were compared by a test for proportions (z).
705 Runs tests were used to evaluate the likelihood of observing the ensemble ΔI_{pos} timeseries by

706 chance. Statistical significance was set at 0.05 for all comparisons. Test statistics, degrees of
707 freedom and effect sizes are provided, in addition to exact p values. These values were computed
708 using SPSS Statistics 28 and Microsoft Excel.
709

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