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 spatial 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 the ability to judiciously use task-relevant information while ignoring salient concurrent information that is currently irrelevant for the task. The consensus view is that the prefrontal cortex (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 [1-3]. The hippocampal role in the cognitive control of spatial and mnemonic information has been investigated using an active place avoidance task [4]. 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 [5]. Avoiding shock at a stationary room location requires using the task-relevant spatial information and ignoring spatial information from the other, task-irrelevant frame. Dorsal hippocampus dysfunction impairs this avoidance [6-9]. During active place avoidance task variants, place cell discharge in hippocampus subfields, and head-direction cell discharge in the medial entorhinal cortical input 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 [4, 5, 10-12].

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 [13, 14]. Recent work indicating that the hippocampus [10] and sensory thalamus [15] 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 [14, 16, 17]. Alternatively, the role of non-PFC brain structures in cognitive control could be explained by a

101 “local-computation” hypothesis; the computations needed for cognitive control can be performed
102 locally in neural networks specialized for the particular information upon which the task depends
103 and on which cognitive control operates. The local-computation hypothesis predicts that PFC
104 lesion can spare cognitive control. We tested these mutually exclusive hypotheses by making
105 medial prefrontal cortex (mPFC) lesions in rats and evaluating their behavior and hippocampal
106 physiology during active place avoidance (Fig. 1A).
107

108 ## Results

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

110 Ibotenic acid, but not vehicle, targeted to mPFC caused lesions that included the cingulate cortex,
111 prelimbic and infralimbic areas (Fig. 1B). To assess the effect of mPFC lesion on behavior, we
112 first examined locomotion during the pretraining sessions (Fig. 1C). There is no effect of lesion
113 on the total distance walked across the session (Fig.1D). We next examined active place
114 avoidance learning during initial training (Days 2-3). Both groups learn to reduce their entrances
115 into the shock zone with training (Fig. 1E). There is no behavioral difference between groups by
116 measuring the number of entrances or time to first enter the shock zone, the clearest estimate of
117 memory (Fig. 1F). The two groups are also indistinguishable on Day 4 during which 24-h memory
118 is assessed by their times to first enter the shock zone and the number of entrances (Fig. 1, Day
119 4 Retention).
120

121 We then trained the rats to avoid the shock zone relocated 180° to assess the impact of mPFC
122 lesion on cognitive flexibility with the additional challenge to distinguish between the current and
123 previously learned location of shock, under the cognitive control challenge [18]. Both groups learn
124 the conflict task variant, measured by the number of entrances and the time to enter the new
125 shock zone (Fig. 1, Days 4-5 Conflict Training). There is a non-significant trend for greater savings

in sham rats, comparing the entrances on the first and second days of conflict trials (sham = 11.12 ± 4.58 entrances, lesion = 4.3 ± 4.09 entrances; t_{16} = 1.11; p = 0.3, d = 0.52). Consequently, we more closely examined the initial experience of the new shock zone location when the rats are first confronted with the change in the location of shock. We compared the number of entrances on the first trial of each day to estimate savings during initial training (Fig. 1F left inset) and during conflict training (Fig. 1F middle inset). During initial training, both sham (t_7 = 4.5, p = 0.003, d = 1.2) and lesion (t_9 = 4.7, p = 0.001, d = 1.5) rats improved. During conflict training, while sham rats all improved across the first two conflict trials of each day (t_7 = 3.8, p = 0.006, d = 1.4) only 6/10 lesion rats improved (t_9 = 0.87, p = 0.4, d = 0.27). We also quantified the improvement for each subject during conflict as a savings index using the first 5 minutes of the first conflict trials of each day (Fig. 1F right inset). The sham rats improved, avoiding more than the lesion rats in the first 5 minutes of the second conflict day compared to the first conflict day (t_{16} = 2.4, one-tailed p = 0.03, d = 0.85), despite equivalent performance across eight trials on the first day. Although, we find no 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, the lesion is sufficient to impair conflict learning after a 24-h delay.

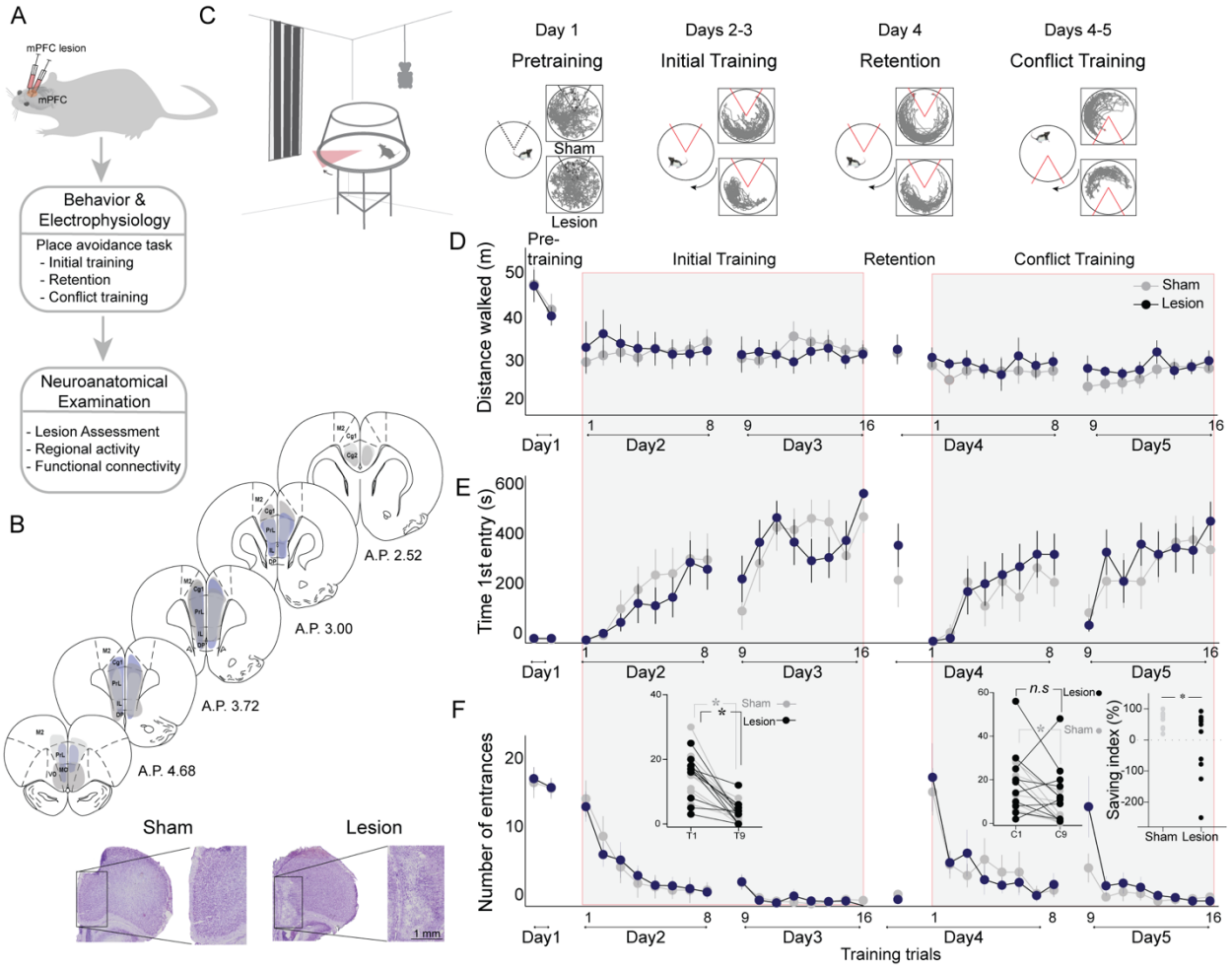

Figure 1. mPFC lesion does not impair initial active place avoidance learning, but impairs cognitive flexibility in the conflict task variant (A) Workflow to assess the impact of mPFC or sham lesions on spatial cognitive control. (**B)** Assessment and impact of the mPFC lesion in three representative subjects (light grey, dark grey, and purple). PrL (prelimbic), IL (infralimbic), Cg (cingulate cortex), M2 (secondary motor cortex). Representative mPFC from a sham and a lesion rat (bottom). **(C)** Behavioral tracks 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. Locomotor activity: During pretraining, there is no effect of lesion on the total distance walked across the two trials ($F_{1,16}$ = 0.04, p = 0. 85, η^2 = 0.002). There is an effect of trial ($F_{1,16}$ = 15.31, p = 0.001, η^2 = 0.09) but there is no effect of the interaction ($F_{1,16}$ = 0.14, p =0.71, η^2 = 10^{-3}). Locomotion does not differ between the groups, across trials, or their interaction during Initial Training (df = 3.17/50.77), or Conflict Training (df = 4.97/79.58; $F'_S \leqslant$ 1.96, p $\geqslant$ 0.09, $\eta^2 \leqslant$ 0.03). Avoidance Memory: (Time to first enter the shock zone) The latency to first enter the new shock zone increases for both groups in Initial training. 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}). Place Learning (Number of entrances): 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 indistinguishable on Day 4 during which 24-h memory is assessed by their times to first enter the shock zone (t_{17} = 1.01, p = 0.3, d = 0.49) and the number of entrances (t_{17}= 0.95, p = 0.4, d = 0.002). There is a non-significant trend for greater savings in sham rats, comparing the first and second days of conflict trials (sham = 11.12 ± 2.89 entrances, lesion = 3.9 ± 4.50 entrances; t_{17} = 1.34; p = 0.20, d = 0.56). In the conflict learning, 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 ($F_{1.89, 30.12}$ = 18.55, p = 10^{-9}, η^2 = 0.28) are significant. The

group interactions are not significant (group x day: $F_{1,16} = 0.55$, $p = 0.47$, $\eta^2 = 10^{-3}$; group x trial: $F_{1.88, 30.12} = 1.38$, $p = 0.27$, $\eta^2 = 0.02$; group x day x trial: $F_{2.30, 36.87} = 1.16$, $p = 0.33$, $\eta^2 = 10^{-3}$). Also, the interaction between day and trial is not significant (day x trial: $F_{2.30, 36.87} = 2.31$, $p = 0.11$ $\eta^2 = 0.019$). The insets compare number of entrances during the first 5 minutes of left: the first (D1T1) and second days of initial training (D2T9) as well as right: 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 for statistical comparison. Sham rats demonstrate greater savings than lesion rats ($t_{16} = 2.4$, one-tailed $^*p = 0.03$, $d = 0.85$), demonstrating effectiveness of the mPFC lesion to impair cognitive flexibility.

mPFC lesion alters functional relationships amongst related brain areas

Cytochrome oxidase (CO), a sensitive metabolic marker for neuronal function [19], 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, S2b; 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

212 a correlation between dorsal CA1 and the central nucleus of the amygdala appears after mPFC
213 lesion. These data indicate that the mPFC lesion causes functional changes beyond mPFC.
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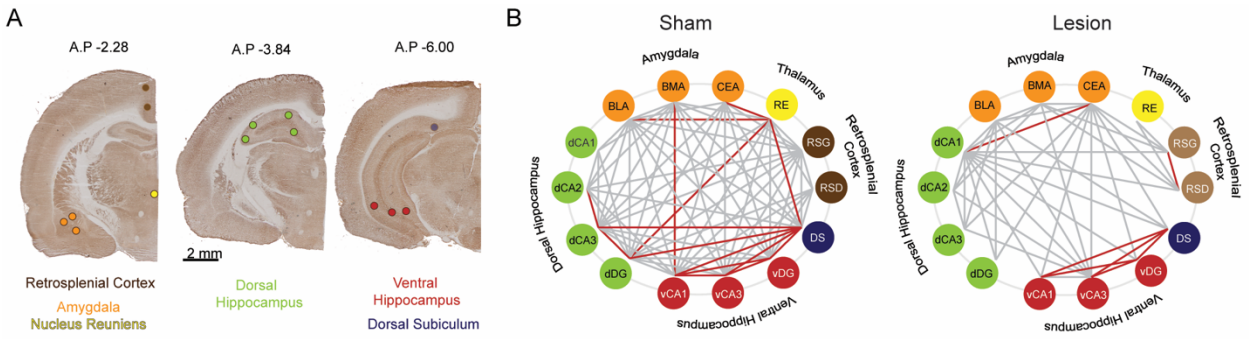

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216 **Figure 2. Cytochrome oxidase analysis demonstrates widespread metabolic**
217 **consequences of mPFC lesion. (A)** Representative cytochrome oxidase staining and locations
218 of the optical density readings. Cytochrome oxidase activity was measured in the dysgranular and
219 granular retrosplenial cortices (RSD and RSG, respectively), the nucleus reuniens (RE), the
220 central nucleus of the amygdala (CEA), basomedial and basolateral amygdala (BMA, and BLA,
221 respectively), the dorsal hippocampus CA1, CA2, CA3 and dentate gyrus areas (dCA1, dCA2,
222 dCA3, dDG, respectively) the ventral hippocampus CA1, CA3 and dentate gyrus areas (vCA1,
223 vCA3, vDG, respectively) and the dorsal subiculum (DS) marked as colored circle areas. **(B)**
224 Interarea covariations of CO activity by graph theory analysis. Each line indicates a significant
225 correlation ($p < 0.05$) between the two brain regions ("nodes") it connects; only the red lines
226 survived False Discovery Rate ($FDR < 0.01$) correction. Sham: $n = 8$; Lesion: $n = 8$.
227

228 ***mPFC lesion does not alter cognitive control of hippocampal neural***
229 ***representations***

230 Cognitive control requires the subject to process and use a class of information purposefully, at
231 the expense of other competing information, which we previously demonstrated in the population
232 dynamics of dorsal hippocampus spatial discharge as rats and mice navigate on a rotating arena

[4, 5, 10, 20]. Thus, we examined spatial frame ensemble preference (SFEP), the representational dynamics of hippocampus CA1 discharge on the rotating arena during pretraining, as well as retention of the conditioned place avoidance of the initial and conflicting shock zone locations (Fig. 3A). Note that the physical conditions were identical in these three trials because the shock was off.

We first examined basic discharge properties of individual CA1 principal cells, which do not differ between the sham and mPFC lesion groups (Fig 3B). We then examined overdispersion of place cell firing, which is known to be reduced by prefrontal inactivation [21]. In contrast, overdispersion is expected to increase with cognitive control and other extra-positional processes that increase discharge non-stationarity [22]. We find that during pretraining, overdispersion of hippocampal discharge is reduced by a factor of two in lesion compared to sham rats, consistent with an effective lesion (Fig. 3C left). Might this also indicate reduced cognitive control in the lesion rats? Remarkably, during conditioned place avoidance the overdispersion in lesion rats increases to the level observed in sham rats, consistent with the increased demand for cognitive control (Fig. 3C middle and right). These findings confirm the effectiveness of the prefrontal lesion and also provide electrophysiological evidence consistent with intact cognitive control in the lesion rats.

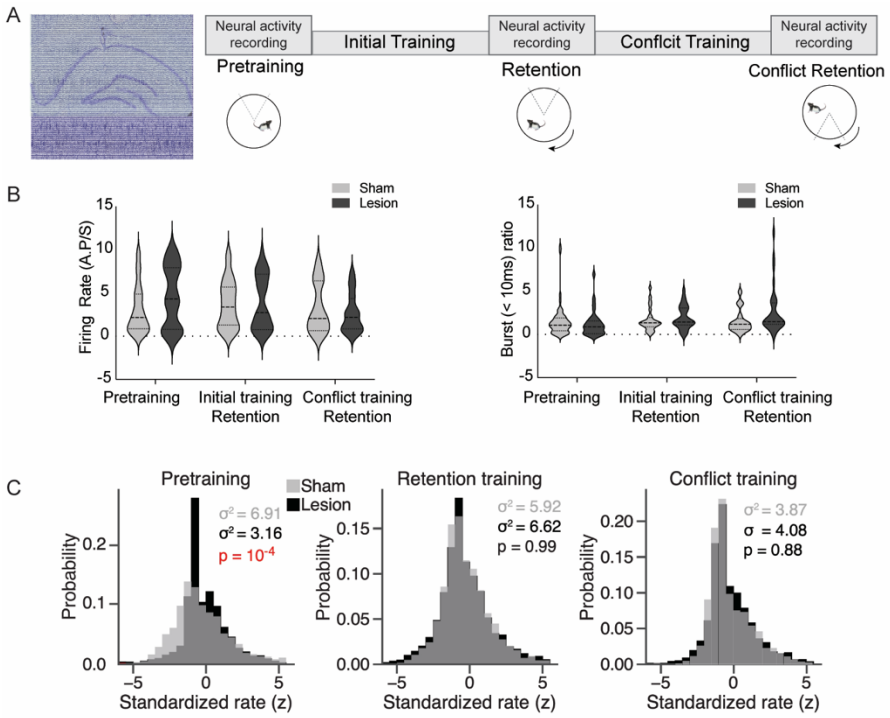

Figure 3. mPFC lesion does not change basic discharge properties, but decreases hippocampus place cell overdispersion only in the absence of the cognitive control challenge. (A) (left) Representative histology with overlaid recording traces from the Neuropixel probe. (right) Recording schedule workflow 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: $F_{2776,3397} = 2.19$, $p = 5.8\times10^{-4}$).

We next examined the spatial frame ensemble preference (SFEP), the electrophysiological signature of cognitive control, during conditioned place avoidance. CA1 ensemble discharge alternates between preferentially representing room locations and arena locations (Fig. 4A; runs tests for all recordings were significant; z's $\geqslant$ 12.3, p's $\leqslant$ 10^{-33}). During pretraining, SFEP is equally likely to signal the current room location or alternatively, the current arena location, in both the sham and lesion rats (Fig. 4A). Importantly, during avoidance of the initial shock location, SFEP favors the arena frame because the rat avoids the room frame location of shock (Fig. 4B) and SFEP is room-preferring near the shock zone and arena-preferring far from the shock zone (Fig. 4C,D), as previously demonstrated [4, 5]. Relocating the shock zone 180° for conflict training changes SFEP, but only in the lesion group such that it is equally probable to be room- or arena-preferring, consistent with needing to decide between avoiding the current and previous shock location throughout the environment (Fig. 4B) [23]. The ability to manipulate SFEP of hippocampal representational dynamics by the presence and location of shock directly demonstrates cognitive control at the level of the hippocampus. Despite an influence of mPFC lesion on cognitive control and the non-stationarity of hippocampal representations of space in hippocampal discharge, the lesion does not impair cognitive control in the place avoidance task.

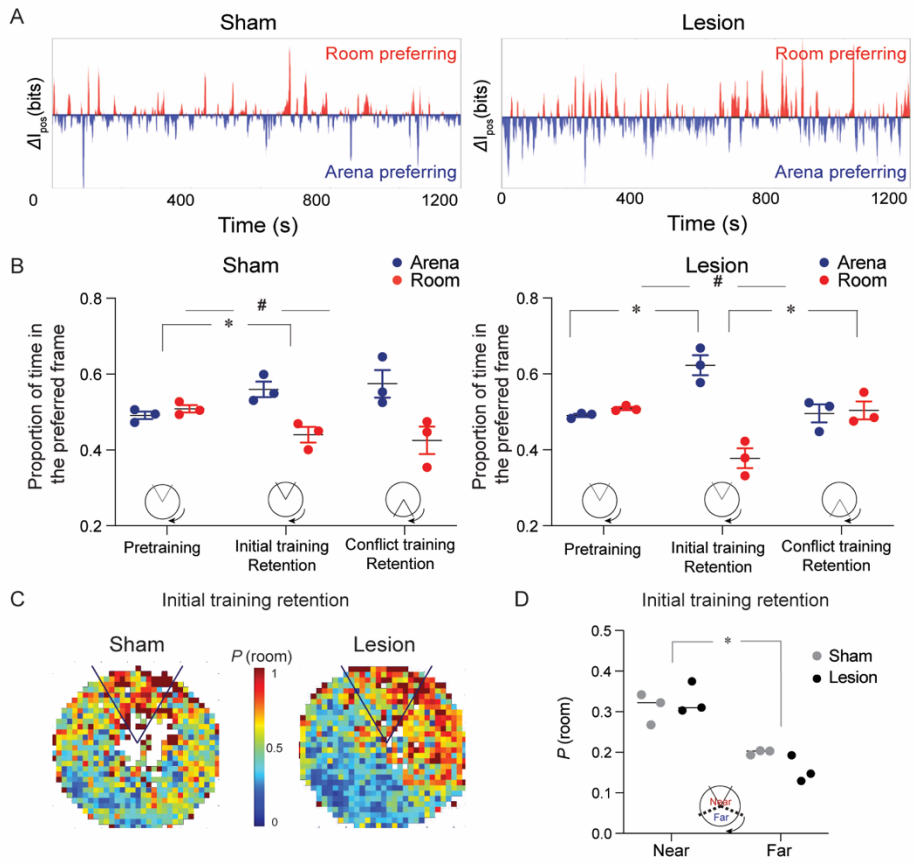

Figure 4. Sham and mPFC lesion rats do not differ in expressing cognitive control of spatial frame-specific representations of location. (**A**) Individual ensemble examples during the Day 4 retention session, and **(B)** group statistics of spatial frame ensemble preference (SFEP), demonstrating cognitive 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 retention session with no shock. **(D)** Summary of average probability of room-preferring SFEP discharge in half the arena near and far from the shock zone. Two-way Group X Location ANOVA: 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 ($F_{1,4} = 2.04$, $p = 0.2$, $\eta^2 = 10^{-2}$).(Sham: n=3, Lesion: n=3)**.**

Discussion

Although permanent lesion of the mPFC alters baseline metabolic coupling of mPFC- and hippocampus-related brain areas (Fig.2, S2), 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 also observed reduced bursting in the discharge of the underlying thalamus in the lesion group compared to sham (Table S2). 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 [24, 25] and loses the metabolic correlation with the nucleus reuniens, which is thought to be a relay between the mPFC and the dorsal hippocampus [26, 27].

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 [28, 29]. When the arena rotates as in the present studies, neural manipulations that impair the place avoidance no longer impair when the irrelevant arena cues are hidden by shallow water [8, 9, 30, 31]. Furthermore, persistent hippocampal neural circuit changes caused by active place avoidance training are not detected when shallow water hides the irrelevant arena cues to reduce the cognitive control demand [4, 32, 33]. While these findings unequivocally demonstrate the salience of relevant stationary room cues to use for avoiding shock and irrelevant arena cues to ignore during active place avoidance,

318 the most compelling evidence of cognitive control comes from recording hippocampal ensemble
319 discharge. Hippocampal ensemble discharge purposefully represents current position using
320 stationary room information when the subject is close to the stationary shock zone and
321 alternatively represents rotating room information when the mouse is far from the stationary shock
322 zone [Fig. 4; 4]. Despite this evidence from task design, behavioral observations, and direct
323 electrophysiological demonstration of cognitive control, one might still argue that it is logically
324 possible that the active place avoidance task does not require cognitive control and this is why
325 the mPFC lesion was not impairing. While we reject such circular reasoning that only tasks that
326 require mPFC can be cognitive control tasks, we nonetheless acknowledge that this may be the
327 opinion of others.
328
329 We assert the evidence is compelling, and together these findings require rejecting the central-
330 computation hypothesis that the mPFC is essential for the neural computations that are necessary
331 for all cognitive control tasks. The present findings do not rule out a role for mPFC and
332 hippocampal interactions in other cognitive processes [2, 34-37], especially those that rely on the
333 ventral hippocampus and perhaps the direct excitatory mPFC-ventral hippocampus and direct
334 mPFC-dorsal hippocampus inhibitory connections [24, 25]. Nonetheless, the present data favor
335 the local-computation hypothesis because bilateral and unilateral inactivation as well as
336 numerous other manipulations of the dorsal hippocampus impair learning, consolidation, and
337 retrieval of the conditioned active place avoidance [6-8, 38], and optogenetic silencing of dentate
338 gyrus impairs conflict learning. Indeed, we directly confirmed that mPFC lesion does not reduce
339 the goal-directed representational switching of dorsal hippocampus (Fig.4) that is a *sine qua non*
340 for cognitive control of spatial information [4, 5, 10, 11, 20, 23], despite detecting other behavioral
341 and electrophysiological effects of the lesion. It is especially important that mPFC lesion impaired
342 conflict avoidance of the relocated shock zone even after eight trials during which both sham and
343 lesion animals learned and performed at a behavioral asymptote (Fig. 1F). We suggest this

344 identifies a key role for the mPFC in cognitive flexibility, specifically the ability to judiciously select
345 between different memories of the location of shock, and that this is demonstrably distinct from
346 judiciously selecting between room- and arena-based classes of spatial information.
347
348 It is possible that acute manipulations of the mPFC, such as optogenetic, chemogenetic or
349 pharmacological inactivation would lead to different results. In which case, post-lesion
350 reorganization of neural circuits is sufficient to compensate for the loss of the mPFC functions
351 that support cognitive control as required by the active place avoidance task. However, this would
352 not change the conclusion to reject the central-computation hypothesis. It is also possible that the
353 role of the mPFC is best evaluated in tasks that rely on egocentric spatial information [39], rather
354 than the allocentric spatial information upon which the present active place avoidance task variant
355 relies, but this possibility would also require rejecting, or at least severely limiting, the central-
356 computation hypothesis. Finally, we observed impaired performance characterized by cognitive
357 flexibility in the conflict task variant, demonstrating not only that the lesion was effective, but a
358 dissociation of the neural substrates needed for different components of cognitive control, as has
359 been previously reported [40, 41]. The mPFC has a crucial role in judiciously selecting between
360 distinct memories of the room-frame shock location, which arguably is a form of memory-guided
361 cognitive control that also depends on hippocampus [5, 23, 42], but not a form of cognitive control
362 that has been demonstrated in the representational discharge of hippocampal cells [5].
363 Taken together, the findings are consistent with the local-computation hypothesis that diverse (but
364 probably not all) brain circuits can perform the computations needed for cognitive control of the
365 information and/or behavior for which that circuit is specialized to process.
366

367 ## Materials and Methods

368 All methods complied with the Public Health and Service Policy on Humane Care and Use of
369 Laboratory Animals and were approved by NYU's University Animal Welfare Committee under
370 protocol 12-1383, which follow National Institutes of Health guidelines.
371
372 *Subjects*
373 Thirty adult, male, Long-Evans rats were purchased from Charles River to arrive at New York
374 University at approximately 40 days old. The rats were given at least one week to acclimate to
375 the facility and were housed two per cage on a 12:12 light:dark cycle with free access to food and
376 water. Fifteen rats were assigned to the lesion group and 14 to the sham group. One animal was
377 used to confirm the coordinates, by injecting fluorogold (Fluorochrome, Denver, CO, 2.5% w/v in
378 distilled water) at the same rate and for the same duration as for the lesions. Three of the sham
379 and three of the mPFC lesions rats were used for the electrophysiology recordings. The behavior
380 of these rats was not included in the behavioral assessment due to the requirement for extended
381 training sessions to record neuronal activity.
382
383 Behavioral analysis followed by cytochrome oxidase activity: One rat in the lesion group was
384 excluded because the lesion was inadequate and one had to be removed from the study due to
385 a skin irritation, resulting in 10 rats in the lesion group. All of these rats underwent behavioral
386 assessment (lesion n=10), eight of which were stained for cytochrome oxidase. The tissue from
387 one lesion and one sham rat could not be used for CO because the tissues were lost to thawing
388 and tissue from one rat from each group was not processed. For the control group, one rat was
389 excluded from performing behavioral experiments because his lesioned cage mate had a skin
390 irritation that prevented the lesion rat from behavioral testing; this control brain was still processed
391 for cytochrome oxidase activity. One rat was excluded from the behavioral experiments due to
392 equipment malfunction during training, and one rat had tissue damage during the sham surgery
393 that appeared as a lesion, so this rat was excluded from the study. Thus, the sham group had

394 eight rats for behavioral assessment and eight for cytochrome oxidase assessment. Our final
395 group numbers for the behavioral assessment were therefore sham group n = 8, lesion group n
396 = 10, and our final group numbers for cytochrome oxidase activity were sham group n = 8 and
397 lesion group n = 8.
398
399 *Lesion Surgery*
400 Between the ages of 48-56 days, the rat received prefrontal cortex or sham lesion under sodium
401 pentobarbital (50 mg/kg, i.p.) anesthesia. Bilateral lesion targeted two sites in each hemisphere
402 at the following stereotaxic coordinates: from Bregma, Site 1: A.P +2.5, ML $\pm$0.6, DV - 5.0, relative
403 to the skull surface, Site 2: AP +3.5, ML $\pm$ 0.6, DV - 5.2, relative to skull surface. Ibotenic acid
404 (0.06 M in PBS) was used to create an excitotoxic lesion. It was injected with a micro-infusion
405 pump at a flow rate 0.2 μL/min through a stainless-steel cannula (0.25 mm outer diameter). Rats
406 in the sham group underwent the same surgery procedure, but only PBS was injected. The rats
407 were given one week to recover.
408
409 *Active place avoidance training*
410 After recovery from surgery, the rats were handled for 5 min per day for 5 days. On the first day
411 of behavior training, animals had a pretraining session that consisted of two trials during which
412 the rats were allowed to explore the stationary arena to habituate to the environment. The
413 following two days, the rats underwent eight training trials per day on a rotating arena, learning to
414 avoid entering a 60° sector shock zone in which the rats received a mild foot shock (500ms, 60Hz,
415 0.4mA). This shock zone was defined by the stationary cues in the room. On the fourth day of the
416 behavioral training, the rats had a single trial with the shock on to test retention of the training.
417 The rats were then trained on days 4 and 5 in a conflict training session in which the rats received
418 eight trials per day with the shock zone located 180° from the initial training position. All trials were

419 10 min with 10 min intertrial intervals. The total distance walked during the session measured
420 locomotion, the time to first enter the shock zone location measured avoidance memory, and the
421 number of entrances into the shock zone was used to measure place learning. Savings in place
422 learning on the conflict trials when the shock zone was relocated 180° was assessed for each rat
423 by a savings index, which compares the number of entrances during the first 5 minutes of the first
424 and second day of conflict training, Conflict Trials 1 and 9 respectively. The difference is
425 normalized by the number of entrances on the first conflict trial and reported as a percentage:

426 $$Savings\ Index = \frac{\left(Number\ of\ Entrances_{conflict1} - Number\ of\ Entrances_{conflict9}\right)}{Number\ of\ Entrances_{conflict1}} X100$$

427 *Electrophysiology procedures*

428 The following procedures have been previously described in detail[12]. Briefly, rats were
429 anesthetized (pentobarbital 50 mg/kg) and received mPFC or sham lesions as described above.
430 A Neuropixel electrode array was implanted in the brain to traverse AP -3.8 mm, ML 2.5 mm for
431 recording dorsal hippocampus and the tip targeted DV 9.3 mm, which allowed recording from the
432 underlying thalamus. The Neuropixel was stabilized and protected by mounting it in a custom 3-
433 D printed appliance. The appliance and five bone screws were cemented to the skull (Unifast, GC
434 America Inc., IL). The rats were allowed at least 1 week to recover before further manipulation.
435
436 The rats received active place avoidance training as described above. In addition, to permit neural
437 ensemble recordings, after the last pretraining, training, and conflict training sessions, shock was
438 turned off and the session was extended for 10 - 20 min during which CA1 neural ensemble
439 discharge was recorded. Signals were filtered between 300 Hz and 10 kHz and sampled at 30
440 kHz for single unit recording. Because of these extended sessions, the behavior from these
441 animals was not included in our behavioral assessment.
442
443 *Electrophysiology data analysis*

Single units were automatically sorted using Kilosort 2[43]. 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[10, 44, 45]. 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[46], 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 fired at high rates and were less likely to discharge in bursts (Table S2).

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[47]. $I_{pos}(t)$ 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: ΔI_{pos} = $I_{pos(room)}$ - $I_{pos(arena)}$, where positive values indicate a momentary preference for signaling the room location, and negative values indicate a preference for signaling the arena location. ΔI_{pos} timeseries were evaluated for significance compared to chance fluctuations around the mean using the z value from a runs test. The spatial frame ensemble preference (SFEP) at each Δt was computed as the average ΔI_{pos} over all cells. This ensemble ΔI_{pos} timeseries (assessed for significance by runs test) was averaged over all times and locations to estimate an overall SFEP as the proportion of time the ensemble activity was room (or arena) preferring[4, 5]. To evaluate if SFEP was purposeful, the arena was divided into approximately two halves based on where individual rats avoided during a retention test with shock off. The "near" half was the largest sector that includes at least 50% of the recording time and surrounds the least visited 20° sector of the room frame (within the shock zone). The "far" half is the remaining sector. The probability of observing room-preferring ΔI_{pos} was computed at each location to make a representational preference map and the average probability in the near and far halves were compared by statistical evaluation.

Overdispersion of hippocampal discharge was computed as previously described[22]. Briefly, The spike and position timeseries is divided into 5-s episodes and the expected firing (*exp*) is computed assuming an inhomogeneous Poisson process. The standardized rate is computed as the normalized difference between the observed (obs) and expected firing: $z = \frac{obs-exp}{\sqrt{exp}}$. Episodes with *exp* = 0 are undefined, and only episodes in which *exp* is greater than the cell's mean firing were analyzed because this criterion selects episodes during which the rat passes through the central region of the firing field. The variance of the distribution of *z* values quantifies overdispersion, which can be compared between conditions using a F test.

494 *Tissue processing and histochemistry*

495 Verification of lesion coordinates

496 Immediately following surgery to inject fluorogold, the rat was transcardially perfused with 0.9%
497 saline and 10% formalin, and the brain extracted and postfixed in 10% formalin for 24h at 4°C.
498 The brain was then cryoprotected in 30% sucrose (w/v in 1x phosphate buffered saline) and stored
499 at 4°C until cut on a cryostat (40 μm). The sections were mounted onto gelatin coated slides and
500 scanned using an Olympus VS120 microscope (fluorescence, 10x). The slides were then placed
501 in e-pure water (2 times, 1 min each) before being dehydrated (50, 70, 80, 95, 100, 100% ethanol,
502 1 min each) and defatted in 50:50 chloroform ethanol for 20 min. The slides were then rehydrated
503 (100, 100, 90, 80, 70, 50% ethanol, 1 min each) before being Nissl stained with Cresyl violet (1
504 min), rinsed in e-pure water, and dehydrated (50% ethanol, 1 min, 70% ethanol until the white
505 matter was white, 95% ethanol with acetic acid until desired intensity, 100, 100% ethanol, 2 min
506 each). The tissues were then cleared in xylenes (3 times, 5 min each) before being coverslipped.
507 The slides were then scanned again (light microscope, 10x). Images were manipulated using
508 Adobe Photoshop CS6 to perform auto-contrast on each image and to remove background from
509 the images. The fluorescent images were then all thresholded in a single operation to remove the
510 background and the result was superimposed on the corresponding Nissl-stained sections using
511 Adobe Illustrator.

512

513 Cytochrome oxidase activity and Nissl staining

514 On the day following the completion of behavior training, the rats were anesthetized with
515 isoflurane, immediately decapitated, and the brains were extracted. The brains were rapidly
516 frozen in isopentane on dry ice and stored at -80 °C. Sets of brains consisting of two to four
517 animals per group were cut simultaneously on a cryostat (40 μm), and sorted into the three series,
518 one of which was Nissl stained and one used for cytochrome oxidase histochemistry. The series

519 used for Nissl staining was stored at room temperature and the other two series stored at -80°C
520 until processed for cytochrome oxidase histochemistry. To control for variability across batches
521 of histochemical staining, 20, 40, 60 and 80 μm sections of fresh rat brain tissue homogenate
522 (prepared as in [48]) were included. Cytochrome oxidase staining was performed according to
523 [49]. Stained slides were scanned with an Olympus VS 120 light microscope (2 x) and the optical
524 densities measured from captured images. Images were converted to 8-bit gray scale using
525 ImageJ [50] and optical densities read from the standard slides and 14 brain regions (Figure 1).
526 These brain regions included the dysgranular and granular retrosplenial cortices (RSD and RSG,
527 respectively), the nucleus reuniens (RE), the central nucleus of the amygdala (CEA), basomedial
528 and basolateral amgydala (BMA, and BLA, respectively), the dorsal hippocampal CA1, CA2, CA3
529 and dentate gyrus areas (dCA1, dCA2, dCA3, dDG, respectively) the ventral hippocampal CA1,
530 CA3 and dentate gyrus areas (vCA1,vCA3, vDG, respectively) and the dorsal subiculum (DS).
531 The optical densities were measured using ImageJ (NIH) and cytochrome oxidase activity was
532 normalized as in [51]. Optical densities were measured while blind to the group identity. Three to
533 six optical density readings were taken for each brain region, from both hemispheres and
534 averaged for each individual subject.
535
536 To confirm the lesion site, one series of sections was stained with Cresyl violet. The slides were
537 placed in the e-pure water (2 times, 1 min each) and dehydrated in a series of ethanol baths (50,
538 70, 80, 90, 100, 100%, 1 min each) prior to clearing the fats in a 1:1 mixture of ethanol:chloroform
539 for 20 min. The slides were then rehydrated (100, 100, 90, 80, 70, 50% ethanol, 1 min each),
540 rinsed in e-pure water, and placed in the Cresyl violet for 10 min. The slides were again
541 dehydrated and cleared in xylenes (3 times, 5 min each) before being coverslipped. Images were
542 captured with an Olympus VS120 light microscope at 10x. Only rats with verified bilateral lesions
543 were included in the data analysis.

544

545 *Statistical analysis*

546 Cytochrome oxidase activity: Group averages of the optical densities were calculated for each
547 brain regions and expressed as mean ± SEM relative cytochrome oxidase activity/ μm of tissue.
548 Interregional metabolic covariation was examined by calculating Pearson correlations between
549 each brain region. The statistical significance of interregional cytochrome oxidase activity
550 correlations was determined by a 0.01 False Discovery Rate. To determine if the interregional
551 correlations were significantly different between groups, we transformed the r value of the
552 correlation to Fisher's z-scores. Significant correlations ($p < 0.05$) were used to generate graph
553 theoretical networks using the Brain Connectivity Toolbox in MATLAB
554 (https://sites.google.com/site/bctnet/).

555

556 Behavior and electrophysiology: Place avoidance task performance and SFEP electrophysiology
557 measures were compared using multivariate analysis of variance. Repeated measure analyses
558 were performed using the Greenhouse-Geisser correction. One-factor group comparisons were
559 performed by t test. Runs tests were used to evaluate the likelihood of observing the ensemble
560 ΔI_{pos} timeseries by chance. Statistical significance was set at 0.05 for all comparisons. Test
561 statistics, degrees of freedom and effect sizes are provided throughout, in addition to exact p
562 values.

563

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