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Disrupting the medial prefrontal cortex with designer receptors exclusively activated by designer drug alters hippocampal sharp-wave ripples and their associated cognitive processes

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Abstract

The hippocampus and medial prefrontal cortex (mPFC) interact during a myriad of cognitive processes including decision-making and long-term memory consolidation. Exactly how the mPFC and hippocampus interact during goal-directed decision-making remains to be fully elucidated. During periods of rest, bursts of high-frequency oscillations, termed sharp-wave ripple (SWR), appear in the local field potential. Impairing SWRs on the maze or during post-learning rest can interfere with memory-guided decision-making and memory consolidation. We hypothesize that the hippocampus and mPFC bidirectionally interact during SWRs to support memory consolidation and decision-making. Rats were trained on the neuroeconomic spatial decision-making task, Restaurant Row, to make serial stay-skip decisions where the amount of effort (delay to reward) varied upon entry to each restaurant. Hippocampal cells and SWRs were recorded in rats with the mPFC transduced with inhibitory DREADDs. We found that disrupting the mPFC impaired consolidating SWRs in the hippocampus. Hippocampal SWR rates depended on the internalized value of the reward (derived from individual flavor preferences), a parameter important in decision-making, and disrupting the mPFC changed this relationship. Additionally, we found a dissociation between SWRs that occurred while rats were on the maze dependent upon whether those SWRs occurred while the rat was anticipating food reward or during post-reward consumption.

KEYWORDS
consolidation, decision-making, foraging, neuroeconomic, Restaurant Row, spatial navigation

1 | INTRODUCTION

The hippocampus and medial prefrontal cortex (mPFC) interact to support memory consolidation and decision-making. Lesion (Churchwell & Kesner, 2011; Spellman et al., 2015; Wang & Cai, 2006) and electrophysiological studies (Shin et al., 2019) have shown that the prelimbic cortex supports hippocampal goal-related cognitive processes. Bursts of high-frequency oscillations (180–220 Hz), known as sharp-wave ripples (SWRs), appear in the local field potential (LFP) of the hippocampus in rats during learning and maze exploration, quiescent times

on a maze, and post-maze rest (Buzsáki, 2015; Buzsáki et al., 1983; Dupret et al., 2010; Joo & Frank, 2018; Lee & Wilson, 2002; O'Keefe & Nadel, 1978; Pfeiffer & Foster, 2013). During SWRs, hippocampal place cells (O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978; Redish, 1999) fire in a temporally compressed manner that recapitulates recent behavioral events (Foster & Wilson, 2006; Karlsson & Frank, 2008; O'Neill et al., 2008). Post-learning SWRs are believed to facilitate the consolidation of information by strengthening the connections within the hippocampus and between the hippocampus and cortical areas, such as the mPFC (Sutherland & McNaughton, 2000). Disrupting SWRs

during sleep impairs spatial learning (Ego-Stengel & Wilson, 2010; Girardeau et al., 2009). In contrast, SWRs exhibited when the rat is performing a cognitive task on the maze are believed to help facilitate planning (Carr et al., 2011; Roumis & Frank, 2015). Disrupting awake SWRs impairs memory-guided decision-making (Jadhav et al., 2012), and artificially prolonging spontaneous SWRs with optogenetic stimulation improve memory performance (Fernández-Ruiz et al., 2019). Taken together, these studies suggest that SWRs facilitate different cognitive processes (Joo & Frank, 2018).

The mPFC receives monosynaptic input from the hippocampus, but only sends input indirectly to the hippocampus (Hoover & Vertes, 2007; Vertes et al., 2007). As such, interactions between SWRs and the mPFC have traditionally been examined by manipulating SWRs or hippocampal projections to the mPFC. However, recent studies suggest that the mPFC may have more control over hippocampal physiology than previously realized (Helfrich et al., 2019; Maingret et al., 2016; Preston & Eichenbaum, 2013; Wang et al., 2015). Recent studies suggest that the mPFC could play a role in triggering hippocampal SWRs during planning (Shin & Jadhav, 2016; Yu & Frank, 2015).

The neuroeconomic spatial decision-making task, Restaurant Row, requires the rat to encounter a series of stay/go decisions for different flavored food rewards (Schmidt et al., 2019; Steiner & Redish, 2014; Sweis et al., 2018). Based on a rat's willingness to wait out the delay, we can measure individual preferences for specific flavors (plain, cherry, banana, chocolate) and in the 4×20 task (see below), reward size (one vs. three pellets). Post-reward SWR rates increase with reward size (Ambrose et al., 2016; Singer & Frank, 2009; Sosa et al., 2020); however, it is not clear how subjective reward value affects SWR rates. In the current study, the mPFC of rodents was transduced with inhibitory (h4MDi) DREADDs and the rats were given daily injections of vehicle (VEH) or CNO (clozapine-N-oxide). LFPs and neural ensembles from the hippocampus were recorded while DREADD-transduced rats performed the Restaurant Row task under VEH and CNO conditions. We hypothesized that disrupting the mPFC would alter hippocampal SWRs, and that in addition to being affected by reward size, SWRs are also modulated by offer value, including both cost (as delay to reward) and reward preferences. Furthermore, given the differences seen between on- and off-maze SWRs (Joo & Frank, 2018), we examined the extent to which SWRs differed between times while the rat was waiting for a reward and times while the rat lingered at the reward site after having just received reward.

2 | METHODS

2.1 | DREADDs transfection

Seven male Brown-Norway rats aged 10–14 months at the start of the experiment were used in this study. Rats were maintained above their 80% free-feeding weight. Prior to training on the task, the mPFC of rats was transfected with mCherry-tagged AAV8-CaMKIIα-hM4Di virus (UNC Vector Core, Chapel Hill, NC) under isoflurane anesthesia. The virus was injected bilaterally into the prelimbic cortex. We infused a total of 4 μl of 3.4×10^{12} mol/ml titer at a rate of 200 nl/min into each site (Pump 11 Elite, Harvard Apparatus). The injector (28 GA cannula) was left in place for an additional 5 min to minimize diffusion up the injector tract. mPFC coordinates for the infusion were 3.0 mm A/P, 0.7 mm M/L, and 3.6 mm D/V. Viral surgeries were conducted under Biological Safety Level 1 practices and procedures as identified by the University of Minnesota's Institutional Biological Safety Committee and all animal-related procedures were approved by the University of Minnesota Institutional Animal Care and Use Committee (IACUC).

2.2 | Pretraining

Following DREADDs transfection surgery and 3 days of recovery, rats received twice-daily training sessions lasting 30 min each (see Figure S1a). Training began with 5 days of habituation to the environment. Delays in this phase remained a constant 1 s at all feeder sites. After 5 days of habituation, the randomized list of delays presented to animals was expanded to 1–2, 1–3, 1–4, and 1–5 s delays on four following days (i.e., on Day 6 of training each restaurant had a random delay between 1 and 2 s, on Day 7 each restaurant had a random delay between 1 and 3 s, etc; Figure S1(a)). Rats then received 10 days of training on which delays were randomly selected from a uniform distribution between 1 and 30 s. After this 19-day sequence of twice-daily, 30-min sessions, rats transitioned to training on once-daily, 60-min sessions in which they could encounter delays between 1 and 30 s. These sessions were presented over a minimum of 5 days until performance was deemed stable (30+ laps). On the rare occasion, the rat did not eat enough food to maintain their weight they would be post-fed to keep them above their 80% free-feeding weight. At this point, five rats received hyperdrive implantation surgery.

2.3 | Hyperdrive implantation surgery

After initial task training, the rats underwent a triple-bundle, 24-moveable tetrode, four-reference, hyperdrive implantation targeting the prelimbic (A/P 3.0; M/L 0.7; 3 tetrodes), ventral striatum (VSTR; A/P 1.2; M/L 2.4; 5 tetrodes), and hippocampus (A/P -3.0; M/L 4.0; 16 tetrodes). Because cell yields were small, prelimbic cortex and ventral striatal data were not analyzed in this paper. Tetrodes were lowered daily until they hit the mPFC and the pyramidal cell layer of CA1. Theta was recorded from the hippocampal fissure from two of the four references, and the other two references were placed in the corpus callosum. Daily recordings were taken while the rat was resting before behavior (5 min, Pre), while on the maze (60 or 80 min, Maze), and resting after behavior (5 min, Post; see Figure 1(b)).

2.4 | Injection sequence

After the hyperdrive surgery, rats were retrained daily on the maze as tetrodes were lowered. A 20-day injection sequence (see Figure S1(a))
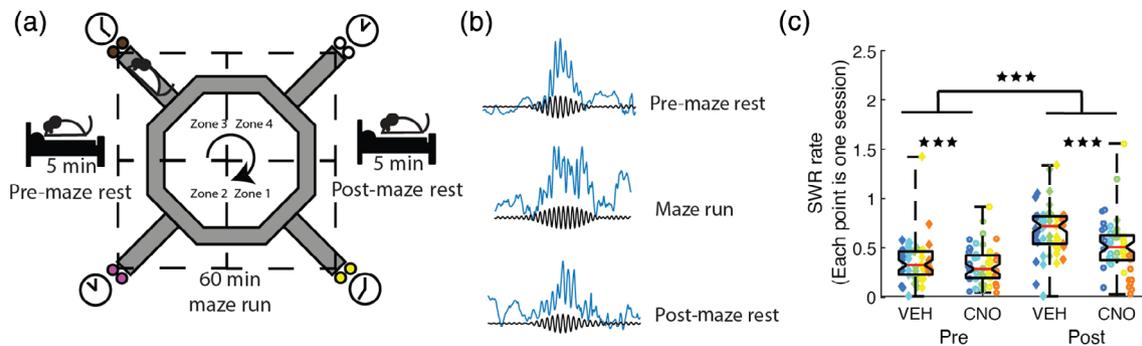
FIGURE 1 Disrupting the mPFC with DREADDs impaired off-line hippocampal SWR rates. (a) Schematic of the daily paradigm. On Restaurant Row, rats are required to make serial stay/skip choices for different flavored food rewards (color reflects flavor: white, plain; yellow, banana; pink, cherry; brown, chocolate). When a rat entered a restaurant/zone (demarcated by the dashed lines), a delay counted down reflecting how long the rat needed to wait to receive the food reward (1–30 s). The rat could wait out the delay to receive the food reward or skip the current restaurant and proceed to the next. The mPFC was transfected with the inhibitory DREADDs (Schmidt et al., 2019) and rats were given daily injections of VEH or CNO before recording. (b) Neuronal ensembles and local field potentials in the hippocampus were recorded during three behavioral epochs: 5-min pre-maze record (Pre), on the maze, and 5-min post-maze record (Post). (c) SWR rates were examined on VEH and CNO days during the Pre- and Post-recordings. SWR rates increased from the Pre-maze to the Post-maze sessions. Disrupting the mPFC with CNO impaired this effect. Though SWR rates increased from the Pre-maze to Post-maze on CNO days, the increase in VEH Post-maze SWR rates versus Pre-maze rates were significantly higher than on CNO days. Boxplot center mark depicts the median (red line), and top and bottom edges represent first and third quartiles. Whiskers extend to extreme data points not considered outliers. Different colors represent different rats. Diamonds = VEH days, circles = CNO days. ***$p < .001$ [Color figure can be viewed at wileyonlinelibrary.com]

followed once the tetrodes had reached their respective areas. Experimenters were blind to the identity of the solution (VEH or CNO) injected on any given day. Experimental and control conditions were presented in matched pairs in pseudorandomized order, controlling for first-order sequence effects. The rats were given CNO (5 mg/kg, s. c.) or VEH 20 min before testing. CNO (NIMH Chemical Synthesis and Drug Supply Program) was dissolved in dimethylsulfoxide (DMSO; Fisher Scientific, Pittsburg; PA) and 0.9% saline to yield a DMSO concentration of 10%. VEH injections also contained 10% DMSO. The blind was broken once all the data were collected.

2.5 | The Restaurant Row task

Restaurant Row is a neuroeconomic spatial decision-making task in which rats make serial stay/skip choices for different flavors of food reward in a naturalistic foraging paradigm (Schmidt et al., 2019; Steiner & Redish, 2014; Sweis et al., 2018) (Figure 1(a)). The Restaurant Row task enables direct measures of value from the flavor preferences revealed by individual rats. Rats were trained to run clockwise around a circular maze (approximately 1 m in diameter) with four evenly spaced spokes; at the end of each spoke was one of four differently flavored rewards ("restaurants": plain, chocolate, banana, cherry). At each restaurant, a feeder (MedAssociates, St. Albans, VT) dispensed two 45-mg food pellets of the given flavor (Research Diets, New Brunswick, NJ). Flavor locations remained constant throughout training. As the rat entered a restaurant perimeter, a tone sounded, where the pitch of the tone indicated the required delay remaining before food would be delivered. The maze was evenly divided up into four quadrants to demarcate restaurant entry and exit (Figure 1(a)

dashed lines indicate restaurant quadrant). Delays were randomized (uniform distribution) between 1 and 30 s on each entry, so the rat did not know what the cost (delay) would be until entering the restaurant. Longer delays were indicated by higher frequency tones and counted down every second in decreasing 250 Hz steps. Rats can discriminate between longer and shorter delays as revealed by their individual thresholds for different flavors, which were different across rats but consistent within rats (Schmidt et al., 2019; Steiner & Redish, 2014; Sweis et al., 2018). If the rat left the restaurant before the countdown completed (skipped), the tone stopped, the offer was rescinded, and the rat was required to proceed to the next restaurant. Restaurants were primed in serial order, forcing the rats to run the maze in a clockwise direction. Rats had 1 h to gather their food for the day (7 days a week) making this an economic task, in which rats had a time budget of 60 min to forage for food. Daily recordings were taken while the rat was resting before the task (5 min, Pre), while on the maze (Maze), and resting after the task (5 min, Post). Behavioral data for these rats on the Restaurant Row task have been previously reported in Schmidt et al. (2019).

2.6 | 4 × 20 task

After 20 days of the VEH/CNO injection sequence (see below) on the Restaurant Row task, rats were trained on the 4 × 20 task for 8 days (Steiner & Redish, 2014) (Figure S1b). In this variant, rats were given four, daily, 20-min epochs to complete the Restaurant Row task (80-min total), but instead of receiving two pellets for each restaurant, the rats received three pellets at one restaurant and one pellet at the other three restaurants. Rats were removed from the maze and returned to their resting pot to mark the end of each 20-min session. In

each of the four 20-min epochs, a different restaurant dispensed three pellets while the other three restaurants dispensed one pellet. As with the Restaurant Row task, daily recordings were taken while the rat was resting before the task (5 min, Pre), while on the maze (four, 20-min sessions; Maze), and resting after the task (5 min, Post).

2.7 | Behavioral and neurophysiological data collection

An overhead camera recorded the rat's position via light-emitting diodes mounted to the hyperdrive. Data were recorded with a Cheetah Digital Lynx SX system (Neuralynx). The task was controlled by software written in-house in MATLAB R2012a (The Mathworks, Natick, MA) using video tracked and time-stamped from the Neuralynx Digital Lynx system.

2.8 | Sharp wave ripple detection

SWRs were detected as described in Jackson et al. (2006). SWRs were examined on LFPs from one tetrode in hippocampus with the best cell yield for each rat. The LFP was bandpass filtered from 180 to 220 Hz. Amplitudes for each signal were found via Hilbert-transform. The distribution of log-transformed average amplitude was used to find events >1 SD above the mean power (similar results were found using 2 and 3 SD above the mean). Events were also required to meet a criterion of movement speed less than 5 cm/s and a theta/delta ratio less than 1 SD above mean power.

2.9 | Sharp wave ripple rate

SWR rate was calculated as the number of SWRs seen on a tetrode divided by the time spent in a condition, providing a per second rate for SWRs. The SWR rate was measured for the Waiting epoch as the rat waited out the delay to receive the food reward. To examine the SWR rates for post-reward epochs, the SWR rate was calculated from the feeder fire to the start of the next restaurant entry.

2.10 | Bayesian decoding

For each SWR that met criteria (see above), the represented path in space was determined using a one-step Bayesian decoding method (Brown et al., 1998; Zhang et al., 1998). Bayesian decoding was done as described in Wikenheiser and Redish (2013). Given spike counts from each cell in the ensemble, the posterior probability of the ensemble was computed representing each position in space. Spatial information was decoded in each SWR using 40 ms time windows with a uniform spatial prior, resulting in a posterior probability distribution across 64 spatial bins. Posterior distributions were normalized to sum to one, and we calculated the decoded position for each time step as the circular mean of the posterior probability distribution. Only time steps with at least one spike were decoded. To examine the decoding for all four restaurants, we categorized and rotated the maze in relation to the rat's current restaurant and calculated the summed posterior probability for the Current, Next, Opposite, and Previous restaurants for each 40 ms bin in a SWR.

2.11 | Delay threshold

To quantify the subjective value of each of the four flavors presented to each rat, we fit a Heaviside step function to the stay/skip decisions as a function of the presented delays by least-squares (Steiner & Redish, 2014). Separate step functions were fit to the data for each restaurant, rat, and session. The delay at which the function predicted an equal likelihood of stay and skip for a given flavor was defined as the threshold for that flavor and provided a measure of the subjective value of the flavor for the rat for the session. The mean threshold across flavors for a session provided the rat's overall willingness to wait for food of any kind.

2.12 | Rate of reinforcement

To quantify the effectiveness of the rats' decision-making, we calculated the overall session reward accumulation for all food. We obtained this measure by summing the total number of pellets that a rat obtained in a session. Higher rates imply that rats made objectively better choices, whereas lower rates imply that rats made objectively less advantageous choices.

2.13 | Vicarious trial-and-error

When making difficult decisions, rats often pause and orient back and forth, a behavior termed "vicarious trial-and-error" (VTE; Muenzinger & Gentry, 1931; Muenzinger, 1938; Redish, 2016; Tolman, 1938). To quantify VTE, we calculated the integrated absolute head angle velocity (IdPhi) in the first 3 s of zone entry (Papale et al., 2012; Schmidt et al., 2013, 2019). The IdPhi values were subsequently Z-scored for each rat across all zone entries made in each drug condition. Large values of Z(IdPhi) (>1) corresponded to trajectories that qualitatively matched the pause-and-orient description of VTE, whereas low values (<1) corresponded to smooth pass through the zone. In the case of behavior-only rats ($n = 2$), position was tracked with backpack-mounted LEDs; in the case of recording rats ($n = 5$), position was tracked from LEDs mounted to recording head stages.

2.14 | Running speed

We computed the running speed as the change in x and y position (dx, dy) using an adaptive windowing of best-fit velocity vectors (Janabi-Sharifi et al., 2000).

2.15 | Statistics and general data analyses

Data analyses were performed in MATLAB (MathWorks, Natick, MA). Two-tailed tests for normally distributed data and nonparametric tests for non-normally distributed data were used for statistical comparisons unless otherwise noted. Student *t*-tests, Wilcoxon signed rank tests of significance, *n*-way ANOVA, and RMANOVA were used and a Tukey–Kramer test for multiple comparisons was used when appropriate.

2.16 | Perfusion/histology

After the end of the experiment, current (100 mA, 10 s) was passed through the electrodes to verify tetrode locations. Three days later, rats were overdosed with sodium pentobarbital (150 mg/kg, Nembutal) and perfused intracardially with formalin. Their brains were transferred to a 30% (wt/vol) sucrose-formalin solution, sectioned on a cryostat, and stained with immunofluorescence for DREADDs or cresyl violet. Immunofluorescence staining was conducted as described in Dong et al. (2010). For further details on the histological methods from these rats, see Schmidt et al. (2019). Tetrode placements were visually confirmed with cresyl violet-stained sections.

3 | RESULTS

3.1 | Disrupting the mPFC impaired SWR rates during consolidation times

The hippocampus and mPFC support the consolidation of long-term memories necessary to support goal-directed decision-making (Eichenbaum, 2017; Foster, 2017; Ito et al., 2015; Redish, 2016; Sutherland & McNaughton, 2000; Tang & Jadhav, 2019; Yu & Frank, 2015). Recent studies have suggested that the mPFC may have control over the retrieval of hippocampal-dependent contextual memories (Navawongse & Eichenbaum, 2013; Place et al., 2016). If the mPFC controls the recruitment of hippocampal representations, we hypothesize that disrupting the mPFC may affect hippocampal SWRs.

The rate of SWRs increased after running on the maze (Pre → Post) (Repeated-Measures ANOVA (*n* = sessions): main effect of Epoch $F_{(1,49)}$ = 130.3, *p* = 2.1e^{-15}; Figure 1(c)), replicating previous results (Ambrose et al., 2016; Dupret et al., 2010; Eschenko et al., 2008; Joo & Frank, 2018; Kudrimoti et al., 1999). However, disrupting the mPFC with DREADDs significantly reduced SWR rates on CNO days (Repeated-Measures ANOVA (n = sessions): main effect of Condition $F_{(1,49)}$ = 8.36, *p* = .0057 and a Condition*Epoch interaction $F_{(1,49)}$ = 10.9, *p* = .0018).

3.2 | Not all on-maze SWRs are created equal

SWRs are not only seen during quiescent rest before and after a training session; SWRs are also seen during quiescent periods on the maze

(Kudrimoti et al., 1999; Pfeiffer & Foster, 2013; Roumis & Frank, 2015). These on-maze SWRs decode non-local information (Davidson et al., 2009; Gupta et al., 2010; Jensen & Lisman, 2000; Pfeiffer & Foster, 2013) and have been suggested to be involved in planning (Davidson et al., 2009; Jensen & Lisman, 2000; Pfeiffer & Foster, 2013; Shin et al., 2019) and learning (Carr et al., 2011; Ego-Stengel & Wilson, 2010; Foster, 2017; Jadhav et al., 2012; Joo & Frank, 2018; Singer et al., 2013). On the Restaurant Row task, rats show two quiescent periods, one while waiting for/anticipating the reward ("Waiting") and a second after having received the reward ("Lingering") (Figure 2(a)). Note that the Waiting period is before reward receipt and the rat can still decide to leave the restaurant, and thus may be involved in planning or decision-making. The Lingering period is after reward, and thus may be more plausibly involved in consolidating the recently completed decisions. Therefore, we hypothesized that SWRs might be different depending upon whether the rat was waiting for a reward or had just received it.

SWR rates were higher after receiving food reward ("Lingering") than while waiting for food reward ("Waiting") (Repeated-Measures ANOVA (n = sessions): main effect of Epoch $F_{(1,49)}$ = 290.87, *p* = 3e^{-22}; Figure 2(b)), replicating previous results that SWR rates increase after reward. Unlike off-maze SWRs, disrupting the mPFC with DREADDs had no effect on SWR rates during either the Waiting or Lingering epochs on the maze (Repeated-Measures ANOVA (n = sessions): no effect of Condition $F_{(1,49)}$ = 1.62, *p* = .21 or Condition*Epoch interaction $F_{(1,49)}$ = 2.31, *p* = .13; Figure 2(b)).

In order to explore the information content of each SWR, we measured the number of cells that fired per SWR event during Waiting and Lingering epochs (Figure 2(c)). We ran a multi-factor ANOVA examining the probably of that at least one cell fired during the SWR, with Epoch and Condition as variables. Lingering epoch SWRs had a higher probability of having cells fire (ANOVA (n = sessions), main effect of Epoch $F_{(1,162)}$ = 56.79, *p* = 3e^{-12}). However, CNO had no measurable effect (ANOVA (n = sessions), no main effect of Condition $F_{(1,162)}$ = 1.28, *p* = .26).

SWRs reflect different cognitive processes such as learning and planning (Pfeiffer & Foster, 2013), and both on and off the maze SWRs may facilitate these different processes (Roumis & Frank, 2015; Wikenheiser & Redish, 2013). Disrupting the mPFC diminished the increase in SWR events typically seen during the post-learning epoch, without affecting SWR events on the maze, supporting the theory that SWRs serve different neural processes on and off the maze. In order to assess this, we examined where hippocampal representations predominantly decoded to during SWRs that occurred during these different maze epochs.

3.3 | Disrupting the mPFC increased non-local decoding

The four different restaurants of the Restaurant Row task allow for the analysis of planning (*what should I do?*) versus memory (*what did I just do?*). Applying Bayesian decoding methods (see Methods) to the
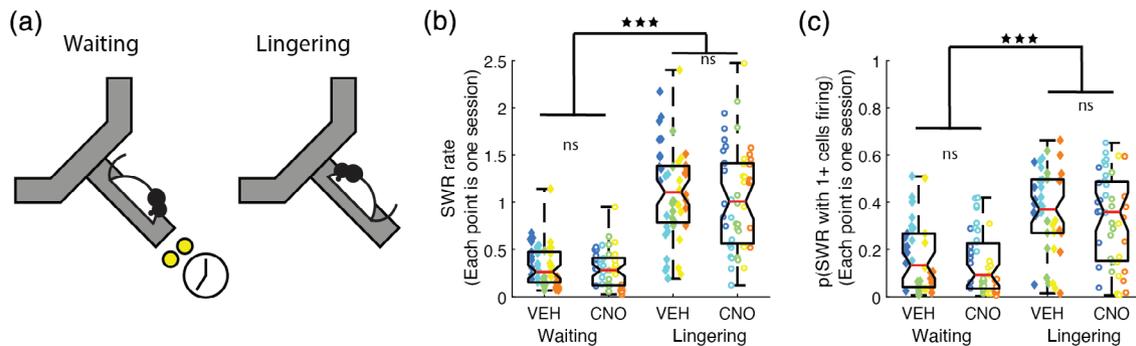
FIGURE 2 Differences between SWRs on the Waiting versus Lingering epochs. (a) SWRs on the maze were measured during two different non-ambulatory times: While waiting out the delay to receive the food reward ("Waiting" epoch) and after eating the food reward ("Lingering" epoch). (b) SWR rates were significantly higher on the Lingering epoch, compared to the Waiting epoch. CNO had no effect on the SWR rate for either epoch. (c) The percentage of SWRs where at least one cell fired was measured for both the Waiting and Lingering epochs. A larger proportion of SWR events had no measured cells firing during the Waiting epoch than during the Lingering epoch. Boxplot center mark depicts the median (red line), and top and bottom edges represent first and third quartiles. Whiskers extend to extreme data points not considered outliers. Different colors represent different rats. Diamonds = VEH days, circles = CNO days. ***p < .001 [Color figure can be viewed at wileyonlinelibrary.com]

neural firing patterns during SWRs revealed that SWRs during the Waiting and Lingering epochs decoded to each restaurant differently. We ran a Repeated-Measures ANOVA with the summed posterior probability of each Restaurant (Current, Next, Opposite, Previous) and Epoch (Waiting vs. Lingering) as variables. Though Waiting and Lingering SWR hippocampal ensembles predominantly decoded the Current restaurant (RM-ANOVA main effect of Restaurant (n = sessions): $F_{(3,66)}$ = 69.70, p = 2e^{-20}; corrected for multiple comparisons, Current vs. Next, Opp, Pre all p < .0006; Figure 3(a),(b)), Waiting SWR non-local representations suggest that hippocampal ensembles were more likely about planning what to do next than about what they just did (multiple comparisons: Next vs. Previous; p = .003), while Lingering epoch SWR representations failed to reach significance (multiple comparisons: Next vs. Previous; p = .059). Hippocampal ensembles during the Lingering epochs decoded more to the local restaurant, but the Waiting epoch decoded more to non-local restaurants (RM-ANOVA Restaurant*Epoch interaction: $F_{(3,66)}$ = 25.18, p = 5e^{-11}).

Disrupting the mPFC with CNO altered the local/non-local decoding pattern seen in Waiting epoch VEH days, while maintaining the Lingering patterns (RM-ANOVA main effect of Restaurant (n = sessions): $F_{(3,66)}$ = 32.7, p = 7e^{-13}; Restaurant*Epoch interaction: $F_{(3,66)}$ = 21.18, p = 1.3e^{-09}; Figure 3(c),(d)). Multiple comparisons revealed that the Current restaurant decoding during the Waiting epoch was not greater than the other three restaurants (only showing significance compared to the Opposite restaurant, p = .006).

In order to examine whether this encoding pattern was consistent, we measured how the decoding changed across time waited. Waiting SWR events overwhelmingly decoded to the Current restaurant, but SWRs more evenly decoded all four restaurants as the rat waited out the delay (Figure 3(e),(g)). Unlike the Waiting epoch, Lingering SWR events initially decoded all four restaurants, but then dramatically shifted predominantly to the Current restaurant (Figure 3(f), (h)). Due to fewer samples, time waited during Lingering after 30 s was not examined.

We similarly measured the SWR rate across time delay. Waiting SWR rates were low as the rat started their wait and gradually increased and plateaued (Figure 3(e)). In contrast, Lingering SWR rates peaked around 5 s after feeder fire and then greatly decreased (Figure 3(f)).

As expected, SWRs predominantly decoded to their Current restaurant location. Waiting SWRs showed more forward information, while Lingering SWRs showed more local information. Impairing the mPFC disrupted representations in Waiting SWRs, increasing their non-local decoding. We interpret decoding to the Previous location as remembering/thinking of the previous restaurant ("what did I just do?") and decoding to the Next restaurant as thinking/planning about approaching the next restaurant ("what should I do?"). VEH days showed that the Next restaurant was decoded to more than the Previous restaurants, something we did not see on CNO days, suggesting that the mPFC affects hippocampal planning SWRs.

3.4 │ SWR rates reflect value and flavor preference

On the Restaurant Row task, rats show flavor preferences, revealed by individual delay thresholds, the delay at which a rat was equally likely to stay or skip (Schmidt et al., 2019; Steiner & Redish, 2014; Sweis et al., 2018). Given that SWR rates are modulated by reward size, we predicted that SWR rates would increase with reward preferences and offer value. For each rat, we ranked the four flavors in order of preference: Most, More, Less, Least. During the Waiting epoch, SWR rates tracked flavor preferences (Figure 4(a)). SWR rates were lowest at the Least preferred restaurant and highest at the Most preferred restaurant (Repeated Measures ANOVA (n = sessions): main effect of Rank, $F_{(3,147)}$ = 15.98, p = 4.8e^{-09}; corrected for multiple comparisons: Least = Less, Least and Less < More, Least and Less < Most, all p < .0001; Figure 4(a)). Disrupting the mPFC reduced the SWR rate/flavor preference relationship, particularly for the preferred restaurants (Condition*Rank interaction $F_{(3,147)}$ = 2.4, p = .071).

FIGURE 3 SWRs during the Waiting epoch decoded to other Restaurants while SWRs during the Lingering epoch decoded to the current Restaurant. (a/b) Bayesian decoding was used on hippocampal ensembles during SWR events to estimate the rat's spatial location (see Methods). Decoded SWR events are shown for (a) Waiting and (b) Lingering SWRs on VEH days in relation to the rat's current restaurant. Though rats primarily decoded to their current restaurant, non-local spatial decoding (decoding to the Next, Opposite, and Previous restaurants) was greater during the Waiting epoch than the Lingering epoch. Decoded SWR events are shown for (c) Waiting and (d) Lingering SWRs on CNO days. Though rats primarily decoded to their current restaurant on CNO days, we found a small increase in non-local representations of space on both Waiting and Lingering epochs. Again, Bayesian decoding was used on hippocampal ensembles during SWR events to estimate the rat's spatial location across the (e) amount of time waited for food reward during the Waiting epoch and (f) the amount of time waited after receiving food reward during the Lingering epoch. Same analyses as e/f but for CNO (g) Waiting and (h) Lingering SWRs. (i) The Waiting SWR rates measured as a function of time waited showed a linear relationship for the first 6 s and plateaued thereafter. (j) Lingering SWR rates as a function of time spent lingering showed an immediate peak and sharp drop thereafter. Curr = current restaurant, Next = next restaurant, Opp = opposite restaurant, Prev = previous restaurant [Color figure can be viewed at wileyonlinelibrary.com]
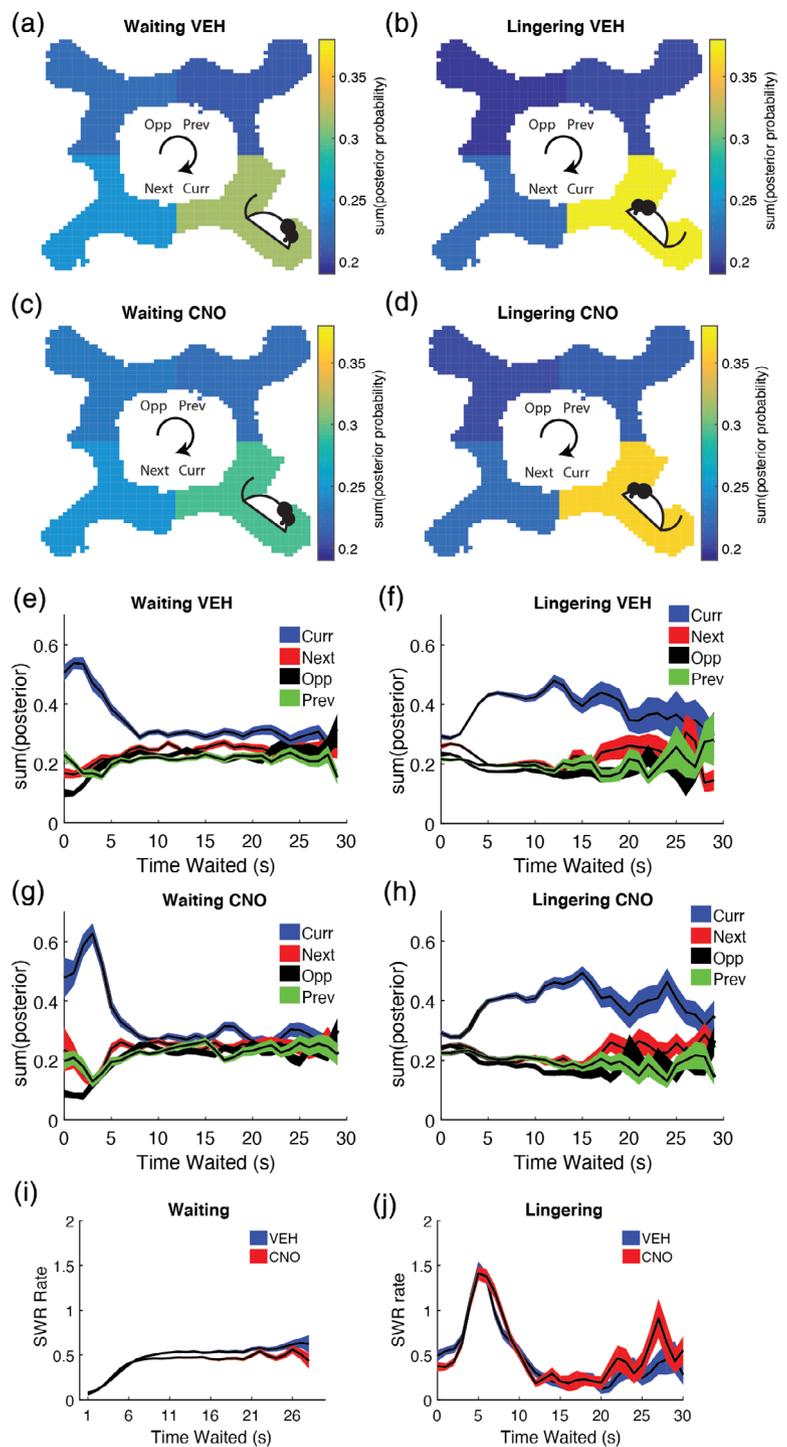
In contrast, Lingering SWR rates did not reflect flavor preferences (Figure 4(b)).

When approaching the zone, the rat can encounter a delay much greater than the individual threshold for that restaurant (a Bad deal), a delay near threshold (a Difficult decision), or a delay much smaller than threshold (a Good deal). Given the strong relationship found between flavor preference and SWR rate, we asked if SWR rates had this same relationship with trial value (Value = Threshold − Delay). Waiting SWR rates increased with trial deal (main effect of Trial Deal (n = sessions): $F_{(2,96)} = 93.25$, $p < 3e^{-23}$). SWR rates were lowest for

Bad deals and highest for Good deals (Figure 4(c); corrected for multiple comparisons, Bad < Difficult < Good, all $p < .001$). Interestingly, only Good Deal SWR rates trended to reduce on CNO days (no main effect of Condition: $F_{(1,48)} = 0.29$, $p = .59$; Trial Deal*Condition interaction: $F_{(2,96)} = 2.76$, $p = .068$). We did not see this same relationship across bad to good deals during Lingering SWRs (Figure 4(d)). SWR rates decreased along the different trial deals (main effect of Trial Deal: $F_{(2,64)} = 4.26$, $p = .018$). Disrupting the mPFC with CNO reduced SWR rates overall for both Waiting and Lingering SWRs (main effect of Condition: $F_{(1,32)} = 4.12$, $p = .0507$).
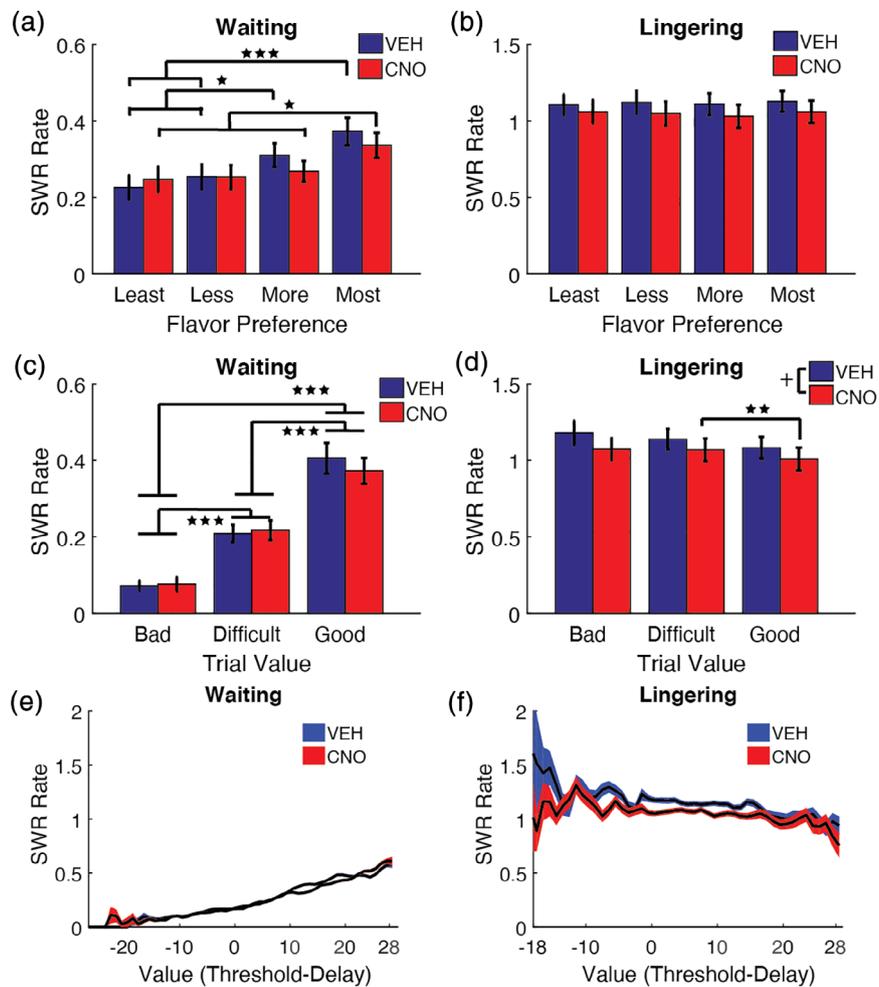
FIGURE 4 Waiting SWRs are modulated by flavor preference and value. (a) The four restaurants (banana, chocolate, plain, and cherry) were ranked for each rat in order of flavor preference (Most = first, More = second, Less = third, Least = fourth). SWR rates tracked with flavor preferences on the VEH Waiting epoch, higher for the most preferred flavors and lower for the least preferred flavors (Most > Less and Least***; More > Less & Least*). This relationship was disrupted on the most preferred restaurants on CNO days (Most > More & Least *). (b) Lingering SWR rates did not track with flavor preference, SWR rates were mostly uniform across flavors. (c) Individual trials were designated a Good Value (delay lower than threshold), Difficult Decision (close enough to threshold that it is not obvious if they should take the deal), or a Bad Value (delay higher than threshold). Waiting epoch SWR rates were linearly correlated with trial value (VEH/CNO: Bad Deals < Difficult and Good***, Difficult < Good***). (d) Lingering SWR rates, in contrast, did not show an effect of Trial Value, though CNO SWR rates were lower on Good deals than Difficult deals. (e) Measuring Waiting SWR rates across the spectrum of trial values showed a positive linear relationship, SWR rates increased as trial value increased. (f) Measuring Lingering SWR rates across the spectrum of trial values revealed a small negative correlation. $+p = .0507$, $*p < .05$, $**p < .01$, $***p < .001$ [Color figure can be viewed at wileyonlinelibrary.com]

Upon examining SWR rates across the distribution of Trial Values, we found a linear relationship between SWR rate and trial value in the Waiting SWRs (Figure 4(e), Pearson's $r = .19$, $p < 1e^{-100}$). Examining the SWR rate during the time waited, this positive correlation was limited to the Waiting epoch, as the lingering epoch showed a small, but significant negative correlation between trial value and SWR rate (Figure 4(f); Pearson's $r = -.07$, $p < 3.1e^{-15}$).

3.5 | The 4 × 20 task

In order to examine the relation of SWRs to changes in reward sizes, learning, and consolidation, rats were tested on a new task, the

4 × 20 variant of Restaurant Row (see Methods; Steiner & Redish, 2014; Figure 5(a)). On the 4 × 20 task, rats were given four, 20-min blocks wherein in each block one restaurant dispensed three pellets and the other three dispensed one pellet. Each of the four restaurants was the three-pellet restaurant for one of the four daily blocks.

We have previously shown that mPFC disruption improved behavior in these rats on the standard Restaurant Row task by increasing the rate of reinforcement and lowering thresholds (Schmidt et al., 2019). Consistent with previous results (Schmidt et al., 2019), rats earned more pellets on CNO days on the 4 × 20 task (Wilcoxon signed rank test $p = 5e^{-06}$; Figure S2(a)). However, unlike on the standard Restaurant Row task, compromising the mPFC with CNO did not measurably alter their willingness to wait for food (threshold;
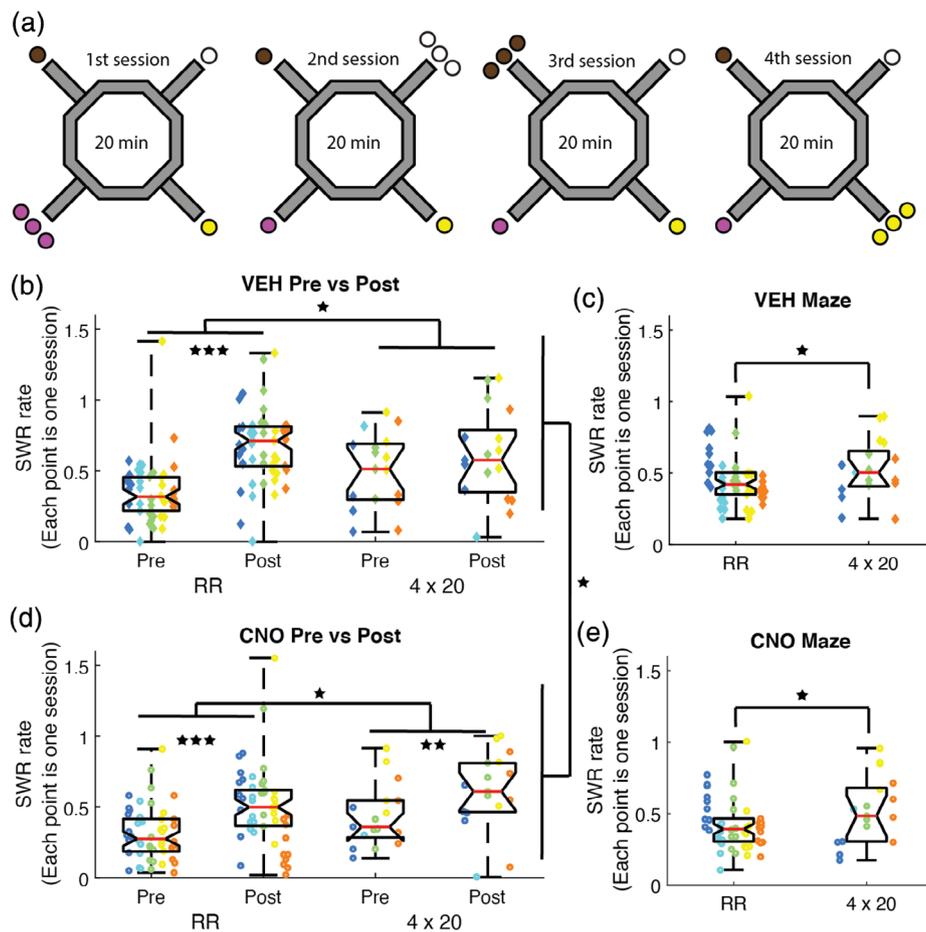
FIGURE 5 The 4 × 20 variant of Restaurant Row included four daily, 20-min sub-sessions. (a) After completing the Restaurant Row task, rats were trained on the 4 × 20 variant. During each 20-min sub-session one restaurant dispensed three pellets and the other three restaurants dispensed one pellet. A different flavor restaurant became the three-pellet restaurant for each of the four daily sub-sessions (brown = chocolate, black = plain, yellow = banana, pink = cherry). (b–e) SWR rates were compared between the over-trained Restaurant Row task and the novel 4 × 20 task. SWR rates were higher after the maze run (Pre → Post). These off-maze (Pre/Post) SWR rates increased on the 4 × 20 task from the Restaurant Row task for both (b) VEH and (d) CNO days. (d) Disrupting the mPFC with CNO reduced SWR rates. Examining on-maze SWR rates revealed the same increase on the 4 × 20 task on both (c) VEH and (e) CNO days, but no overall effect of CNO. Boxplot center mark depicts the median (red line), and top and bottom edges represent first and third quartiles. Whiskers extend to extreme data points not considered outliers. Diamonds = VEH days, circles = CNO days; different colors represent different rats *p < .05, **p < .01, ***p < .001 [Color figure can be viewed at wileyonlinelibrary.com]

Wilcoxon signed rank test $p = .60$; Figure S2(b)). This effect was possibly mediated by the learning component of the 4 × 20 task, unlike the Restaurant Row, which was an overly trained task.

We measured two behavioral variables of deliberative planning: the reaction time to skip a trial (hesitation time) and the probability of vicarious trial-and-error behavior (pVTE; Schmidt et al., 2019). On the 4 × 20 task, CNO reduced the rat's hesitation time (Wilcoxon signed rank test (n = sessions), $p = 3e^{-07}$; Figure S2(c)) and the pVTE behavior (Wilcoxon signed rank test (n = sessions), $p = .034$; Figure S2(d)).

As noted above, the 4 × 20 task allows for the comparison of flavor preference and reward size. In order to examine flavor value preference between the four different restaurants, we measured the lingering time at the reward site after consumption. Both rats and mice linger longer after reward consumption for more preferred rewards (Sweis et al., 2018). Similarly, on 4 × 20, mPFC disruption

reduced the time rats spent at the feeder after eating the reward (Wilcoxon signed rank test (n = sessions), $p = 2e^{-05}$; Figure S2(e)).

As rats are less likely to sit and wait at a restaurant (hesitation time and lingering time) under mPFC disruption, they also run faster under mPFC disruption (Wilcoxon signed rank test (n = sessions) $p < 1.0e^{-09}$; Figure S2(f)). We ran a general linear model with pVTE, thresholds, lingering time, hesitation time, and drug condition as explanatory variables of the rate of reinforcement. Lingering time had the most significant effect on rate of reinforcement ($\beta = -1.7$, $t = -22$, $p = 5.1e^{-55}$). Threshold was the only other variable found to have a significant effect on rate of reinforcement ($\beta = -.46$, $t = -2.41$, $p = .017$).

Taken together, most of the mPFC disruption behavioral results from the Restaurant Row task were replicated on the 4 × 20 task; the only incongruity was thresholds. mPFC disruption had no detectable effect on thresholds, which could be a result of changes in pellet sizes (three or one pellet vs. two pellets) between the two tasks (4 × 20

vs. Restaurant Row, respectively) or due to the amount of training on each task (newly learned vs. overtrained).

3.6 | SWR increased on the novel 4 × 20 task

SWR rates increase during novelty (Cheng & Frank, 2008; Eschenko et al., 2008; Karlsson & Frank, 2008; O'Neill et al., 2008); therefore, we predicted that SWR rates would increase on the 4 × 20 task. We ran an ANOVA on SWR rate with Condition (VEH vs. CNO), Task (Restaurant Row vs. 4 × 20), and Epoch (Pre-maze rest vs. Post-maze rest) as variables (n = sessions). SWR rates significantly increased on the 4 × 20 task in general (main effect of Task: $F_{(1,261)} = 4.6$, $p = .033$), but significantly decreased on CNO days (main effect of Condition: $F_{(1,261)} = 4.1$, $p = .04$; Figure 5(b),(d)), and significantly increased on the Post-maze rest (main effect of Epoch: $F_{(1,261)} = 32$, $p < .001$).

To examine SWRs on the maze, we ran an ANOVA on SWR rate with Condition (VEH vs. CNO) and Task (Restaurant Row vs. 4 × 20) as variables (n = sessions). On the maze, we found a significant increase in SWR rates on the novel 4 × 20 task (main effect of Task: $F_{(1,130)} = 5.1$, $p = .025$), but no effect of Condition (no main effect of Condition: $F_{(1,130)} = 0.14$, $p = .71$; Figure 5(c),(e)). As expected, training rats on a novel task resulted in an increase in SWRs. We found this effect on SWRs both on the maze and during the off-maze rest. Interestingly, the increase in SWR rates due to novelty was primarily driven by an increased rate in SWRs during the Pre-maze rest (Pre-Restaurant Row vs. Pre-4 × 20; t-test: $t_{132} = -3.2$, $p = .002$) and not an overall increase in SWR rates across the two epochs (Post-Restaurant Row vs. Post-4 × 20; t-test: $t_{132} = -0.25$, $p = .80$).

3.7 | The mPFC is necessary to anticipate an increase in reward

On the Restaurant Row task, rats show consistent flavor preferences for each restaurant, revealed by individual delay thresholds (the delay at which a rat was equally likely to stay or skip; Steiner & Redish, 2014). The 4 × 20 task allowed for the comparison of different reward sizes in each restaurant. We examined thresholds for the one- and three-pellet sessions within the same restaurant across the four, daily sessions (Figure 6(a)).

Rats wait longer for the three-pellet rewards than the one-pellet rewards on the 4 × 20 task (Steiner & Redish, 2014). We replicated this result on VEH days (one-pellet vs. three-pellet restaurant thresholds (n = sessions): $t_{(74)} = -2.97$, $p = .004$, CI [−5.0, −1.0]; Figure 6(b), left). This effect required learning, as there were no differences in thresholds between one-pellet and three-pellet restaurants on their first few days of the 4 × 20 task (first day: $p = .51$, second day: $p = .44$), but there was on the last few days (third day: $p = .032$; last day: $p = .001$; Figure S3(a), top row). Disrupting the mPFC impaired the rats' ability to anticipate the increase in reward size (one-pellet vs. three-pellet restaurant thresholds: $t_{(74)} = -1.38$, $p = .17$, CI [−3.4, 0.62]; Figure 6(b), right). Additionally, mPFC disruption impaired the rat's ability to recognize the

increase in pellet reward (first day: $p = .59$; second day: $p = .48$; third day: $p = .33$; last day: $p = .019$; Figure S3(a), bottom row).

Disrupting the mPFC impaired the rat's ability to anticipate the difference in pellet size. *We hypothesize that this could result from (1) the rat's inability to recognize the difference between 1 and 3 pellets, (2) an impaired ability to remember the difference in reward size, or (3) an inability to link the memory to the actions taken.*

Post-reward evaluation can be measured in the amount of time the rat lingers at a restaurant post consumption. Animals linger longer after more preferred flavors (Sweis et al., 2018). Similar to threshold measures, rats lingered longer after receiving three pellets of reward rather than one pellet (one-pellet vs. three-pellet restaurant lingering time VEH: $t_{(74)} = -7.29$, $p = 2.8^{e-10}$, CI [−9.1, −5.2]; CNO: $t_{(74)} = -9.65$, $p = 9.9^{e-15}$, CI [−7.2, −4.7]; Figure 6(c)). This implies that rats were still able to recognize the difference in reward size after mPFC disruption. Examining the lingering time across training revealed that this effect did not require learning (Figure S3(b)).

Disrupting the mPFC did not affect the behavioral consequences of reward preference equally. Rats had an increased threshold for higher value rewards, but only with an intact mPFC. However, disrupting the mPFC impaired the rat's ability to anticipate the increase in three-pellet restaurants. Nonetheless, CNO left the post-reward evaluation intact; *rats recognized the difference between one and three pellets under both VEH and CNO conditions.* This implies that disrupting the mPFC left post-reward evaluation intact but leaves open the question of whether it impaired the ability to remember the difference in reward size and/or the ability to link the memory to the mPFC action-selection system.

3.8 | Waiting SWR rates reflect the anticipation of higher value reward

SWR rates increase with reward size (Ambrose et al., 2016; Singer & Frank, 2009; Sosa et al., 2020). We predicted that SWR rates would be higher for three-pellet restaurants versus one-pellet restaurants if the animal could recognize and remember the difference. However, the differences seen between Waiting and Lingering epochs suggest that the effect of reward size on SWR rates during post-reward evaluation may not be the case during reward anticipation.

On the 4 × 20 task, Waiting SWR rates tracked reward size (one-pellet vs. three-pellet restaurant SWR rates (n = session) VEH: $t_{(50)} = -2.87$, $p = .006$, CI [−0.16, −0.029]; CNO: $t_{(50)} = -3.66$, $p = 6.1^{e-04}$, CI [−0.087, −0.025]; Figure 6(d)). On VEH days, thresholds and SWR rates were higher for larger reward restaurants. On CNO days even when rats failed to show an increase in threshold for larger reward restaurants, they still showed increased SWR rates during the Waiting period. This implies that the difference in thresholds was not due to an impaired ability to remember the reward size, as the SWR rate during waiting did increase proportionally.

The Lingering epoch also demonstrated this effect. SWR rates were greater for three-pellet restaurants than one-pellet restaurants (one-pellet vs. three-pellet restaurant SWR rates VEH: $t_{(50)} = -6.24$,
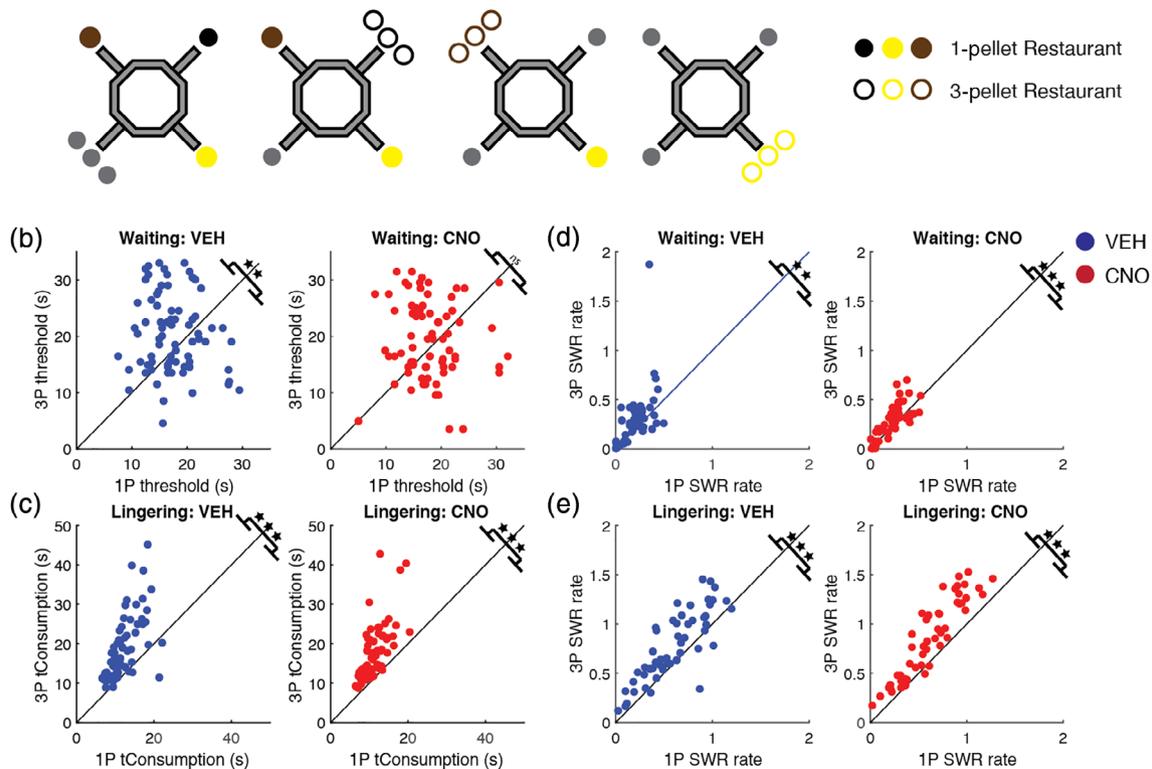
FIGURE 6 Rats showed behavioral and electrophysiological differences with increased reward value. (a) The 4 × 20 task allowed for the direct comparison of each restaurant when it dispensed three pellets (unfilled circle) and one pellet (filled circle). (gray circles represent restaurants/pellet configurations not examined in the current figure). (b) A rat's willingness to wait for food reward (threshold) tracked with reward size on VEH days (left), but not CNO days (right). (c) Post-reward lingering time was greater on higher reward restaurants on both VEH and CNO days. (d) Waiting SWR rates were higher for three-pellet restaurants on both VEH and CNO days. (e) Lingering SWR rates also tracked with reward size on VEH and CNO days. VEH = blue circle, CNO = red circle. **$p < .01$; ***$p < .001$ [Color figure can be viewed at wileyonlinelibrary.com]

$p = 9.2^{e-08}$, CI [−0.23, −0.12]; CNO: $t_{(50)} = −9.79$, $p = 3.3^{e-13}$, CI [−0.28, −0.19]; Figure 6(e)).

3.9 | The memory of value is carried over from sub-session to sub-session

Rats waited longer for three-pellet rewards (Figure 6(b)). SWR rates increased on three-pellet restaurants. This implies that thresholds and SWR rates reflected expected value or reward. If the rats remember the increased pellet reward, the increased thresholds and SWR rates on three-pellet restaurants should carry over to the next within-day sub-session, even though the reward value decreased back to one pellet in the subsequent sub-session (Figure 7(a)). In order to test this, SWR rates were compared between restaurants categorized as a "one-pellet restaurant" (the restaurant in the sessions such that it had only dispensed one pellet up until the examined sub-session) and as a "previous three-pellet restaurant" (the restaurant after it had dispensed three pellets in a previous sub-session (of that day) but was then dispensing one pellet again). This categorization allowed us to track behavioral and physiological variables across sub-sessions in order to determine whether the

memory of getting three pellets at a restaurant persisted by comparing to other restaurants that had only ever dispensed one pellet.

In anticipation of the reward, rats valued one-pellet and previous three-pellet restaurants similarly, (VEH: $t_{(49)} = −0.85$, $p = .40$, CI [−3.2, 1.3]; CNO: $t_{(49)} = 1.20$, $p = .24$, CI [−1.0, 4.0]; Figure 7(b)). Interestingly, during the post-reward evaluation, rats lingered longer at the previous three-pellet restaurants than one-pellet restaurants on (VEH: $t_{(49)} = −3.02$, $p = .004$, CI [−29, −0.58]; CNO: $t_{(49)} = −2.15$, $p = .037$, CI [−1.5, −0.05]; Figure 7(c)). This implies that the rats did remember that these restaurants had provided three pellets in the previous sessions.

Going from a three-pellet restaurant back to a one-pellet restaurant ("previous three-pellet") resulted in an increase in SWR rates during the Waiting period (VEH: $t_{(33)} = −4.79$, $p = 3.4^{e-05}$, CI [−0.12, −0.046]; CNO: $t_{(33)} = −2.83$, $p = .008$, CI [−0.12, −0.019]; Figure 7 (d)). This increase in SWR reward value representation from the previous sub-session carried over to the current sub-session, despite the fact that the reward size received was only one pellet, implying that the rats remembered the anticipated reward.

Given that Lingering SWR rates were affected by reward size (Figure 6(e)), we predicted that Lingering SWR rates would also differentiate between previous three-pellet and one-pellet restaurants.
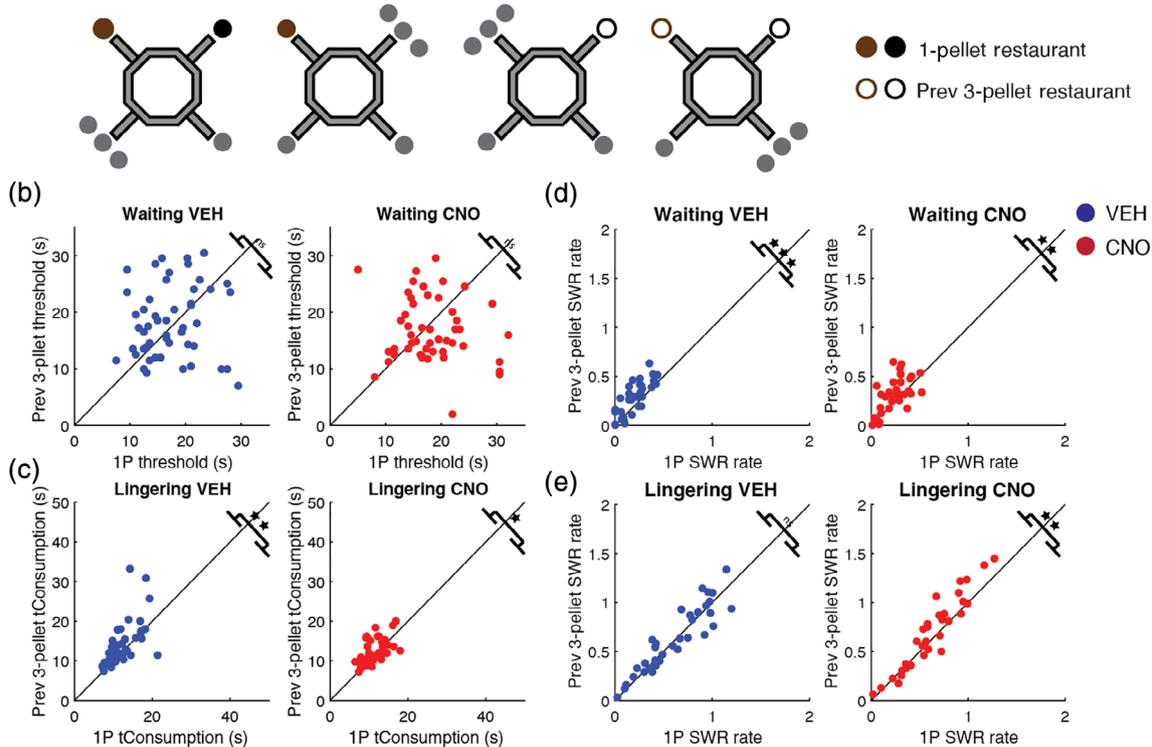
FIGURE 7 Rats showed behavioral and electrophysiological differences to changes in reward value. (a) In addition to measuring when a restaurant increased from 1 to 3 pellets, we also measured different variables after the restaurant dispensed three pellets ("previous three") (i.e., currently dispensing one pellet (filled circle), but dispensed three pellets on a previous sub-session of that day (unfilled circle)). (b) The rats waited for one-pellet restaurants similarly as long as previous three-pellet restaurants on both VEH (left) and CNO days (right). (c) Interestingly, post-reward lingering revealed that previous three-pellet restaurants were valued more than one-pellet restaurants, as the rats lingered longer at these restaurants post-reward consumption. (d) SWR rates during the Waiting epoch were greater for previous three-pellet restaurants on both VEH (left) and CNO (right) days. (e) SWR rates during the Lingering epoch did not differentiate between previous three-pellet restaurants and one-pellet restaurants on VEH days (left), though it did on CNO days (right). VEH = blue circle, CNO = red circle. * $p < .05$; **$p < .01$; ***$p < .001$ [Color figure can be viewed at wileyonlinelibrary.com]

That was not the case under VEH; SWR rates during the Lingering epochs were similar for both one-pellet and previous three-pellet restaurants ($t_{(33)} = -0.73$, $p = .47$, CI [−0.062 0.029]; Figure 7(e), left). However, SWR rates increased on previous three-pellet restaurants on CNO days ($t_{(33)} = -2.86$, $p = .007$, CI [−0.11, −0.019]; Figure 7(e), right), implying that the rats were surprised by the change.

Given that the previous three-pellet restaurants only dispensed one pellet, the increase in Waiting SWR rates between previous three-pellet over one-pellet restaurants likely reflected the changed expectations from the memory of receiving three pellets—an effect that carried over from sub-session to sub-session. This precluded our second hypothesis as to why CNO disrupted the rat's ability to recognize the increase in pellet reward, *CNO did not impair the ability to remember the difference in reward size.* Unlike the Waiting epoch, we did not see this effect on the Lingering epoch, thereby further supporting the hypothesis that SWRs on the maze reflected different cognitive processes.

How does the memory of the previous three-pellet restaurant compare to the restaurant when it dispensed three pellets (Figure 8

(a))? There were no significant differences in threshold between three-pellet and previous three-pellet restaurants on VEH days ($t_{(74)} = 1.59$, $p = .12$, CI [−0.45 4.0]; Figure 8(b), left). In contrast, on CNO days, three-pellet restaurant thresholds had a small, but significant, increase over previous three pellets ($t_{(74)} = 2.16$, $p = .034$, CI [0.18, 4.5]; Figure 8(b), right). Though previous three-pellet restaurants had a higher post-reward valuation over one-pellet restaurants (Figure 7 (c)), they were not evaluated as high as three-pellet restaurants. Rats lingered longer at three-pellet restaurants than previously three-pellet restaurants (VEH: $t_{(74)} = 8.34$, $p = 2.9^{e-12}$, CI [3.1, 5.1]; CNO: $t_{(74)} = 8.42$, $p = 2.1^{e-12}$, CI [3.2, 5.1]; Figure 8(c)). This implies that the Lingering time reflected the gradient of reward value with one pellet being evaluated as least rewarding, previous three pellets evaluated as more rewarding, and three pellets being evaluated as most rewarding.

If the increase in reward size was reflected in SWR rates and this increase is carried over from sub-session to sub-session, then SWR rates on three-pellet restaurants should remain high even when the reward drops back down to one pellet on the subsequent sub-sessions (i.e., becomes a previous three-pellet restaurant). This was
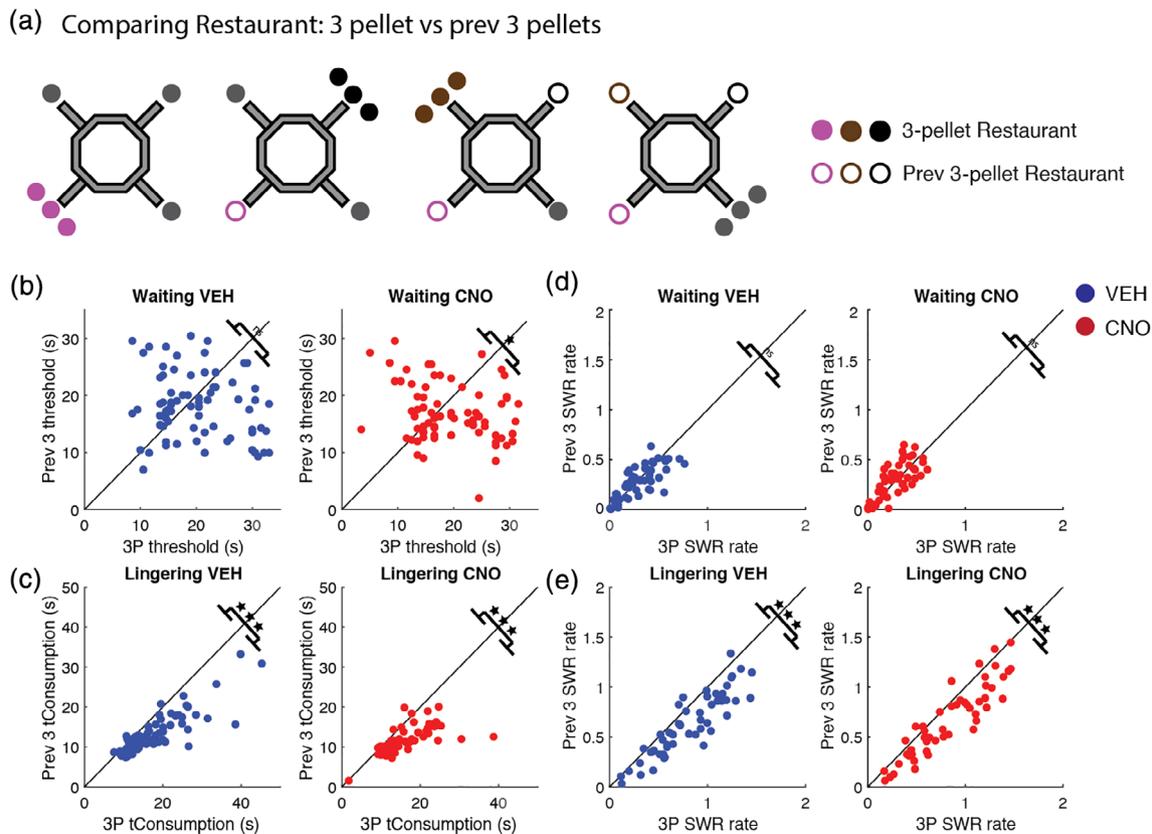
FIGURE 8 Rats showed different behavioral and electrophysiological responses to decreased reward value. (a) The 4 × 20 task allowed for the direct comparison of a restaurant on the sub-sessions after it dispensed three pellets ("previous three"; unfilled circle) and to that same restaurant when it had dispensed three pellets (filled circle). (b) Interestingly, the rats waited as long for the previous three-pellet restaurants as they did when the same restaurant dispensed three pellets on VEH (left), but not, CNO days (right). (c) Though rats were willing to wait as long for previous three-pellet restaurant, post-reward lingering revealed that three-pellet restaurants were valued more. (d) SWR rates during the Waiting epoch did not differentiate between previous three-pellet restaurants and three-pellet restaurants on both VEH and CNO days. (e) SWR rates during the Lingering epoch were greater for the three-pellet restaurants than the previous three-pellet restaurants on both VEH and CNO days. VEH = blue circle, CNO = red circle.*p < .05; ***p < .001 [Color figure can be viewed at wileyonlinelibrary.com]

the case—Waiting SWR rates were similar between previous three-pellet restaurants and three-pellet restaurants (VEH: $t_{(50)} = 1.1$, $p = .26$, CI [−0.015, 0.054]; CNO: $t_{(50)} = -0.74$, $p = .46$, CI [−0.047, 0.022]; Figure 8(d)). Consistent with the previous comparisons, Lingering SWR rates were greater for three-pellet restaurants than previous three-pellet restaurants (VEH: $t_{(50)} = 8.24$, $p = 6.9^{e-11}$, CI [0.14, 0.23]; CNO: $t_{(50)} = 7.24$, $p = 2.53^{e-09}$, CI [0.12, 0.20]; Figure 8(e)).

mPFC disruption impaired the rat's ability to recognize the changes in pellet reward size. We hypothesized that this could result from either (1) the rat's inability to recognize the difference between one and three pellets, (2) an impaired ability to remember the difference in reward size, or (3) an inability to link the memory to action selection. The rats were able to accurately evaluate larger rewards post-consumption. The rats showed increased SWR rates for larger rewards, suggesting that their ability to remember the difference in reward size was intact. Taken together, this leaves open the third hypothesis to account for disruption of mPFC on this task. We suspect that the memory of the larger reward within the hippocampus was intact, but by disrupting the mPFC this memory was not reaching or accessible to the action-selection system, likely mediated by the mPFC.

4 | DISCUSSION

During post-learning rest, SWRs are hypothesized to facilitate a process of consolidation by recapitulating behaviorally relevant information in a coordinated manner with neo-cortical unit firing, delta oscillations, and sleep spindles (Battaglia et al., 2004; Maingret et al., 2016; Siapas & Wilson, 1998; Tang et al., 2017). In contrast, during awake behavior, SWRs are hypothesized to facilitate planning (Jadhav et al., 2012; Ólafsdóttir et al., 2017; Pfeiffer & Foster, 2013; Shin et al., 2019) and value-learning functions (Ambrose et al., 2016; Ólafsdóttir et al., 2017; Shin et al., 2019). Our data show that (1) disrupting the mPFC with DREADDs impaired post-learning SWR rates, (2) disrupting the mPFC with DREADDs altered SWRs differently depending upon whether the rat was waiting for a reward or after having just received it, and (3) SWRs were modulated by offer value, including both cost (as delay to reward) and reward preferences and the memory of the offer value carried over from daily sub-session to sub-session.

Disrupting the mPFC with DREADDs diminished the post-learning increase in SWR rates typically seen after learning/decision-making. Disrupting post-task SWRs affects learning and retention of novel

tasks (Ego-Stengel & Wilson, 2010; Girardeau et al., 2009). Global and neuronal mPFC activity correlates with SWRs during these post-task SWRs (Battaglia et al., 2004; Euston et al., 2007; Maingret et al., 2016; Siapas & Wilson, 1998; Sirota et al., 2003; Wierzynski et al., 2009). Our data suggest that the mPFC has a causal functionality in generating these SWRs; disrupting mPFC diminished the number and rate of SWRs emitted during post-task rest.

Internally disrupting hippocampal SWRs impairs spatial memory (Ego-Stengel & Wilson, 2010; Girardeau et al., 2009; Jadhav et al., 2012) and artificially prolonging SWRs improves memory (Fernández-Ruiz et al., 2019). Ours is the first study to show that internally disrupting the mPFC impairs hippocampal SWRs. Previous studies have shown that SWR rates increase during novelty (Cheng & Frank, 2008; Eschenko et al., 2008; Karlsson & Frank, 2008; O'Neill et al., 2008) and after reward receipt (Ambrose et al., 2016; Singer & Frank, 2009). Taken together, these studies imply that the mPFC may facilitate the post-learning/reward increase in SWR rate.

SWR rates increase during novelty (Cheng & Frank, 2008; Eschenko et al., 2008; Karlsson & Frank, 2008; O'Neill et al., 2008) results we replicated on the 4×20 task. Interestingly, the increase seen off the maze was primarily driven by the pre-maze rest epoch. This implies that novelty increases SWR rates in anticipation of learning new contingencies each day. Post-maze rest SWR rates between the Restaurant Row and 4×20 tasks were comparable. This could potentially be due to a ceiling effect, as SWRs during post-learning rest are already increased compared to pre-learning rest.

SWRs on the maze and SWRs during rest are believed to support planning and consolidation, respectively, though it is possible these two functions are two sides of the same coin (Joo & Frank, 2018). Even on the maze, during tasks, representational differences have been found, both in the representational component of SWRs themselves (Carey et al., 2019; Ólafsdóttir et al., 2017) and in the correlation between hippocampal and mPFC activity (Jadhav et al., 2016; Shin et al., 2019). Though fewer in number than SWRs after receiving food reward, SWRs during the anticipation of food reward (Waiting epoch) showed more non-local decoding than those emitted after having received the food reward (Lingering epoch). This was particularly prominent for the *Next* restaurant, suggesting that these anticipatory SWRs were more related to planning (comparing *Current* and *Next* restaurants) than consolidation (which we would expect would entail representations of *Previous* restaurants). Not only did we find a dissociation between SWRs as a rat was anticipating food reward versus after having received food reward, we found that mPFC disruption affected SWRs differently at these two times, with a larger effect on Lingering (post-reward) than Waiting (pre-reward) SWRs, suggesting a diversity in how mPFC causally impacted different SWRs.

Previous studies have reported that SWR rate tracks with reward size (Ambrose et al., 2016; Singer & Frank, 2009; Sosa et al., 2020). We replicated these results, and furthermore, found that this increase in SWR rate for greater reward size restaurants carried over from session to session in the 4×20 variant. As rats were waiting out the delay for food reward (Waiting), restaurants that previously provided three pellets (but currently provided one pellet)

showed higher SWR rates than when these same restaurants had only ever dispensed one pellet (Figure 7(d)). This effect was seen only while the rats were waiting out the delay for food reward; SWR rates during the lingering session (post reward delivery) did not show this SWR rate carry-over effect within the daily sessions. Previous studies have shown that stabilization of a memory trace is contingent upon the memory salience (Salvetti et al., 2014) and increased SWR rates correlate with memory performance (Norman et al., 2019). Taken together, these data suggest that the mPFC may play a role in stabilizing salient events that will later be used for future goal-directed decision-making.

Our data provide evidence for a causal role of mPFC in hippocampal SWR emission rates and SWR representations. However, as the current study did not apply CNO to a cohort of non-DREADD rats, we cannot rule out that the results stemmed from a general CNO effect. Importantly, however, we found that mPFC disruption did not affect all hippocampal SWRs equally. This implies that differences seen between SWRs at different behavioral times likely facilitate different cognitive processes. SWRs while waiting for food are likely involved in anticipation and planning (Jadhav et al., 2012; Ólafsdóttir et al., 2017; Pfeiffer & Foster, 2013; Shin et al., 2019), whereas SWRs while lingering after reward post-task rest are likely involved in consolidation and learning (de Lavilléon et al., 2015; Girardeau et al., 2009; Wikenheiser & Redish, 2013). Each depends differently on the mPFC-hippocampal interaction.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

A. D. Redish and Brandy Schmidt designed experiments and analyses. Brandy Schmidt collected data. A. D. Redish and Brandy Schmidt wrote analyses programs. Brandy Schmidt and A. D. Redish analyzed data, discussed results, and wrote the paper.

DATA AVAILABILITY STATEMENT

The dataset and code generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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