Network oscillatory activity driven by context memory processing is differently regulated by glutamatergic and cholinergic neurotransmission

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1. Introduction

Memory retrieval requires the coordination of intra- and inter-regional activity in networks of brain structures. Dysfunction of these networks and memory impairment are seen in many psychiatric disorders, but relatively little is known about how memory retrieval and memory failure are represented at the level of local and regional activity. To address this question, we measured local field potentials (LFPs) from mice as they explored a novel context, retrieved memories for contextual fear conditioning, and after administration of two amnestic agents: the NMDA receptor antagonist MK-801 and muscarinic acetylcholine receptor antagonist scopolamine (SCOP). LFPs were simultaneously recorded from retrosplenial cortex (RSC), dorsal hippocampus (DH), and anterior cingulate cortex (ACC), which are involved in processing contextual memories, and analyzed for changes in intra-regional power and inter-regional peak coherence of oscillations across multiple frequency bands. Context encoding and memory retrieval sessions yielded similar patterns of changes across all three structures, including decreased delta power and increased theta peak coherence. Baseline effects of MK-801 and SCOP were primarily targeted to gamma oscillations, but in opposite directions. Both drugs also blocked memory retrieval, as indicated by reduced freezing when mice were returned to the conditioning context, but this common behavioral impairment was only associated with power and peak coherence disruptions after MK-801 treatment. These findings point to neural signatures for memory impairment, whose underlying mechanisms may serve as therapeutic targets for related psychiatric disorders.
Episodic memories are particularly dependent upon hippocampal-cortical interactions (Kim, 2016). This network activity may help define brain states, such as consciousness, arousal, and emotional state, which are permissive for successful memory retrieval. These psychological processes have all been associated with patterns of oscillatory activity embedded in local field potentials (LFPs). Because the processes associated with these oscillations are interrelated, and our regions of interest (RSC, DH, and ACC) are interconnected, we recorded LFPs from all three regions, and examined oscillatory activity across six frequency bands: delta (1–4 Hz), low (4–8 Hz) and high (8–12 Hz) theta, beta (13–30 Hz), and low (30–55 Hz) and high (55–80 Hz) gamma. Intraregional power and inter-regional coherence were converted to state-space vectors, allowing us to identify specific patterns of oscillations at which such network-level coordination occurs in three experiments: (1) during encoding of context memory, (2) during retrieval of memory for contextual fear conditioning, and (3) during retrieval testing after injection of MK-801 and SCOP, drugs that block memory retrieval.

2. Methods

2.1. Subjects

A total of forty-four nine-week-old male C57BL6/N mice obtained from a commercial supplier (Harlan, Indianapolis, IN) were used in this study. Mice were individually housed in a facility on a 12/12 h light/dark cycle (lights on at 7 a.m.), and allowed free access to food and water. All procedures were approved by Northwestern University’s Animal Care and Use Committee in compliance with National Institutes of Health standards.

2.2. Surgery

Mice were anesthetized with Avertin (1.2%) and implanted with insulated silver wires (100 μm diameter) aimed at RSC (1.8 mm posterior, 0.4 mm lateral, 0.75 mm ventral to bregma), DH (1.5 mm posterior, 1.0 mm lateral, 1.75 mm ventral), and ACC (1.3 mm anterior, 0.4 mm lateral, 1.75 mm ventral). All electrodes were placed in the left hemisphere. A gold screw lowered into the skull near the right parietal/occipital bone suture served as a reference and ground electrode. Two stainless steel jeweler’s screws were inserted in the skull to anchor the headcap. All wires were soldered to a 6-pin connector to which the recording devices were later attached, and the assembly was fixed to the skull with acrylic. Mice were allowed at least 72 h to recover from surgery prior to behavioral procedures. At the end of behavioral testing, electrode placements were verified using Nissl-stained coronal sections taken from RSC, ACC, and DH.

2.3. Context enocoding, fear conditioning, and memory retrieval testing

All behavioral testing occurred in a 35 × 20 × 20 cm Plexiglas conditioning chamber with a stainless steel rod floor (4 mm diameter, 0.9 cm center-to-center) in a sound-attenuating cabinet with black inner walls (TSE Systems Inc., Bad Homburg, Germany). For context encoding, naïve mice were placed in the novel chamber for 3 min and returned to their home cages. Contextual fear conditioning occurred the following day, and consisted of mice being placed back in the chamber for 3 min, followed by presentation of a mild footshock (2 s, 0.7 mA, constant current). Testing for memory retrieval in the conditioning context consisted of a 3 min session during which no shocks were presented. For drug testing, mice were not exposed to the conditioning chamber prior to fear conditioning. On every day, the chamber was cleaned after each mouse with 70% ethanol.

2.4. LFP acquisition

On each test day, LFP recordings began as soon as the mice were connected to wireless 4-channel NeuroLogger recording devices (TSE Systems), and continued until the end of each test session (up to 55 min total). Continuous recordings were made with a sampling rate of 500 Hz. Pre-amplification, analog-to-digital conversion (unity gain buffer, AC input range ± 750 μV, 1000x gain, ADC resolution 8 bits), and data storage all occurred on the NeuroLogger. After each session, the NeuroLogger was removed and data were downloaded to a computer for later analysis.

2.5. Drugs

Mice were injected (0.2 mL i.p.) with saline (0.9%), MK-801 (0.10 mg/kg; Sigma, St. Louis, MO), and scopolamine (SCOP; 2.0 mg/kg; Sigma). MK-801 and SCOP were dissolved in 0.9% saline. Injections were made ∼ 34 min prior to memory retrieval tests in the conditioning context. Each mouse received each injection on separate days. The order of injections was the same for all mice; injections were separated by 1–7 d to allow for washout prior to the subsequent test.

2.6. Data collection and analysis

LFP recordings were converted to a Matlab-compatible format for spectral analyses using open-source Chronux algorithms (http://Chronux.org; see Rojas-Libano, Frederick, Egaña, & Kay, 2014 for a detailed description). Power and coherence spectra were computed for the delta (1–4 Hz), low theta (4–8 Hz), high theta (8–12 Hz), beta (13–30 Hz), low gamma (30–55 Hz), and high gamma (55–80 Hz) frequency bands across each 3 min recording session using 35 half-overlapping 10 s windows with 4 tapers (resulting in a frequency resolution of 1.4 Hz). Coherence was transformed to z-coherence using the inverse hyperbolic tangent transform as described by Kay and Freeman (1998). There was no filtering. The frequency within each band at which coherence was highest was taken as the center frequency, and coherence at this peak was used as the dependent measure.

Although our LFP recording sessions lasted up to 55 min, we focused our analyses on 3 min subsets of the total recordings. For context encoding and retrieval test days (Fig. 1), we focused our analyses on the 3 min period before mice were exposed to the context and during the 3 min context exposure. On each drug test day (Figs. 3 and 4), we focused our analyses on the 3 min period before drug injection, a 3 min period beginning 30 min post-injection, and during the 3 min test in the conditioning chamber. No recordings were made on the fear conditioning day.

Average power and peak coherence within each frequency band were calculated for each mouse in each session, and then converted to ratios to determine between-session changes using the formula X/ﬀ(X1 + X2), where X is power or peak coherence within each band, and S1 and S2 are the recording sessions being compared (e.g., pre- and post-injection in the home cage). Thus, a ratio of 0.5 indicates no difference between recording sessions. These ratios were analyzed using two-way ANOVA, with factors of frequency band and region (for power) or site-pair (for peak coherence). Significant interaction effects indicated differences in the patterns of power and peak coherence ratios between regions/site-pairs across frequency bands, and were followed by post hoc one-sample t tests to compare power and peak coherence ratios for each region/site-pair against 0.5 to determine significant changes between recording sessions. Where interaction effects were non-significant, we only highlight instances where there was both a significant main effect of frequency band and all three regions/site-pairs showed a consistent and significant difference from 0.5 within at least one frequency band.

To better quantify differences in LFP activity between experimental conditions, we z-scored each of the 36 LFP variables (6 frequency bands × 3 brain regions × 2 measurements [power and peak coherence]) across each subject and then created LFP state vectors for each recording session containing all 36 LFP variables. One mouse was
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