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Ketamine disrupts theta synchrony across the septotemporal axis of the CA1 region of hippocampus

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Hinman JR, Penley SC, Escabí MA, Chrobak JJ. Ketamine disrupts theta synchrony across the septotemporal axis of the CA1 region of hippocampus. *J Neurophysiol* 109: 570–579, 2013. First published October 31, 2012; doi:10.1152/jn.00561.2012.—The hippocampal theta signal reflects moment-to-moment variation in the synchrony of synaptic input to hippocampal neurons. Consistent with the topography of hippocampal afferents, the synchrony (coherence) of the theta signal varies across the septotemporal axis. Septotemporal variation in the theta signal can also be observed in relation to ongoing and past experience. Thus there is a systematic decrease in the relationship between locomotor speed and theta power across the septotemporal axis, septal hippocampus exhibiting the strongest relationship. Conversely, theta in temporal hippocampus decrements over repeated behavioral experience (running episodes), while theta in the septal hippocampus does not. Ketamine is an *N*-methyl-D-aspartate (NMDA) antagonist that can decrease theta power. The present study examined whether ketamine treatment could alter theta coherence across the long axis independent of changes in locomotor behavior. Rats were well trained to navigate a linear runway and outfitted with electrodes at different septotemporal positions within CA1. Locomotor behavior and theta coherence and power were examined after administration of 2.5 and 10 mg/kg ketamine. Ketamine (2.5 mg/kg) decreased theta coherence between distant CA1 electrode sites without altering running speed or theta power. Both doses of ketamine also blunted and reversed the decrement in theta power observed at midseptotemporal and temporal electrodes over repeated run sessions. The results demonstrate the sensitivity of global network synchronization to relatively low doses of ketamine and septotemporal differences in the influence of ketamine on hippocampal dynamics in relation to past experience.

NMDA; theta rhythm; schizophrenia; habituation; rat

THE HIPPOCAMPAL THETA local field potential (LFP) reflects moment-to-moment variation in intrahippocampal and entorhinal excitatory (glutamatergic) inputs to hippocampal neurons. The LFP theta signal exhibits both laminar and areal variation across the somatodendritic fields of CA1 neurons (Bragin et al. 1995; Royer et al. 2010; Sabolek et al. 2009), reflecting the topographical organization of intrahippocampal (CA3) and entorhinal inputs (Dolorfo and Amaral 1998; Ishizuka et al. 1990; Ruth et al. 1982). The signal is also sculpted by a broad network of GABAergic interneurons (Brankack et al. 1993; Buzsáki et al. 1983; Klausberger and Somogyi 2008), as well as the septal GABAergic input and a number of subcortical modulatory inputs (Bland 1986; Bland et al. 2007; Pignatelli et al. 2012).

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During the awake state, CA1 theta reflects the processing of ongoing sensory inputs as filtered by neocortical associative networks and provided directly by the theta-related discharge of entorhinal cortical (EC) neurons (Alonso and Garcia-Austt 1987; Bragin et al. 1995; Chrobak and Buzsáki 1994, 1998; Deshmukh et al. 2010). The CA1 signal also reflects the theta-related output of the CA3 network (Kocsis et al. 1999), which is presumed to store and output “patterns” of activity in relation to prior experience (O’Reilly and McClelland 1994). Both CA3 and EC inputs provide theta frequency synaptic potentials to the dendritic field of CA1 neurons, and the precise timing of both inputs plays a fundamental role in the amplitude modulation of the signal (Ang et al. 2005 as well as Sabolek et al. 2009 for discussion).

In association with a variety of sensory, associative, and motor events, the theta signal clearly changes with regard to amplitude and frequency. These changes have suggested an association between theta and the processing of sensory input, attention to novelty or meaningful stimuli, sensorimotor integration, as well as memory processing during both ongoing experience and subsequent REM sleep (Benchenane et al. 2010; Bland 1986; Buzsáki 2002; Montgomery et al. 2008; Vinogradova 1995). The clearest quantifiable relationship in the rodent literature exists between locomotor speed and the amplitude and frequency of theta (Teitelbaum and McFarland 1971; see Hinman et al. 2011 for additional references).

A goal of our studies is to understand the conditions that promote unitary activity (increased synchrony) across the long axis of the hippocampus (HPC) versus conditions that may isolate or dynamically differentiate septotemporal areas. Greater synchrony across the long axis may suggest integrated computational processing across the entire hippocampal network, while decreased synchrony may suggest segregate computational processing. We have described variation in the coherence of the theta signal across the long axis (Penley et al. 2012; Sabolek et al. 2009; see also Royer et al. 2010) and a systematic decrease in the relationship between running speed and theta power with distance from the septal pole of the HPC (Hinman et al. 2011; see also Maurer et al. 2005). Such findings highlight the independent generation of theta at multiple laminar and areal sites across the somatodendritic field of HPC neurons (Montgomery et al. 2009), which nonetheless are interdependent and exhibit considerable coherence across the entire long axis (Buzsáki 2002).

While examining how various manipulations might influence power and coherence, we discovered variation in the dynamics of theta power over the course of repeated trials of

running on a linear runway (Hinman et al. 2011). Briefly, the amplitude of theta LFP decreases over sessions of running within a daily session; this effect is quite prominent in temporal HPC sites, moderate at midseptotemporal sites, and generally negligible at septal HPC electrodes. Thus theta at septal HPC sites exhibits the strongest relation to running speed, and the amplitude is relatively stable over repeated running sessions. Theta at more temporal HPC sites exhibits weaker relationships with running speed, and the amplitude of the theta signal decreases over daily run sessions. Such findings indicate the relative independence of theta generation across the long axis and highlight functional differentiation across the long axis of the HPC.

Many of the brain's neurons use glutamate as their neurotransmitter. Glutamate receptors are thus important for sensory, motor, and cognitive processes. *N*-methyl-D-aspartate glutamate receptors (NMDARs) play a permissive role in synaptic change (Collinridge et al. 1983; Lynch et al. 1988) and exhibit distinct developmental and regional expression patterns (Monyer et al. 1984; Sanz-Clemente et al. 2012). NMDARs thus have a profound influence on the function and plasticity of association cortices including the HPC. Ketamine is an antagonist of NMDARs (Anis et al. 1983; Millan 2005) that can produce a unique constellation of cognitive dysfunction including delay-dependent impairments on hippocampus-dependent memory tasks (see Bannerman et al. 2004; Morris et al. 1986; Robbins and Murphy 2006 for review, as well as Chrobak et al. 2008). Systemic and intrahippocampal administration of NMDAR antagonists decrease the theta signal but also produce subtle and significant changes in motor behavior

(Leung and Shen 2004). The presented study tested the hypothesis that ketamine treatment would decrease theta coherence across the long axis independent of speed-related changes in the theta signal. Well-trained rats were administered saline and two doses of ketamine (2.5 and 10 mg/kg; see Fig. 1A). The effects of each treatment on theta power and coherence at distinct septotemporal positions within CA1 were assessed over multiple 5-min run sessions (up to 120 min) after injection.

MATERIALS AND METHODS

Animals and surgical procedures. Six adult male Fischer 344 rats were individually housed in a temperature-controlled room and maintained on a 12:12-h light-dark cycle. All procedures presented in the present report were reviewed and approved by The University of Connecticut's Institutional Animal Care and Use Committee and strictly adhered to guidelines set forth by the National Institutes of Health.

The surgical procedures employed have been described previously (Hinman et al. 2011; Penley et al. 2012). Briefly, burr holes were drilled in the rats' skull over the HPC after the induction of anesthesia with a ketamine cocktail (4 ml/kg consisting of 25 mg/ml ketamine, 1.3 mg/ml xylazine, and 0.25 mg/ml acepromazine). Several electrode arrays, each consisting of four 50- μ m tungsten wires (12 total electrodes; California Fine Wire, Grover Beach, CA), were implanted in each animal at three distinct sites across the septotemporal axis of the HPC [septal HPC: AP -3.0 , ML 2.5, DV 3.0; intermediate HPC: AP -5.0 , ML 5.0, DV 5.0; temporal HPC: AP -6.5 , ML 5.5, DV 7.0; all coordinates are relative to bregma (Swanson 1998)]. Stainless steel watch screws positioned over the cerebellum served as indifferent and ground electrodes. Support screws were positioned in the anterior aspect of the skull as well as over the contralateral hemisphere, and

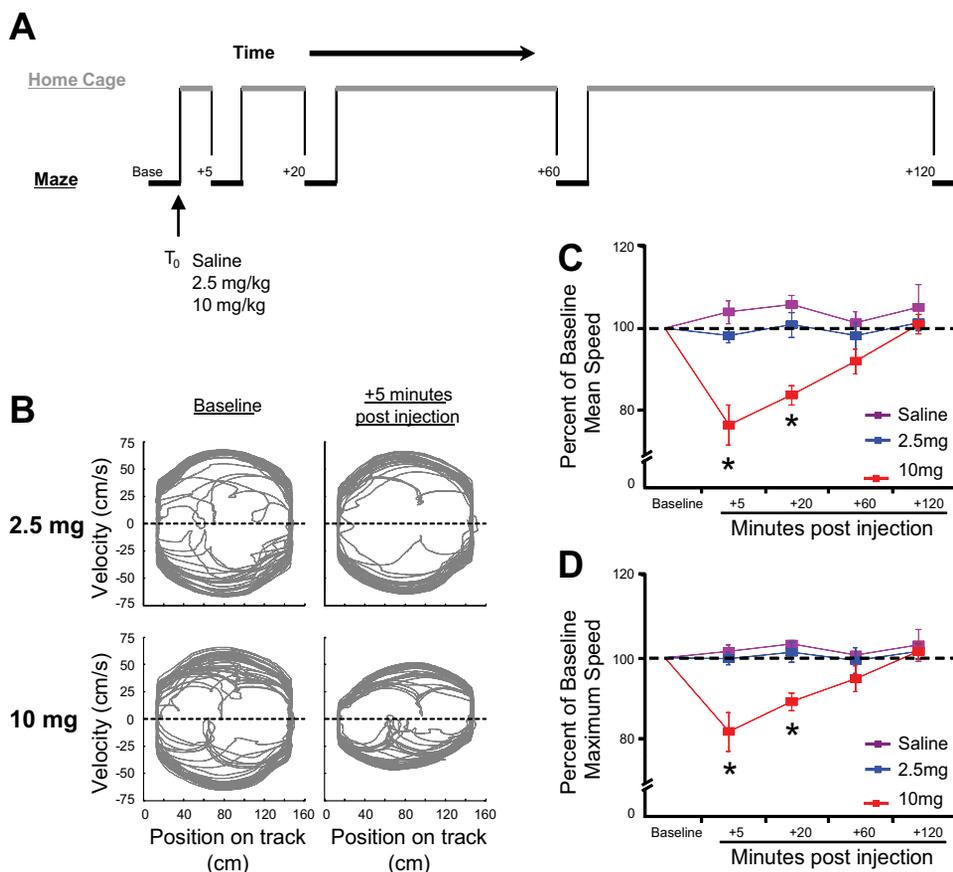


Fig. 1. Experimental procedure and locomotor behavior. **A:** timeline of the recording procedure with a baseline recording followed by an injection of saline or 2.5 or 10 mg/kg ketamine and postinjection recordings starting 5, 20, 60, and 120 min after the injection. Each recording required the rat to run 50 trials on a linear track. **B:** each plot shows a single rat's velocity as a function of position on the linear track during baseline (left) and 5 min after (right) 2.5 (top) and 10 (bottom) mg/kg ketamine. Track traversals from left to right and from right to left are represented as positive and negative velocities, respectively. Note that there was no change in locomotor behavior after 2.5 mg/kg ketamine but maximum and average velocity were reduced after 10 mg/kg. **C:** as a group, rats ($n = 6$) ran at slower mean speeds during the +5 and +20 min postinjection recordings after 10 mg/kg ketamine but showed no change in mean running speed at any time point after 2.5 mg/kg. **D:** the same pattern of changes was observed for the maximum speed achieved per trial, with rats achieving lower maximum speeds after 10 mg/kg ketamine but not after either saline or 2.5 mg/kg ketamine. * $P < 0.01$, paired sample *t*-test.

dental acrylic was used to bind the ensemble together. Rats were allowed to recover for 1 wk after surgery.

Ketamine treatments. Prior to electrode implantation, rats were food deprived to 85% of their ad libitum weight and extensively trained to shuttle between ends of a linear track (10 × 140 cm) for chocolate sprinkles. Ketamine hydrochloride (Ketaset, 100 mg/ml; Fort Dodge Laboratories, Fort Dodge, IA) was prepared in physiological saline, and all injections were administered intraperitoneally in volumes of 1 ml/kg. Each recording day started with a baseline recording (5 min) at the end of which intraperitoneal injections of either ketamine (2.5 or 10 mg/kg) or saline were administered, the injections marked T_0 . Four subsequent recordings were initiated at T_5 , T_{20} , T_{60} , and T_{120} min after the injection (Fig. 1A). During each recording rats were required to complete a minimum of 50 trials, each of which simply required the rat to move from one end of the track to the other. Between recording sessions, rats waited in their home cage on a table adjacent to the linear track until the beginning of the next recording.

Doses of ketamine and saline were administered in counterbalanced order, each rat receiving each treatment once, with 3 or 4 days intervening between each treatment. Rats were run on the maze task for each intervening day between treatments. Doses of ketamine were chosen based on our experience in giving ketamine prior to radial water maze performance (see Chrobak et al. 2008). Briefly, rats receiving 2.5 mg/kg ketamine exhibit memory encoding deficits but do not exhibit any overt behavioral changes, and experienced observers would be unable to detect ketamine treatment at this dose even when handling the rat. In contrast, at roughly 5 mg/kg and clearly at 10 mg/kg, an experienced observer/handler would detect some mild atonia (limb weakness) within 1–5 min while handling the animal. At these doses, however, rats will nonetheless run on a maze task, perform learned tasks, and swim, and the sensorimotor disruptions could be characterized as relatively mild. At doses of roughly 15–25 mg/kg, rats exhibit varying degrees of atonia with motor incoordination and mild head-weaving behavior for roughly 10 min after treatment.

Electrophysiological data acquisition and analyses. The Neuralynx data acquisition system (Bozeman, MT) was used to record wide-band electrical activity (3,787 samples/s). An overhead camera recorded light-emitting diodes attached to the headstage, which provided the animal's position on the track over time and allowed for the calculation of locomotor speed by getting the positional difference between successive tracking samples (33 samples/s).

All data analysis was conducted with custom-written programs in MATLAB (The MathWorks, Natick, MA) or in SPSS (SPSS, Chicago, IL). Movement-related data were visualized as a state-space plot (position vs. velocity; Fig. 1B). All analyses were restricted to periods of locomotion by exclusion of data recorded during the consumption of sprinkles and turning behavior. A physical threshold 14 cm from each end of the maze was set in order to exclude the just-mentioned behaviors, and any trial during which the rat's speed decreased below 5 cm/s was discarded from further analysis.

Spectral indices. The average power in the 6–12 Hz band was calculated from the power spectral density estimates obtained by Welch's averaged modified periodogram method (Welch 1967) for each trial. To calculate coherence, EEG signals from individual trials were concatenated into continuous 20-s-long strings of data (Roark and Escabi 1999; see also Sabolek et al. 2009), with each recording generating a series of such strings with different associated mean speeds. To achieve this, trials were sorted based on mean speed and then the slowest trials totaling 20 s were concatenated, then the next slowest 20 s worth of data, and so forth for the rest of the data. Coherence values (Bullock et al. 1990) for each channel pair were computed with the Welch periodogram estimation procedure with a spectral resolution of ~2 Hz obtained through the use of a B-spline window with a temporal half-width of 0.48 s.

Statistics: coherence analysis. A significance estimation procedure was devised in which the coherence estimate was compared with that of signals with identical magnitude spectrum but with zero phase coherence. For each channel pair, the cumulative distribution of the frequency-dependent coherence values was created by randomizing the phase spectrum of the signals while preserving the magnitude spectrum, calculating the coherence for the phase-randomized signals, and bootstrapping the procedure 250 times (Efron and Tibshirani 1993). This procedure guarantees that the signal magnitude spectra are identical but have no linear association, because the phase or time information has been removed. The coherence distribution obtained via bootstrapping the procedure was used to determine a significance threshold for each frequency band (2-Hz resolution), below which 95% of the shifted null hypothesis coherence values fell (i.e., the Null hypothesis; see also Sabolek et al. 2009).

Only regions of the experiment coherence spectrum falling above the 95% threshold were considered statistically significant. For each channel pair, the statistically significant area between the experiment coherence spectrum and the bootstrapped coherence spectrum in the theta (6–12 Hz) range was calculated and normalized by the maximum possible coherence within the theta range, which consists of the total area above the bootstrapped coherence spectrum. Finally, the normalized coherence area was divided by the frequency bandwidth, thus yielding values expressed as average coherence value per hertz.

Statistics: linear regression. To control for any changes in the locomotor speed of the rats, a linear regression analysis was utilized. The mean speeds and four orthogonally coded dummy categorical variables for the five recording time points (e.g., T_5 , T_{20} , etc.) were included as explanatory variables. Each electrode site (or electrode pair) yielded a single standardized regression coefficient (β -value,

where $\beta = b \frac{SD_x}{SD_y}$) for each of the explanatory variables. Thus the

regression equation takes the form: $y = \beta_{T5}X_1 + \beta_{T20}X_2 + \beta_{T60}X_3 + \beta_{T120}X_4 + \beta_{speed}X_5 + \epsilon$. The resulting β -values for the different time points indicate how theta power changes in relation to the baseline recording while controlling for speed. Thus a negative β_{T5} value indicates that theta power for a particular electrode was decreased during the recording 5 min after an injection compared with the baseline recording, having controlled for speed. Distributions of β -values were assessed with a repeated-measures (RM) ANOVA followed by post hoc Dunnett *t*-tests (Lorch and Myers 1990).

Histology. After the final recording, rats were anesthetized with Euthasol (pentobarbital sodium solution) before being transcardially perfused with saline and then 4% paraformaldehyde in 0.1 M phosphate buffer. Brains were removed from the skull and sliced (50- μ m sections) with a vibratome (Vibratome Series 1500). Sections were then mounted and Nissl stained with thionin. Electrode placements were then verified and categorized based on laminar and septotemporal position. Electrodes positioned in all laminae of CA1 were grouped together, and thus all subsequent references to CA1 electrodes include those positioned in all laminae of CA1. All final placements were indicated on a flatmap representation of the hippocampus (Swanson et al. 1978) and were documented by photomicrographs with a Nikon microscope connected to a Spot RT camera system, digitized, and prepared for presentation with Adobe Photoshop 7.0.

RESULTS

Electrodes were implanted at multiple septotemporal levels of CA1 (see Fig. 3A), and LFPs were recorded while rats shuttled between ends of a linear track before and after intraperitoneal injections of ketamine (2.5 or 10 mg/kg) or saline (Fig. 1A). A series of five recording sessions were obtained for each dose, which included a baseline recording and four postinjection recordings (Fig. 1A). Injections were administered at the end of the baseline recording, and postinjection

recordings were initiated 5, 20, 60, and 120 min after the injection. Each recording session required the rat to complete 50 trials, where a single trial simply constituted a traversal from one end of the maze to the other.

Effect of ketamine on locomotion. Since ketamine is known to acutely alter locomotive behavior (see, e.g., Littlewood et al. 2006), we used the tracking data obtained during each recording to investigate whether the animal's running performance changed as a result of either dose of ketamine or across the multiple recording sessions. Both the maximum speed per trial and the mean speed per trial were dose-dependently affected by ketamine (see Fig. 1, *B–D*). RM ANOVAs on dose \times time trial speed data indicated a significant interaction between dose and time on both measures [$F(8,40) > 5.57$, $P < 0.001$; Fig. 1, *C* and *D*]. Post hoc analyses indicated that only the 10 mg/kg dose of ketamine decreased ($\sim 20\%$) running speed at both the 5 and 20 min time points [$t(5) > 3.9$, $P < 0.01$]. By 60 and 120 min after injection, rats receiving 10 mg/kg were running at the same average and maximum speeds as during baseline. Note that there were no significant changes in the maximum speed per trial or the mean speed per trial as a function of the multiple recording sessions after either saline or 2.5 mg/kg ketamine injections. The latter indicates that rats did not become fatigued or less motivated after having run multiple sessions within a single day. This is notable because decreases in theta power are observed at certain electrode sites as a function of multiple run sessions (see Fig. 3*B* as well as Hinman et al. 2011) and this is not obviously related to decreased running speed or the motivational level that speed indicates.

Theta coherence. Our main finding was that 2.5 mg/kg ketamine decreased theta coherence across the long axis as a function of the septotemporal distance between electrodes (Fig. 2, *A* and *B*) during the first 5 min postinjection recording session. A decrease in theta coherence was also observed after 10 mg/kg ketamine, but the decrease was relatively constant with respect to septotemporal distance between electrodes. Figure 2*A* shows coherence before and 5 min after saline and each dose of ketamine for two pairs of electrodes within a single animal, with Fig. 2*A*, *insets*, showing the theta frequency range. The three electrodes are positioned in quartile 1 (Q1), quartile 2 (Q2), and quartile 3 (Q3) of CA1, and thus the two pairs span different distances of the septotemporal axis. It can be seen that regardless of the distance between the electrodes there is no change in theta coherence after a saline injection, but there are decreases after injections of both 2.5 and 10 mg/kg ketamine. In particular, after 2.5 mg/kg ketamine the decrease is larger for the pair positioned farther apart than the pair located closer together (Fig. 2*A*, *center*, *top vs. bottom*; see also Fig. 2, *B* and *C*), while both pairs are similarly decreased after 10 mg/kg ketamine (Fig. 2*A*, *right*, *top vs. bottom*).

A simple linear regression analysis on the change in theta coherence from baseline in relation to the distance between electrodes is plotted in Fig. 2*B*. In the first 5 min after saline injection there was no change in theta coherence regardless of the distance between the electrodes, as indicated by the non-significant intercept and slope (intercept = 0.01, $P = 0.18$; slope = -0.0003 , $P = 0.94$; Fig. 2*B*, *left*). The low dose of 2.5 mg/kg ketamine resulted in a septotemporally differential change in theta coherence, such that electrodes positioned close together underwent a small decrease in theta coherence while electrodes positioned farther apart decreased by greater

amounts (intercept = -0.028 , $P < 0.01$; slope = -0.015 , $P < 0.0005$; Fig. 2*B*, *center*). The significant change in intercept indicates that even pairs of electrodes positioned at the same septotemporal level displayed decreased theta coherence; the significant negative slope indicates that theta coherence decreased by greater amounts the farther apart the electrodes were separated. This graded effect was not observed after administration of 10 mg/kg ketamine, but instead theta coherence was decreased similarly regardless of the distance between the electrodes (intercept = -0.10 , $P < 0.001$; slope = -0.001 , $P = 0.89$; Fig. 2*B*, *right*).

As noted in the introduction, theta power is highly correlated with locomotor speed, particularly at septal CA1 sites (see Fig. 4*A*). To ensure that the changes in coherence did not result from the changes in running speed after 10 mg/kg, a multiple regression was conducted regressing locomotor speed on theta coherence between each electrode pair across the multiple recordings of each dose. The regression analysis confirmed each change observed in theta coherence described above, with no changes resulting after saline injection (intercept = 0.07, $P = 0.21$; slope = -0.005 , $P = 0.87$; Fig. 2*C*, *left*), a significant graded decrease after 2.5 mg/kg ketamine (intercept = -0.16 , $P < 0.01$; slope = -0.10 , $P < 0.001$; Fig. 2*C*, *center*), and a uniform decrease in theta coherence regardless of the distance between the electrodes after 10 mg/kg (intercept = -0.93 , $P < 0.001$; slope = -0.03 , $P = 0.39$; Fig. 2*C*, *right*). The latter analyses in fact mirrored the changes observed independent of the speed measures, indicating that the changes in theta coherence at either dose were independent of any speed-related differences.

Theta power: habituation across sessions after saline. As noted in the introduction, minimally three key factors predict variability in theta power at a given electrode site over multiple run sessions: 1) running speed, 2) the septotemporal position of the recording electrode, and 3) the number of run sessions. In line with previous observations, mean theta power in the second and third quartiles significantly decreased across the multiple recording sessions after saline injections: a RM ANOVA on all data obtained prior to (baseline) and subsequent to (+5, +20, +60, and +120 min) saline treatment indicated a significant time \times quartile interaction [$F(8,88) = 3.97$, $P < 0.001$]. Post hoc analyses at each time interval (e.g., +5 min) indicated that significant decreases ($P < 0.05$) were observed in the second and third quartiles by the first session (+5 min) and all subsequent sessions (Fig. 3*B*, *left*). Note that no changes were observed among Q1 electrodes even by the fifth run session (+120 min; Fig. 3*B*, *top left*).

Despite the decreases in theta power in Q2 and Q3 during the second run session, there was no decrease in theta coherence at any electrode pair across the septotemporal axis. This illustrates the important point that changes in the power of a signal(s) do not necessitate changes in the coherence of those signals; changes in theta power can alter theta coherence, but the biological mechanisms mediating changes in power at single sites and coherence across sites can be relatively independent.

Theta power: acute decrease only after 10 mg/kg ketamine dose. As evidenced in Fig. 3*B*, the effects of ketamine treatment on theta power varied as a function of dose, time, and quartile. An omnibus dose \times quartile \times session RM ANOVA indicated significant interactions across all main factors ($P < 0.05$). Surprisingly, we observed a clear alteration of the

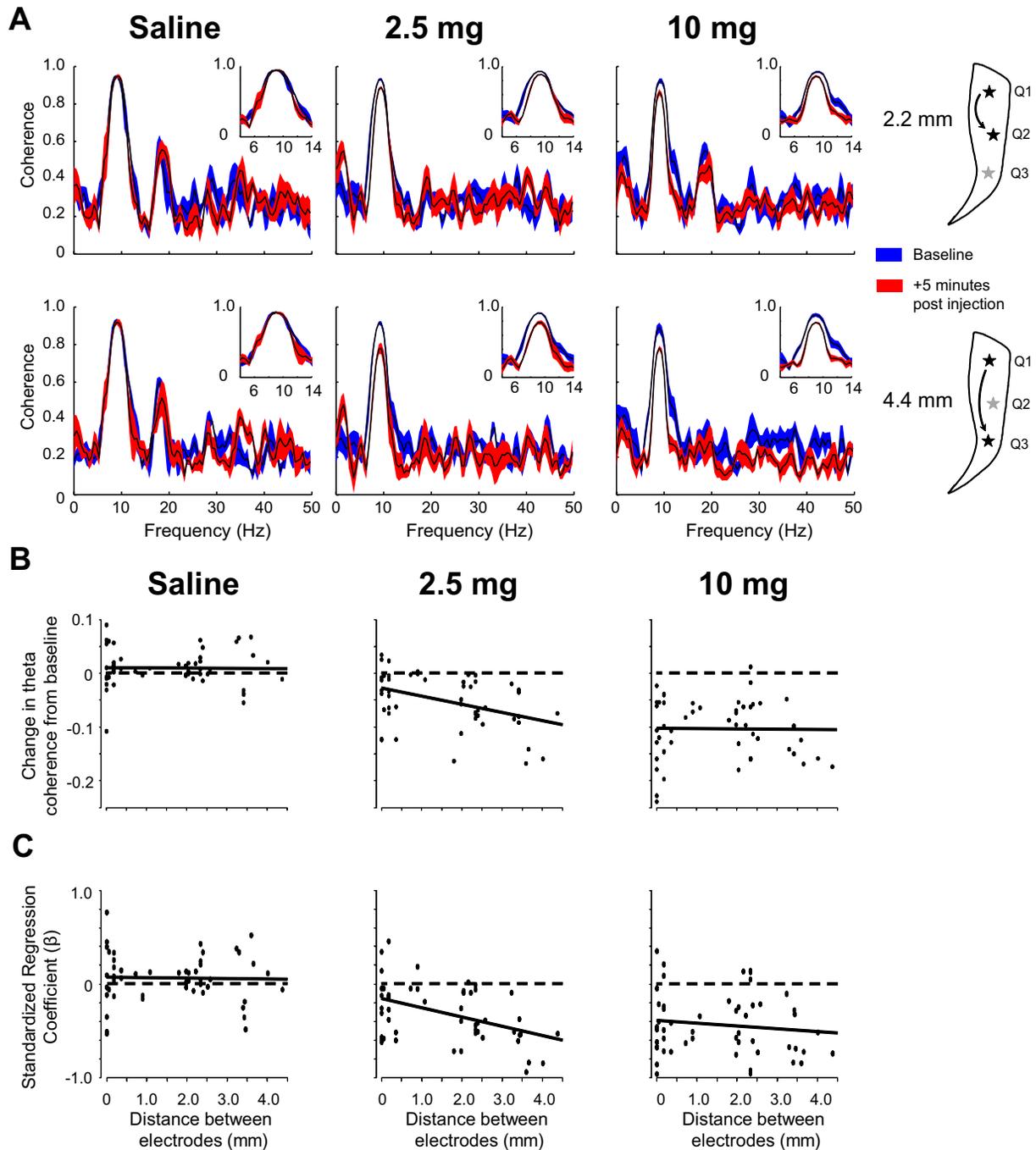


Fig. 2. Ketamine disrupts theta coherence across the septotemporal axis. *A*: coherence within the theta range is shown for 2 pairs of electrodes from a single animal (*top* and *bottom*) differing in the distance across the septotemporal axis between the electrodes (*right*). No change in theta coherence is observed between either pair of electrodes after the saline injection, but there is a selective decrease in theta coherence between the more distant pair of electrodes after 2.5 mg/kg ketamine. Theta coherence is similarly decreased between both electrode pairs after 10 mg/kg ketamine despite the difference in distance between the electrodes. *Insets*: theta frequency range. *B*: change in mean theta coherence during the +5 min postinjection recording from baseline is shown as a function of distance between the electrodes. There is no change in mean theta coherence after saline injection, but theta coherence decreased as a function of distance between electrodes across the septotemporal axis after 2.5 mg/kg ketamine and decreased similarly regardless of distance between electrodes after 10 mg/kg. *C*: same as in *B* but for the standardized regression coefficients. The same pattern of changes was observed when controlling for the speed of the animal.

habituation in theta power observed at Q2 and Q3 electrodes (compare time series of changes after saline vs. doses of ketamine in Fig. 3*B*). Given this alteration of the habituation effect, we ran separate RM ANOVAs (dose \times quartile) for each run session (+5, +20, etc.) with subsequent post hoc comparisons to the saline treatment within each quartile (e.g., +5 min saline in Q3 vs. +5 min 2.5 mg/kg ketamine in Q3).

The 2.5 mg/kg dose had no effect on theta power compared with saline treatment during the initial +5 and +20 min run sessions ($P > 0.05$; Fig. 3*B*, *center*) regardless of electrode position. This is particularly noteworthy given that theta coherence is altered during these initial run sessions (Fig. 2). The higher dose of ketamine (10 mg/kg) did decrease theta power relative to saline during the +5, +20, and +60 min run

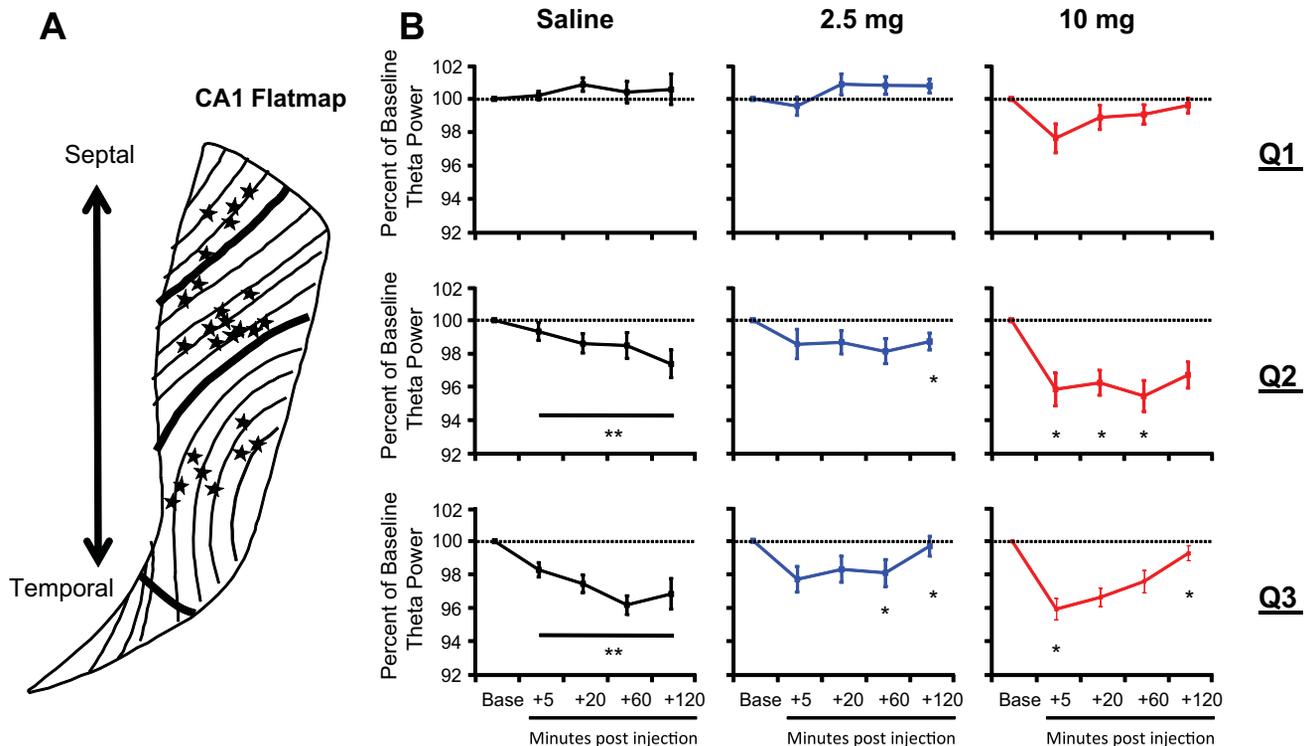


Fig. 3. Ketamine acutely decreases theta power and blocks experience-dependent theta power habituation. *A*: locations of all electrode recording sites are marked with stars on the flatmap representation of CA1. Bold lines mark the boundaries between quartiles. *B*: theta power as % of baseline is shown for each quartile after each dose of ketamine and saline. Theta power habituated as a function of repeated experiences on the track in the second and third quartiles after saline administration (*left*) (** $P < 0.001$, repeated-measures ANOVA). There were no acute effects on theta power after 2.5 mg/kg compared with saline, but the experience-dependent habituation observed after saline was blocked by 2.5 mg/kg ketamine (*center*); 10 mg/kg ketamine both decreased theta power acutely and blocked theta power habituation (*right*) (* $P < 0.01$, paired sample *t*-test).

sessions in Q1 and Q2 and during the first run session in Q3 ($P < 0.01$; see Fig. 3*B*, *right*).

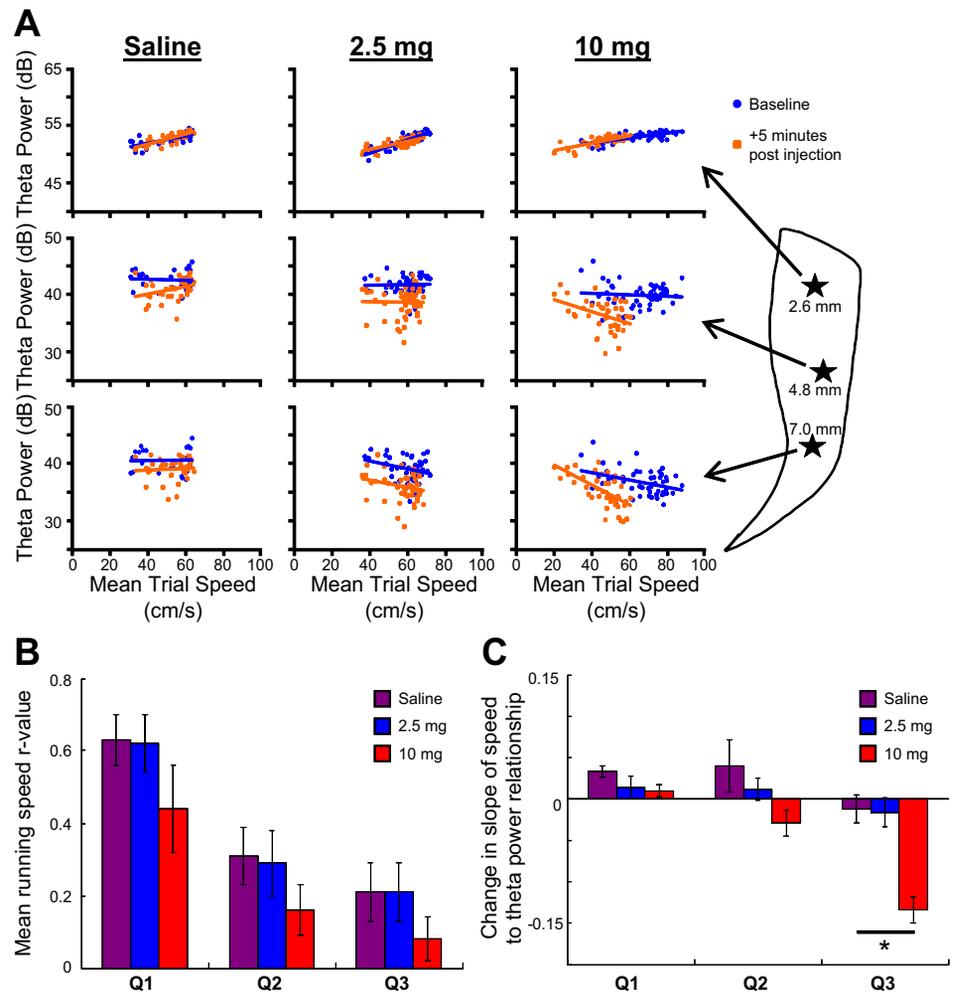
Theta power: blunting of habituation. The only effect of 2.5 mg/kg ketamine on theta power was to decrease the degree of habituation observed during the later run sessions. In Q2 during the last run session and Q3 during the last two run sessions, theta power was elevated relative to the time-matched sessions after saline treatment ($P < 0.01$; see Fig. 3*B*, *center*). A similar pattern was observed after 10 mg/kg, with Q3 electrodes having theta power elevated relative to saline treatment during the last run session ($P < 0.005$; Fig. 3*B*, *bottom right*). The data suggest that NMDARs directly contribute in some way to the theta habituation effect. Given that the effect is observed later in the course of repeated runs (e.g., +60, +120 min), it may be that this effect relates to alterations in the rat's sensory experience as the effects of ketamine wear off. It is certainly the case that the encoding of spatial memory is impaired within the first 10–15 min after ketamine administration (Chrobak et al. 2008), and it may be the case that the altered habituation reflects an altered recognition of recent experience.

Relationship between speed and theta power under ketamine. Consistent with previous findings (Hinman et al. 2011; Maurer et al. 2005), the relationship between theta power and running speed varied as a function of the septotemporal position of the electrodes during the baseline recording session (Fig. 4). To examine what, if any, effect ketamine treatment had on the relationship between locomotor speed and theta power, we examined the correlations between speed and theta power in

each quartile during the baseline period and during subsequent run sessions. Figure 4*A*, *left*, illustrates the decrease in this relationship across a set of CA1 electrodes at different septo-temporal positions in a single animal during the baseline and first postinjection saline run session. Theta recorded from a septal electrode (Q1; Fig. 4*A*, *top*) increased as a function of running speed, while theta recorded from a midseptotemporal (Q2; Fig. 4*A*, *middle*) and a more temporal (Q3; Fig. 4*A*, *bottom*) site exhibited relatively flatter slopes. Mean *r* values for all electrodes, in all animals, during the baseline recording session were 0.63 ± 0.07 , 0.31 ± 0.08 , and 0.21 ± 0.08 for Q1–Q3, respectively.

Ketamine (10 mg/kg) decreased the speed-to-power correlation at all CA1 electrode sites (Fig. 4*B*) and decreased the slope value only at Q3 electrodes (Fig. 4*C*). A RM ANOVA on the *r* values indicated a significant dose effect [$F(2,44) = 17.44$, $P < 0.001$]; subsequent post hoc tests indicated that only the 10 mg/kg dose was significant in all quartiles (see Fig. 4*B*). The decrease in the speed-to-power relationship was most prominent after the 10 mg/kg dose, particularly at midseptotemporal and temporal sites (Fig. 4*A*, *right*). There was also a significant decrease in the slopes of the speed-to-power relationship after 10 mg/kg at more temporal electrode sites (Q3), while the speed-to-power slopes were relatively constant at all sites after saline and 2.5 mg/kg ketamine (Fig. 4, *A* and *B*). Thus the higher dose of ketamine (10 mg/kg) decreased the variability in theta power explained by speed at all septotemporal sites and altered the slope of the speed-to-power relationship at the most temporal electrode sites (Fig. 4, *A* and *B*).

Fig. 4. Ketamine alters the relationship between speed and theta power. *A*: relationship between speed and theta power for 3 electrode sites from a single animal is shown for baseline (blue) and 5 min postinjection (orange) recordings for both doses of ketamine and saline. *Right*: a flatmap representation of CA1 is shown with 3 electrode sites marked by stars and their distance from the septal pole indicated. Note particularly that the slopes of the relationship between speed and theta power show a septotemporally differential decrease after 10 mg/kg ketamine but remain unchanged after 2.5 mg/kg ketamine and saline. *B*: ketamine dose-dependently decreased the amount of variability in theta power explained by running speed in all 3 quartiles. *C*: slope of the speed-to-theta power relationship is decreased selectively in the third quartile, without a change to slopes in the first and second quartiles (* $P < 0.01$, paired sample t -test).



Such findings minimally indicate that NMDARs play a more prominent role in the speed-to-power transformation within hippocampal circuits at more temporal electrodes, despite the fact that these electrodes exhibit a much more limited relationship to speed in general. While speculative, these findings hint that subcortical inputs responsible for the speed-to-power relationship in the septal HPC do not directly engage more temporal levels of the HPC; rather, intrahippocampal glutamatergic circuits may convey speed-modulated information down the long axis.

Delta coherence and power. Previous reports have demonstrated that NMDAR antagonism can increase the prevalence of delta frequency (1–4 Hz) activity (Leung and Desborough 1988; Zhang et al. 2012) and the presence of delta frequency oscillations may disrupt theta coherence in the stationary rat (Leung et al. 1982). Since all of the data included in the present analysis were restricted to periods of locomotion, we first determined whether delta power varied as a function of running speed. Across all three quartiles of CA1, delta power decreased as a function of running speed ($P < 0.05$; Fig. 5, *A* and *B*). Delta power was not altered at any time point at any septotemporal position after the 2.5 mg/kg dose ($P > 0.05$), while delta power did increase in Q2 and Q3 positions after the 10 mg/kg dose ($P < 0.05$). Multiple regression analysis indicated that when running speed is taken into consideration delta power actually decreased in Q1 ($P < 0.05$) but remained

unchanged in Q2 and Q3 after 10 mg/kg ketamine ($P > 0.05$), indicating that the increases in delta power observed in Q2 and Q3 were a consequence of the slower running speeds after 10 mg/kg ketamine. Coherence within the delta frequency range remained unchanged after injections of saline and 2.5 mg/kg ketamine regardless of the distance between the electrodes (intercepts: $P > 0.05$, slopes: $P > 0.05$; Fig. 5, *C* and *D*). After injections of 10 mg/kg ketamine delta coherence actually increased among nearby electrodes, while delta coherence approached zero for electrodes positioned farther apart, as indicated by the negative slope (change in delta coherence: intercept = 0.12, $P < 0.05$; slope = -0.02 , $P < 0.05$; standardized regression coefficient: intercept = 0.56, $P < 0.05$; slope = -0.09 , $P < 0.05$; Fig. 5, *C* and *D*). Thus the decreases in theta coherence described above (especially after 2.5 mg/kg ketamine) are unlikely to be a result of increased delta frequency oscillations.

DISCUSSION

The present study tested the hypothesis that ketamine treatment would decrease theta coherence across the septotemporal axis of the HPC independent of alterations in running speed. Our main finding is that a relatively low dose of ketamine (2.5 mg/kg), a dose that produces no overt changes in sensorimotor performance, decreases theta coherence across the septotem-

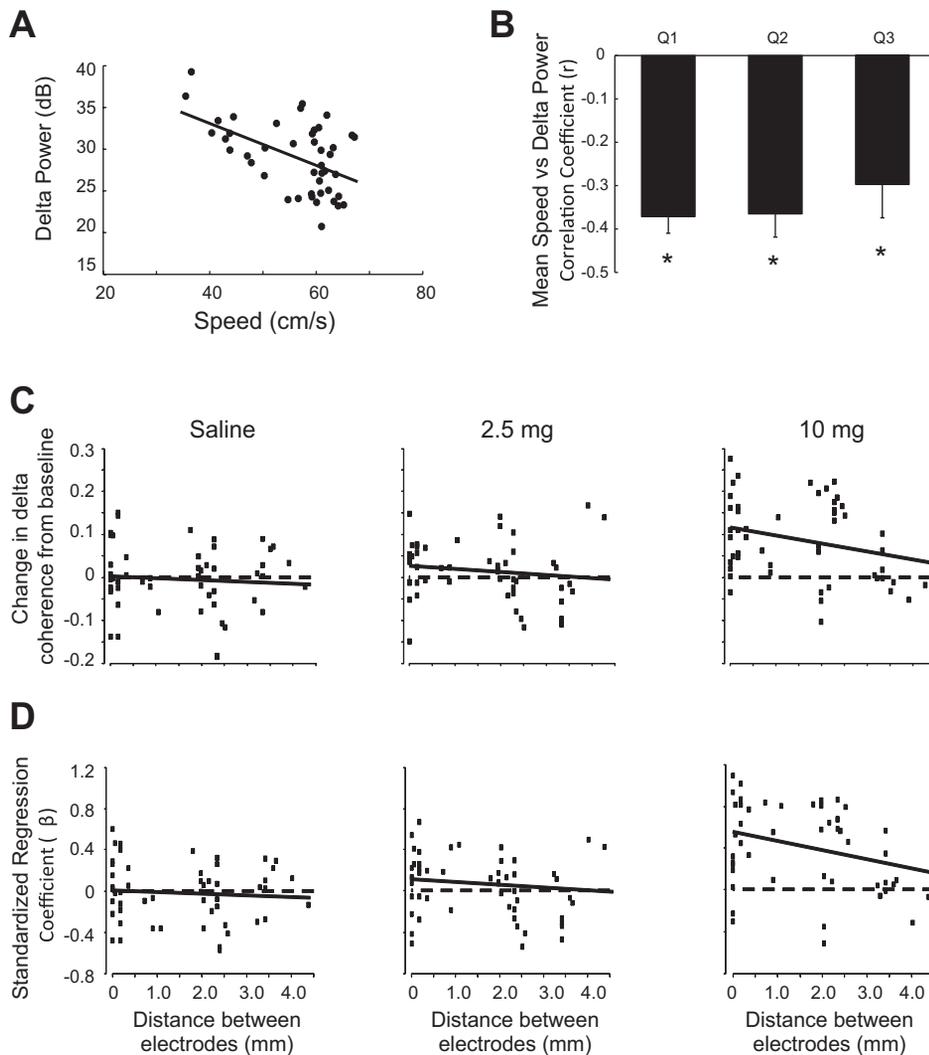


Fig. 5. Effect of running speed and ketamine on delta. *A*: a clear negative relationship between running speed and delta power is shown for a single electrode. *B*: mean correlation coefficients for each quartile of CA1 investigated. Note that the relationship is negative in each quartile, thus indicating that delta power decreases as a function of running speed ($*P < 0.01$, t -test). *C*: change in delta coherence 5 min after injection as a function of distance between the electrodes is shown for both doses of ketamine and saline injection. No change in delta coherence is observed after saline and 2.5 mg/kg ketamine, but 10 mg/kg ketamine increases delta coherence between closely positioned electrodes. *D*: same as in *C* but for standardized regression coefficients.

poral CA1 network. Ketamine at 2.5 mg/kg did not alter running speed, or the power of theta, but decreased the coherence of the theta signal across the long axis. The decrease in coherence across the long axis was greater with increasing distance between CA1 electrode pairs. The latter suggests that long-range intrahippocampal synchronization, and perhaps hippocampal-entorhinal or hippocampal-prefrontal communication, may be highly dependent on NMDARs. We suggest that the dynamic and presumably highly plastic interactions among large ensembles of hippocampal and neocortical neurons are highly sensitive to low doses of NMDA blockade and that such disruption likely mediates the cognitive and memory dysfunctions consequent of NMDAR antagonist administration.

Two other observations were noteworthy. First, ketamine (10 mg/kg) not only decreased running speed and theta power but also significantly altered the speed-to-power relationship (altering the slope of the linear relationship between speed and theta power) prominently at midseptotemporal and temporal electrode positions. The latter suggests that there is a differential contribution of NMDAR activation to the speed-to-power relationship across the septotemporal axis. In this regard, we have observed a decrease in theta power at sites distal from the septal pole over repeated running sessions (habituation). This

characteristic “habituation” in theta power increases in magnitude with distance from the septal pole (see Fig. 6 in Hinman et al. 2011). The septotemporal variation in habituation, and the sensitivity of speed-to-power relationships to ketamine treatment, suggest that the speed-to-power relationship may be highly variable or exhibit short-term “plasticity.” We are currently exploring the consistency of the speed-to-power relationship at individual electrode sites over multiple sessions and days of recording.

More surprising was our second observation that the habituation of theta power observed at more temporally located CA1 sites was blunted by ketamine treatment at both 2.5 and 10 mg/kg. The habituation (degree of decrease) of theta power at CA1 sites increases (theta decreases more) over multiple repeated running sessions (5 min of running spaced tens of minutes apart). The greatest habituation (decrease) was observed during the last session of the day (2 h after an initial baseline recording). The largest decrement (blunting or reversal) of this habituation was also most evident during latter sessions, hours after ketamine treatment.

NMDA receptors may contribute to speed-to-power relationships. Glutamatergic input clearly contributes to the generation of the theta LFP, and glutamatergic antagonists administered peripherally or centrally decrease characteristics of theta as well as

gamma signals (Leung and Shen 2004; Zhang et al. 2012). Many studies examining the effects of pharmacological manipulations on theta have not necessarily controlled for changes in motor performance while examining changes in either theta power or frequency. Subtle modifications in the behavior of the rat (e.g., changes in speed) following both central and peripheral drug administration may contribute to changes in theta as opposed to any direct effect on the intrahippocampal or extra-hippocampal circuits generating theta (see Buzsaki et al. 1979, 1981 for discussions). The results reported in the present study illustrate how ketamine at a fairly low dose (10 mg/kg) can alter theta power at specific electrode sites likely as a consequence of changes in locomotor speed, while lower doses (2.5 mg/kg) alter theta indexes independent of any changes in locomotor speed.

It is important to note that the present results, obtained after peripheral drug administration, do not directly speak to modulation of intrahippocampal NMDARs. Rather, they speak more directly to ketamine-induced changes in hippocampal physiology that likely result from actions of ketamine at multiple NMDARs in the brain and as would occur in relation to memory/cognitive dysfunction in association with peripheral ketamine treatment (e.g., Chrobak et al. 2008).

Ketamine treatment and memory dysfunction. Peripheral NMDAR blockade can disrupt the encoding, retention, and retrieval of memories (Bannerman et al. 2004; Newcomer and Krystal 2001; Robbins and Murphy 2006), including performance on HPC-dependent memory tasks (see Chrobak et al. 2008 for review and references). Given the widespread distribution of NMDAR in cortical areas, it is likely that multiple memory systems (e.g., procedural and declarative) and processes (e.g., encoding and retrieval) contribute to task-related deficits. The information processing functions of the HPC and prefrontal cortex, as well as many areas of limbic cortex, are adapted to provide maximal plasticity to allow for flexibility in sensori-sensory and sensori-motor circuits. Such flexibility may be highly sensitive to pharmacological manipulation of NMDARs.

In this regard, we have observed that the lower dose of ketamine (2.5 mg/kg) used in the present study can impair the encoding of one-trial, episodic memories (HPC dependent) in a task in which the performance and procedural memory skills are well learned (Chrobak et al. 2008) when drug is administered just prior to to-be-remembered events. Such studies suggest that low doses of ketamine can selectively weaken the “strength” of encoded representations (see also Kentros et al. 1998). Our present study highlights that long-range coherence is likely the most sensitive measure of neurophysiological activity altered by peripheral ketamine administration. A few recent studies have highlighted hippocampal-prefrontal coherence in relation to behavioral/cognitive performance in rodents (Sigurdsson et al. 2010). The present findings illustrate that long-range coherence is disrupted by ketamine treatment, and we suggest that future studies should examine whether lower doses disrupt hippocampal-prefrontal coherence.

Putative neurophysiological mechanisms. Ketamine induces a range of physiological effects consistent with the wide distribution of NMDARs in the brain. The present data make no statement about the underlying mechanisms, although we suggest that the alterations of hippocampal theta may depend on physiological changes subsequent to NMDAR blockade in

both hippocampal and widespread brain regions. Our evidence indicates that fairly low doses (2.5 mg/kg) disrupt theta coherence most prominently at millimeter-distant electrode sites in septal and temporal HPC. In this regard, our studies highlight the disruption of long-range communication as a central feature of ketamine-induced neurophysiological events in contrast to a focal site of action at any of the numerous NMDARs in the brain.

Summary. The hippocampal theta (LFP) signal reflects moment-to-moment variation in synaptic inputs to hippocampal neurons. One source of variation in the amplitude of theta is locomotor speed, and the relationship of this variable to theta power varies across the septotemporal axis. The theta signal also habituates in amplitude in relation to “experience”; thus simply running across a linear track over time decreases the amplitude of theta. This phenomenon also exhibits variability across the septotemporal axis. The present studies demonstrate that doses of the NMDA antagonist ketamine that alter memory and cognitive performance in the rat can alter theta indexes independent of overt changes in behavior (locomotor speed). Furthermore, they illustrate dynamic variability in the relationship between locomotor speed and theta power and that this variability is sensitive to alteration by ketamine treatment. Most importantly, the study demonstrates that long-range synchronization of the theta signal across the septotemporal or long axis of the HPC is highly sensitive to the lowest dose of ketamine. We suggest that a neural network account of the effects of ketamine includes a disruption of long-range communication in cortico-cortico networks.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: J.R.H. and J.J.C. conception and design of research; J.R.H. and S.C.P. performed experiments; J.R.H. and M.A.E. analyzed data; J.R.H. and J.J.C. interpreted results of experiments; J.R.H. prepared figures; J.R.H. and J.J.C. drafted manuscript; J.R.H. and J.J.C. edited and revised manuscript; J.R.H., S.C.P., M.A.E., and J.J.C. approved final version of manuscript.

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