The psychotomimetic ketamine disrupts the transfer of late sensory information in the corticothalamic network.

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Running title :

Ketamine reduces sensory-induced gamma oscillations

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ABSTRACT

In prodromal and early schizophrenia, disorders of attention and perception are associated with structural and chemical brain abnormalities, and with dysfunctional, highly distributed corticothalamic networks exhibiting disturbed brain rhythms. The underlying mechanisms are elusive. The non-competitive NMDA receptor antagonist ketamine simulates the symptoms of prodromal and early schizophrenia, including the disturbances in ongoing and task/sensory-related broadband gamma frequency (30-80 Hz) oscillations in corticothalamic networks. In normal healthy subjects and rodents, complex integration processes, like sensory perception, induce transient, large-scale synchronized gamma oscillations in a time window of a few hundreds of ms (200-700 ms) after the presentation of the object of attention (e.g., sensory stimulation). Our goal was to use an electrophysiological multisite network approach to investigate, in lightly anesthetized rats, the effects of a single psychotomimetic low-dose (2.5 mg/kg, subcutaneous) of ketamine on sensory stimulus-induced gamma oscillations. Ketamine transiently increased the power of baseline gamma oscillations and decreased sensory-induced gamma oscillations. In addition, it disrupted information transferability in both the somatosensory thalamus and the related cortex and decreased the stimulus-induced gamma-frequency band thalamocortical connectivity. In conclusion, the present findings support the hypothesis that NMDA receptor antagonism disrupts the transfer of perceptual information in the somatosensory cortico-thalamo-cortical system.

INTRODUCTION

In neuropsychiatric illnesses, like schizophrenia, sleep disorders and deficits in attention-related sensorimotor and cognitive integration processes are common. These disorders insidiously start to occur during the prodromal phase (McGhie & Chapman, 1961; Lunsford-Avery *et al.*, 2013; Manoach *et al.*, 2014; Zanini *et al.*, 2015; Mayeli *et al.*, 2021). It can be simulated with the non-competitive NMDA receptor antagonist ketamine following its administration at a subanesthetic dose in healthy humans (Krystal *et al.*, 1994; Hetem *et al.*, 2000; Anticevic *et al.*, 2015; Hoflich *et al.*, 2015; Rivolta *et al.*, 2015; Grent-'t-Jong *et al.*, 2018) and other species, including rodents (Chrobak *et al.*, 2008; Pinault, 2008; Pitsikas *et al.*, 2008; Ehrlichman *et al.*, 2009; Hakami *et al.*, 2009; Kocsis, 2012).

Sensory-related perception is a very complex and relatively long-lasting (~2 s) process, which involves early (<200 ms) and late (>200 ms) stages. These two-time stages represent a continuum through highly distributed systems involving diverse cortical areas during the perceptual process (Portella *et al.*, 2012; Portella *et al.*, 2014; Saradjian *et al.*, 2019). The dynamics of the cortico-thalamo-cortical (CTC) network in the late stage of perception remains little known in psychotic disorders. Literature suggests the existence of a link between late sensory-related activities and perception. In a visual perception task, participants show sensory perception-related gamma activity increases in two separate components, early and late (Rodriguez *et al.*, 1999). Likewise, in a study conducted in humans and mice two, early (< 300 ms) and late (> 300 ms), response activities are recorded after visual stimulation, the latter response believed to be involved in visual perception (Funayama *et al.*, 2015).

In schizophrenia patients, deficits in perception are associated with a reduction of phase synchrony in beta-gamma-frequency (20-60 Hz) oscillations at this period (Uhlhaas *et al.*, 2013). These results suggest a decrease in induced sensory-related gamma oscillations during the late period of perception. There are lines of evidence of a decrease in induced-gamma oscillations in individuals at clinically at-risk mental state for transitioning to psychosis (Haenschel *et al.*, 2009; Reilly *et al.*, 2018). The decrease in power and synchrony of task/sensory-induced gamma oscillations may be due to the abnormal amplification of basal gamma oscillations recorded in such patients (Ramyead *et al.*, 2015). Indeed, in the acute rodent ketamine model, early sensory-evoked gamma oscillations decrease whereas ongoing gamma oscillations increase, supporting the hypothesis of a reduction in the signal-to-noise ratio (Hakami *et al.*, 2009; Kulikova *et al.*, 2012; Anderson *et al.*, 2017).

So, we wanted to study whether and how late sensory-induced gamma oscillations are disturbed by NMDA receptor antagonism. For that, we investigated the low-dose ketamine effects in the somatosensory thalamocortical (TC) system during the late sensory stimulus-related period (200-700 ms post-sensory stimulation), involving highly distributed CTC systems (Alitto & Usrey, 2003; Briggs & Usrey, 2008; Urbain *et al.*, 2015; Homma *et al.*, 2017). Since sensory-induced gamma oscillations can be recorded in anesthetized rats (Neville & Haberly, 2003), the experiments were conducted in the pentobarbital-sedated rat. Spectral analysis and coherence connectivity were used in an attempt to estimate, respectively, the level of synchronization and the functional connectivity between the recording sites (Kam *et al.*, 2013). Unlike amplitude measures, coherence measurement shows the synchronization level between two signals based on the phase consistency (Srinivasan *et al.*, 2007). EEG and extracellular signals are relatively complex as they are generated by multiple interacting cortical and subcortical oscillators. The complexity of such signals, related to functional aspects of the corresponding neural networks, can be assessed with non-linear analyses such as the multiscale entropy analysis (MSE) (Costa *et al.*, 2005; Miskovic *et al.*, 2019). The MSE has been applied to EEG from psychiatric patients (Fernandez *et al.*, 2013). Higher MSE can indicate increases in the complexity of time-varying signals and may represent disruptions in long-range temporal connectivity or temporal integration (Breakspear & Stam, 2005). So, in an attempt to measure the dynamical complexity in the TC system at multiple timescales, MSE was applied to the extracellular recordings. The present findings show that, in the somatosensory CTC system, ketamine disrupts the transfer of sensory-induced gamma oscillations.

MATERIAL AND METHODS

Animals and drugs

Seven adult (3-6-month-old, 285-370 g), Wistar male rats were used. All animal care procedures were performed under the approval of the Ministère de l'Education Nationale, de l'Enseignement Supérieur et de la Recherche. Animals were housed and kept under controlled environmental conditions (temperature: 22 ± 1°C; humidity: 55 ± 10%; 12/12 h light/dark cycle; lights on at 7:00 am) with food and water available *ad libitum*. Every precaution was taken to minimize stress and the number of animals used for each series of experiments. Ketamine (Imalgene 1000, MERIAL), pentobarbital sodique (CEVA santé animale) and fentanyl (Fentadon$^{@}$ DECHRA) were from CENTRAVET.

Surgery under deep narco-analgesia

Narcosis was initiated with an intraperitoneal injection of pentobarbital (60 mg/kg). An additional dose (10–15 mg/kg) was administered as soon as there was a nociceptive reflex. Analgesia was achieved with a subcutaneous injection of fentanyl (7.5 µg/kg) every 30 min. The depth of the surgical narco-analgesia was continuously monitored using an electrocardiogram, watching the rhythm and breathing, and assessing the nociceptive withdrawal reflex. The rectal temperature was maintained at 36.5°C (peroperative and protective hypothermia) using a thermoregulated pad. The trachea was cannulated and connected to a ventilator (50% air–50% O^2, 60 breaths/min). Under local anesthesia (lidocaine), an incision of the skin on the skull was done, and the periosteum was removed to set the skullcap bared and to perform the stereotaxic positioning of the recording electrodes on the frontoparietal skull. The deep narco-analgesia lasted about 2.5 h, the time needed to complete all the surgical procedures.

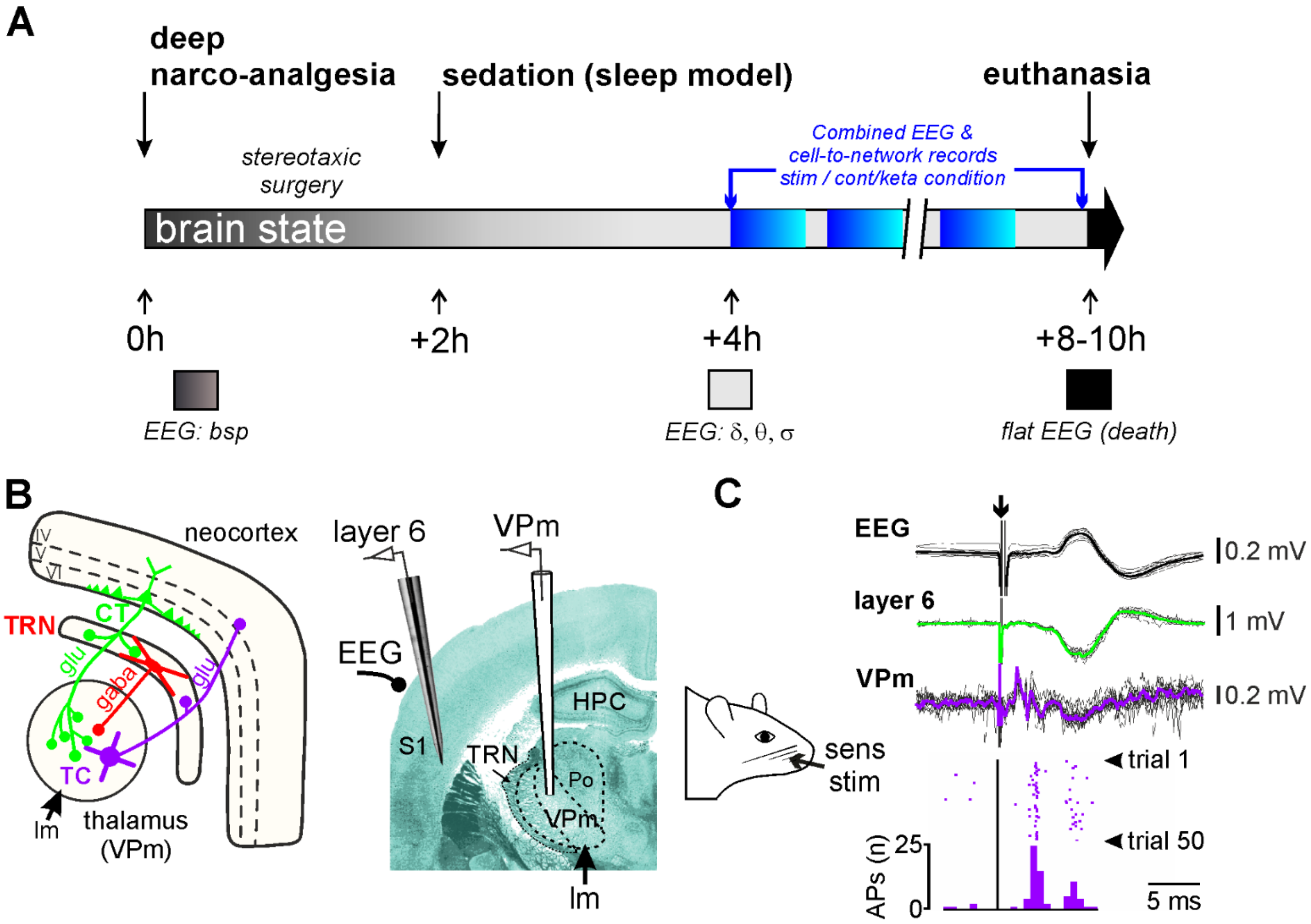


Figure 1: Experimental design. (A) Timeline illustrating the key events during the experimental procedure with repeated measures in one animal. One to three low-dose ketamine challenges can be done during one animal-experiment. At the bottom, the color code of the brain state is dark gray for deep narco-analgesia, light gray for sedation (light narco-analgesia), and dark for death. bsp, Burst Suppression Pattern. During the sedation, the EEG is characterized principally by delta- (1-4 Hz), theta- (5-9 Hz) and sigma- (10-17 Hz) frequency oscillations (δ, θ, and σ, respectively). **(B)** Simplified hodology of the thalamocortical (TC, in blue purple) and corticothalamic (CT, in green) pathways of the somatosensory system linked to the vibrissae. This involves the inhibitory afferents originating from the thalamic reticular nucleus (TRN, red). CT and TC neurons are glutamatergic and TRN neurons GABAergic. The right panel shows multi-site recordings within the thalamus (VPm) and neocortex (layer VI and cortical EEG) within the rat somatosensory system. The VPm receives lemniscal afferents (lm). **(C)** The teguments of the vibrissae are electrically stimulated every 15 seconds (sens stim). Sensory evoked potentials are recorded simultaneously within the cortex and the thalamus. For each recording site are shown an overlay of 15 recordings and their averaging. Extracellular field potentials can be accompanied by cellular discharges. In this example, the number of action potentials from the recordings within the VPm are shown (50 trials). HPC: Hippocampus; Po: Posterior nucleus of the thalamus.

Pentobarbital-induced sedation

At the end of the surgery, the body temperature was set to and maintained at 37.5°C. The analgesic pentobarbital-induced sedation (light narco-analgesia) was initiated about 2 h after the induction of the surgical narco-analgesia (Figure 1A) and was maintained by a continuous intravenous infusion of the following regimen (average quantity given per kg and per hour): Pentobarbital (7.2 ± 0.1 mg), fentanyl (2.4 ± 0.2 µg), and glucose (48.7 ± 1.2 mg). In order to help maintain the ventilation stable and to block muscle tone and tremors, a neuromuscular blocking agent was used (d-tubocurarine chloride: 0.64 ± 0.04 mg/kg/h). The cortical EEG and heart rate were under continuous monitoring to adjust, when necessary, the infusion rate to maintain the sedation. The EEG recordings began 2 hours after the beginning of the infusion of the sedative regimen. During the recording session and every 2 hours, drops of the local anesthetic lidocaine were applied to the surgical wounds.

Electrophysiology

For the EEG recordings of the frontoparietal somatosensory cortex (stereotaxic coordinates relative to bregma (Paxinos & Watson, 1998): posterior 2.3 mm, lateral 5 mm), the section of the Ag/AgCl wires (diameter 150 µm), insulated with Teflon, was placed on the inner plate of the bone. Extracellular field potential and multi-unit activities were recorded in the somatosensory thalamus, especially in the medial part of the ventral posterior nucleus (VPm, bregma -2.8 mm, lateral 2.8 mm), and in the medial part of the posterior group (PoM, bregma -2.8 mm, lateral 2.8 mm, depth 5.6 mm.) using glass micropipettes (tip diameter of 5-10 µm) filled with artificial cerebrospinal fluid and 1.5 % Neurobiotin). Semi-micro quartz/platinum-iridium electrodes were used for recordings in the layer 6 (depth 1.6-2.0 mm) of the related somatosensory cortex (Figure 1B). All regions of interest were recorded simultaneously, and the electrophysiological signals were sampled with a rate of 20 kHz (Digidata 1440A with pCLAMP 10 Software, Molecular Devices). The recording electrodes were moved down until the identification of the receptive field (Figure 1C). Sensory-evoked potentials were recorded after electrical stimulation of the vibrissae teguments using a pair of subcutaneous needles (duration: 75 µs; intensity: 50–60% of the intensity that gives maximal amplitude evoked potential, 1.0 to 1.5 mA; frequency: 0.06 Hz). Every trial contained recorded signals after one stimulation (10 trials/rat).

Pharmacology and repeated measures in one animal

During the recording session under the sedation condition, every rat was its own control. Saline (vehicle, NaCl 0.9%) and ketamine (2.5 mg/kg) were subcutaneously administered (1ml/kg). As long as the pentobarbital-induced sedation is stable (4 to 6 hours) and knowing that, under the present experimental conditions, the ketamine effect (peaking at 15–20 min) lasts significantly less than 90 min (Anderson *et al.*, 2017; Mahdavi *et al.*, 2020), two to three conditions (20-40-minutes saline condition followed by one or two ketamine challenges) could be performed in one animal (Figure 1A).

Data Analysis

Data analyses were performed with Clampfit 10, SciWorks (Datawave Technologies) and MATLAB softwares. Spectral analysis was done with 2 Hz resolution, hamming windowing, none overlay. Recorded signals were analyzed in five frequency bands: delta (1-4 Hz), theta (5-9 Hz), sigma (10-16 Hz), beta (17-29 Hz), and gamma (30-80 Hz). Sensory stimulus-induced gamma power was calculated by subtracting the evoked and basal power from the total power.

Total power spectral: In total, data of 40 trials (10 x 4 rats) were acquired. The total power in a given frequency range v was the sum of powers across the defined spectral range. We consider the 500 ms period before each stimulus as baseline. The baseline power for each trial is denoted as P_{b1}, P_{b2}, P_{b3}, …P_{b40}; stimulus-related power each successive post-stimulus 500-ms epoch is denoted as P_{e1}, P_{e2}, P_{e3}, … P_{e40}. Therefore, the average normalized power P_v for the frequency v range is computed as:

$$P_\nu = \sum_{i=1}^{N=40} \left(\frac{P_{e_i}}{P_{b_i}}\right)/N$$

Similarly, in ketamine conditions, P_{kbi} and P_{kei} stand for the baseline and stimulus-related power respectively for each trial i. Thus, average normalized ketamine power P_{kv} is computed as:

$$P_{k\nu} = \sum_{i=1}^{N=40} \left(\frac{P_{ke_i}}{P_{kb_i}}\right)/N$$

Multi-scale entropy (MSE): The information complexity of extracellular recordings was measured by MSE. Although the definition of complexity is various, it is associated with “meaningful structural richness” and “information randomness” (Costa *et al.*, 2005; Hager *et al.*, 2017). The MSE is calculated with 2 steps. First, coarse-graining is applied to the time series $\{x_1, \ldots, x_i, \ldots, x_N\}$. It is constructed by averaging data points from non-overlapping time-windows of interest, τ. Every coarse-grained time series, y_j^τ, is calculated as :

$$y_j^\tau = \sum_{i=(j-1)\tau+1}^{j\tau} x_i/\tau \qquad\qquad 1 \leq j \leq N/\tau$$

Where N/τ is the length of each resulting coarse-grained time series. Then the sample entropy is calculated for each series y_j^τ and plotted as function of the scale factor. When τ equals one, y_j^1 is equivalent to the original time series. The higher scale factor is, the longer temporal range it is. The MSE values for low scales reflect short-range temporal irregularity, while high scales reflect long-range temporal irregularity. Other parameters for MSE calculations were adopted from previous studies (Lake *et al.*, 2002; Richman *et al.*, 2004; Takahashi *et al.*, 2010).

Coherence connectivity: Coherence was calculated by the MATLAB mscohere function.

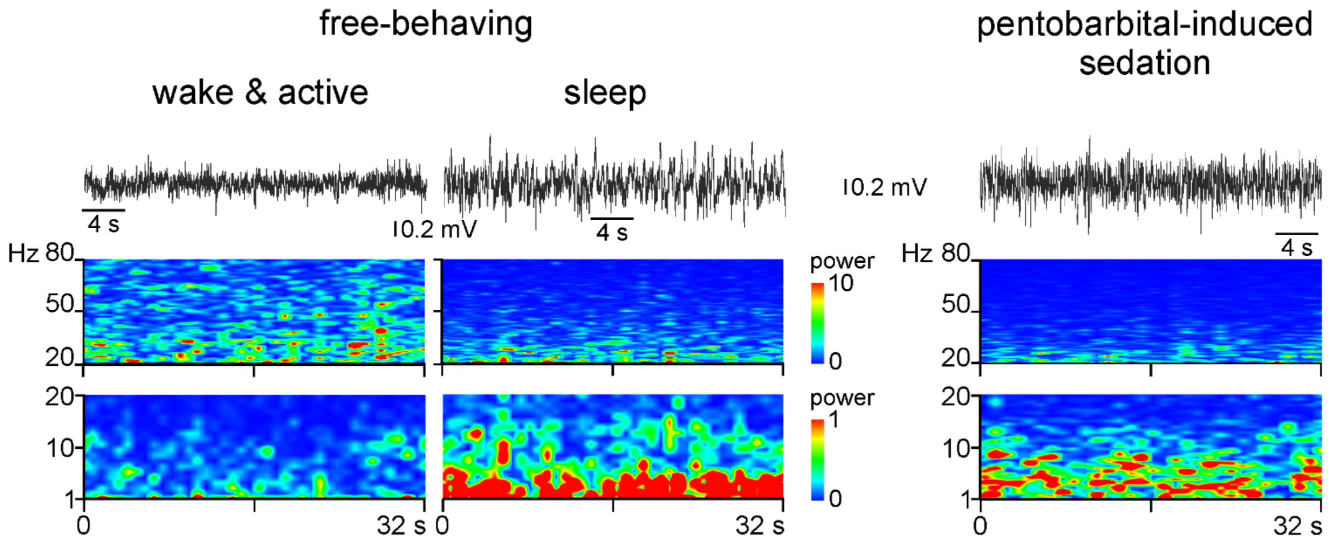
Statistics: All statistics tests were calculated using MATLAB or Graphpad Prism 9. For comparing the baseline and stimulus-related activities in different frequency bands, we used one-way ANOVA test with Holm-Šidák's multiple comparisons test as post-hoc analysis. For comparing normalized gamma total power under ketamine and saline conditions, paired t-tests were applied to each group, each animal being its own control. For testing the effect of ketamine on induced gamma oscillations, we computed whether there was a significant interaction using a two-way ANOVA for time and condition (saline or ketamine). When assessing the coherence between recording sites, we used the Wilcoxon matched pairs signed-rank test.

RESULTS

The detailed statistical data are presented in the supplementary material (S1).

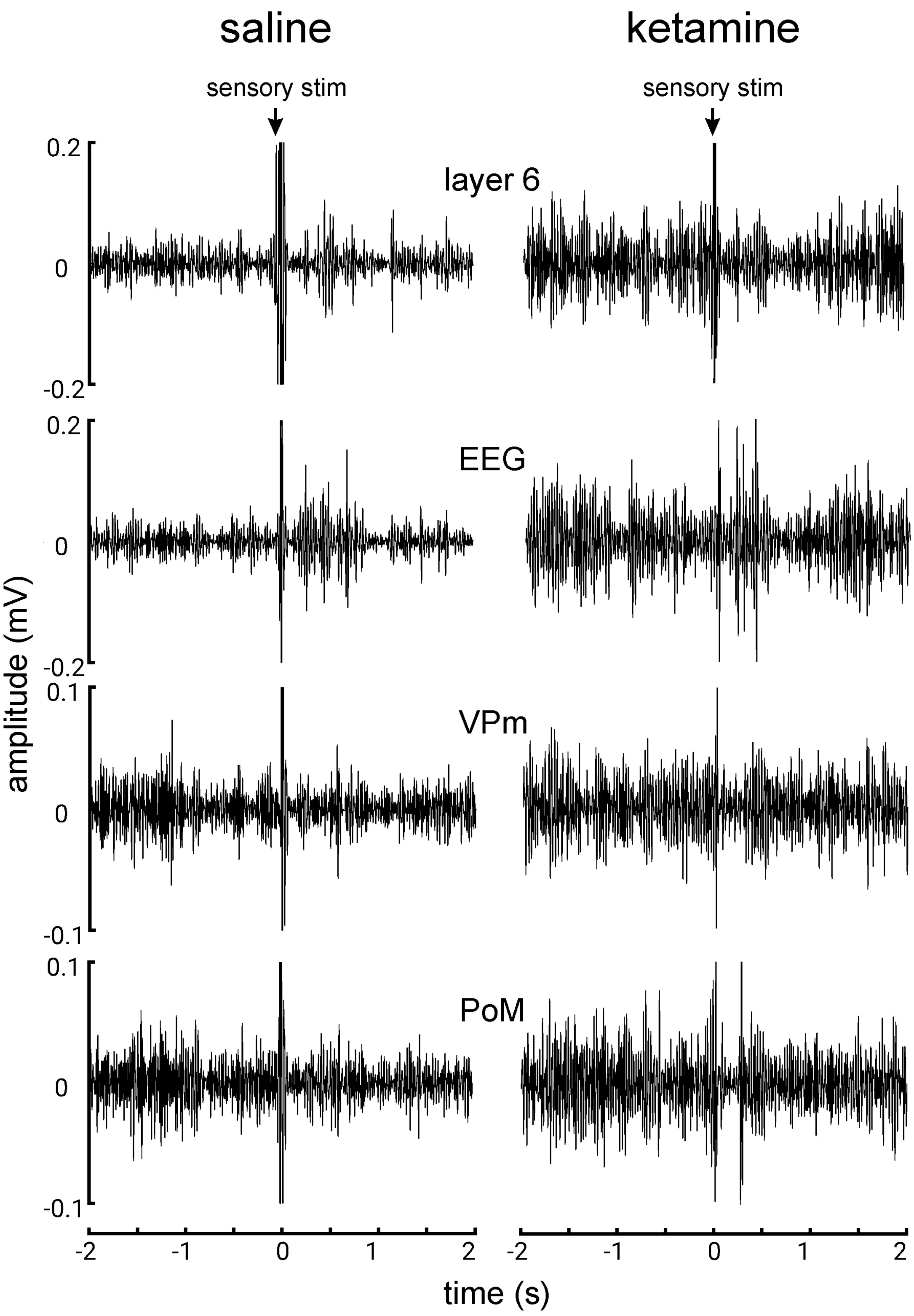
Ongoing and sensory-induced gamma oscillations under pentobarbital sedation

Ongoing oscillations: Under the pentobarbital-induced slow-wave sleep (ketamine-free) condition, the EEG recordings principally displayed oscillations in the delta-frequency band (1–4 Hz or slow-waves) accompanied by oscillations in the sigma band (10–17 Hz or "spindle-like" activities) (Pinault *et al.*, 2006; Mahdavi *et al.*, 2020). These oscillations were qualitatively similar to slow-wave sleep with spindles recorded in free-behaving rats in stage II sleep (S2). The slow-wave sleep-type oscillations were sometimes interspersed with smaller and faster oscillations, including, among others, broadband gamma- and higher-frequency oscillations.



S2: Cortical EEG oscillations in the free-behaving or pentobarbital sedated rat. Top: 32-s bouts of desynchronized, during wake state, and synchronized, during non-REM sleep, cortical EEG recorded in a free-behaving rat during a 90-minutes recording session; the right trace is from a pentobarbital-sedated rat. Bottom: Time-frequency spectral analysis (resolution: 0.03 Hz, hamming, 50 % overlap) of a 32-s recording episode for each condition. The power scale (z scale in color) is not the same for the two frequency bands 1-20 Hz (x1) and 20-80 Hz (x10). The records from the free-behaving rat are from the study performed by Pinault (Biol Psychiatry, 2008).

Sensory stimulus-induced oscillations: Under the control (saline) condition (S3, Figure 2A), the total power of all cortical frequency-band oscillations strongly increased following sensory stimulation during the 200-700 ms post-stimulus period. Both cortex and thalamus demonstrated power increases in a wide frequency spectrum from theta to gamma frequencies. Regarding the delta-frequency oscillations, a power increase was recorded in the cortex (cortical EEG and extracellular layer 6 recordings) but not in the thalamus. The statistical comparison between each period and baseline was done by one-way ANOVA, with Geisser Greenhouse correction, Holm-Šidák's multiple comparisons.



S3: Simultaneous cortical (EEG & layer 6) and thalamic (VPm & PoM) recordings under saline and ketamine conditions from a lightly anesthetized rat. They are filtered in the gamma frequency band (25-50 Hz). Each trace (sweep) shows the 2-s pre-stimulus and 2-s post-stimulus periods. The teguments of the vibrissae are stimulated (sensory stim). The traces under the saline condition were recorded 10 minutes before the ketamine administration. The ketamine traces were recorded 20 minutes after the subcutaneous administration of ketamine (2.5 mg/kg).

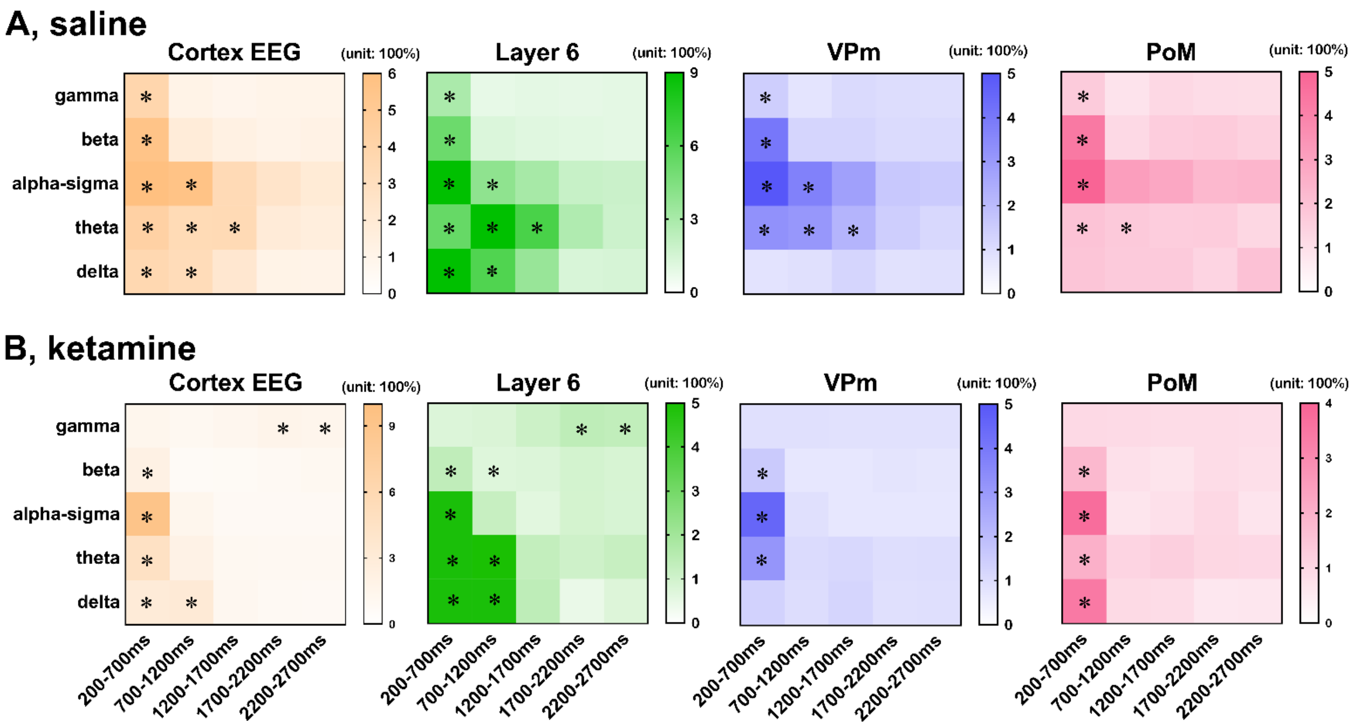
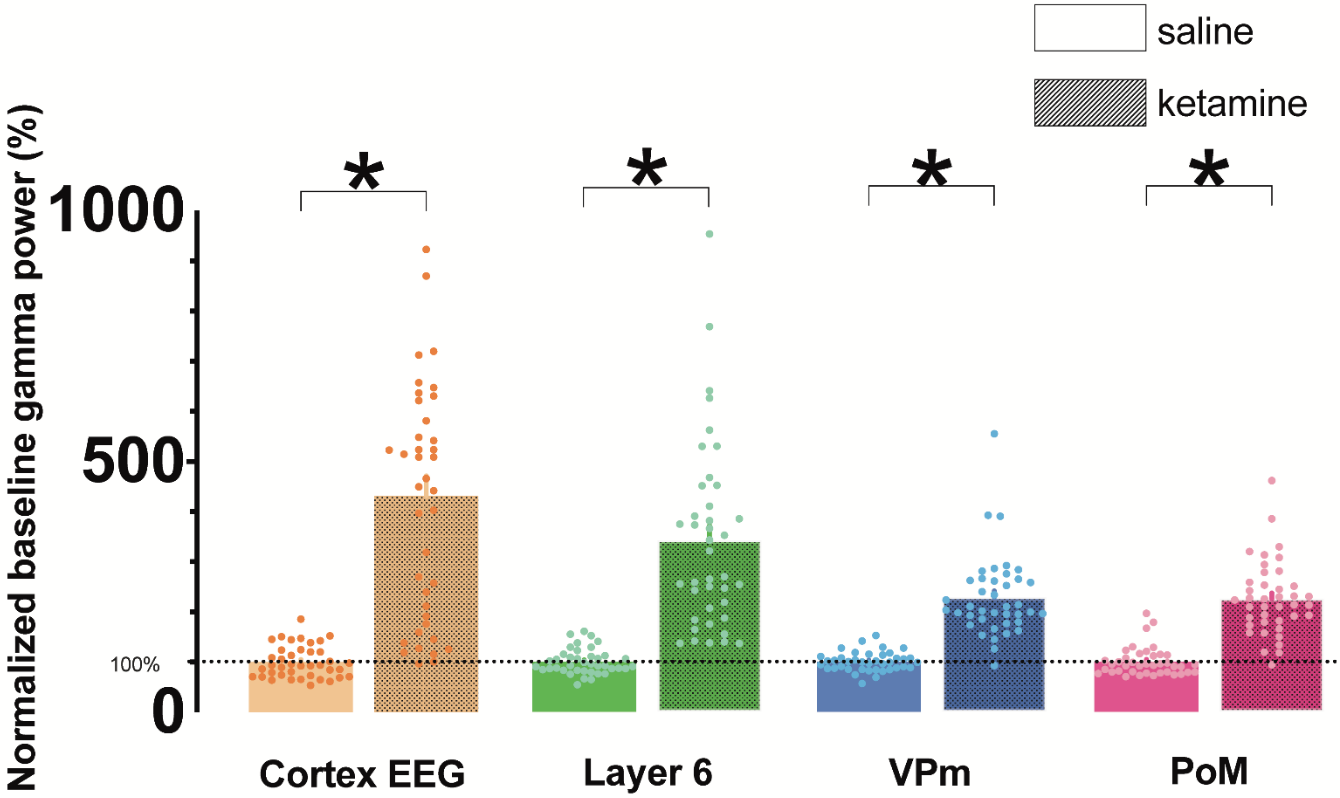


Figure 2. Ketamine elicits power changes of all frequency bands in the somatosensory thalamocortical network from 200 to 2700 ms. In the eight time-frequency heatmaps, each cell stands for average (from 40 values, 10 per rat, 4 rats) of the total power (normalized to pre-stimulus baseline) under the saline (A) and ketamine (B) conditions. Note that, under the ketamine condition, during the post-sensory stimulation 200-700 ms, the gamma power is not significantly changed. On the other hand, a significant gamma increase is recorded in the cortex 1700 ms after the sensory stimulation. VPm, medial part of the ventral posterior of the thalamus; PoM, medial part of the posterior complex of the thalamus. Asterisks when significant ($p < 0.05$, all: one-way ANOVA and Holm-Sidak test multiple comparisons. Check supplement for statistic results details).

Ketamine increases baseline and decreases induced gamma oscillations

Under the ketamine condition (Figure 2B), the power increase in sensory-related theta, sigma, and beta oscillations was still observed at all recording sites during the 200-700 ms post-stimulus period. However, this power increase was reduced from 700 to 1700 ms, especially in the theta and sigma frequency bands. Furthermore, gamma-frequency oscillations decreased in power during the 200-700 ms post-stimulus period in both the cortex (EEG and layer 6) and the thalamus (VPm and PoM). On the other hand, gamma oscillations increased during the 1700-2700 ms post-stimulus period only in the cortex.

To investigate further the effects of ketamine on sensory-related gamma oscillations, we first compared the baseline gamma recorded under the ketamine and saline conditions. At all recording sites, ketamine strongly increased the power of baseline gamma (S4, t-test with Welch's correction). We then compared sensory-related gamma oscillations recorded under the ketamine and saline conditions (Figure 3). Ketamine largely decreased the magnitude of these changes.



S4. Ketamine substantially increases in power baseline gamma oscillations. Each column stands for the average (± SEM, from 40 values, 10 per rats, 4 rats) of the normalized total power of gamma oscillations relative to saline baseline. Asterisks when significant (paired t-test, all P value < 0.0001, check supplement for statistic details).

Ketamine disrupts information transferability in the corticothalamic (CT) network

Ketamine decreased sensory-induced gamma oscillations at all recording cortical and thalamic sites during the 200-700 ms post-stimulus period (Figure 2B). This time lapse is long enough to encode, integrate, and perceive the incoming sensory signal (Rodriguez *et al.*, 1999). We hypothesized that ketamine can interrupt information processing during this period. To test it, we measured the uncertainty of information based on MSE in the gamma band during the 200-700 ms post-stimulus period (Figure 4). The measurement of entropy can be used as an estimation of “complexity” in physiological systems. Higher entropy means the system is likely in a more ”complex/dynamic” state (Costa *et al.*, 2005; Hager *et al.*, 2017). In Figure 4, we show that the entropy of the VPm and that of layer 6 were significantly increased along with different time scales. This indicates that the information contained in the VPm and layer 6 extracellular potential was biased toward a random or “noisy” state. No difference was observed in the PoM (Paired t-test, p<0.05).

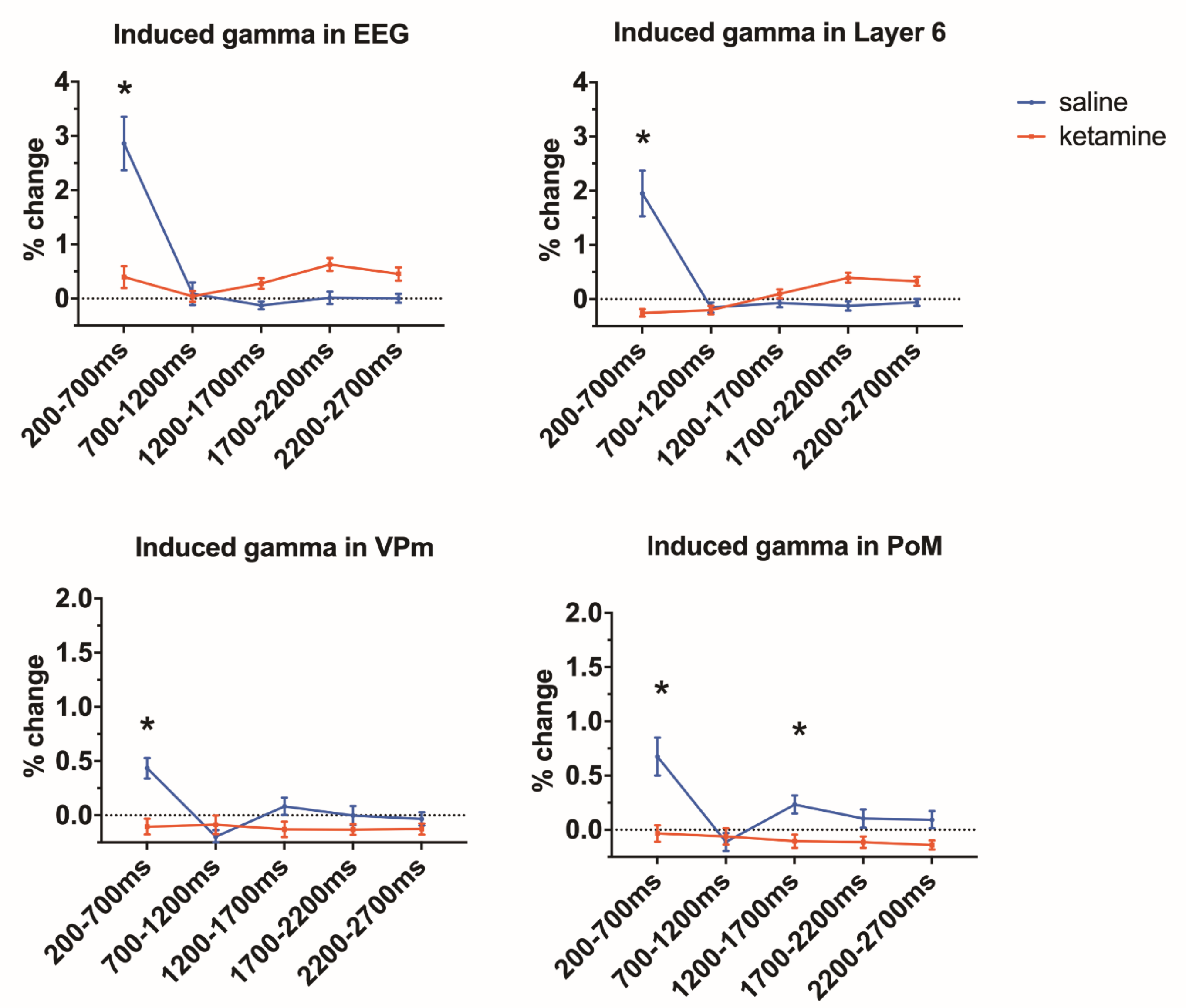


Figure 3. Ketamine decreases the power of sensory-induced gamma oscillations at 200-700 ms. The power of the induced gamma oscillations was obtained when subtracting the power of the baseline gamma from the power of the sensory-elicited total gamma. Each value (± SEM, from 40 values, 10 per rats, 4 rats) is the % change relative to the baseline gamma recorded before the sensory stimulation. Asterisks when significant (< 0.05, two-way ANOVA, corrected with Holm-Sidak, check supplement for details).

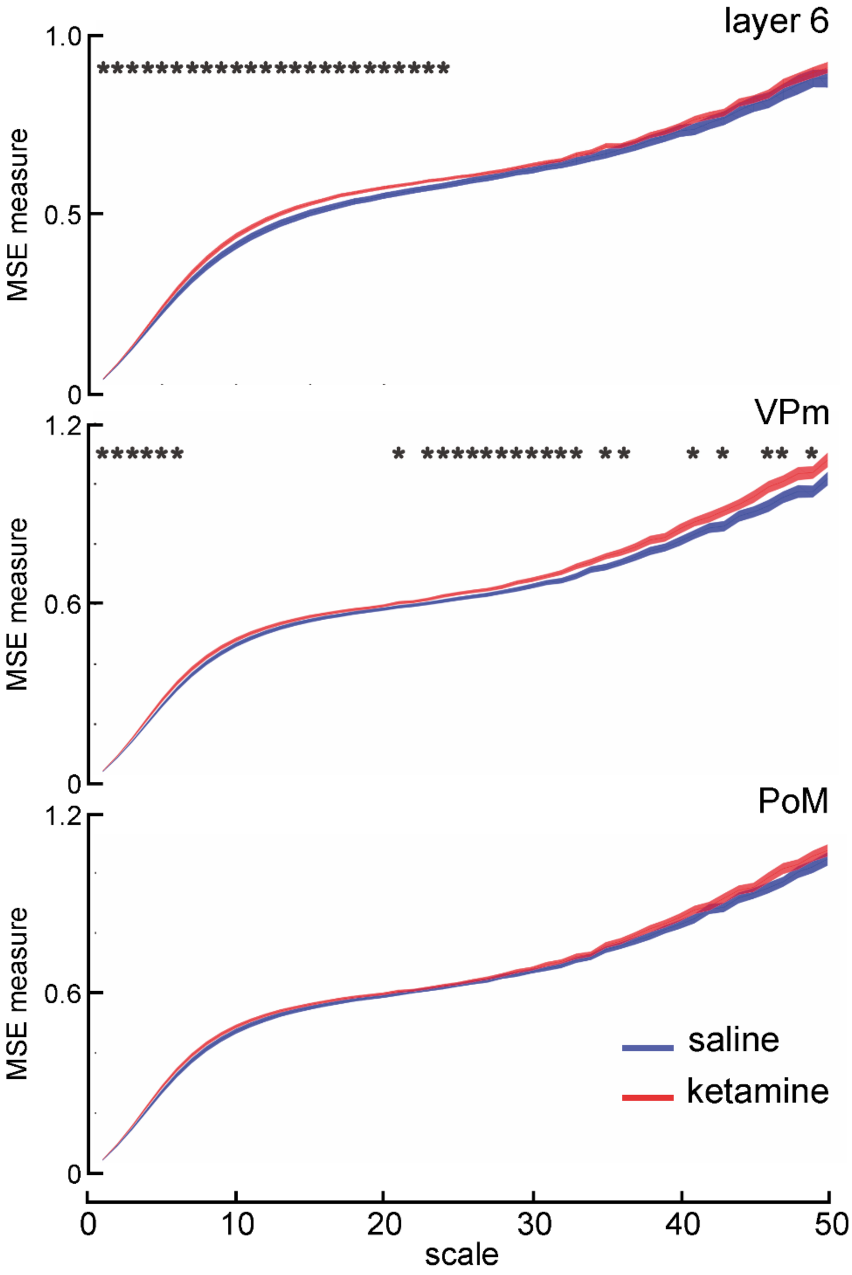


Figure 4. Ketamine increases multi-scale entropy of the VPm and layer 6. Comparison of the multi-scales entropies of saline (blue) and ketamine (red) conditions at all recording sites during the 200-700 ms post-stimulus period. Layer 6 and VPm show a significant increase in entropy. Each scale point is the average entropy (± SEM, from 40 values, 10 per rats, 4 rats). Asterisks when significant (< 0.05, paired t-test).

The present study shows that ketamine had a strong effect on information in the specific thalamic nucleus (VPm) and in the related layer 6, indicating that the connectivity of the whole network might also be dysfunctional. We used the coherence coefficient to measure the induced gamma-band connectivity between the VPm and layer 6. We applied the magnitude-squared coherence to measure similarities between two signals during the 200-700 ms post-stimulus period. We found that ketamine dramatically decreased (nearly 40 %) the coherence coefficient between layer 6 and the VPm. Furthermore, no significant change of coherence was observed between PoM and VPm, or layer 6 and PoM (Figure 5, Wilcoxon matched-pairs signed-rank test).

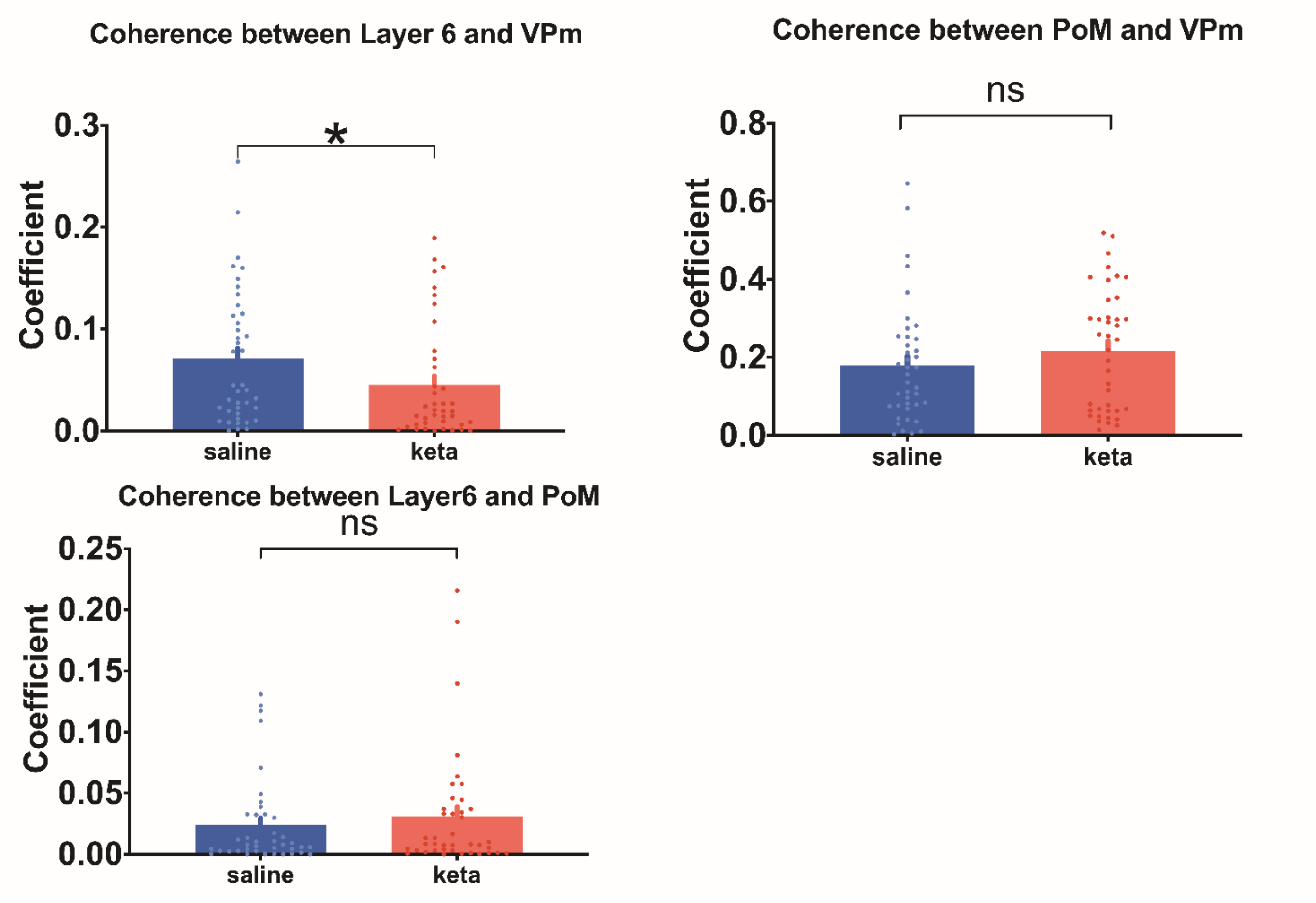


Figure 5. ketamine decreases coherence connectivity between layer 6 and VPm. Comparison of coherences connectivity of gamma band within CT-TC network under saline and ketamine conditions. Blue and red columns stand for the average coefficients (± SEM, from 40 values, 10 per rats, 4 rats) of the coherences of gamma oscillation in saline and ketamine conditions, respectively. Asterisks when significant (< 0.05).

DISCUSSION

The findings presented here demonstrate that the parietal CTC system significantly contributes to sensory stimulus-induced thalamic gamma frequency oscillations, which occur at the late post-stimulus stage (200-700 ms), and that the administration of the NMDA receptor antagonist ketamine disrupts the transfer of perceptual information in the system.

Low-dose ketamine decreases the signal-to-noise ratio.

In the lightly-anesthetized rat, vibrissae stimulation generates a wide-band frequency response in extracellular recordings simultaneously in the VPm, PoM, and in the related somatosensory cortex (layer 6). Theta- to sigma-frequency response activities were sustained across time (up to 1200-1700 ms) in both cortex and thalamus. On the other hand, the power (synchronization) in delta-frequency oscillations substantially increased only in the cortex (up to 1200 ms). This is not surprising because the experimental conditions (pentobarbital-induced sedation) force the brain to sleep (non-REM sleep), and knowing that the cortex is predominantly involved in the generation and transfer of delta waves to the dorsal thalamus (Murphy *et al.*, 2009; Knyazev, 2012; Urbain *et al.*, 2019). Notably, sensory-induced beta- and gamma-frequency oscillations were significantly decreased in a smaller post-stimulus time window (200-700 ms).

Under the ketamine condition, the sensory-related delta to sigma responses were attenuated in amplitude and duration, a finding that is coherent with the arousal-promoting effect of low-dose ketamine (Mahdavi *et al.*, 2020); the gamma responses were completely abolished during the post-stimulus 200-700 ms time window. On the other hand, the power of gamma oscillations started to increase beyond 1700 ms to retrieve power values of pre-stimulus spontaneous gamma activities. The ketamine-induced obliteration of the sensory stimulus-induced gamma at 200-700 ms may be the result of the ketamine-elicited abnormally and diffusely amplified basal gamma oscillations, which lead to disruption of information transferability in the somatosensory CTC system as assessed, in the present study, by an increase in MSE and a decrease in coherence connectivity in the specific CT system.

The fact that ketamine aberrantly and diffusely amplifies ongoing gamma oscillations at all recorded cortical and thalamic sites supports the concept that NMDA receptor hypofunction-related generalized gamma hypersynchronies represent an aberrant diffuse network noise that contributes to disrupting the ability of neural networks to process/integrate input signals. In other words, NMDA receptor antagonism decreases the signal-to-noise ratio (Hakami *et al.*, 2009; Gandal *et al.*, 2012; Kulikova *et al.*, 2012; Anderson *et al.*, 2017). The disruption of the transfer of sensory information would start to occur at least during the very first stages (up to ~15 ms) of information processing, that is, at the gate of cognitive processes (Briggs & Usrey, 2008; Kulikova *et al.*, 2012; Anderson *et al.*, 2017; Homma *et al.*, 2017). The aberrant diffuse network gamma noise may be a potential electrophysiological correlate of a psychosis-relevant state as increased gamma synchrony has been recorded in patients during somatic and visual hallucinations (Baldeweg *et al.*, 1998; Behrendt, 2003; Spencer *et al.*, 2004; Becker *et al.*, 2009) and, importantly, in clinically at-risk mental state patients for psychosis transition and naïve in antipsychotic medication (Ramyead *et al.*, 2015; Perrottelli *et al.*, 2021).

Ketamine-induced increase in randomness or complexity in a signal.

Our MSE results show that the sensory thalamic nuclei (VPm) and related layer 6 somatosensory cortex have increased sample entropy (i.e. complexity) following ketamine administration, which is consistent with previous studies on human patients with schizophrenia (Takahashi *et al.*, 2010). Of particular interest is that both layer 6 and the VPm showed increased MSE in the lower time scale factors, meaning those with the most detailed temporal information (i.e., with more high-frequency information incorporated in the complexity measure at these time scales). Interestingly, there is a tendency for younger, medication-free patients with higher positive symptoms to display higher levels of complexity in EEG (Fernandez *et al.*, 2013), a finding that matches our interpretation of ketamine administration to model a psychotic-like state. It has further been suggested that these increases in neural complexity measures are evidence for the "disconnection hypothesis" (Friston *et al.*, 2016) whereby disruption (aberrant or reduced) in connectivity increases EEG signal complexity (Takahashi *et al.*, 2010). In healthy humans submitted to a cognitive-visual task, ketamine increases the power of broadband gamma oscillations and disrupted feedforward and feedback signaling, leading to hypo- and hyper-connectivity in CTC networks (Grent-'t-Jong *et al.*, 2018).

Increased entropy may also be interpreted as an increase in "randomness" in a signal (with a truly random signal having maximal entropy (Ahmed & Mandic, 2011). Applying such an interpretation to our present results would reflect ketamine administration adding "noise" to the system increasing ongoing gamma power, resulting in a more random signal. The increased ongoing gamma power reflects an aberrant and pathological increase in non-relevant gamma activity that effectively attenuates sensory-related induced gamma interfering with its sensory transmission. This decreases the overall gamma signal-to-noise in the CTC system, disconnecting these areas and impairing sensory perception. Accompanying this disconnection hypothesis, we also observed a functional disconnection of phase coherence measures in the gamma frequency band between layer 6 and VPm, but not between PoM and layer 6 or VPm. This result supports the interpretation that sensory-generated gamma activity has been disrupted between cortex and thalamus under the ketamine condition. Disorders in the intrinsic properties (amplification/noise, complexity) and spatial dynamics (coherence) of gamma oscillations somehow reflect a fundamental disturbance of basic integrated brain network activities.

Possible underlying mechanisms.

The CTC system is involved in multiple integrative functions, including sensory, perceptual, and attentional processing (Pinault, 2004; Van Essen, 2005; Wolff *et al.*, 2021). Sensory-to-perceptual responses of the CTC system result from dynamic interactions between TC (bottom-up) and CT (top-down) processing (Alitto & Usrey, 2003; Briggs & Usrey, 2008; Homma *et al.*, 2017). Both TC and CT pathways are glutamatergic. In thalamic neurons, the response pattern depends on the brain state (Castro-Alamancos, 2002; Urbain *et al.*, 2015) and thalamic GABAergic inhibition mediated principally by the external source thalamic reticular nucleus (TRN) (Pinault, 2004). Under the present experimental sleep conditions, almost all the thalamic glutamatergic and GABAergic neurons are hyperpolarized and fire in the burst mode (Pinault *et al.*, 2006; Mahdavi *et al.*, 2020), and the arousal promoting effect of ketamine switches the spontaneous firing pattern of both the glutamatergic TC and the GABAergic TRN neurons from the burst to the tonic mode (Mahdavi *et al.*, 2020).

The post-inhibitory rebound excitation is a cellular intrinsic property, which occurs during physiological and pathological brain oscillations or following the activation of prethalamic (e.g., sensory) or cortical inputs. For instance, during slow-wave sleep, a long-lasting hyperpolarization gives rise, in the thalamic relay and reticular neurons, to a rebound excitation caused by a low-threshold calcium-dependent potential, de-inactivated by membrane hyperpolarization, and can be topped by a high-frequency burst of action potentials (Deschenes *et al.*, 1984; Jahnsen & Llinas, 1984; Llinas, 1988; Grenier *et al.*, 1998; Urbain *et al.*, 2019). Such a post-inhibitory rebound excitation is also recorded under anesthesia in TC neurons following the activation of prethalamic or cortical inputs (Deschenes *et al.*, 1984; Grenier *et al.*, 1998). There is evidence that TC bursting may serve as a “wake-up call” in the initiation of perceptual/attentional processes (Sherman, 2001; Swadlow & Gusev, 2001). Two potential mechanisms of the effect of the NMDA receptor antagonist ketamine could be responsible alone or in combination: 1) reduced TRN-mediated inhibition (see discussion by Mahdavi et al, 2020), and 2) a reduction of the hyperpolarization-activated cationic current Ih (Kim & Johnston, 2020). Of course, ketamine also acts at multiple cortical and subcortical structures, and there is increasing evidence that it suppresses the activity of GABAergic interneurons leading to disinhibition of glutamatergic neurons (Homayoun & Moghaddam, 2007; Ali *et al.*, 2020).

The late (200-700 ms post-stimulus) sensory-induced gamma oscillations were, on average, measurable in the sedated rat. These late response activities would be involved in the perceptual process (Funayama *et al.*, 2015). In sedated rats, the level of perception and the underlying neural activities are expected to be attenuated because of the presence of rhythmic GABAergic mediated inhibitions at least in the delta- and sigma-frequency bands (slow-wave sleep with spindles). Ketamine, by reducing the slow waves, spindles, and burst activities, depolarizes and switches the burst firing pattern to the irregular tonic mode (Mahdavi *et al.*, 2020). This means that ketamine brings a persistent depolarizing pressure to the membrane potential (persistent UP state) of the glutamatergic and GABAergic neurons, which is expected to disrupt the tonic firing pattern associated with a sensory-perceptual process. Moreover, it was demonstrated that, in the rat, NMDA receptor antagonism disrupts synchronization of action potential firing in the prefrontal cortex, which would lead to a disruption of the transfer of information processing dependent on the timing of action potentials (Molina *et al.*, 2014).

Downsides and upsides.

As the experiments were performed in the pentobarbital-sedated rat (non-REM sleep model), the present findings do not allow drawing definitive conclusions. However, the combined two models, one for the brain state (sleep model) and one for the ketamine psychosis-relevant challenge (Mahdavi *et al.*, 2020), provide interesting tools to conceptually and mechanistically advance in the understanding of the neurobiology of psychotic disorders. The major requirement of the present study was to have the equivalent of a stationary stage II non-REM sleep, during which we could perform repeated measures. Furthermore, under the present experimental conditions, a single systemic administration of ketamine at a psychotomimetic dose (2.5 mg/kg, estimated from a study conducted in free-behaving rats (Pinault, 2008) induces most of the oscillopathies (especially basal gamma hyperactivity and delta/spindle hypoactivity) recorded in patients having psychotic disorders (Mahdavi *et al.*, 2020). One advantage of the pentobarbital-induced sedation was its relative stability over time allowing repeated measures.

Under the present experimental conditions, the degree of perception and attention would have been weakened because the pentobarbital induces a slow-wave sleep with spindle-like activities by increasing the GABAergic neurotransmission (Maldifassi *et al.*, 2016). In short, the experimental conditions, which promote cortical slow waves (Pinault *et al.*, 2006; Murphy *et al.*, 2009; Knyazev, 2012; Urbain *et al.*, 2019), would have prevented or attenuated the full corticalization of sensory-perception processing and, subsequently the full implication of the CT (feedback) and cortico-cortical (feedforward) pathways. However, the CTC system, which includes the TRN (Pinault, 2004), is functionally polyvalent in a state-dependent way as it is involved in sensory-perception processing (Saalmann & Kastner, 2011), the wake-sleep brain oscillations (Steriade *et al.*, 1993), and in attention-sensory processes (Chen *et al.*, 2015; Wimmer *et al.*, 2015). So, it is not surprising that the highly distributed CTC systems play a central role in the disorders of sleep integrity, sensorimotor, perception, and attentional processes observed in patients with psychotic disorders (Steriade *et al.*, 1993; Shipp, 2004; Ferrarelli & Tononi, 2011; Pinault, 2011; Chen *et al.*, 2015; Wolff *et al.*, 2021).

Conclusion and perspectives.

The present results provide anatomo-functional relevance to understanding the neural dynamics underlying ketamine-induced impairment of encoding processes (Hetem *et al.*, 2000), perception-related (feedforward and feedback) dysconnectivity, and abnormal amplification of gamma oscillations in human CTC systems (Driesen *et al.*, 2013; Anticevic *et al.*, 2014; Hoflich *et al.*, 2015; Rivolta *et al.*, 2015; Grent-'t-Jong *et al.*, 2018). The NMDA receptor hypofunction-related gamma hypersynchronies (power increases) are neurophysiological abnormalities that may represent a core biological feature of the psychotic transition. Although the interpretation of measures using complexity estimators (like MSE) of neural signals is not simple, in recent years there is accumulating evidence that increased and abnormal complexity may also be a hallmark of psychosis (Fernandez *et al.*, 2013; Yang *et al.*, 2015; Ibanez-Molina *et al.*, 2018). Abnormal and diffuse amplification of spontaneously-occurring broadband gamma oscillations in neural networks (gamma noise) associated with reductions in sensory-related, evoked, and induced gamma-band responses (gamma signal) are potentially predictive translational biomarkers of psychosis transition (Hakami *et al.*, 2009; Gandal *et al.*, 2012; Kulikova *et al.*, 2012; Anderson *et al.*, 2017). The sensory-evoked potential is also an appropriate index to evaluate the expression of the plasticity of neural circuits (Kulikova *et al.*, 2012). Because of their spatio-temporal structure and stereotyped pattern, sensory-evoked and induced gamma oscillations represent potential reliable and suitable variables (Spencer *et al.*, 2008; Hong *et al.*, 2010; Leicht *et al.*, 2016; Tada *et al.*, 2016; Reilly *et al.*, 2018) for the development of innovative therapies preventing the psychotic transition.

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DISCLOSURES

All authors have approved the final version of the article. The authors report no competing biomedical financial interests or potential conflicts of interest.

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