The N-Methyl D-Aspartate Glutamate Receptor Antagonist Ketamine Disrupts the Functional State of the Corticothalamic Pathway

Paul M. Anderson¹,²,³,⁴, Nigel C. Jones³, Terence J. O’Brien³ and Didier Pinault¹,²

¹Neuropsychologie cognitive et physiopathologie de la schizophrénie, INSERM U1114, Strasbourg, France, ²FMTS, Faculté de Médecine, Université de Strasbourg, Strasbourg, France, ³Department of Medicine, Royal Melbourne Hospital, University of Melbourne, Parkville, VIC, Australia and ⁴Current address: Department of Cognitive Neuroscience, Radboud University Medical Centre, Nijmegen, The Netherlands

Abstract

The non-competitive N-methyl D-aspartate glutamate receptor (NMDAR) antagonist ketamine elicits a brain state resembling high-risk states for developing psychosis and early stages of schizophrenia characterized by sensory and cognitive deficits and aberrant ongoing gamma (30–80 Hz) oscillations in cortical and subcortical structures, including the thalamus. The underlying mechanisms are unknown. The goal of the present study was to determine whether a ketamine-induced psychotic-relevant state disturbs the functional state of the corticothalamic (CT) pathway. Multisite field recordings were performed in the somatosensory CT system of the sedated rat. Baseline activity was challenged by activation of vibrissa-related prethalamic inputs. The sensory-evoked thalamic response was characterized by a short-latency (∼4 ms) prethalamic-mediated negative sharp potential and a longer latency (∼10 ms) CT-mediated negative potential. Following a single subcutaneous injection of ketamine (2.5 mg/kg), spontaneously occurring and sensory-evoked thalamic gamma oscillations increased and decreased in power, respectively. The power of the sensory-related gamma oscillations was positively correlated with both the amplitude and the area under the curve of the corresponding CT potential but not with the prethalamic potential. The present results show that the layer VI CT pathway significantly contributes in thalamic gamma oscillations, and they support the hypothesis that reduced NMDAR activation disturbs the functional state of CT and corticocortical networks.

Key words: electrophysiology, gamma oscillations, network noise, schizophrenia, sensory-evoked potential

Introduction

In schizophrenia, disorders in sensorimotor and cognitive information processing are associated with dysfunctional brain circuits, including corticocortical and corticothalamic (CT) networks (Clinton and Meador-Woodruff 2004; Cronenwett and Csernansky 2010; Pinault 2011; Zhang et al. 2014), which exhibit disturbed gamma-frequency (30–80 Hz) oscillations (GFOs; Spencer et al. 2004; Herrmann and Demiralp 2005; Uhlhaas and Singer 2006; Stephan et al. 2009; Uhlhaas et al. 2013). The underlying mechanisms are the object of intensive studies testing the N-methyl D-aspartate glutamate receptor (NMDAR) hypofunction hypothesis of schizophrenia. In healthy subjects, a single injection of a subanesthetic dose of the noncompetitive NMDAR antagonist ketamine induces cognitive deficits and schizophreniaiform psychosis (Krystal et al. 1994; Hetem et al. 2000; Corlett et al. 2007). These ketamine-elicited effects are associated with a state of functional hyperconnectivity, which models high-risk mental states for developing psychosis and early stages of
schizophrenia (Driesen et al. 2013; Anticevic et al. 2014). Furthermore, ketamine increases the power of GFO and decreases slower oscillations during both the resting state (Rivolta et al. 2015) and the auditory-evoked network oscillations (Hong et al. 2010), as predicted by comprehensive preclinical studies (Ma and Leung 2007, Pinault 2008; Ehrlichman et al. 2009; Hakami et al. 2009; Kocsis 2012; Wood et al. 2012). In addition, ketamine increases functional connectivity in the thalamus and of CT pathways originating from the somatosensory cortex (Höflich et al. 2015). The neural dynamics underlying the acute effects of ketamine are yet to be elucidated. In the rat somatosensory thalamocortical (TC) system, ketamine increases the power of resting-state baseline GFO (Pinault 2008; Hakami et al. 2009) and coincidently decreases both the power of sensory-evoked TC-mediated cortical GFO and the synaptic potentiation at TC synapses (Kulikova et al. 2012). These findings support the hypothesis that psychotic-relevant states impair the ability of the CT–TC system to encode and integrate incoming/relevant sensory signals from the persistent network gamma hyperactivity. It was further demonstrated that the power of sensory-evoked TC-mediated cortical GFO is positively correlated with the amplitude of the corresponding cortical potential, indicating that sensory-evoked GFO represents a “true” sensory-related component at least during the very first stage (100-ms poststimulus epoch) of information processing. The cortical GFO must also involve the activation of multisynaptic corticocortical and corticofugal pathways, including CT axons that originate from layer VI and massively innervate both the dorsal thalamus (principally composed of glutamatergic TC neurons) and the GABAergic thalamic reticular nucleus (TRN; Bourassa et al. 1995; Zhang and Deschênes 1997), the only source of inhibition of the rodent somatosensory thalamus. The goal of the present study was to determine whether ketamine alters the functional state of the CT pathway.

For this purpose, we investigated the rat somatosensory layer VI CT–TRN–TC circuit, an appropriate three-neuron circuit, common in all sensory systems (Alitto and Usrey 2003), to understand the neurodynamics occurring during the first stages of information processing, that is, at the gate of cognitive processes. Paired cortex–thalamus extracellular local field potentials (LFPs) combined with sensory stimulation were performed in sedated (resting-wakefulness) rats to identify the different components of thalamic sensory-evoked potentials (SEPs). Cortical application of tetrodotoxin (TTX), a blocker of sodium-dependent activities, was used to reduce or block the CT component in the thalamic SEP. This component was used to assess the impact of a single subcutaneous administration of ketamine, at a subanesthetic dose (2.5 mg/kg), on the functional state of the CT pathway.

Materials and Methods

Animals

Twenty-four adult (3–6-month-old) male Wistar rats (347 ± 10 g) were used in accordance with European Union Guidelines (directive 2010/63/EU) and with the approval of the National and Regional Ethics Committee (Comité Regional d’Éthique en Matière d’Expérimentation Animale, Université de Strasbourg).

Surgery and Sedation

The surgical procedures were performed under deep general pentobarbital (40 mg/kg, intraperitoneal)–ketamine (45 mg/kg, intramuscular) anesthesia. The trachea was cannulated and connected to a ventilator (50% air–50% O₂, 60 breaths/min). The rectal temperature was maintained at 37 °C using a thermoregulated pad. Animals were placed in a stereotaxic frame and a micro-cranioduratomy (Pinault 2005) was performed for the insertion of the recording micropipettes. Surface electrocorticogram (ECOG) recordings of the frontoparietal somatosensory cortex (relative to bregma: posterior 2.3 mm and lateral 5 mm) were done with Ag/AgCl wires (diameter 150 µm) insulated with Teflon, their section being in contact with the inner plate of the bone. The ear bars had a foam tip and their interauricular pressure was relaxed after the surgery to alleviate stress.

The sedation was initiated about 2 h 30 min after the beginning of the general anesthesia, that is, when the rat started to recover (reflex response when pinching the hind paw). It was induced and maintained by a continuous intravenous injection (0.29 ± 0.01 mL/h, 20 rats) of the following mixture (average quantity given per kg and per hour, 20 rats): 1.93 ± 0.07 µg fentanyl, 193.3 ± 6.7 µg haloperidol, and 48.3 ± 1.7 mg glucose. Muscle rigidity and tremors were blocked with δ-tubocurarine chloride (0.75 ± 0.03 mg/h). The ECoG and heart rate were under continuous monitoring to adjust the level of sedation–analgesia, which was considered adequate when the ECoG displayed desynchronized and synchronized episodes (Pinault et al. 2001).

Because the neuroleptic haloperidol partially reduces the power of both the baseline GFO and the ketamine-induced increase in the power of baseline GFO (Jones et al. 2012), 4 experiments were done under pentobarbital–fentanyl sedation as used in pediatric patients undergoing MRI investigation (Connor et al. 2003). Pentobarbital was administered intravenously at a subanesthetic dose (0.71 ± 0.06 mg/kg/h, 4 rats) with fentanyl (2.01 ± 0.20 µg/kg/h) and δ-tubocurarine chloride (0.60 ± 0.03 mg/kg/h). Under this experimental condition, in all 4 rats, the somatosensory system exhibited desynchronized and synchronized episodes similar to those recorded in free-moving resting-state and neuroleptanalgesic-sedated rats.

The recordings started 2–3 h after the induction of the sedation–analgesia.

Electrophysiology

Glass micropipettes (pulled from 1.5 mm glass capillaries) were used to record extracellular LFP and multunit activity in the medial part of the somatosensory ventral posterior nucleus (VPM; stereotaxic coordinates (Paxinos and Watson 1998): bregma –3.2 mm, lateral 2.8 mm, depth 5–5.8 mm below the cortical surface), in the postero medial complex (PoM: bregma –3.6 mm, lateral 2.2 mm, depth 4.8–5.6 mm below the cortical surface), in the motor ventral lateral (VL) nucleus of the thalamus (VL: bregma –2.2 mm, lateral 2 mm, depth 5.5–5.5 mm below the cortical surface), in the TRN (bregma –2.5–3.2 mm, lateral 3.5–3.7 mm, depth 4.4–5.6 mm), and in the layer VI (depth 1.6–2.0 mm) of the somatosensory (vibrissa-related) cortex. The micropipettes were filled with artificial cerebrospinal fluid (ACSF) and neurobiotin (1.5%) and had a tip diameter of 5–10 µm and a resistance of 0.5–1.0 MΩ. Glass micropipettes or quartz/platinum–iridium fiber electrodes (Thomas Recording, GmbH) were used for layer VI recordings (Fig. 1A,D1). Multisite LFP recordings (bandpass: 0.1–5 kHz) were done along with the ECoG (0.1–800 Hz) with low-noise differential amplifiers (DPA-2FL, npi electronic GmbH). All signals were sampled at 20 kHz 16-bit (Digidata 1440A with pClAMP10 Software, Molecular Devices). The recording sites were first electrophysiologically identified on the basis of their receptive field (vibrissae) then anatomically following multunit juxtacellular labeling (Pinault 1996) with neurobiotin.
performed at the end of the recording sessions (Fig. 1). 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, ~2 mA; frequency: 0.1 Hz).

**Pharmacology**

Recordings were made under the 2 pharmacological conditions, saline (vehicle) control (1 mL/kg, subcutaneous, s.c.) and then ketamine (2.5 mg/kg, s.c.). The open area (about 1 mm²) of the somatosensory vibrissae-related cortex was preserved using

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**Figure 1.** Characteristics of the thalamic and cortical sensory-evoked potentials. (A) Simplified hodology of the somatosensory vibrissae-related TC–CT pathways and experimental design showing the location of the recording electrodes. Also shown is the sensory stimulation (sens stim) of the vibrissae, which activates the lemniscal (lm) inputs of the somatosensory part of the thalamus (medial part of the VPm). (B) Sensory-evoked potentials (SEPs) recorded in the cortex and thalamus along with the surface ECoG. For each location, from top to bottom: averaged SEP (15 trials), a single trial, and a drawing of the action potentials of the larger unit detected in the corresponding trials. (C) The waveform of the thalamic SEP varies with the stereotaxic location of the recording electrode in the thalamus. The thalamic SEP includes 2 principal, early and late negative-going potentials. The micro-photographs of the histological coronal 100-µm thick sections show the neuronal labeling with neurobiotin left by the recording micropipettes (following extracellular iontophoresis) in the cortical (layer VI), TRN, and in the VPm at the end of the recording session. The recording sites are indicated by the arrows. (D) Experimental design showing multisite thalamic (VPm and PoM) and cortical (ECoG and layer VI) recordings in the rat somatosensory system. The vibrissae are stimulated every 15 s (sens stim). The VPm and PoM receive lemniscal (lm) and para-lemniscal (plm) inputs, respectively. (D2) Staining of the recording sites following extracellular iontophoretic application of neurobiotin at the end of the recording session. (D3) Blood track left by the recording quartz/platinum–iridium fiber electrode into the primary somatosensory cortex. The green arrow indicates the location of the electrode tip (depth from the cortical surface = 2.555 mm). (D4) Sensory-evoked potentials recorded at all sites, indicating that they are located in the same functional register. A–C are from neurolept-sedated rats and D1–D4 from pentobarbital sedated rats. Brg, bregma; CPu, caudate–putamen; HPC, hippocampus; IC, internal capsule; LD, lateral dorsal; MD, medial dorsal; PoM, medial part of the posterior group of the thalamus; VM, ventral median; VPI, lateral part of the ventral posterior nucleus of the thalamus; WM, white matter.
ACSF-impregnated surgical gelatin sponges. To interrupt sodium current-dependent cortical activities, ACSF was replaced by TTX (100 μM) in ACSF.

Data Analysis
Data analysis was performed with Clampfit 10, Matlab (Mathworks), and SciWorks, v8 (Datawave Technologies) software packages. Action potentials were detected on the basis of their waveform. Spectral analysis of ongoing spontaneously occurring activity was performed with fast Fourier transformation at a resolution of 2.5 Hz (Hamming window). The power of baseline activity was analyzed in 4 frequency bands: slow- (1–14 Hz), beta- (16–29 Hz), gamma- (30–80 Hz), and higher-frequency oscillations (81–250 Hz). In a band, the total power was calculated as the sum of all power values within the frequency range. The time course of gamma-frequency changes was calculated using gamma power in 2-min blocks, then normalizing all data to the mean gamma power in the 20-min saline control condition and expressing all values as a percentage of this.

For sensory-evoked calculations, time–frequency analysis was performed on 1-s long epochs, extracted from the continuous data, and centered on the time of stimulation. Epochs were visually inspected for artifacts and slow-wave activity; only trials occurring during a desynchronized state were used for analysis. Amplitude, latency, and area under the curve (AUC) of sensory-evoked responses in the thalamus were calculated by determining the minimal voltage and the absolute value of the area below the baseline (using the 100-ms period before stimulus onset) in 2 windows 1–7 ms poststimulus for the “early” and 7–15 ms poststimulus for the “late” response. The same process was used in the cortical recordings using the absolute area above and area below the curve and identifying minima and maxima across a single window, 3–25 ms poststimulus.

Spectral power was calculated for all trials using the newtimef function from the EEGLAB Matlab toolbox (Delorme and Makeig 2004; Kulikova et al. 2012). Morlet wavelets were used in 80 evenly spaced frequency bands from 20 to 100 Hz, with wavelet cycles ranging from 3 at the lowest frequency to 10 at the highest frequency. Baseline GFO power was calculated for each individual trial as the average power in the gamma-frequency range from 100 ms before stimulus onset. Evoked GFO power was calculated in the span 0–100 ms poststimulus. Gamma signal was defined as the per trial difference between the evoked and baseline gamma power (i.e., gamma signal = evoked gamma – baseline gamma).

Gamma power measures were averaged into minute blocks (6 data points). Correlation between gamma signal and the amplitude and AUC of the “early” and “late” thalamic responses was calculated using Pearson’s correlation between the mean thalamic gamma signal and the mean late amplitude of all recordings. Drug condition means were calculated using the period 10–20 min post-drug administration (60 data points). Statistical significance of the observed effects was evaluated with ANOVA, Student’s t-test, and Wilcoxon signed-ranked test performed in Prism 6 (GraphPad Software); spectral power and specific frequency bands were compared using the nonparametric statistical Wilcoxon signed-ranked tests as the normality of the distribution of spectral power cannot be assumed (Korotkova et al. 2010).

Results
All data analyses were restricted to ECoG episodes exhibiting desynchronized oscillations, which were most comparable to those recorded in nonanesthetized, resting-state animals (Pinault 2008; Hakami et al. 2009; Kulikova et al. 2012). Desynchronized bouts of ECoG typically contain GFO and are a cortical state typically observed in awake, behaving animals (Pinault 2008; Hakami et al. 2009; Ahmed and Cash 2013). Furthermore, neural responses to repeated sensory stimuli display less adaptation while in a desynchronized condition making it an ideal condition for studying neural responses to recurrent sensory stimuli (Harris and Thiele 2011), which was the case in the present study.

Characteristics of the Thalamic and Cortical Sensory-Evoked Potentials
To evaluate the functional state of the CT pathway, paired recordings were conducted in the primary somatosensory system at both ends of the CT pathway, that is, in the VPM and layer VI, along with the ECoG (Fig. 1A). Both the ECoG and the layer VI SEPs were biphasic and stereotyped across trials and individuals. The ECoG SEP had a positive potential component (P1 peak at 9.50 ± 0.08 ms, Table 1) followed by a negative potential component (N1 peak at 15.79 ± 0.03 ms), and the layer VI SEP had 2 successive, negative (N1 peak at 8.77 ± 0.05 ms) and positive (P1 peak at 17.26 ± 0.08 ms) potentials. The layer VI N1 potential was, in contrast to the following P1 potential, often accompanied with single-unit or multiunit firing (Fig. 1B), suggesting that the N1 potential corresponded to intracortical excitation while the P1 potential to intracortical inhibition.

The thalamic (VPM) SEP had 3 components (Fig. 1B): A short-latency negative-going potential (“early” component: 3.74 ± 0.01 ms, Table 1), medium-latency positive potential (measurable in 9 of 13 rats: 5.75 ± 0.05 ms), and long-latency negative potential (“late” component: 10.30 ± 0.05 ms). The early component, triggered by presynaptic synchronized lemniscal volleys—indicated by a miniature negative potential that appeared just before the early negative component (Fig. 1B and also see Fig. 5B)—systematically preceded the layer VI negative N1 potential. The second thalamic positive and third (late) negative components resulted from multisynaptic activities. Single- or multiunit firings could be recorded in the trough of the 2, early and late, negative components (Fig. 1B) and never during the intermediary positive component, suggesting that this positive potential component reflected in part a TC–TRN-driven GABAergic-mediated feedback

Table 1 Peak latencies in milliseconds (mean ± SEM, >100 values/rat) of the thalamic and cortical (bold values) SEP components (n = number of rats)

<table>
<thead>
<tr>
<th></th>
<th>VPM (n = 13)</th>
<th>PoM (n = 4)</th>
<th>TRN (n = 5)</th>
<th>VL (n = 3)</th>
<th>ECoG (n = 13)</th>
<th>Layer VI (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early N1</td>
<td>3.74 ± 0.01</td>
<td>3.58 ± 0.03</td>
<td>3.17 ± 0.01</td>
<td>4.08 ± 0.04</td>
<td>NA</td>
<td>8.77 ± 0.05</td>
</tr>
<tr>
<td>Early P1</td>
<td>5.78 ± 0.05</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>9.50 ± 0.08</td>
<td>17.26 ± 0.08</td>
</tr>
<tr>
<td>Late N2</td>
<td>10.30 ± 0.05</td>
<td>11.48 ± 0.16</td>
<td>10.90 ± 0.03</td>
<td>9.36 ± 0.05</td>
<td>15.79 ± 0.03</td>
<td>NA</td>
</tr>
</tbody>
</table>

Note: N and P for negative- and positive-going components, respectively, of the sensory-evoked potentials. The data are from both neurolept (VPM, TRN, VL, ECoG, and layer VI) and pentobarbital (VPM, PoM, ECoG, and layer VI) sedations.
NA, not available (unmeasurable component).
and/or lateral inhibition. The peak latencies measured from recordings (at least from VPm) performed under the neurolept and pentobarbital sedations are statistically not different (see Supplementary Table 1).

The respective amplitudes of the 3 thalamic components varied as a function of the location of the recording electrodes (Fig. 1C). Both the temporal order of the sensory-evoked thalamic and cortical potentials (Table 1) and our knowledge of the hodology of the neural pathways that make the CT–TC system (Guillery et al. 1998; Crabtree 1999) give strong support to the idea that the thalamic late negative component (at ∼10 ms) was initiated by CT neurons.

Knowing that the CT pathway that originates from layer VI innervates both the TRN and the dorsal thalamus, including the PoM in a topographic manner (Crabtree 1999; Pinault 2004), we expected to record a multicomponent SEP in both the TRN and the PoM roughly similar in waveform to that recorded in the VPm. This was indeed the case, with 2 successive, early (TRN: 3.17 ± 0.01 ms; PoM: 3.58 ± 0.03 ms; see Supplementary Table 1) and late (TRN: 10.90 ± 0.03 ms; PoM: 11.48 ± 0.16 ms), negative-going components (Fig. 18C,D). These 2 negative potentials could be associated with firing, suggesting that they were not the result of volume conduction of remote thalamic field potentials. Their peak latencies were not significantly (two-way ANOVA, effect of sedation F_{1,72} = 0.33, P = 0.56) different from those of VPm neurons (Table 1). Therefore, on the basis of our anatomical knowledge, the TRN early negative potential was, like for the VPm, triggered by synchronized TC volleys and the late negative component by CT volleys. In PoM recordings, the early negative-going component was triggered by the paralemniscal, whereas the late component (at ∼10 ms) was triggered by the CT feedback.

TTX Effect on the Sensory-Evoked Cortical and Thalamic Field Potentials

To determine whether the thalamic late SEP-negative component was actually due to a CT feedback, cortical sodium-dependent activities were blocked following local application onto the cortical surface of TTX, which then progressively diffuse into deep layers (Fig. 2A1). These experiments were done in rats sedated with the neurolept–fentanyl protocol. Under the TTX condition, spontaneously occurring layer VI and thalamic firings (when detectable in the LFP) were significantly reduced but much more in layer VI than in thalamic neurons (−80–100% vs. 30–50%, Fig. 2A2). The decreased firing of thalamic neurons is likely due to the dramatic decrease in the firing of cortical, including CT, neurons. The amplitudes of ECoG and layer VI SEPs were almost completely abolished following TTX application (Fig. 2B1,C1,D1). The residual small-amplitude potentials were likely the result of volume conducted evoked potentials at remote cortical areas. Of importance, in the VPm, only the late negative-going component was, likewise, almost completely abolished (Fig. 2A3,B2,C2,D2).

It is well known that the layer VI CT pathway of the somatosensory system innervates, in a topographic manner, large territories in the somatosensory thalamus (Murphy et al. 1999; Rouiller and Welker 2000; Guillery and Sherman 2002). Also, layer VI contains a significant population of corticocortical neurons innervating motor cortical areas (Zhang and Deschênes 1998), which in turn innervate the motor thalamic (VL) nucleus (Aldes 1988). So, we performed a series of experiments [under the neurolept sedation] designed to record LFP activities simultaneously in the VPm and VL along with the surface ECoG (Fig. 2A1). The location of the recording sites was identified histologically after extracranial application of the neuronal tracer neurobiotin (not shown). Following the sensory stimulation, the VL exhibited an early (4.08 ± 0.04 ms, Table 1) and a late (9.36 ± 0.05 ms) negative-going potentials followed by a long-lasting positive potential (Fig. 2B2). The latencies of the VL early- and late negative potentials were not significantly different with those of the VPm (Table 1; early: P = 0.457, late: P = 0.248, two-way repeated-measures ANOVA). Following TTX cortical application, the mean amplitude of the VL early component showed, when measurable, no discernible effect, whereas that of the late component was slightly reduced (Fig. 2B2,C2,D2). Two-way ANOVA showed no effect of drug on the early response, but the location was statistically significant (F_{1,8} = 11.09, P < 0.05). For the late response, both drug (F_{1,8} = 18.35, P < 0.005) and location (F_{1,8} = 6.89, P < 0.05) were significant effects, with post hoc tests showing the late VPm response was different (P < 0.05, Bonferroni’s multiple comparisons). Two-way ANOVA of the amplitudes of the sensory-evoked cortical responses in the period 10–20 ms after TTX or ACSF application showed significant effects for drug on both early and late responses (F_{1,15} = 12.19, P < 0.005 and F_{1,15} = 25.10, P < 0.0001 for early and late effects, respectively). Post hoc tests showed significant differences in the layer VI LFP amplitude at both early and late responses and significant changes only in the late response in the frontoparietal ECoG (P < 0.05, Bonferroni’s multiple comparisons).

To sum up, TTX blockade of cortical sodium-dependent activity, combined with simultaneous recordings in the thalamic somatosensory and motor nuclei, revealed converging evidence indicating that the thalamic late negative component (at ∼10 ms) was initiated by CT neurons.

Contribution of the CT Pathway in Thalamic Sensory-Evoked Gamma Oscillations

Then, we investigated the impact of TTX cortical application on the CT pathway in the somatosensory thalamus through time-frequency analysis of the cortical and thalamic SEP. Using Morlet wavelet decomposition of the LFP and ECoG recordings, we assessed the effects of TTX application on sensory-evoked gamma signals (Fig. 3A). Unsurprisingly, TTX markedly decreased the power of both the ongoing and the sensory-evoked (signal) gamma-frequency activities recorded simultaneously in the somatosensory cortex and the related thalamus (Fig. 3A,B1,B2). Two-way ANOVA of the mean gamma signal recorded in the 10–20 min following TTX or ACSF cortical application revealed significant effects of TTX (F_{1,22} = 107.7, P < 0.0001) and a significant interaction between TTX administration and the location recorded from (F_{1,22} = 5.82, P < 0.01). Post hoc analysis revealed significant differences between the conditions ACSF and TTX in the frontoparietal ECoG, layer VI LFP, and VPm LFP (P < 0.0001, Bonferroni’s multiple comparisons test; Fig. 3C). There was no significant difference in the gamma signal recorded in the VL between ACSF and TTX conditions. Interestingly, we also demonstrated a strong positive correlation between the gamma power and both the amplitude (Fig. 3D; r = +0.93, P < 0.0001) and the AUC (see Supplementary Fig. 2; r = +0.96, P < 0.0001) of the corresponding late CT-mediated evoked response; the correlation between the gamma power and the early evoked response was weakly negatively correlated (r = −0.14, P < 0.005).

Ketamine Reduces the Gamma Signal-to-Noise Ratio in both the Thalamus and the Cortex

Now we wished to assess the effects of a single administration of ketamine (2.5 mg/kg, s.c.) on the functional state of the CT

Supplementary Table 1.

Table 1. The respective amplitudes of the 3 thalamic components var-
pathway using the sensory-evoked late (~10 ms) negative-going potential, first under the neurolept sedation. Spectral analysis of the cortical and thalamic pre-stimulus baseline activity demonstrated, in all cases (ECoG and VPm, n = 7; layer VI, n = 3), a significant (Wilcoxon matched-pairs test: P < 0.001) ketamine-induced increase in the total power of ongoing GFO and higher-
frequency oscillation. The ketamine effects on baseline GFO were quick, robust, and transient. This is illustrated in the representative heatmaps of the time-frequency data from the cortical (layer VI) and thalamic (VPm) LFP recordings taken from a single experiment (Fig. 4A2; baseline: before 0 ms). The time course of the ketamine-induced increase in thalamic and cortical baseline GFO was similar at both ends of the CT pathway (Fig. 4B1, B2, top charts) with maximal effects of 227% and 210% in the VPm and layer VI, respectively, whereas in the surface ECoG maximal change was 360%. The ketamine effects on baseline GFO returned to predrug levels within approximately 45–60 min, in agreement with previous studies (Pinault 2008; Hakami et al. 2009; Jones et al. 2014). Under the ketamine condition (10–30 min after administration), the ECoG displayed significant increases in the beta-frequency oscillation (16–29 Hz; Wilcoxon matched-pairs test, P = 0.014), GFO (P < 0.001), and higher-frequency (P < 0.001) oscillation. As well as the distinct frequency bands, analysis of the total spectra showed significant differences under saline and ketamine conditions in each recording site (P < 0.0001, Wilcoxon matched-pairs test).

To determine whether the ketamine effects recorded under the neurolept–fentanyl sedation were general and not specific to this condition, we repeated the experiments in rats sedated with the pentobarbital–fentanyl regimen. Under this experimental condition, the ketamine-induced reduction of the gamma signal-to-noise ratio in both the cortex (layer VI and ECoG) and the thalamus (VPm and PoM) was likewise recorded (see Supplementary Fig. 3). In addition, the data obtained under the pentobarbital sedation were quantitatively and statistically not different from those recorded under the neurolept sedation. Ketamine’s effects

Figure 3. The contribution of the CT pathway in the late component of sensory-evoked field gamma oscillations. (A) Representative heatmaps generated through time-frequency analysis of the sensory-evoked waveforms from the parietal ECoG and the LFP of the related thalamus (VPm). The top panels show spontaneous activity followed by sensory-evoked activities (at time = 0 ms) under control conditions (local, topical application of ACSF onto the somatosensory cortex). The bottom panels show both spontaneous and sensory-evoked activity 20–30 min after TTX application onto the cortical surface. The evoked response in the ECoG is greatly diminished and the response in the related VPm is also reduced. (B1 and B2) Time course of TTX’s effects on cortical (B1) and thalamic (VPm and VL, B2) sensory-evoked gamma signal. The sensory-evoked gamma signal is greatly diminished in the cortex and related VPm. A nonsignificant slight decrease is recorded in the VL. Each point represents the mean ± SEM of ECoG and VPm n = 7, VL and layer VI n = 6 animals. (C) Histograms demonstrating TTX’s effects on sensory-evoked gamma signal, group data being taken from 10 to 20 min post-drug application and represent 100 trials from ECoG and VPm n = 7, VL and layer VI n = 6 animals. TTX administration causes a decrease in all areas, with this reaching significance in ECoG, layer VI, and VPm, *P < 0.05, Bonferroni’s multiple comparisons test. (D) Correlation between the amplitude of sensory-evoked responses recorded in the VPm and the corresponding gamma signal; data points are from 20 min before to 40 min after TTX application to the cortical surface and represent the mean of 7 animals. The amplitude of the early VPm negative-going component has a weak negative correlation to the strength of the gamma signal, whereas the second late component is highly positively correlated to the sensory gamma signal, both correlations are significant (P < 0.001, Pearson’s correlation). The open symbols are from ACSF condition.
on sensory-related gamma signal were opposite to those measured on ongoing GFO (Fig. 4B1,B2). In both the cortex (B1) and the thalamus (B2), ketamine simultaneously (with a similar time course) increased the ongoing GFO (top charts) and decreased the sensory-evoked GFO (bottom charts). Two-way ANOVA’s revealed that the effects of ketamine were significant on both baseline gamma ($F_{1,23} = 106.3, P < 0.0001$) and gamma signal ($F_{1,23} = 138.9, P < 0.0001$), with post hoc tests revealing significant differences between saline and ketamine conditions in all recording sites for both baseline gamma and gamma signal ($P < 0.001$, Bonferroni’s multiple comparisons test, Fig. 4C1,C2). We obtained equivalent quantitative and statistical data under the 2 types of sedation (Fig. 4B1,B2 and see Supplementary Fig. 3). These results predict that the baseline and signal gamma oscillations are highly negatively correlated (see Supplementary Fig. 4).
Furthermore, ketamine caused a significant decrease of the AUC of the sensory-evoked cortical (ECoG and layer VI) components that appeared during a time window of approximately 8–17 ms (see Supplementary Fig. 5A, A2) and only in the thalamic (TRN, VPm, and PoM) late (~10 ms) component (see Supplementary Fig. 6). The AUC of the cortical components is positively correlated with the strength of the gamma signal (see Supplementary Fig. 5B, B2). In the thalamus (TRN, VPM, and PoM), the gamma signal is more positively correlated with the AUC of the sensory late component than with the early component (see Supplementary Fig. 7A–C). Interestingly, here it is revealed that the correlation of the gamma signal is higher with the AUC than with the amplitude of the sensory-evoked cortical and thalamic potentials (see Supplementary Fig. 57A, D). This result makes sense since the AUC reflects more information than the peak itself. On the other hand, ketamine had no effect on the peak latencies of the sensory-evoked cortical and thalamic responses (see Supplementary Table 8).

**Discussion**

The present findings demonstrate that the layer VI CT pathway significantly contributes in ongoing and sensory-evoked thalamic GFO (network noise and signal, respectively), and that the NMDAR antagonist ketamine disrupts the functional state of this substantial glutamatergic pathway. The network model investigated here provides anatomic-functional features to understand the neurodynamics underlying the ketamine-induced impairment of encoding processes (Hetem et al. 2000), the hyperconnectivity, and the increased gamma power in human CT–TC systems (Driesen et al. 2013; Anticevic et al. 2014; Hőflich et al. 2015; Rivolta et al. 2015). Understanding the effects of reduced NMDAR activity in such highly distributed systems, which are involved in sensorimotor and cognitive processes, can help to gain insights in the etiology and pathophysiology of schizophrenia.

It is worth mentioning that the present results, recorded under 2 types of sedation–analgies (neurelopt–fentanyl and pentobarbital–fentanyl), were statistically equivalent and similar to those recorded in nonanesthetized rats (Pinault 2008; Hakami et al. 2009; Kulikova et al. 2012). This indicates that the 2 types of sedation are appropriate to investigate at least the early stages of sensory processing (see below), and that the effects on the ongoing and sensory-evoked GFO recorded after the subcutaneous administration of ketamine were indeed specific to this non-competitive NMDAR antagonist.

**The Layer VI CT Pathway Shapes the Thalamic Sensory-Evoked Activities**

Layer VI CT neurons innervate the TRN and the related specific (or first-order, such as the VPM) and nonspecific (higher-order, like the PoM and medial dorsal) thalamic nuclei (Guillery and Sherman 2002). The layer VI CT pathway exerts a substantial (~10-fold more important than the corresponding TC pathway (Sherman and Koch 1986) and widespread influence in the first- and higher-order thalamic nuclei. The primary somatosensory layer VI CT–TRN–TC circuit of the rodent is an appropriate three-neuron circuit, common in all sensory systems (Alitto and Usrey 2003), to understand the neurodynamics that occur during the first stages of information processing, at the gate of cognitive processes (Fig. 5A). Interestingly, the TRN is involved in both bottom-up and top-down information processing (Pinault 2004).

Taking these anatomical properties into consideration, it is reasonable to conclude that the late (~10 ms) negative-going potential component of the VfM SEP was almost exclusively caused by the layer VI-mediated cortical feedback (Fig. 5B). Indeed, 1) the late component was likewise recorded in both the FoM and the TRN, which are also innervated by the layer VI CT axons. 2) Blocking or reducing the activity of the neocortex, using TTX (present study), muscimol (Krupa et al. 1999), lidocaine, or cooling (Kublik et al. 2003), abolished or reduced the late negative component recorded in the VPM, VL (when measurable, present study), and in the medial part of the PO (Kublik et al. 2003). It must be said that the late component that is mediated by layer VI CT neurons includes, in agreement with findings from in vitro investigations (Landisman and Connors 2007; Lam and Sherman 2010), monosynaptic glutamate-mediated excitation (layer VI–VPM and layer VI–PoM) and disynaptic GABA-mediated inhibition (layer VI–TRN–VPM and layer VI–TRN–PoM). 3) Whatever the experimental conditions, the VPM early (~4 ms) potential component was never affected during and after manipulating the activity of the related cortex, confirming its lemniscal origin. 4) The axonal conduction time of the layer VI CT neurons is about twice longer (1.78 ± 0.89 ms, Kelly et al. 2001) than that of the TC neurons (0.80 ± 0.17 ms, Pinault and Pumain 1988). This means that the very beginning of the sensory-related CT feedback from layer VI is expected to happen approximately 3–4 ms after the early component (first thalamic postsynaptic TC activity, Fig. 5A) and taking into consideration a couple of synaptic delays (TC + CT –– 2 ms). In agreement with previous findings (Temereanca and Simons 2004), the peak latency of the CT feedback occurs at approximately 10 ms.

The layer VI CT pathway also exerts a great influence in the ongoing and sensory-evoked thalamic GFO. Moreover, whatever the type of sedation and our experimental conditions (control, TTX, or ketamine), the power of the sensory-evoked thalamic GFO was positively correlated with both the peak amplitude and the AUC of the corresponding CT-mediated late negative potential component of the thalamic SEP, whereas it was almost not correlated with the peripherally mediated early negative component. Similarly, the power of the sensory-evoked, TC-mediated cortical GFO was positively correlated with the peak amplitude of the first (CT-mediated) component of the cortical SEP, which appears at a latency of approximately 10 ms (Kulikova et al. 2012).

The possible mechanisms underlying the CT-related thalamic ongoing and sensory-evoked field GFO are currently uncertain. For cortical structures, the current literature consensually highlights the involvement of functional interactions between GABAergic (parvalbumin-positive) and glutamatergic neurons (Bartos et al. 2007; Buzsaki and Wang 2012). We believe that this theory can also apply for the thalamic TC–TRN networks. Indeed, the membrane of the GABAergic TRN neurons is endowed with pacemaker properties to generate intrinsic subthreshold and threshold gamma oscillations, which result in rhythmic GABA(A) receptor-mediated inhibitory postsynaptic potentials in related TC neurons (Pinault and Deschénes 1992a). Most of the TRN cells have the calcium-binding protein parvalbumin (Cslilik et al. 2005). Furthermore, cortical cooling reduced by 30–50% the firing rate of TRN neurons, supporting the hypothesis of a CT regulation of thalamically generated GFO (Pinault and Deschénes 1992b). The relative contribution of the thalamus and neocortex in the emergence of ongoing and function-related GFO in CT–TC systems is still the object of investigation (Bastos et al. 2014; also see below).

**Ketamine Disrupts the Functional State of the CT Pathway**

The layer VI CT pathway, as the major glutamatergic constituent in the CT–TC circuits, mediates most of the excitatory neuronal
transmissions through the activation of ionotropic (NMDA and AMPA receptors) and metabotropic glutamate receptors. Interestingly, NMDAR-mediated excitatory postsynaptic currents are much greater in CT than in lemniscal synapses (Miyata and Imoto 2006; Crandall et al. 2015). Furthermore, NMDARs are involved more in the late than in the early (lemniscal-mediated) component of the thalamic SEP at least in the VPM (Salt 1986). In addition, the corresponding NMDA-related response is antagonized by the noncompetitive NMDAR antagonist ketamine or MK-801 (Salt et al. 1988), which significantly disturbs GFO in highly distributed systems (Pinault 2008; Hakami et al. 2009; Anderson et al. 2014).

In the present study, in line with previous works (Hakami et al. 2009; Kulikova et al. 2012; Anderson et al. 2014; Jones et al. 2014), we considered the gamma signal-to-noise ratio as a potential electrophysiological marker of the functional state of neural circuits. It is well established that the administration of a single low dose (<10 mg/kg, s.c.) of ketamine dramatically amplifies the power of ongoing beta-frequency oscillation, GFO, and high-order-frequency oscillation in highly distributed cortical–subcortical systems.

Figure 5. The CT neurodynamics underlying the early stages (up to ∼15 ms) of sensory information processing. (A) Left: simplified schema of the anatomical relations between the dorsal thalamus (at least VPM and PoM), which is innervated by the lemniscal inputs (Im), the GABAergic TRN, and the related primary somatosensory area of the neocortex. This three-neuron circuit is common in both first-order (VPM) and higher-order (PoM) thalamic nuclei. The arrowheads indicate the innervation sites. More precisely, the TC pathways innervate principally the layer IV (from VPM) and infra- and supragranular layers (from PoM) of the cortex. In the cortex, any information is computed through vertical and horizontal circuits (dotted lines). The electrocorticographic electrode (ECoG) is in contact with the inner plate of the cranial. Right: timeline of the early stages of sensory-evoked flow information through the primary somatosensory thalamo-cortico-thalamic system. The sensory (vibrissae-related) information reaches, via the presynaptic lemniscal (Im, to VPM) and para-lemniscal (plm, to PoM) inputs (pre), the VPM and PoM, which contain only TC neurons and which are reciprocally connected with the TRN, and the related somatosensory area of the neocortex. The numbers give the averaged peak latencies (in ms) of the negative (N) and positive (P) components of the sensory-evoked potentials recorded simultaneously in the VPM/PoM, TRN, layer VI, and surface ECoG. The arrows provide the functional links between the 3 principal structures of the primary somatosensory thalamo-cortico-thalamic system during the early stages of sensory-evoked responses. Note that the TRN is involved twice (bottom-up then top-down) during the first 15 ms of sensory information processing. The N1 and N2 components of the thalamic sensory-evoked potential are considered as the early and late components recorded in the VPM and PoM. (B) Sensory-evoked potentials (5 superimposed trials + average of 15) recorded simultaneously in the surface ECoG, the related layer VI, and in the VPM. Each colored area under the layer VI and VPM curve (average potential) reflects the synaptic and intrinsic membrane events due principally to the activities of the TC, CT, or corticofugal pathways, and to those generated by the GABAergic TRN. The initial activity is synaptically triggered by the synchronous prethalamic (pre) volleys conveyed by the lm pathway. The resulting synchronous TC volleys in turn trigger cortical synaptic and intrinsic events, which lead to corticocortical and corticofugal volleys. The CT volleys that originate from layer VI pyramidal neurons propagate to their 2 corticalpostsynaptic targets, the TRN and VPM, the latter nucleus containing only TC neurons. (C) A single systemic administration of ketamine disturbs the functional state of the simplified three-neuron circuit (layer VI CT-TRN-TC). Ketamine increases the amplitude and power of spontaneously occurring GFO and decreases the power of the sensory-evoked cortical and CT gamma signals during the early stages of information processing. Thereby, ketamine disturbs the mental state and decreases the gamma signal-to-noise ratio in the thalamo-cortical-thalamic system. SEP, averaged (N = 15) sensory-evoked potential considered as an index of the sensory-related signal.
systems involved in sensorimotor, limbic, and cognitive processes (Pinault 2008; Hakami et al. 2009). This means that ketamine generates an aberrant, generalized, and excessive network gamma noise, which would interfere with incoming/relevant sensory information (Fig. 5C). The present study shows that ketamine transiently and in similar proportions amplified the network gamma noise in both the cortex and the thalamus. In addition, ketamine decreased the sensory-related gamma signal in both the thalamus (present study) and the cortex (Kulikova et al. 2012).

The possible mechanisms underlying the ketamine-induced effects in both gamma noise and signal in CT–TC systems remain elusive. Some of them are discussed in recent reports (Hakami et al. 2009; Kulikova et al. 2012; Kocsis et al. 2013). Anatomo-functional studies indicate that CT neurons exert a simultaneous effect on both the center (excitation) and the surround (suppressive) of the receptive fields (Murphy and Sillito 1987; Ghazanfar et al. 2001; Sillito and Jones 2002; Alitto and Usrey 2003; Temereanca and Simons 2004). The CT synapses would thus exert a crucial role in sharpening the thalamic receptive field via increasing both the center and the surround mechanisms. The CT influence is dynamic with an excitatory-inhibitory balance fluctuating in an activity-dependent manner (Crandal et al. 2015). For instance, sustained cortical GFO can enhance thalamic activity, like during states of focused attention (O’Connor et al. 2002; McAloon et al. 2008). So, on the basis of these anatomofunctional properties, we propose that ketamine can elicit a pathophysiological uncontrolled “hyper-attentional” state, during which both cortex and thalamus become hyperactive at least in the gamma-frequency band. Such ketamine-induced hyperactivity would be due to loss of lateral inhibition, at least in the dorsal thalamus. During such a state, layer VI CT neurons might play a key role in the genesis of abnormal perception (e.g., hallucinations) whatever the activity level of peripheral inputs (Henke et al. 2014). In summary, the present findings support the hypothesis that the psychotomimetic ketamine lessens thalamic TRN-mediated lateral inhibitions and subsequently disturbs attention-related global brain operations (Pinault 2011).

Furthermore, as above-mentioned, the axonal conduction delay of layer VI CT neurons is approximately 2 times lower than that of TC neurons, and both TC and CT synapses work with AMPA and NMDA receptors. So, we predict that the impact of ketamine should be higher in strength and duration in the thalamus and TRN (at CT synapses) than in the cortex (at TC synapses). Assuming that GABAergic neurons are more sensitive to NMDAR antagonists than glutamatergic neurons (Grunze et al. 1996) and that the ketamine-elicited global neurochemical effect is to generate a hypoGABAergic–hyperglutamatergic state (Moghaddam et al. 1997; Razouk et al. 2007; Pittman-Polletta et al. 2015), the hyperglutamatergic state would be higher at CT than TC synapses.

It is worth reminding that the principal neurons of the cortical layer VI are CT (~46%) and corticocortical (~44%), meaning that layer VI is the source of strategic networks for both CT and corticocortical communication (Zhang and Deschênes 1997). This suggests that ketamine might also disturb the functional state of short- and long-range corticocortical pathways.

Limitations of the Study
It is well known that anesthetizing and sedating substances both through their direct action and their side-effects can influence the outcomes, which might compromise the conclusion of any study (Bazin et al. 2004; Stokes et al. 2009). Two points should be discussed, the pentobarbital–ketamine general anesthesia necessary for the surgery, and the sedation protocols used for the recordings. The first point is the use of a single intraperitoneal administration of pentobarbital (40 mg/kg), followed by a single intramuscular injection of ketamine (45 mg/kg) for the induction of the general anesthesia. It is worth specifying that ketamine has a faster effect than pentobarbital, with a half-life of 10–15 min in alpha-phase and of 2.5 h in beta-phase (Wieber et al. 1975), and that the recordings performed in the present study started at least 5 h after the anesthesia induction. In the rodent, the levels of ketamine and its metabolite norketamine in blood sera and brain tissues are almost unmeasurable 2–3 h after a single systemic administration of ketamine (<80 mg/kg, i.p. or s.c.; Palenicek et al. 2011; Nagy et al. 2016). Therefore, in the present study, the ketamine used for the anesthesia was almost completely eliminated by the beginning of our recordings, which displayed patterns similar to those recorded in nonanesthetized resting-state rats (Pinault 2008; Hakami et al. 2009; Kulikova et al. 2012). However, a comprehensive study (Zanos et al. 2016) showed that one of the ketamine metabolite (2R,6R)-hydroxynorketamine increases glutamatergic signaling involving the upregulation of synaptic AMPA receptors, which may lead to their activation at the time of experiments. Although we should not exclude that, under our experimental conditions, ketamine can rapidly increase synaptogenesis (Duman et al. 2012), and that pentobarbital exerts a powerful depression of synaptic transmissions, further experiments are needed to better appreciate the impact, if any, of the anesthetizing pentobarbital–ketamine regimen on the neurolept or pentobarbital sedation designed for the recordings. Of importance, in the present study, the kinetics of the ketamine (a single injection of 2.5 mg/kg, s.c., made more than 5–6 h after the induction of the general anesthesia) on behavior and GFO are quite consistent with plasma and brain half-life measured following injection of ketamine (White et al. 1976; Palenicek et al. 2011). In addition, the present findings fully agree with previous results obtained independently in other laboratories working on other neural systems in different species and under different experimental conditions (Gandal et al. 2012; Saunders et al. 2012). Interestingly, these findings (ketamine-induced reduction in the gamma signal-to-noise ratio in sensory systems) are no longer recorded once ketamine is cleared from the body (Nagy et al. 2016).

The second point is the use of the neurolept–fentanyl sedation. In an attempt to demonstrate that the ketamine effects under investigation were general and not specific to the experimental (pharmacological) condition, we used 2 types of light sedation (haloperidol or pentobarbital) with the analgesic fentanyl. The 2 sedation protocols used in the present study set the brain state similar to a resting-state or resting-wakefulness (quiet immobile wakefulness), characterized by an ECoG fragmented by desynchronized and synchronized episodes. The sedated rats could even make spontaneous wake-sleep transitions. These sedation protocols allowed maintaining a stable brain state during long-lasting periods (>5 h) without measurable pain and distress, each animal serving as its own control. Under both sedation protocols, the electrophysiological recordings consistently reproduced the ketamine-induced increase in the power of ongoing GFO in cortical and subcortical networks (Hakami et al. 2009) recorded in free-moving rats (Ma and Leung 2007; Pinault 2008). In addition, the sensory-related cortical oscillations were similar to those recorded in the nonanesthetized head-restrained preparation (Kulikova et al. 2012). In the present study, we demonstrated that the ketamine effects on both the baseline and the sensory-related gamma oscillations are
statistically equivalent under the 2 types of sedation. The similarities measured during both the sedation and the nonanesthetized conditions make both the neurolept–fentanyl and pentobarbital–fentanyl sedations suitable for investigating the early stages of neural processing in sensory systems.

**Conclusion**

The present results substantiate the hypothesis that reduced NMDAR activation disrupts the functional state of CT and corticothalamic networks. Furthermore, they can help in designing experiments to investigate the potential links between dysfunctional CT–TC systems and abnormal behaviors associated with mental health disorders like psychosis. They also show that the gamma signal-to-noise ratio of neural networks can be a useful neurophysiological marker to test their functional state. Such a quantifiable bioelectrical marker might be a promising translational tool to develop innovative therapies designed to prevent the development of chronic forms of schizophrenia.

**Authors’ Contributions**

P.M.A.: design, data acquisition and analysis, and writing. N.C.J.: design and writing. T.J.O.: design and writing. D.P.: design, data acquisition and analysis, and writing.

**Supplementary Material**

Supplementary material can be found at: [http://www.cercor.oxfordjournals.org/](http://www.cercor.oxfordjournals.org/).

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