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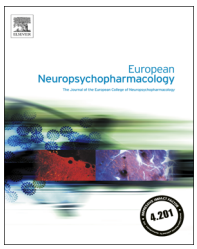

# NMDA receptor antagonist-enhanced high frequency oscillations: Are they generated broadly or regionally specific?

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**Abstract**
Systemic administration of NMDA receptor antagonists, used to model schizophrenia, increase the power of high-frequency oscillations (130–180 Hz, HFO) in a variety of neuroanatomical and functionally distinct brain regions. However, it is unclear whether HFO are independently and locally generated or instead spread from a distant source. To address this issue, we used local infusion of tetrodotoxin (TTX) to distinct brain areas to determine how accurately HFO recorded after injection of NMDAR antagonists reflect the activity actually generated at the electrode tip. Changes in power were evaluated in local field potentials (LFPs) recorded from the nucleus accumbens (NAc), prefrontal cortex and caudate and in electrocorticograms (ECoGs) from visual and frontal areas. HFO recorded in frontal and visual cortices (ECoGs) or in the prefrontal cortex, caudate (LFPs) co-varied in power and frequency with observed changes in the NAc. TTX infusion to the NAc immediately and profoundly reduced the power of accumbal HFO which correlated with changes in HFO recorded in distant cortical sites. In contrast, TTX infusion to the prefrontal cortex did not change HFO power recorded locally, although gamma power was reduced. A very similar result was found after TTX infusion to the caudate. These findings raise the possibility that the NAc is an important neural generator. Our data also support existing studies challenging the idea that high frequencies recorded in LFPs are necessarily generated at the recording site.


## 1. Introduction

There is good evidence from clinical, preclinical and theoretical studies that the NMDAR complex is involved in the pathophysiology of several psychiatric diseases, such as schizophrenia, bipolar depression and drug addiction (Paul and Skolnick, 2003; Krystal et al., 2003). NMDAR antagonists have long been used to model some of the psychiatric symptoms of schizophrenia (Abi-Saab et al., 1998) and over the last decade this class of compounds has been found clinically useful in the treatment of bipolar depression (Mathew et al., 2012). Therefore, understanding how

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NMDAR antagonists influence brain activity may shed important light on the possible mechanisms underlying these diseases.

Local field potential (LFP) oscillations, part of the extracellular potential encompassing frequencies below 300 Hz, are receiving increased attention for the role they may play in health and disease. Previously, we showed in freely moving rats that subanesthetic doses of ketamine produce rapid (within tens of seconds) and substantial increases in the power of high-frequency oscillations (130–180 Hz, HFO) (Hunt et al., 2006). Spontaneous HFO occur in the nucleus accumben NAc during waking and rapid-eye movement sleep, but are reduced during slow-wave sleep and attenuated by anesthesia (Hunt et al., 2009). Notably, large increases in power also occur during emergence from ketamine anesthesia (Hunt et al., 2006) which may be related to emergence reactions known to occur in humans. We have also found HFO in the NAc can be modulated by antipsychotic compounds (Olszewski et al., 2012). NMDAR antagonists have also been reported to increase the power of HFO in many other structurally and functionally distinct brain regions, including the caudate nucleus, motor cortex, visual cortex, hippocampus, medial septum, substantia nigra pars reticulata, subthalamic nucleus and posterior thalamus (Nicolas et al., 2011; Phillips et al., 2012; Hunt et al., 2011). Small but significant increases in the power of HFO in electroencephalograms have been recorded in the methylazoxymethanol developmental rat model, and these animals also display an exaggerated response post NMDAR antagonist injection (Phillips et al., 2012). Together, these findings indicate the neural networks mediating the generation of HFO may have relevance to the pathophysiology of schizophrenia.

A number of studies, mostly based on recordings from cortical areas, have presented compelling evidence that LFP oscillations $>40$ Hz are highly localized to the electrode tip (Gray and Singer, 1989; Liu and Newsome, 2006). This would indicate that NMDAR antagonist-enhanced HFO are a spatially well localized neuronal signal that is generated in structurally and functionally diverse areas. As such synchronous HFO may represent a mechanism whereby altered brain functioning occurs through the formation of aberrant neuronal networks and loops. In support of this Nicolas et al. (2011) provided evidence, from imaginary coherence studies, that HFO, at least for basal ganglia areas, are likely to be generated locally. However, such an interpretation is at odds with our current source and sink density analyses, which indicate good localization to the ventral but not dorsal striatum (Hunt et al., 2011). Recently, a series of studies have begun to challenge the notion that the generation of high frequency LFP oscillations is necessarily localized to the vicinity of the recording electrode. For example, cortical tissue can transmit all frequencies comparably well (Logothetis et al., 2007) and the spread of LFP may reach a centimeter and is chiefly a function of amplitude, rather than intrinsic frequency (Kajikawa and Schroeder, 2011). Understood in this way, the widespread nature of NMDAR antagonist-enhanced HFO may instead represent spread from more distant generator(s).

As emphasized by many, distinguishing the authentic LFP is pivotal for correct understanding of the nature of LFP recordings and what they functionally mean. To address this issue, we used local infusion of TTX to distinct brain areas to determine how accurately HFO recorded in LFPs in distinct brain areas could be explained based on local neural activity occurring at the recording site.

## 2. Experimental procedures

### 2.1. Surgery

Male Wistar rats (250–350 g) were assigned to three experimental groups. The NAc group consisted of 12 rats implanted bilaterally with 22 gauge stainless steel guides (Bilaney, Germany) [AP 1.6, ML 0.8, DV 7 mm] (Paxinos and Watson, 1986) with a pair of twisted stainless steel electrodes (125 μm, Science Products, Germany) placed along one guide (to permit monopolar and derived-bipolar analyses). For simultaneous NAc and ECoG recordings, 6 rats were implanted as the NAc group but with additional stainless steel screws above the frontal [AP 5.0, ML 2.0] and visual [AP −6.0, ML 5.5] cortices. In the prefrontal group, 7 rats were implanted with guides and electrodes in the dorsal prelimbic area of the PFC [AP 3.2, ML 0.5, DV 2–3 mm] and electrodes in the NAc. In the caudate putamen group, 8 rats were implanted with guides and electrodes in the caudate [AP 0.5, ML 3.5, DV 4 mm] and electrodes in the NAc. In all cases, a silver wire was used as the ground/reference electrode connected to a screw above the olfactory bulb. Rats were housed with access to water and food ad libitum. All experiments were conducted in accordance with the European Community guidelines on the Care and Use of Laboratory Animals (86/609/EEC) and approved by a local ethics committee.

### 2.2. Recording

Animals were placed in a recording chamber 35 cm wide, 35 cm long, and 42 cm high. LFPs and ECoGs were recorded through a JFET preamplifier. The signal was relayed through a commutator (Crist Instruments, USA) amplified $\times 1000$, filtered 0.1–1 kHz (A-M Systems, USA), digitized 4 kHz (Micro1401, CED, Cambridge, UK), allowing the rat free movement inside the recording chamber, and data stored on a PC for offline analysis.

LFPs were recorded for 20 min, followed by i.p. injection of 0.1 mg/kg MK801, 30 min later followed by infusion of TTX (10 ng/side) or saline to the NAc ($N$=12), PFC ($N$=7) or caudate ($N$=8). In a separate study, muscimol (1 μg/side) was infused, followed 10 min later by i.p. injection of 25 mg/kg ketamine ($N$=6 rats). For infusion, cannulae (28 gauge, Bilaney) that extended 2 mm below the tip of the guide were inserted for 60 s, followed by infusion (1 μl, 0.5 μl/min) and left in place for a further 60 s. Experiments were conducted in a Latin square design, whereby each rat received TTX/saline or muscimol/saline infusions in a randomised order separated by at least 72 h. The location of tips of cannulae and electrode (electrolytic lesion) was determined on 40 μm Cresyl violet stained sections.

### 2.3. Data analysis

Mean power spectra of the raw monopolar LFP and derived-bipolar signal (difference between the two monopolar recordings) were carried out on successive 60-s data blocks using a fast Fourier transform of 4096 points. Total power (130–180 Hz) and power of dominant frequency (maximal power at the dominant frequency in the spectra) were calculated. Total power of the gamma band (30–90 Hz) was also computed for the same 60-s data blocks. Coherence between pairs of raw monopolar LFP signals was calculated using a script available from the CED website http://www.ced.co.uk/upu.shtml. Coherence analyses (4096 points) were done for 300 s periods at the end of baseline, immediately prior to