The NMDA Receptor Antagonist Ketamine Exerts Biphasic Effects on Mismatch Negativity in the Rat

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Introduction

Mismatch negativity (MMN) is a component of event-related potentials recorded in the scalp EEG. MMN is diminished in many neuropsychiatric disorders including schizophrenia. Antagonists of the N-Methyl-D-aspartate (NMDA) receptor, such as ketamine and MK-801, mimic symptoms of schizophrenia and disrupt MMN in healthy volunteers. MMN can be measured in rodents as well. To examine the back-translational potential of the MMN assay, we tested whether ketamine and MK-801 could impair MMN in the rat similar to humans.

Methods

EEG surgery and recording
24 adult (200-250 g) male CD rats (Charles River, UK) were surgically implanted with telemetry transmitters for fronto-parietal EEG and EMG recording. Briefly, we placed a telemetry transmitter (HD-S02; DSI, USA) into the peritoneal cavity and the tip of EEG leads epidurally over the frontal (2 mm anterior / 1 mm lateral to Bregma) and parietal (0 mm anterior / 1.5 mm lateral to Lambda) cortices under isoflurane (2-5%) anesthesia. After recovery, the rats were placed individually in sound attenuated recording chambers, equipped with audio speakers. EEG signals were analogue filtered (1-100 Hz), sampled at 500 Hz, and then stored on a PC for offline analysis (Spike2; CED, UK). Tonal stimuli were generated by a custom sequencer script and their timestamps were recorded together with the EEG signal.

'Flip-flop' oddball paradigm and EEG power spectral analysis
MMN was elicited in awake, freely-behaving rats by the auditory oddball paradigm. "Flip-flop" (FF) blocks were presented consecutively, in which the first "flip" sequence consisted of 1000 randomized, 50 ms long tones of either 6.0 kHz (standard, 90% probability, 900 tones) or 8.0 kHz (deviant, 10% probability, 100 tones). The subsequent "flop" sequence consisted of the same number of tones, but the frequencies were reversed for standards and deviants. The interstimulus interval was 350 ms. Components of the auditory evoked potential (AEP) were measured in difference waves (MMN) that were generated by subtracting standard (STD) waves from deviant (DEV) waves.

EEG power spectra was computed using fast-Fourier transformation (FFT size: 1024, Hanning window).

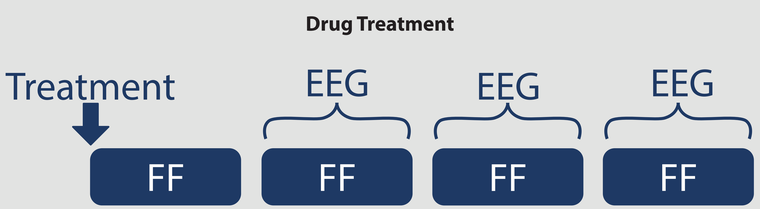

Figure 1. Daily study design.
After establishing the baseline MMN, the rats were treated with either ketamine (3, 10 and 30 mg/kg, s.c.), MK-801 (0.3 mg/kg, i.p.) or their vehicles in a cross-over design with 3-4 days washout between the treatments. The MMN protocol was started immediately after the treatment. The EEG recorded during the 2nd-4th FF blocks (ketamine) and 2nd-3rd FF blocks (MK-801) were used for data analysis.

Results

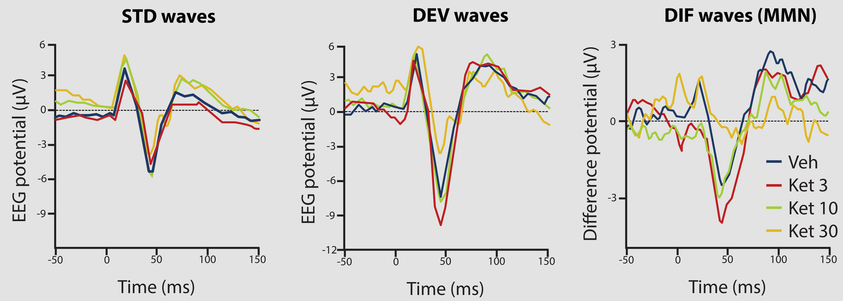

Figure 2. High but not low doses of the NMDA antagonist ketamine disrupted MMN in the rat.
The effects of acute treatment with ketamine (3, 10 and 30 mg/kg, s.c.) or its vehicle (saline, 5 ml/kg) on MMN was assessed in the rat 20-80 min post-treatment. Data are presented as mean in 1 ms intervals.

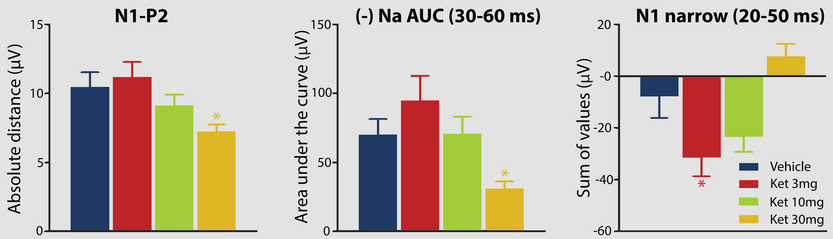

Figure 3. Ketamine reduced N1-P2 distance and (-) N1 AUC at a high dose, but increased N1 in the 20-50 ms region at low doses.
The effects of acute ketamine (3, 10 and 30 mg/kg, s.c.) or vehicle treatment on the components of MMN was evaluated in the rat. Data are presented as mean ± SEM. *P<0.05 compared to vehicle (Dunnett post-test).

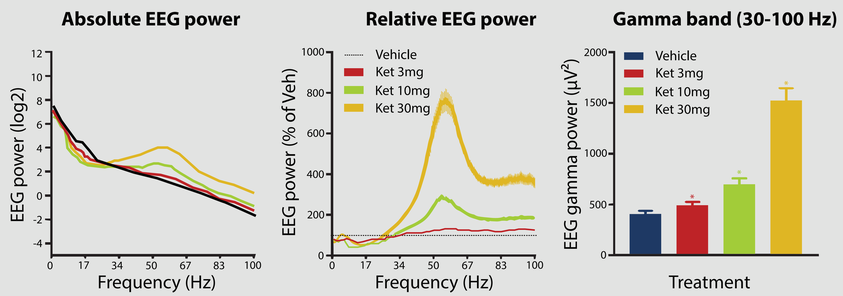

Figure 4. Besides altering MMN, ketamine also increased EEG gamma (30-100 Hz) oscillation in a dose-dependent manner.
Changes in absolute and relative power values of EEG spectra, as well as in the gamma band (30-100 Hz) of the EEG are shown 20-80 min after treatment with vehicle or ketamine (3, 10 and 30 mg/kg, s.c.). Data are presented as mean ± SEM. *P<0.05 compared to vehicle (Dunnett post-test).

Results

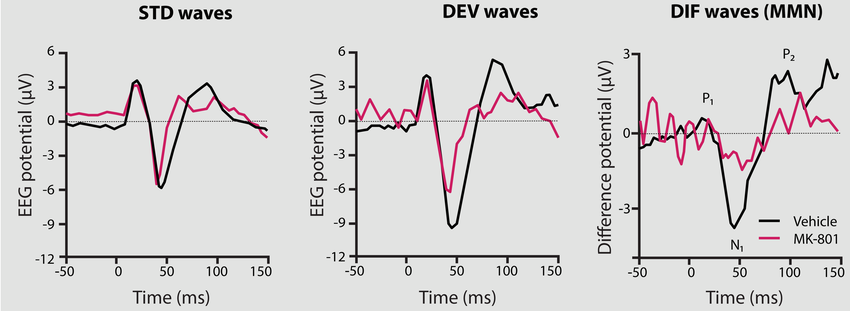

Figure 4. The NMDA antagonist MK-801 disrupted the MMN in the rat.
Changes in MMN are presented 20-60 min after acute treatment with MK-801 (0.3 mg/kg, i.p.) or its vehicle (saline, 1 ml/kg). Data are presented as mean in 1 ms intervals.

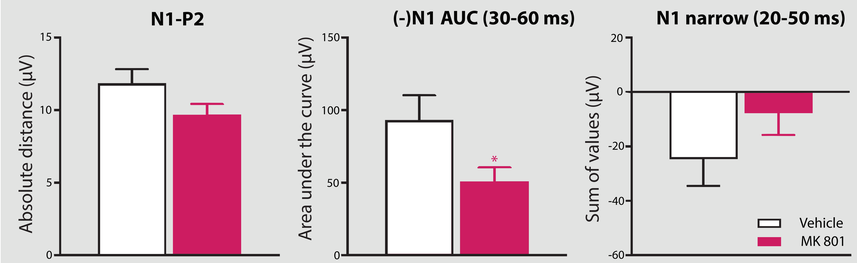

Figure 5. Acute treatment with MK-801 decreased (-) N1 AUC of MMN.
The effects of acute MK-801 (0.3 mg/kg, i.p.) or vehicle (saline, 1 ml/kg) treatment on the components of MMN was evaluated in the rat. Data are presented as mean ± SEM. *P<0.05 compared to vehicle (paired t-test).

Conclusions

- Schizophrenia-like MMN deficits are induced in the rat by acute treatment with MK-801 and with a high dose of ketamine.

- Low and high doses of ketamine have similar effects on EEG gamma power, namely they increase it, but opposing effects on MMN suggesting that different mechanisms are responsible for these changes.

- The changes seen in MMN after MK-801 treatment are similar to the ones reported previously (Upton et al., 341.05 SFN 2017 Online). However, different doses of MK-801 didn't produce a biphasic effect, suggesting that ketamine and MK-801 may modulate MMN by different mechanisms.

- Our data suggest that MMN can be a valuable translational tool for testing therapeutics targeting neuropsychiatric disorders including schizophrenia.

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