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Electroencephalographic Spectral and Coherence Analysis of Ketamine in Rats: Correlation with Behavioral Effects and Pharmacokinetics

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Key Words

Ketamine · Sensorimotor gating · Prepulse inhibition · Open field · Locomotion · Electroencephalography, coherence · Electroencephalography, power spectra · Schizophrenia · Functional connectivity

Abstract

Aims: This study was designed to evaluate the changes in EEG power spectra and EEG coherence in a ketamine model of psychosis in rats. Analyses of behavioral measurements – locomotion and sensorimotor gating – and the pharmacokinetics of ketamine and norketamine were also conducted. ***Methods:*** Ketamine and norketamine levels in rat sera and brains were analyzed by gas chromatography-mass spectrometry after ketamine 30 mg/kg (i.p.). Ketamine 9 and 30 mg/kg (i.p.) were used in the behavioral and EEG experiments. Locomotor effects in an open field test and deficits in prepulse inhibition of acoustic startle reaction (PPI ASR) were evaluated in the behavioral experiments. EEG signals were simultaneously recorded from 12 implanted active electrodes; subsequently, an EEG power spectral and coherence analysis was performed. ***Results:*** Ketamine had a rapid penetration into the brain; the peak concentrations of the drug were reached within 15 min after administration. Ketamine induced marked hyperlocomotion and deficits in the PPI ASR. EEG spectral analysis mainly showed increases in EEG power as well as coherence. These were most robust at 10–15 min after the administration and influenced all parts of the spectrum with ketamine 30 mg/kg. ***Conclusions:*** Ketamine at behaviorally active doses induces a robust increase in EEG power spectra and coherence. The maximum levels of change correlated with the kinetics of ketamine.

Introduction

The important role of the glutamatergic system in the etiopathogenesis of schizophrenia has been supported by findings on various levels from molecular interactions up to the structural layout of the neuronal network in the human brain [1, 2]. The glutamate *N*-methyl-D-aspartate (NMDA) receptor theory of schizophrenia proposes that a dysfunction of NMDA receptors underlies the schizophrenia pathophysiology. Analogously, NMDA antago-

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nists such as dizocilpine (MK-801), phencyclidine (PCP) and ketamine mimic symptoms of schizophrenia in healthy humans. Both NMDA dysfunction and NMDA antagonists exert specific effects on inhibitory circuits that lead to disinhibition of neurotransmitter systems [3]. Disinhibition of glutamate activity resulting in increased excitatory transmission was confirmed in the prefrontal cortex of patients with schizophrenia [4, 5] and of rodents, humans and nonhuman primates after administration of NMDA antagonists [6, 7]. The use of these substances changes behavior in both humans and animals and induces schizophrenia-like manifestations [7, 8].

However, the individual NMDA antagonists exert slightly different behavioral and pharmacological profiles [9–12]. The substantial problem is that in the majority of studies on animal models of schizophrenia, MK-801 or PCP was used [8, 9]; on the other hand, only ketamine is used nowadays in schizophrenia modeling in humans [6, 13–17].

Changes in locomotor activity and sensorimotor gating deficits are frequently analyzed in animal models of psychosis. Locomotor activity in the open field is one of the most frequently used behavioral parameters describing the behavioral activity of a substance. In glutamatergic models of psychosis induced by NMDA antagonists, hyperlocomotion and movement disorganization are continuously observed; this productive behavior has been postulated to be a model of positive symptoms of psychosis [8, 18–20]. Sensorimotor gating reflects the ability of an individual to appropriately filter inputs from the environment and to appropriately respond to them. Prepulse inhibition (PPI) of acoustic startle reaction (ASR) is the most frequently used method of analyzing sensorimotor gating. It represents the ability of a weak sensory event to inhibit the motor response of an intense stimulus [21, 22]. PPI is typically disrupted in schizophrenic patients [23, 24] as well as in animal models of psychosis based on glutamatergic NMDA receptor dysfunction [8, 9]. Thus, the clear advantage of this method in glutamatergic models is its predictive validity for testing potential antipsychotics [24].

Quantitative EEG (QEEG; spectral analysis, coherence) can bring a new and fundamental approach to describing the electrophysiological changes induced by NMDA antagonists in animal models. Whilst spectral EEG analysis describes the voltage/power distribution in frequency bands under each electrode, EEG coherence represents a quantitative measure of the correlation between two EEG signals in the frequency domain, thereby indexing anatomical and/or functional coupling between the brain regions under the electrodes [25, 26]. EEG coherence is therefore a measure of functional connectivity between two regions. Whilst in schizophrenia QEEG analysis revealed several abnormalities [27–36], to date only limited information on the QEEG effects of NMDA antagonists in rats is available. Several authors have described alterations in EEG spectra in these models [37–40]; however, no information on EEG coherence is available to our knowledge.

The aim of this study was to evaluate the effects of the NMDA antagonist ketamine on EEG spectra and coherence in freely moving rats. We have used a human recording and analytical system with the intention of allowing the translation of our findings to humans; this also led us to use the frequency range of 1–40 Hz. Subanesthetic doses of ketamine in the range known to produce schizophrenia-like behavior were chosen according to a literature search [40–47]. Two doses of ketamine, low (9 mg/kg) and high (30 mg/kg), were used. Based on our pilot/preliminary results, a lower dose was chosen to induce little or no change in behavior (mainly locomotion), whereas a high dose should show more pronounced behavioral effects [48–50]. Hence, the EEG findings following both doses would discriminate between the electrophysiological changes mediated by the behavioral effect (higher dose) and the 'pure' pharmacological effect without behavioral (locomotor) sequelae. We performed EEG recordings simultaneously from 12 subdural electrodes placed in 6 cortical regions of each hemisphere. With respect to the above mentioned facts, locomotor activity in the open field and PPI were analyzed to verify the behavioral activity of ketamine and the validity of this model. Ketamine undergoes an extensive liver metabolism by cytochrome P450 N-demethylation to norketamine, which is also an NMDA receptor antagonist [51]. In order to determine the role of both compounds, we analyzed the relationship between ketamine and norketamine blood and brain levels. The pharmacokinetics of ketamine were also used for the appropriate temporal organization of the behavioral and EEG experiments. The goal was to cover the peak effects of ketamine where the symptoms of psychosis-like behavior are expected to be the most pronounced.

Materials and Methods

Animals

All experiments were carried out on adult male Wistar rats (SPF animals; Hannover breed, Konárovice, Czech Republic) weighing 200–300 g. In the behavioral experiments 9–10 animals,

and in EEG experiments 12 animals per group were used. Each subject was tested only once. All experiments respected the Guidelines of the European Union (86/609/EU) and followed the instructions of the National Committee for the Care and Use of Laboratory Animals.

Drugs and Chemicals

Ketamine hydrochloride (Narketan 10 A.U.V. inj 50 ml, Chassot) was diluted in a physiological saline to the appropriate concentration. The drug or a vehicle was administered intraperitoneally in a volume of 2 ml/kg. Doses of 9 and 30 mg/kg (i.p.) were used in the behavioral as well as the EEG experiments. Only the highest dose was used in the pharmacokinetic experiments. Reference standards necessary for gas chromatography-mass spectrometry (GC-MS) analyses of ketamine, norketamine and deuterated ketamine were purchased from Cerilliant in the form of methanolic solutions, ketamine and norketamine in concentrations of 1 mg/ml, and deuterated ketamine in concentrations of 0.1 mg/ml, with all values expressed as free bases.

Pharmacokinetics

For the kinetic study, a ketamine single-bolus dose of 30 mg/kg (i.p.) was injected into rats, and subsequently 7–9 animals per time period were sacrificed after 5, 10, 20, 30, 60, 120 and 240 min. For control purposes, a physiological saline solution was injected as well. Separated sera and whole brains were kept at –20°C until the toxicological analyses.

Method of Determination of Ketamine and Norketamine in Rat Samples

0.5 ml of serum was mixed with a phosphate buffer at pH 6 and 100 ng of the internal standard deuterated ketamine. Ketamine and norketamine were extracted by solid phase extraction-drugs-of-abuse urine (SPEC-DAU) discs with mixed solid phase, and the obtained extract was derivatized by acetylation for the GC-MS analysis. For the brains, 1 g of brain tissue was homogenized with 5 ml methanol with the addition of 500 ng of the internal standard deuterated ketamine. After separation, the supernatant was evaporated and transferred to the phosphate buffer at pH 6. Ketamine and norketamine were extracted by SPEC-DAU discs with mixed solid phase, and the obtained extract was derivatized by acetylation for the GC-MS analysis.

Gas Chromatography-Mass Spectrometry

The Hewlett-Packard GC-MS system HP 6890/5973 (Agilent, Waldbronn, Germany) equipped with an autosampler, splitless injector and HP-5ms capillary was used for the analysis. Helium was used as the carrier gas. Electron-impact ionization and the selected ion monitoring mode were used for detection and quantification.

Method Validation and Determination of Ketamine and Norketamine

Blank rat serum and tissue samples spiked with the appropriate amounts of standard substances were used for calibration and validation purposes. The internal standard method was used for quantification purposes. The calibration curves were based on linear regression analysis using the ratio of the analyte peak area related to the internal standard. The concentration range of calibration in serum was linear in the range of 4–1,000 ng/ml for both analytes, with appropriate regression coefficients greater than 0.99. The range of calibration in the brain tissue was linear in the range of 10–5,000 ng/ml for both analytes, with appropriate regression coefficients greater than 0.99.

Behavioral Experiments

Open Field

Locomotor activity (trajectory length) and its spatial characteristics (thigmotaxis and time spent in the center) in a novel environment were registered and analyzed by an automatic video tracking system for recording behavioral activities (EthoVision Color Pro v. 3.1.1; Noldus, The Netherlands). A square black plastic box arena (68 × 68 × 30 cm) was situated in a soundproof and evenly lit room. Each rat was placed into the center of the arena 5 min after drug administration (ketamine 9 and 30 mg/kg or saline), and locomotor activity was registered for 30 min. The EthoVision program was also used to calculate locomotor data in 5-min time intervals. For evaluating the spatial characteristics of the movement in the open field (thigmotaxis and time spent in the center), the arena was virtually divided by the EthoVision program into 5 × 5 identical, square zones, with 16 being located on the periphery and 9 in the center. Initially, the total number of appearances of the animal in each zone (frequency, f) was calculated by the program. Thigmotaxis (i) was calculated as $i = f_{\text{peripheral zones}}/f_{\text{all zones}}$. Thus, thigmotaxis is a relative number which varies from 0 to 1 and indicates the probability of an appearance in any of the peripheral zones of the arena. Time spent in the center of the arena (T_{center}) was analyzed as a complementary measure, equaling the summation of time spent in the 9 central zones (Σt_{1-9}) [52, 53].

Prepulse Inhibition of Acoustic Startle Reaction

All of the rats were habituated to the testing apparatus in a short session (a 5-min acclimatization period plus 5 single pulses) 2 days before the experiment. On the day of the experiment, ketamine (9 and 30 mg/kg or saline i.p.) was administered 5 min before the start of the testing session.

All testing was performed in 2 startle chambers (SRLAB; San Diego Instruments, San Diego, Calif., USA) consisting of a soundproof, evenly lit enclosure with a Plexiglas stabilimeter with an 8.7-cm inner diameter. A piezoelectric accelerometer detected all peak and average amplitudes of the startle response. These were digitized and stored on a computer hard drive. A dynamic calibration system was used to ensure comparable stabilimeter sensitivity across the test chambers. Sound levels were measured using a RadioShack sound level meter. A high-frequency loudspeaker mounted 24 cm above the Plexiglas cylinder inside the chamber produced both a background noise of 75 dB and an acoustic stimulus (pulse) of 125 dB. The experimental design was adopted from previous studies [53, 54]. After the acclimatization period (5 min), the test began with a first session consisting of 4 initial startle stimuli (125 dB). It was followed by a second session which consisted of 4 different trial types presented in a pseudorandom order: (1) single pulse – 125 dB broadband burst, 20 ms duration; (2) prepulse-pulse – prepulse 13 dB above the background noise, 20 ms duration, presented 100 ms before the onset of the 125-dB pulse alone; (3) prepulse alone – 13 dB above the background noise, 20 ms duration, and (4) no stimulus. Five presentations of each trial type were given, with a floating interstimulus interval of about 30 s. The PPI was expressed as the percentage of PPI [100 – (mean response for the prepulse-pulse trials/startle re-

sponse for the single-pulse trials) × 100]. The 4 single-pulse trials at the beginning of the test session were not included in the calculation of the PPI values. Animals with an average startle value lower than 10 were excluded from the calculation of the PPI and were marked as nonresponders.

EEG Experiments

Stereotactic Surgery

Rats were stereotactically implanted with 14 silver electrodes under halothane anesthesia, 7 days before the EEG recording. Twelve active electrodes were implanted into the surface of the cortex in homologous frontal, parietal and temporal regions of the right and left hemispheres. The coordinates for implanting the electrodes were adopted from a stereotactic atlas [55] and were calculated from the bregma: 5 mm anteriorly and ±2 mm laterally for the frontal association cortex (electrodes F3/F4); 2.2 mm anteriorly and ±3.2 mm laterally for the primary motor cortex (electrodes C3/C4); 3.8 mm posteriorly and ±2.5 mm laterally (electrodes P3/P4), and 4.5 mm posteriorly and ±4.5 mm laterally (electrodes P5/P6) for the medial and lateral parietal association cortex; 3.6 mm posteriorly and ±7.2 mm laterally for the temporal association cortex (electrodes T3/T4), and 8.3 mm posteriorly and 5.8 mm laterally for the secondary auditory cortex (electrodes T5/T6). The reference electrode was implanted above the olfactory bulb (fig. 1), and the ground electrode subcutaneously in the occipital region. All electrodes were fixed to the skull with Dentalon Plus dental cement. After surgery, each of the animals was individually placed in a plastic cage where it remained until the EEG recording. The day before EEG recording, a 14-pin connector was plugged to the electrodes and fixed with dental cement under short-term total halothane anesthesia.

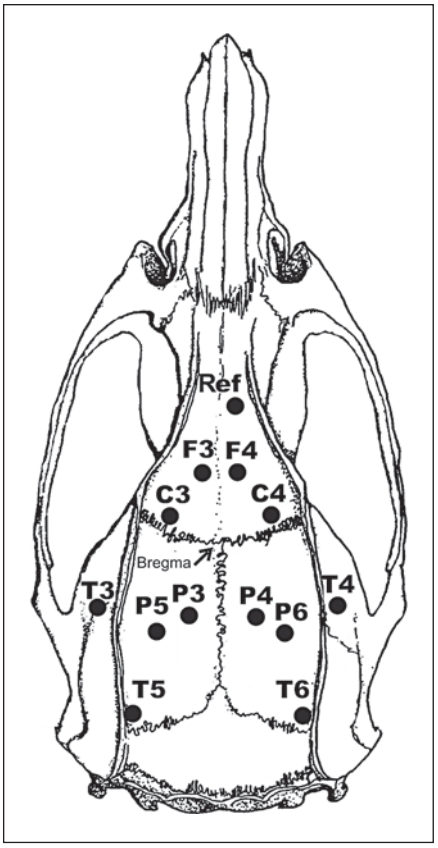

Fig. 1. Position of electrodes on the rat's skull. Coordinates refer to the bregma and are adopted from Paxinos and Watson [55]. F3/F4: frontal association cortex (A = +5.0 mm, L = ±2.0 mm). C3/C4: primary motor cortex (A = +2.2 mm, L = ±3.2 mm). P3/P4: medial parietal association cortex (A = –3.8 mm, L = ±2.5 mm). P5/P6: lateral parietal association cortex (A = –4.5 mm, L = ±4.5 mm). T3/T4: secondary auditory cortex (A = –3.6 mm, L = ±7.2 mm). T5/T6: temporal association cortex (A = –8.3 mm, L = ±5.8 mm). Ref: reference electrode (above bulbus olfactorii). A = Anteriorly (+) or posteriorly (–) from the bregma; L = laterally from the bregma.

EEG Recordings

All EEG recordings were performed between 8.00 and 12.00 h. Approximately 15 min before administration of the compound, the animals were deprived of food and water and connected to the EEG system in their home cages. A 10-min recording session was conducted immediately before treatment to provide a baseline condition. Subsequently, ketamine (9 or 30 mg/kg) or saline was administered intraperitoneally, and registration continued for another 30 min (total length of record: 40 min). The rats were able to move freely in their cage during all EEG recordings while being connected by a cable to a data acquisition system. Raw EEG signals were recorded using the BrainScope data acquisition system (Unimedis, Prague, Czech Republic) with an EADS-221 amplifier having a frequency band of 0.15–70 Hz. The system acquired the data with a 16-bit depth and 7.63 nV/bit resolution (i.e. approx. 130 bit/μV) with a dynamic range of ±500 μV. The data were recorded using a sampling rate of 250 Hz. EEG data were stored on a PC hard disk for offline processing and analysis. Each rat was recorded only once with the specific treatment. Animals were handled for a few seconds by an observer when there was suspicion of sleep (animals did not move and tended to close their eyes). Concomitantly, a mark in the EEG trace was made to signify this epoch, and these epochs were subsequently excluded from the analysis. However, this only happened in vehicle-treated animals.

EEG Signal Analysis

Eight animals for ketamine 9 mg/kg, and 10 animals for 30 mg/kg were included for signal analysis, with the others being excluded due to technical difficulties during recording and/or insufficient data quality. The EEG data were bandpass filtered with a linear finite impulse response (FIR) filter with 111 coefficients in the range of 0.5–45 Hz using WaveFinder version 2.3 software (Unimedis, Prague, Czech Republic). For a detailed description of FIR filters see Principe and Smith [56]. For each EEG recording session, 4 EEG segments (5 min in duration) were edited for further processing. The first EEG segment was selected from the baseline EEG record, the second segment of EEG was taken between 2.5 and 7.5 min, the third between 10 and 15 min, and the fourth between 20 and 25 min after the administration of the substance. Each 5-min EEG segment was subjected to editing procedures using the Neuroguide software (Neuroguide© NG-2.4.6; Applied Neuroscience Inc., St. Petersburg, Fla., USA), in which a 1- to 2-second template of 'clean', artifact-free EEG was selected.

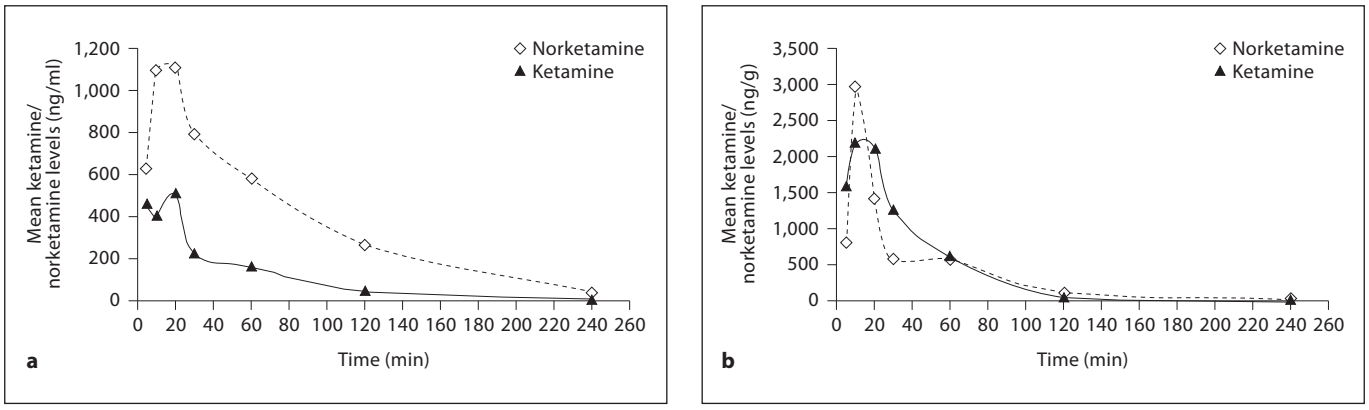

Fig. 2. Mean values of ketamine and norketamine levels in serum (**a**) and brain homogenate tissue (**b**).

This template was then used to compute matching amplitudes of EEG using flexible criteria of equal amplitudes for amplitudes that are ≤1.25 times larger. The decision as to which clean EEG sample multiplier was used was determined by the length of the sample (50 s as a minimum) and visual inspection of the digital EEG, and when split-half reliability and test retest reliability measurements were ≥0.95. Split-half reliability is the ratio of variance between the odd and even seconds of the time series of selected digital EEG, while test retest reliability is the ratio of variance between the first half versus the second half of the selected EEG segments (variance = sum of the square of the deviation of each time point from the mean of the time points). A test retest reliability of >0.90 is commonly accepted in the scientific literature. For a detailed description of editing procedures, see Thatcher et al. [57, 58]. After multiple visual inspections and selection of clean EEG samples, the edited samples varied in length from 50 to 179 s (mean: 91.24 s; SD: 4.42 s).

The spectral content of the EEG was quantified by fast Fourier transform analysis. The EEG was downsampled to 128 Hz, and spectra between 1 and 40 Hz were calculated at a 0.5-Hz resolution for each 2-second epoch. The autospectra of individual electrodes and cross-spectra of selected electrode pairs were obtained for the following frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–25 Hz), high beta (25–30 Hz) and gamma (30–40 Hz). EEG coherence was derived from autospectral and cross-spectral values for 30 intrahemispheric electrode pairs (F3-C3, F3-P3, F3-P5, F3-T3, F3-T5, C3-P3, C3-P5, C3-T3, C3-T5, P3-P5, P3-T3, P3-T5, P5-T3, P5-T5 and T3-T5 on the left hemisphere, and analogously on the right) and 6 interhemispheric electrode pairs (between electrodes F3-F4, C3-C4, T3-T4, P3-P4, P5-P6 and T5-T6).

Statistical Analysis

Statistical analysis of all data from behavioral experiments was performed using the program SigmaStat version 3.0 by one-way analysis of variance (ANOVA). When appropriate, comparisons between treatment groups and controls were made, using the Bonferroni post hoc test. For analysis of locomotor effects in 5-min intervals, a two-way repeated-measures (RM) ANOVA with treatment as between-subject factor and time as repeated-measures factors was initially used. This was followed by one-way RM ANOVA for each treatment group (with time as a repeated-measures factor and a first interval as a control interval for post hoc analysis) and finally by one-way ANOVA for treatment effects in each time interval. All post hoc analyses were again conducted using a Bonferroni post hoc test. The differences between groups with $p < 0.05$ and lower were considered significant.

EEG data were analyzed by Neuroguide software version 2.4.6. (Applied Neuroscience Inc.). The mean power was calculated from individual values from each animal, and a statistical analysis was made by SigmaStat version 3.0, using a paired t test. EEG coherence statistical analysis was made by Neuroguide software, also using a paired t test. The difference between groups with $p < 0.05$ was considered significant. Each animal served as a control for itself (baseline data were compared to data from each of the 3 intervals after administration).

Results

Time Profile of Serum and Brain Levels of Ketamine and Norketamine

The levels of ketamine and its metabolite norketamine determined in blood sera and brain tissues of rats sacrificed 5, 10, 20, 30, 60, 120 or 240 min after the intraperitoneal dose are summarized in figure 2. The concentration values are expressed as free bases. There was a rapid increase in ketamine levels both in serum and brain after drug administration. Production of the metabolite norketamine was rapid, and its abundance in serum exceeded that of the parent drug. The peak level of ketamine in the brain was achieved within 10 min and remained until 20 min after administration with only a slight temporal delay after peak serum levels. Subsequently, the concentration continuously declined to 240 min. Brain concentrations of ketamine were significantly higher compared

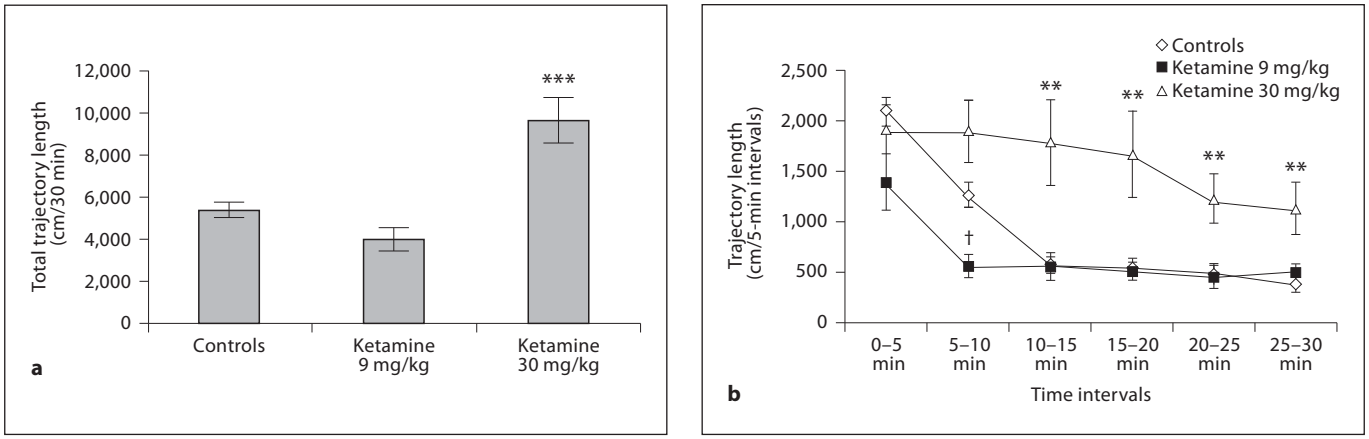

Fig. 3. The total distance travelled was significantly increased by ketamine 30 mg/kg (**a**). While ketamine 30 mg/kg significantly increased locomotion during the last 4 intervals, ketamine 9 mg/kg decreased locomotion during the second interval (**b**). Means ± SEM. ** $p < 0.01$, *** $p < 0.001$ versus the control group for ketamine 30 mg/kg. † $p < 0.05$ versus the control group for ketamine 9 mg/kg.

to those in serum: the mean concentrations were elevated approximately 3–5 times. The incorporation of the more polar metabolite norketamine into brain tissue from the blood was less efficient in relation to the parent drug; the levels of norketamine in brain slightly surpassed those in serum only shortly after dosage.

Behavioral Experiments

Open Field

The total distance travelled was significantly influenced by ketamine treatment [$F(2, 26) = 16.747$; $p < 0.001$]. Post hoc analysis showed that ketamine 30 mg/kg significantly increased locomotion compared to the control animals ($p < 0.001$), while the low dose was without effect (fig. 3a).

Analysis of 5-min intervals by two-way RM ANOVA showed an effect of treatment [$F(2, 173) = 19.341$; $p < 0.001$] and time [$F(5, 173) = 14.516$; $p < 0.001$], and an interaction of treatment × time [$F(10, 173) = 2.369$; $p = 0.013$]. Subsequent one-way RM ANOVA revealed the effect of time in control animals [$F(5, 45) = 53.557$; $p < 0.001$] and in animals treated with ketamine 9 mg/kg [$F(5, 45) = 7.796$; $p < 0.001$], but not in those treated with ketamine 30 mg/kg [$F(5, 40) = 1.356$; $p = 0.261$]. Post hoc analysis showed that the total distance travelled decreased constantly in controls and in animals treated with ketamine 9 mg/kg ($p < 0.001$ for all intervals vs. the first one); in contrast, there was no such effect in animals treated with ketamine 30 mg/kg. Subsequent one-way ANOVA for treatment effect revealed a significant effect of ketamine treatment in all intervals except the first one: $F(2, 26) = 11.783$, $p < 0.001$ for 5–10 min; $F(2, 26) = 7.807$, $p = 0.002$ for 15–20 min; $F(2, 26) = 7.797$, $p = 0.002$ for 15–20 min; $F(2, 26) = 8.237$, $p = 0.002$ for 20–25 min, and $F(2, 26) = 6.107$, $p = 0.007$ for 25–30 min. Post hoc analysis showed that ketamine 30 mg/kg significantly increased locomotion in the last 4 intervals ($p < 0.01$), whereas ketamine 9 mg/kg slightly decreased locomotion during the second interval ($p < 0.05$) (fig. 3b).

Thigmotaxis was not affected by ketamine treatment [$F(2, 26) = 2.414$; $p = 0.109$]. On the contrary, there was a slight effect on time in the center [$F(2, 26) = 3.466$; $p = 0.046$]. While ketamine 9 mg/kg slightly decreased the time spent in the center when compared to controls, ketamine 30 mg/kg did the opposite. However, post hoc analysis did not reveal any difference for either 9 or 30 mg/kg ketamine treatment versus the control group. An additional post hoc analysis revealed a significant difference only between ketamine 9 and 30 mg/kg treatments ($p < 0.05$) (table 1).

Prepulse Inhibition of Acoustic Startle Reaction

Ketamine at either dose does not influence the startle amplitude in a way to reach statistical significance [$F(2, 26) = 1.454$; $p = 0.525$] (table 2). In contrast, PPI was significantly disrupted by ketamine administration [$F(2, 26) = 9.934$; $p < 0.001$]. Post hoc analysis revealed that both doses induced a deficit in PPI ($p < 0.01$ and $p < 0.001$) (fig. 4).

Table 1. Thigmotaxis results and time spent in center of arena

	Controls	Ketamine 9 mg/kg	Ketamine 30 mg/kg
Thigmotaxis	0.85 ± 0.02	0.92 ± 0.02	0.86 ± 0.03
T_{center}, s	82.6 ± 15.1	37.8 ± 18.7	153.5 ± 51.1

Data are presented as means ± SEM.

Table 2. ASR aplitude

	Controls	Ketamine 9 mg/kg	Ketamine 30 mg/kg
ASR amplitude, mV	124.44 ± 13.5	110.56 ± 8.36	98.26 ± 10.35

Data are presented as means ± SEM.

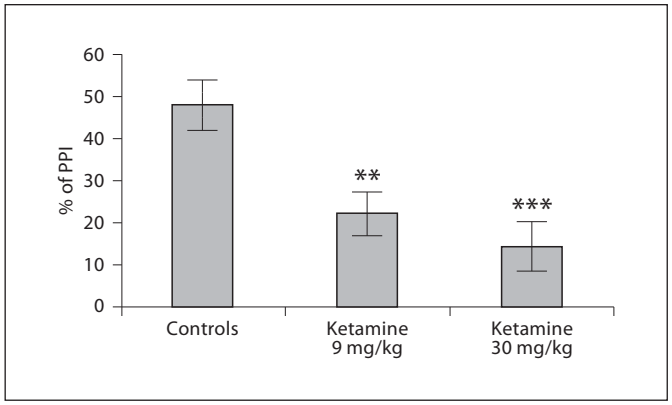

Fig. 4. PPI was significantly disrupted by ketamine. Means ± SEM. ** $p < 0.01$, *** $p < 0.001$ versus control group.

EEG Experiments

Absolute Power Spectra

There were no significant differences at any time in mean absolute EEG power for all EEG frequency bands in the control animals (fig. 5a). Ketamine 9 mg/kg produced a significant increase in absolute EEG power in the high beta and gamma bands at 2.5–7.5 min after administration, with mean powers of 114% ($p = 0.008$) and 122% ($p = 0.004$) of the baseline. The changes were present at almost all electrodes. Some minor changes (increases as well as decreases at 1–3 electrodes) were also seen in other frequency bands, mainly in the left hemisphere. At 10–15 min after administration, ketamine 9 mg/kg increased the mean absolute EEG power in the delta band; the mean power increased to up to 168% of the baseline ($p = 0.012$) at these times, and the effect was apparent at all electrodes. The effect was still apparent at 20–25 min after administration (mean power: 124% of the baseline), though it was insignificant. There were also some other changes (mainly increases) at single electrodes throughout the spectrum at these times; again they were more robust in the left hemisphere (fig. 5b).

Ketamine 30 mg/kg increased the mean absolute EEG power in all frequency bands and in all time intervals. The increases were present at all electrodes. The most robust were changes in the delta band (up to 230% of the baseline; $p < 0.001$ for all time segments), the high beta band (up to 222% of the baseline; $p < 0.001$ for 2.5–7.5 and 10–15 min, $p < 0.01$ for 20–25 min after administration) and the gamma band (up to 304% of the baseline; $p < 0.001$ for all time segments). In the theta band, the increase was up to 177% ($p < 0.001$ for 2.5–7.5 min and 10–15 min, $p < 0.01$ for 20–25 min after administration); in the alpha band, it was up to 187% ($p < 0.001$ for all time segments), and in the beta band, it was up to 175% ($p < 0.001$ for 2.5–7.5 and 10–15 min, $p < 0.05$ for 20–25 min after administration) of the baseline (fig. 5c, 6).

EEG Coherence

There were only minor changes in the control animals. These were mainly slight increases in frontoparietal and frontotemporal coherence in the delta and theta bands, and decreases in frontotemporal and temporoparietal intrahemispheric, and temporal and parietal interhemispheric coherence in the high beta and gamma bands, during 10–15 min and 20–25 min after administration of the vehicle (fig. 7).

Ketamine 9 mg/kg induced an increase as well as decreases in coherence throughout the spectrum. At 2.5–7.5 min after administration, it induced minor changes in coherence. Most changes were in the gamma band (fig. 8a). At 10–15 min after administration, the changes became more apparent, with the main findings being increases in frontal, frontoparietal and frontotemporal intrahemispheric, and frontal and temporal interhemispheric coherence in the delta, beta, high beta and gamma bands (fig. 8b). At 20–25 min after administration, the most prominent changes were increases in frontal, frontoparietal, frontotemporal and parietotemporal intrahemispheric, and frontal and temporal interhemispheric

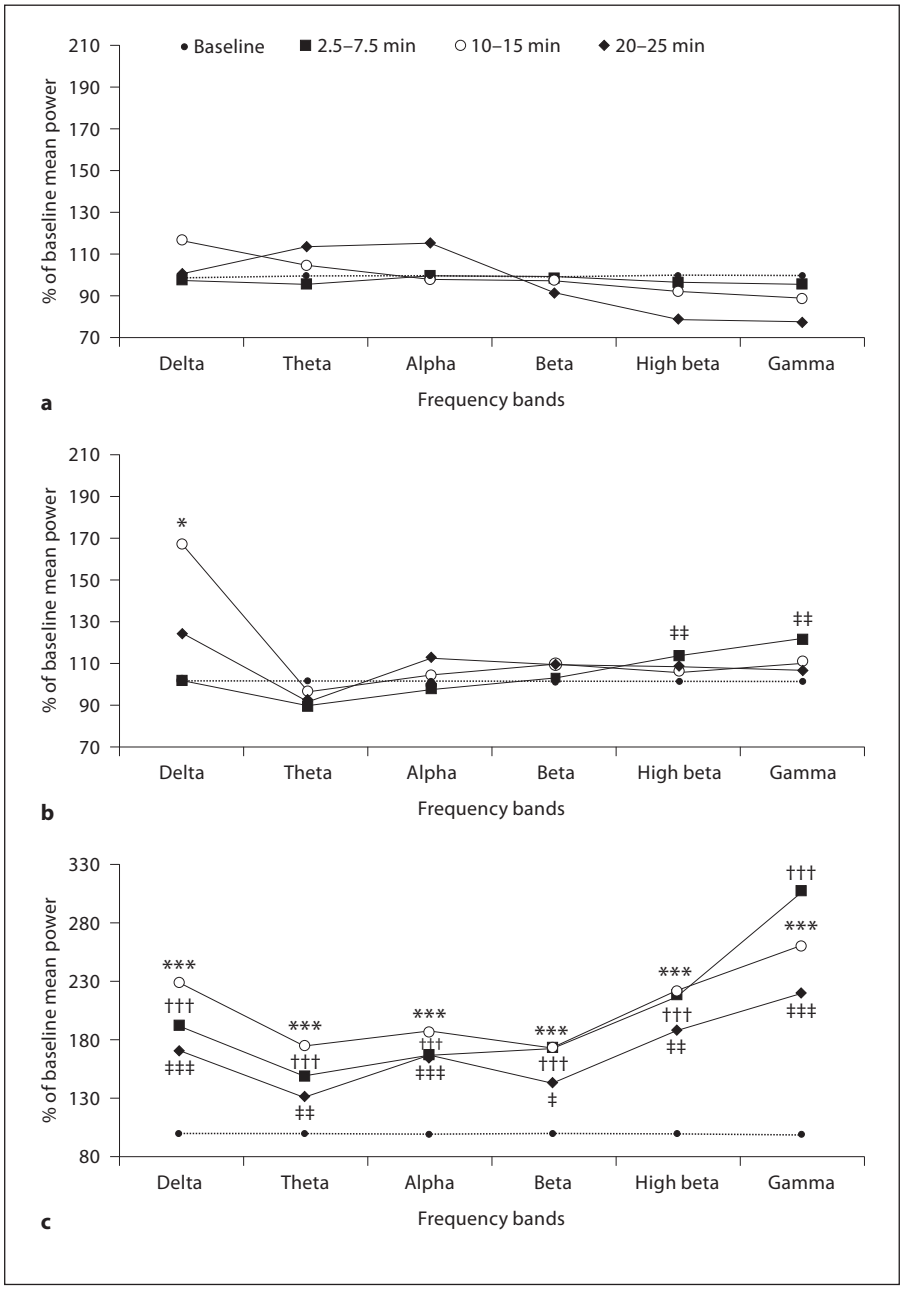

Fig. 5. Mean absolute power. Comparison of baseline record versus 2.5–7.5 min, 10–15 min and 20–25 min after ketamine 9 (**b**) or 30 mg/kg (**c**) or vehicle (**a**) administration. All data are expressed in percentages. † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ versus baseline for 2.5–7.5 min (paired t test). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus baseline for 10–15 min (paired t test). ‡ $p < 0.05$, ‡‡ $p < 0.01$, ‡‡‡ $p < 0.001$ versus baseline for 20–25 min (paired t test). **a** In control animals, the mean absolute EEG power did not significantly change in any of the tested periods and in any part of the spectrum. **b** Mean absolute power for ketamine 9 mg/kg. Ketamine 9 mg/kg increased the power in the theta band at 10–15 min after administration, and the power was significantly increased in the high beta and gamma bands at 2.5–7.5 min after administration. No other significant changes were observed. **c** Mean absolute power for ketamine 30 mg/kg. Ketamine 30 mg/kg increased the mean absolute power in all bands. The most robust changes were in the delta and gamma bands.

coherence in the beta, high beta and gamma bands. In the theta and alpha bands, only a minor decrease in frontotemporal intrahemispheric coherence was observed (fig. 8c).

Ketamine 30 mg/kg induced mainly increases in coherence throughout the spectrum and between almost all electrodes intra- as well as interhemispherically. At 2.5–7.5 min after administration, the only significant decrease observed was in frontotemporal and parietotemporal intrahemispheric coherence in the delta band. In all other frequency bands, only increases were present, with maxima in the beta, high beta and gamma bands (fig. 9a). At 10–15 min after administration, the overall increase in coherence became very robust throughout the spectrum (fig. 9b), and similarly so at 20–25 min after administration (fig. 9c). The dominating changes were most strongly expressed in the delta, beta, high beta and gamma bands during these 2 time segments. The most prominent

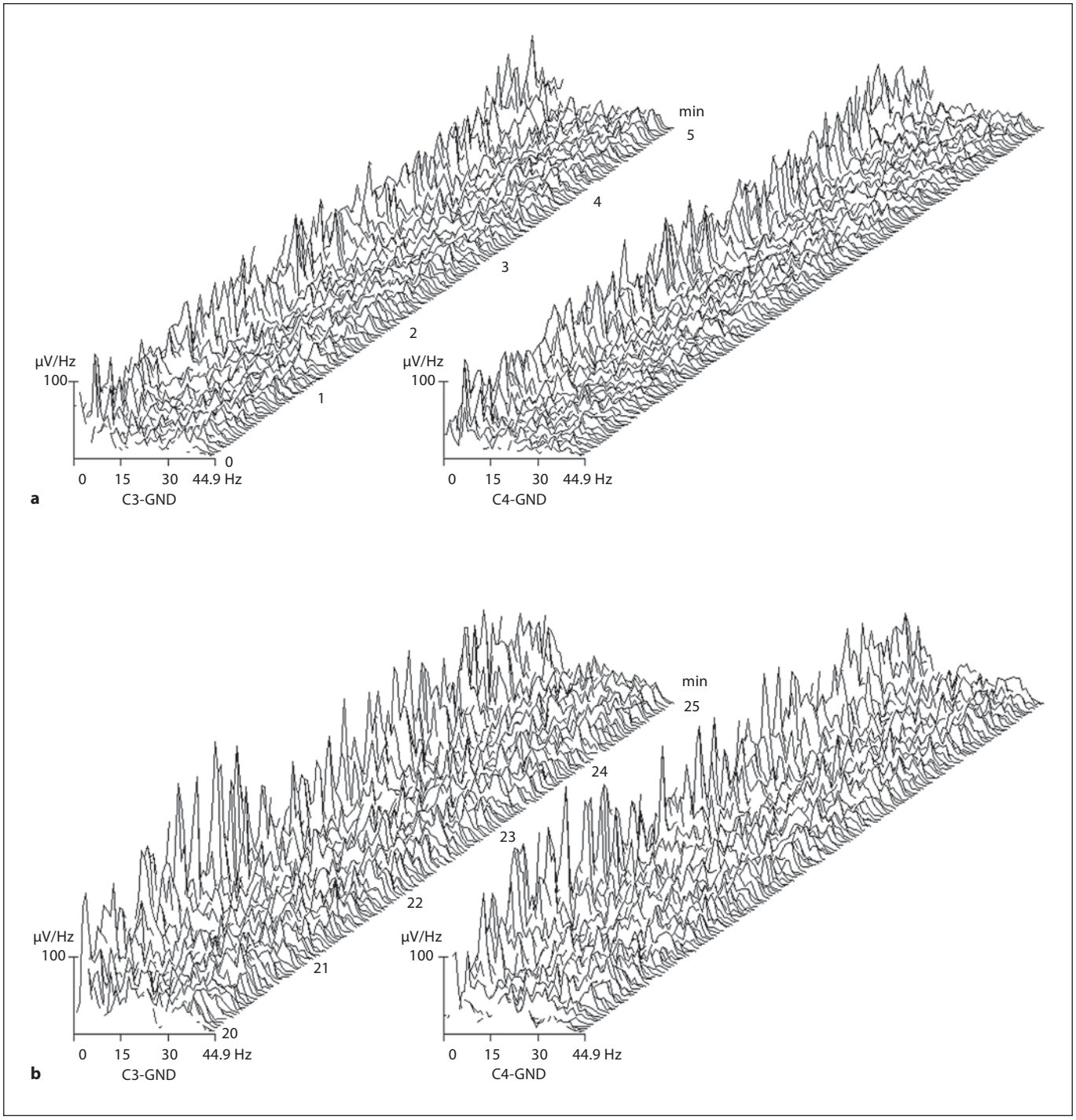

Fig. 6. An example of EEG spectra from a single animal treated with ketamine 30 mg/kg. Signals from electrodes C3/C4 are presented at 0–5 min (**a**) and 20–25 min (**b**) since the beginning of recording. The first epoch corresponds to drug-free baseline EEG, the second epoch corresponds to the peak effects of ketamine at 10–15 min after administration. These examples of EEG spectra were exported from WaveFinder version 2.3 software.

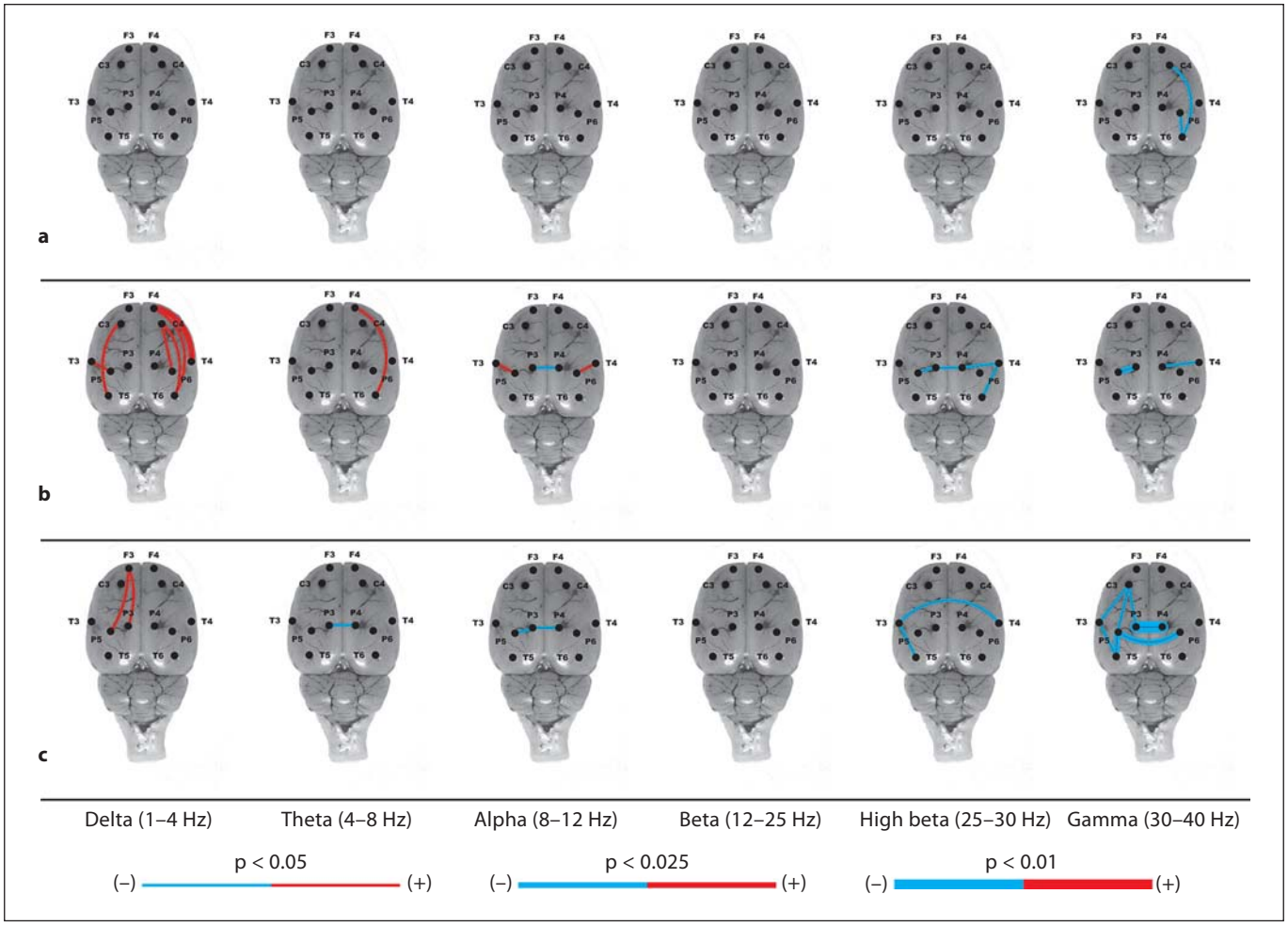

Fig. 7. EEG coherence for control animals 2.5–7.5 min (**a**), 10–15 min (**b**) and 20–25 min (**c**) after the administration of vehicle. Significant changes in EEG coherence after vehicle administration compared to the baseline record. Red: increase in coherence. Blue: decrease in coherence. The statistical significance of the changes found (p; paired t test) is expressed by the thickness of the line as displayed below the images.

changes were increases in frontal, frontoparietal, frontotemporal and parietotemporal intrahemispheric, and frontal and temporal interhemispheric coherence.

Discussion

As stated above, administration of NMDA antagonists at subanesthetic doses to rodents usually produces hyperlocomotor effects and disrupts sensorimotor gating. This was confirmed by our findings, where ketamine 30 mg/kg induced hyperlocomotion, and both doses of ketamine led to deficits in PPI. Even though we did not scale qualitative behavioral parameters, we observed severe ataxia along with hyperlocomotion, head waving and other stereotypy as well as flat body posture after ketamine 30 mg/kg during the EEG registration. Only minor behavioral changes and slight ataxia along with hypolocomotion were associated with ketamine 9 mg/kg. The hypolocomotion most likely reflects initial ataxia as is common with other psychedelic drugs, rather than stereotyped behavior as with the higher dose [44, 53–59]. The pharmacokinetics of ketamine revealed that behavioral experiments were performed in a period of time which corresponds to the highest brain concentrations of the compound and its main metabolite norketamine. Since hyperlocomotor effects of NMDA antagonists are interpreted as a model of positive symptoms of psychosis

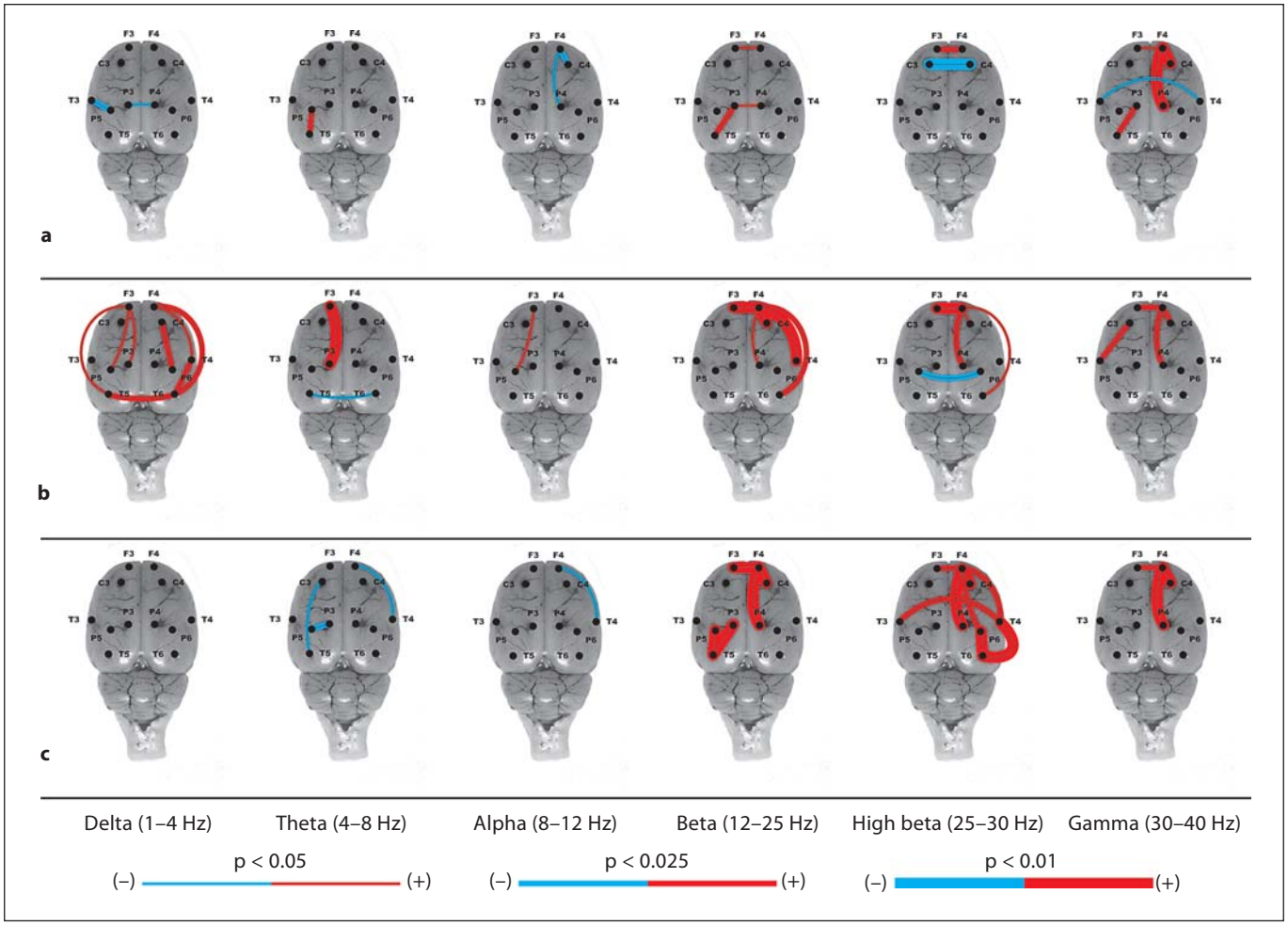

Fig. 8. EEG coherence for ketamine 9 mg/kg 2.5–7.5 min (**a**), 10–15 min (**b**) and 20–25 min (**c**) after administration. Significant changes in EEG coherence after ketamine 9 mg/kg administration were found compared to the baseline record. Red: increase in coherence. Blue: decrease in coherence. The statistical significance of changes found (p; paired t test) is expressed by the thickness of the line as displayed below the images.

[18–20], and the disruption of PPI indicates deficits in sensorimotor gating which are consistently present in schizophrenic patients [24], we can conclude that the behavioral effects of ketamine confirmed the reliability of this model.

The main findings of our study are represented by the analyses of the influence of ketamine on EEG. We have found specific dose-dependent changes in the QEEG parameters analyzed. Spectral analysis showed an increase in absolute power after both doses; the highest increases were achieved in the delta, beta and gamma bands. Changes were most prominent at 10–15 min after administration, which temporally correlates with the highest ketamine and norketamine levels in the brain. Previous EEG studies in rats based on visual analysis revealed that PCP and MK-801 produce effects in 3 dose-dependent stages: (1) cortical desynchronization, (2) an increase in amplitude of the high-frequency low-voltage cortical background, and (3) the appearance of slow wave-sharp wave complexes [60, 61]. Spectral analyses of NMDA antagonists have been performed by many authors; however, most of them concentrated on specific regions and usually used 1–4 electrodes. Various alterations have been described, most of which more or less congruently represent an increase in EEG power with increased wave amplitudes mainly in the delta-to-alpha bands (1–10 Hz). Some authors also positively correlate the delta-to-theta peak with locomotor changes and stereotypy [47, 62–66].

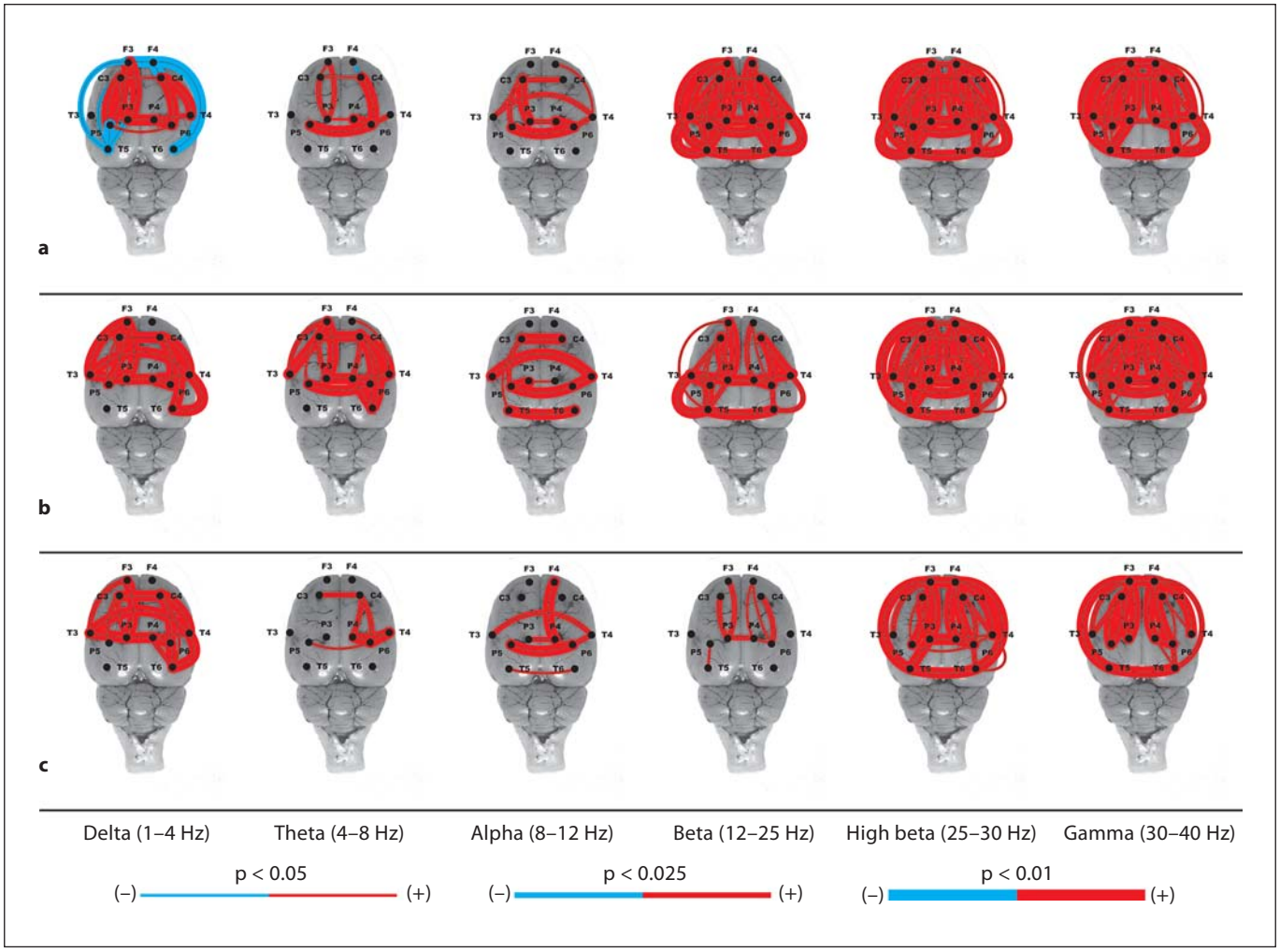

Fig. 9. EEG coherence for ketamine 30 mg/kg 2.5–7.5 min (**a**), 10–15 min (**b**) and 20–25 min (**c**) after administration. Significant changes in EEG coherence after ketamine 30 mg/kg administration were found compared to the baseline record. Red: increase in coherence. Blue: decrease in coherence. The statistical significance of changes found (p; paired t test) is expressed by the thickness of the line as displayed below the images.

Congruently, in our recent study with 4-bromo-2,5-dimethoxyphenethylamine (2C-B) and amphetamine, we have also found that both drugs induce a peak in theta (2C-B) and theta-to-alpha (amphetamine) power, which seems to correspond to their hyperlocomotor effects [48, 49, 67]. In line with these findings is that ketamine 30 mg/kg increased power in theta-to-beta bands along with hyperlocomotion; in contrast, the lower dose – which induced slight hypolocomotion – did not have such an effect. Comparably to our results, another group of authors has described increased hippocampal [39, 68] and subcortical and neocortical [38, 69] gamma power/oscillations after either PCP and/or MK-801 and/or ketamine. Interestingly, these oscillations do not seem to have a direct link to the hyperlocomotor effects of these compounds [69]. Sebban et al. [37] reported results similar to our findings. They found that in the frontal and sensorimotor cortices of the rat there was increased power at 1–3 Hz with low doses of PCP and MK-801, and decreased power between 9 and 30 Hz; however, higher doses of the drugs increased power in almost all frequency bands. Partly contradictory were the results by Dimpfel and Spuler [70], who described dose-dependent biphasic effects of NMDA antagonists on EEG spectra, with an initial decrease in power in most frequency bands with low doses of drugs, followed by increases with higher doses.

The most frequently reported EEG effect of ketamine on theta and gamma oscillations also seems to be valid for rats and mice [71, 72]. Interestingly, while the theta-to-beta bands were altered only with the higher ketamine dose and seemed to be specific for locomotor behavior, delta and gamma bands were influenced by both treatments and did not correlate to locomotion. As ketamine at both doses induced a deficit in PPI, these power increases might be specific for altered sensorimotor gating, but not for hyperlocomotion. Hence, taking into account our findings characterized by increased power in the delta and gamma bands with ketamine 9 mg/kg and by a global power increase with ketamine 30 mg/kg, most of the above mentioned studies are in good accordance with our recent results. Some similarities in EEG (changes in absolute as well as relative[1] theta-to-delta power) can be found between our experiments and in ketamine-anesthetized rats [46, 47]. However, the anesthetic doses in rats are typically in the range of 100–300 mg/kg and induce deep sedation; on the other hand, subanesthetic doses of ketamine within the range of 30–100 mg/kg induced stereotyped behaviors and ataxia [47] similarly to our setting. Thus, we assume that the power changes observed in the delta and theta bands are rather specific for the drug itself and do not correspond to the anesthetic effects.

The main finding in EEG coherence was an increase in coherence throughout the spectrum, most evident for ketamine 30 mg/kg. Some decreases in delta coherence were also observed during the onset of its action. Again, the magnitude of changes corresponded with brain levels of the drug and its main metabolite. In contrast, with ketamine 9 mg/kg there initially was little change in coherence, characterized by a decrease as well as increase, but later more increases were present. Thus, the effects of ketamine seem to be dose dependent and also biphasic. Since, to our knowledge, we have reported such analyses of EEG signals in rats for the first time, it is difficult to compare our coherence analysis to those by other authors. The only comparable data are from our laboratory, with 2C-B and amphetamine. These results show that 2C-B has biphasic effects on coherence: lower doses lead to general decreases in coherence, whereas higher doses induce an increase in coherence mainly in the high beta and gamma bands. However, some minor increases in the theta and alpha bands were also observed. On the other hand, amphetamine induced a robust increase in coherence in the theta and alpha bands, and a slight decrease in coherence in the beta band [48, 49, 67]. Again, observed increases in coherence correspond to locomotor changes. Interestingly, the lower-dose ketamine treatment, which was associated with hypolocomotion, initially induced some decrease in coherence. However, only minor increases in coherence were observed when compared to the higher dose. To date, other coherence analyses have successfully been applied to rats only in non-pharmacological settings [73–77]. A link to our results may be found in a study by Maloney et al. [76], who found an increase in coherence within the gamma range during 'active behavior' of the rat (e.g. moving, eating, grooming). Thus, the observed increase in coherence might be associated with hyperlocomotion and other behavior, e.g. stereotypy, induced by ketamine. Alternatively, the global increase in coherence in our setting may reflect cortical synchronization. It has been proposed by Lisman and Buzsaki [78] that gamma and theta oscillations in humans occur during cognitive processes. Based on animal studies, the authors proposed that theta and gamma oscillations together create a specific neural code, the function of which is to allow representation of multiple items in a defined order. They described the synchrony of theta and gamma waves in hippocampal place cell ensembles. According to their hypothesis, each of these neuronal ensembles is activated at a specific place of the environment. As the animal moves in the environment, a different ensemble is activated. In addition, each neuron systematically changes its preferred phase of spiking within the theta cycle in response to a different position on the track. Further firing occurs in earlier theta phases as the rat moves along a track and through the place field. Thus, it can be presumed that the hypersynchrony in theta as well as gamma bands induced by ketamine results in attenuation of these mechanisms. This in turn would make it impossible to appropriately interpret the place where this occurs and might lead to a disorganization of behavior in the open field and to concomitant hyperlocomotion and stereotypy. Thus, hypersynchrony induced by ketamine may reflect disturbed informational processing and could also reflect the alterations in place perception in our setting.

Despite several mechanisms underlying the increased EEG power and EEG coherence observed, we propose one explanation based on the recent theory of gamma oscillation generation [78]. Briefly, the increased coherence represents a higher synchrony of signals from two differ-

[1] We do not present relative spectra here since we have recorded the signal directly from the surface of the cortex, thus variables like bone thickness, skull resistance and impedance which change with age did not play a role in our setting.

ent regions [25, 26]. The blockade of NMDA receptors leads to partial elimination of cortical glutamatergic connections. Consequently, the feedback loop via γ-aminobutyric acid interneurons is not working properly and disinhibits glutamatergic pyramidal neurons [78], which become unplugged from regulatory inputs. This would allow subcortical structures to synchronize the cortical oscillations across the spectrum. Furthermore, the increase in EEG power can be explained by two different mechanisms – an increased synchrony of neurons under the electrode and/or an increased number of active neurons under the electrode [79]. Thus, hypersynchrony, which was mentioned in relation to coherence, can also be the direct cause of the increased power observed across the spectrum. Similarly, while there is an absence of the feedback loop, the animal cannot appropriately control its behavior. This might underlie mechanisms leading to stereotypy and disruption of sensorimotor gating.

Our intention in using a higher number of cortical electrodes than is usual in rodent experiments was to optimize the transfer of our findings to human schizophrenia QEEG studies. Most replicated QEEG findings in subjects with schizophrenia include an increase in low (delta and theta) and fast (beta) activities, and a decrease in alpha power [27, 28]. A recent metaanalysis evaluating delta and theta increases in QEEG studies of schizophrenia patients yielded effect sizes of 0.462 and 0.426, respectively [29]. Thus, a link between our model and these findings is evident. Connectivity studies made on schizophrenic patients are divided into resting and task-related conditions. Those comparable to our setting would be in the resting condition. However, irrespective of the condition, most studies found a decrease in coherence in schizophrenic patients [32–35, 80–86]. In contrast, in a few other studies, an increase [30, 31] as well as no difference [36] between patients and healthy controls were found. Also, there are some discrepancies between our preliminary results from comparable ketamine experiments in humans and those from our animal study: the EEG power was decreased in the delta-to-beta bands, while gamma power was increased; further, a robust decrease in EEG coherence in alpha and beta bands in contrast to an increase in all other frequency bands was present [87].

Thus, the results of our animal experiments, where mainly an increase was observed, do not correspond to the majority of these findings. There are many reasons which might underlie these discrepancies. Firstly, we have to accept that schizophrenia is a specifically human disease with a chronic course which has a much more complex pathophysiology (myelination abnormalities, altered pruning, altered dopamine turnover, serotonergic dysfunction, etc.) than the simple hypofunction of NMDA receptors [8, 88]. Secondly, even though animals can help us understand many mechanisms, there are always differences between animal and human models, e.g. different dosage regimens (intravenous infusion, much lower total doses of the drug), and different metabolism, blood-brain barrier and affinity of receptors. Thus, our animal ketamine model of psychosis represents a rough approximation to human conditions and schizophrenia. Another plausible explanation which might lend better insight into the discrepancy between the ketamine rodent model and human models and schizophrenia is related to the recording conditions. In most of the studies on schizophrenia (and also in relevant human ketamine studies [89]), the EEG is recorded during a resting state with the eyes closed. In contrast, in our experiments the rats had opened eyes and were freely moving, expressing hyperlocomotion after ketamine administration which temporally correlated with the most robust changes on the EEG. Experiments which would include splitting the EEG signal into active and passive behavior, as used by Maloney et al. [76], might better correspond to the human recording conditions. In relation to this, we evaluated the effects of ketamine in correlation with locomotor-behavioral activity in our recent experiments. Interestingly, the preliminary analysis of epochs corresponding to passive behavior showed that ketamine increased the power in delta and gamma bands and decreased coherence [90]. However, further investigations have to be carried out to confirm these preliminary findings.

Conclusions

To conclude, we have found that ketamine 30 mg/kg was effective in inducing hyperlocomotion, and that both doses (ketamine 9 and 30 mg/kg) induced deficits in sensorimotor gating as markers of psychosis-like behaviors. Ketamine induced robust and dose- and time-dependent increases in absolute EEG power in the delta and gamma bands, independently of locomotor changes. Ketamine 30 mg/kg also induced an increase in theta-to-beta power, which seemed to correlate to its hyperlocomotor effects. EEG coherence was also increased throughout the spectrum, mainly after the higher dose when compared to the drug-free condition. All EEG changes were most pronounced at 10–15 min after administration and correlated with the highest concentrations of ketamine and

its metabolite norketamine in the brain. While power analysis revealed some similarities to findings in schizophrenic patients, the increased coherence is in contradiction to the generally described disconnection. We propose that the different recording conditions ('resting' in humans vs. 'freely moving' in rats) may underlie these discrepancies.

Acknowledgments

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