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The effect of ((−)-2-oxa-4-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY379268), an mGlu2/3 receptor agonist, on EEG power spectra and coherence in ketamine model of psychosis

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ABSTRACT

In the present study we investigated the potential antipsychotic effects of the mGlu2/3 agonist LY379268 on changes in EEG power spectra and coherence in the ketamine model of psychosis. In order to use behaviorally active drug doses, experiments detecting changes in locomotor activity and sensorimotor gating were also conducted. In EEG experiments, adult male Wistar rats were injected with ketamine 30 mg/kg i.p. and LY379268 3 mg/kg i.p. Cortical EEG was recorded from twelve (2 × 6) electrodes placed homolaterally on each hemisphere. To avoid interference with the behavioral hyperactivity of ketamine challenge, the behavioral activity of animals was simultaneously registered at the time of recording. Subsequent power spectral and coherence analyses were assessed in epochs corresponding to behavioral inactivity. Analysis of segments with behavioral activity compared to inactivity was also performed. The effects of LY379268 3 mg/kg i.p. on the deficits in sensorimotor processing and on hyperlocomotion induced by ketamine were evaluated in the test of prepulse inhibition of acoustic startle reaction (PPI ASR) and in the open field. LY379268 reversed the ketamine-induced hyperlocomotion but had no effect on ketamine-induced PPI deficits. In EEG epochs corresponding to behavioral inactivity ketamine decreased the power in the delta band, induced a power increase in the high frequency bands and globally decreased EEG coherence. Pretreatment with the LY379268 completely reversed the ketamine-induced power increase in high frequency bands and had a partial effect on EEG coherence. LY379268 alone induced a decrease of beta, high beta and low-gamma power, and an increase in coherence in high frequency bands. Additional analysis revealed that behavioral activity increases power as well as coherence in most frequency bands. In conclusion, agonism of mGlu2/3 receptors was effective in reversing most of the changes induced by ketamine, however due to the lack of effectiveness on PPI deficits its potential antipsychotic properties remain disputable.

1. Introduction

Functional brain imaging techniques in schizophrenia, including quantitative electroencephalography (qEEG), have yielded to a theory that the disorder can be characterized as a functional brain disconnection syndrome. In schizophrenic patients, qEEG studies consistently show an increase in power in slow waves (delta–theta) over frontal regions (Bourtos et al., 2008; Itil, 1977; Sponheim et al., 1994, 2000) in resting conditions and abnormalities in the high frequency range (gamma) in both pre-stimulus and stimulus evoked paradigms (Gandal et al., 2011; Krishnan et al., 2009; Sun et al., 2011). Gamma oscillations are thought to mediate perception processes and cognitive functions which are typically disturbed in schizophrenia. Another qEEG parameter, EEG coherence — a measure of brain functional connectivity — is also frequently affected in patients. However, due to various EEG recording conditions, medication and the heterogeneity of the disease, results obtained from schizophrenic patients are inconsistent, showing an increase as well as decrease in coherence (Bob et al., 2008; Bucci et al., 2007; Nagase et al., 1992). Nevertheless, most authors state that neuroleptic-free schizophrenic patients show a decreased fronto-temporal coherence in resting as well as task-related conditions (Ford et al., 2002; Higashima et al., 2007; Tauscher et al., 1998; Yeragani et al., 2006). An abnormal fronto-temporal connectivity has been described most consistently in other imaging studies (Friston and Frith, 1995; Horacek et al., 2006; Lawrie et al., 2002).

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Studies using NMDA antagonists as models of psychosis (Krystal et al., 1994; Lahti et al., 2001) have led to a theory of dysfunctional NMDA receptors in schizophrenia (Bubenikova-Valesova et al., 2008). It was proposed that the blockade of NMDA receptors on gamma-aminobutyric acid (GABA)ergic interneurons results in disinhibition of cortical excitatory pathways producing the hyperglutamatergic state (Bubenikova-Valesova et al., 2008; Olney et al., 1999). According to the recent theory, activated fast-spiking interneurons as well as thalamo-cortical loops and primary sensory cortices both play a fundamental role in gamma oscillation generation. In as much, an increase in baseline gamma oscillations in awakened rats has been observed after the acute administration of NMDA antagonists (Ehrlichman et al., 2009; Hakami et al., 2009; Pinault, 2008). This is also consistent with our previous study (Palenicek et al., 2011b) where ketamine showed an increase in absolute power in delta, beta and gamma bands in EEG traces that comprised segments corresponding to behavioral activity. Since metabotropic glutamate mGlu2/3 receptors play a crucial role in the regulation of glutamate release at the synapse, agonism at these receptors has been proposed to have antipsychotic potential (Chaki, 2010; Marek, 2010; Moghaddam and Adams, 1998; Patil et al., 2007). In line with this hypothesis, agonist activation of these receptors reduces glutamate excitatory postsynaptic potentials (EPSPs) (Anwyl, 1999) and glutamate release (Imre et al., 2006; Imre, 2007). In agreement, mGlu2/3 agonists also showed a unique ability to normalize aberrant gamma oscillations induced by an NMDA antagonist in rats (Jones et al., 2012).

Assuming that the glutamatergic dysfunction might be an underlying mechanism leading to psychosis, gamma abnormalities and disconnection, we examined the effect of the mGlu2/3 agonist LY379268 on EEG power spectra and coherence after acute administration of ketamine in freely moving rats. Before the EEG experiments we also examined the effects of the mGlu2/3 agonist on hyperlocomotion and on disruption of prepulse inhibition (PPI) induced by ketamine (parameters generally used as models of positive symptoms and deficits in sensorimotor processing in psychosis (Bubenikova-Valesova et al., 2008)). The reasons were: 1) to evaluate/confirm the potential antipsychotic activity of the mGlu2/3 agonist in a behavioral study and 2) to determine a behaviorally efficient dose of the drug to be further used in the EEG experiments.

With the intention of obtaining EEG data with translational validity to human findings, the following approaches were combined: 1) a simultaneous recording of EEG from multiple (12 active) cortical electrodes from frontal, parietal and temporal regions was performed and 2) to avoid interference of the EEG signal with the stimulatory activity of ketamine (Palenicek et al., 2011b, 2012), the EEG signal was split and analyzed only in epochs corresponding to behavioral inactivity (a model of "resting EEG"). In addition, a comparison of EEG signals from epochs corresponding to behavioral activity versus inactivity was made to elucidate/confirm the direct impact of behavior on EEG.

2. Material and methods

2.1. Animals

All experiments were performed on adult male experimentally naive Wistar rats (specific pathogen free, 250–350 g b.w.) obtained from Biotest Inc. (Konárovice, Czech Republic). Each rat was tested only once. Animals were habituated to the animal facility a minimum of 5 days prior to testing. The rats were housed by pairs in plastic cages and maintained on a 12 h light/dark cycle beginning at 6 a.m., ambient temperature of 21–24 °C and humidity of 40% with standardized diet and water available ad libitum. All experiments were carried out between 7 a.m. and 2 p.m. The experimental groups consisted of 12 rats (EEG experiments) or 10 rats (behavioral experiments). All experimental procedures were approved by the Expert Committee for Protection of Experimental Animals of the 3rd Medical Faculty of Medicine, Charles University, Prague, Czech Republic and were performed in accordance with the Animal Protection Act of the Czech Republic and respected the Guidelines of the European Union Council (86/609/EU).

2.2. Drugs

Ketamine hydrochloride (Narketan 10 A.U.V. inj 50 ml, Chassot, United Kingdom) was diluted in physiological saline to achieve the appropriate concentration. Doses of 9 and 30 mg/kg were used in the behavioral experiments, while in the EEG experiments only the higher dose was used (known to exert full behavioral effects on locomotion as well as PPI (Palenicek et al., 2011b)). A selective mGlu2/3 agonist, LY379268 ((−)-2-oxa-4-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid, Tocris, United Kingdom) in the dose of 3 mg/kg was dissolved in a physiological saline solution (0.9% NaCl w/v). The dose was chosen based on literature research as being active in behavioral as well as electrophysiological experiments (Galici et al., 2005; Imre et al., 2006; Jones et al., 2012). Control animals were given a saline solution injection. The drugs and/or vehicle were administered intraperitoneally (i.p.) in a volume of 2 ml/kg of body weight.

2.3. Behavioral experiments

In order to minimize the number of animals and due to the fact that the behavioral experiments were performed at a similar time as to our previous study (Palenicek et al., 2011b), identical data from animals treated solely with ketamine were used. Locomotor activity and prepulse inhibition were also analyzed in a design comparable to our previous studies e.g. (Palenicek et al., 2008, 2011a).

2.3.1. Locomotor activity in the open field test

Animals were injected with LY379268 (3 mg/kg i.p.) 15 min and ketamine (9 or 30 mg/kg i.p.) 5 min before the start of the experiment. Each rat was then placed into the center of a square black plastic box arena (68 * 68 * 30 cm) and was registered for 30 min. The arena was located in a soundproof and equally-lit room. The locomotor activity (trajectory length in a novel environment) was recorded and analyzed by an automatic video tracking system for recording behavioral activities (EthoVision Color Pro v. 3.1.1, Noldus, Netherlands).

2.3.2. Prepulse inhibition of the acoustic startle reaction (PPI ASR)

Drugs were administered in the same way as in the locomotor experiments. The startle reaction and prepulse inhibition were measured in startle chambers (SRLAB, San Diego Instruments, California, USA). Each chamber was ventilated, illuminated and contained a clear Plexiglas restraint cylinder with an 8.7 cm inner diameter resting on a platform connected to a piezo-electric accelerometer, which detected the startle response and amplitude. A high-frequency loudspeaker, mounted 24 cm above the Plexiglass cylinder, produced a continuous background noise of 75 dB and the various acoustic stimuli. A Radioshack sound level meter was used to dynamically acquire precise sound levels. The experiment started with an acclimatization period of 5 min, where the background noise (a 75 dB white noise) was presented. The background noise then continued throughout the remainder of the test session. After the acclimatization period (5 min), the test began with a first session consisting of 4 initial startle stimuli (125 dB). This 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 session contained a total of 24 trials and lasted approximately 17 min. The PPI was expressed as the percentage of PPI [100 − (mean response for the prepulse–pulse trials/startle response

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 non-responders.

2.4. EEG experiments

2.4.1. Stereotactic surgery and EEG recording

EEG experiments were performed comparably as described in our previous studies (Palenicek et al., 2011b, 2012).

2.4.2. EEG surgery

Seven days before EEG recording, the rats were anesthetized with halothane and 14 silver-plated electrodes (12 active) were implanted on the top of the cortex above the frontal, parietal and temporal cortices. The stereotactic coordinates from bregma (Paxinos and Watson, 2005) were: A +5 mm and L ±2 mm for the frontal association cortex (electrodes F3/F4), A +2.2 mm and L ±3.2 mm for the primary motor cortex (electrodes C3/C4), A −3.8 mm and L ±2.5 mm (electrodes P3/P4) and A −4.5 mm and L ±4.5 mm (electrodes P5/P6) for the medial and lateral parietal association cortex, A −3.6 mm and L ±7.2 mm for the temporal association cortex (electrodes T3/T4) and A −8.3 mm and L ±5.8 mm for the secondary auditory cortex (electrodes T5/T6). The reference electrode was implanted above the olfactory bulb and the ground electrode subcutaneously in the occipital region. All electrodes were fixed with dental cement. The position of the active electrodes is shown in Fig. 1. One day before EEG recording, a 14 pinned connector was mounted to the electrodes and fixed with dental cement under short-term (10 min) total halothane anesthesia.

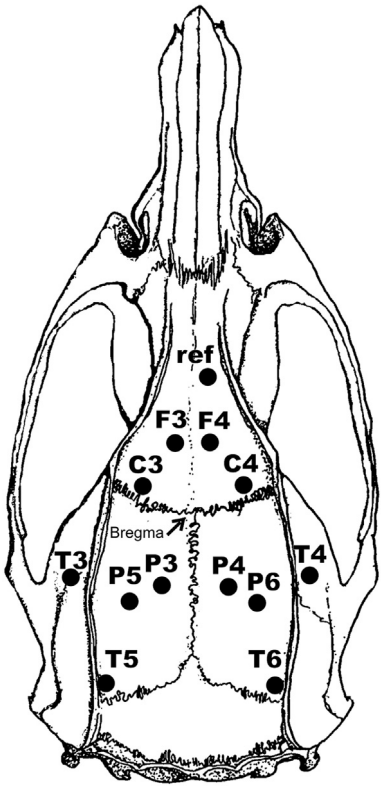

Fig. 1. Position of electrodes on the rat's skull. F3/F4 corresponds to electrodes on the left and right frontal association cortex, C3/C4 to the primary motor cortex, P3/4 and P5/6 to the medial and lateral parietal association cortex, T3/4 to the temporal association cortex and T5/6 to the secondary auditory cortex (electrodes T5/T6). Ref = reference electrode.

2.4.3. EEG recordings

The rats were connected with a cable suspended from an above arm holder (and attached to the digital amplifier system BrainScope (Unimedis, Prague). The rats were able to move freely in their cages. The total length of each recording was 50 min. The first 10 min corresponded to the baseline recording, subsequently the drugs were administered. Ketamine 30 mg/kg i.p. or LY379268 3 mg/kg i.p. alone were injected immediately after the first 10 min of the baseline EEG recording. When the drugs were co-administered, LY379268 3 mg/kg i.p. was applied after 10 min of the baseline recording followed by ketamine 30 mg/kg i.p. another 10 min later. During the 50 minute recording period, the animal's behavior was continuously observed and registered in the Activities © program by an experienced observer in order to differentiate between active (walking, running, grooming, rearing, sniffing while moving the whole body) and quiet behavior/behavioral inactivity (immobility, sniffing without moving the whole body, small head movements and small movements without displacing the limbs). Epochs corresponding to the drug administration were marked as artifacts and were excluded from the analysis. Finally, the animals were handled for a few seconds by an observer when a suspicion of sleep was present (no movement with a tendency to close their eyes). Concomitantly, a mark in the EEG trace was made to signify this epoch and the epochs were subsequently excluded from the analysis.

2.4.4. EEG signal analysis

The control group consisted of 10 animals, 13 animals were in the ketamine 30 mg/kg group, 10 in the LY379268 3 mg/kg group and 11 animals in the ketamine 30 mg/kg + LY379268 3 mg/kg group. Others from the total number of animals (n = 48) were excluded from the analysis due to technical difficulties (e.g. inefficient/no signal during recording). WaveFinder v. 2.6. software (Unimedis, Prague, CZ) was used to separate the epochs of the signal corresponding to behavioral activity and inactivity according to the matrix obtained from the Activities © program. A bandpass filter with a linear FIR (Finite Impulse Response) filter and 111 coefficients in the range 0.5–40 Hz was applied to the EEG data during this splitting procedure (for a detailed description of the FIR filters see Principe and Smith, 1986).

Subsequently, traces were imported while being automatically downsampled to 128 Hz in Neuroguide software v. 2.4.6. (c. 2002–2008 Applied Neuroscience Inc., St. Petersburg, FL, USA) for further analysis. Two EEG segments were carefully selected by visual inspection from the traces corresponding to behavioral inactivity by an experienced observer for further processing. The first EEG segment consisted of the baseline EEG recording; the second was selected from the data after the administration of the substances. Selection of the traces after the drug administration was made in a time window that covered the peak effect of the ketamine, which is 10–20 min after i.p. administration (Palenicek et al., 2011b). Since pretreatment with LY379268 was 10 min before the ketamine administration, data in this subgroup were selected 10 min after ketamine administration. Congruently, the same time window but starting 20 min after drug administration was included in the analysis of the vehicle and LY379268 treated animals. In the vehicle and ketamine treated animals, EEG segments were also selected corresponding to behavioral activity after the administration of the vehicle or ketamine. The semiautomatic data selection process consisted of 3 steps: 1) Initially, a two to five second template of “clean”, artifact-free EEG was visually selected (covering all typical EEG patterns present within the recorded signal) using the Neuroguide software. 2) This template was then used to compute the matching amplitudes of EEG using flexible criteria of equal amplitudes to amplitudes that are ≤1.25 times larger and to select the corresponding data. 3) The decision as to which clean EEG sample multiplier is used was determined by the length of the sample (30 s as a minimum), visual inspections of the digital EEG and when split-half reliability and test re-test reliability

measurements were ≥0.90.[1] After multiple visual inspections and selection of clean EEG samples, the samples varied in length from 32 to 217 s. The mean length (±SEM) of the selected signal for baseline inactivity was: 1) 75.9 s (±7) for the vehicle, 2) 98.2 s (±10.6) for ketamine, 3) 81 s (±3.01) for LY379268 and 4) 71.6 s (±7.3) for ketamine + LY379268. For periods of inactivity after administration it was: 1) 81.9 s (±3) for the vehicle, 2) 101.5 s (±12.7) for ketamine 3) 81 s (±3.69) for LY379268 and 4) 75.7 s (±9.7) for ketamine + LY379268. The mean length of the selected signal from active periods was: 1) 105.2 s (±11.3) for the vehicle and 2) 126.9 s (±7.8) for ketamine.

A Fast Fourier Transformation (FFT) was then applied to the selected data. Absolute as well as relative power spectra between 1 and 40 Hz were calculated at a 0.5 Hz resolution for each 2-s epoch. The FFT mean, variance, standard deviation, sum of squares, and squared sum of the real (cosine) and imaginary (sine) coefficients of the cross-spectral matrix were computed across the sliding average of the selected EEG for all 12 leads for the total number of 101 frequencies and 1919 log transformed elements for each subject at a 0.5 Hz resolution (0.5–40 Hz). This created the basic spectral measurement sets and their derivatives. Cross-spectral power was calculated as a square root of the sums of squares of the real and imaginary coefficients and auto-spectral power which is the diagonal of the cross-spectral matrix where the imaginary coefficient = 0 and power = sine square. The auto-spectra of the individual electrodes and cross-spectra of the selected electrode pairs were obtained in 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 low-gamma (30–40 Hz). EEG coherence — a quantitative measure of similarity between two EEG signals recorded over different brain regions — was calculated as a square of the cross-spectrum divided by the product of the two auto-spectra for 30 intra-hemispheric 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, T3–T5 on the left hemisphere and analogically on the right) and 6 inter-hemispheric electrode pairs (between electrodes F3–F4, C3–C4, P3–P4, P5–P6, T3–T4, T5–T6).

2.5. Statistical analyses

Two-way Analysis of Variance (ANOVA) followed by the Student–Newman–Keuls post hoc test was performed using the program Statistica v. 9.0 in the behavioral experiments and in the analysis of time spent in behavioral activity during the EEG registration. The mean absolute and relative power (from all electrodes) was calculated from the individual values exported from the Neuroguide software. EEG has a high inter-individual variability but high intra-individual stability, leading to possible false positive differences in baseline recordings when relatively small groups are used. Therefore, the data were initially analyzed by the paired *T*-test where each animal served as a self-control (baseline data vs data after the administration or segments corresponding to behavioral activity vs inactivity; Sigmastat v. 3.0.). Subsequently, to determine the differences between the treatment groups, power spectra were analyzed by ANCOVA with a post-hoc Student–Newman–Keuls test where the treatment factor was within the subject factor and the baseline was used as a covariate (Statistica v. 9.0). Using the baseline as a covariate prevents the risk of type I errors where the baseline recordings are different between groups. Coherence statistics were calculated between all of the available pairs of EEG recordings by the paired *T*-test (NeuroStat version 2.0, part of Neuroguide software). In all of the analyses, the level of significance was set at $p < 0.05$.

[1] Split-half reliability is the ratio of variance between the odd and even seconds of the time series of selected digital EEG, while test re-test reliability is the ratio of variance between the first half vs. 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). Tests re-test reliability of >0.90 is commonly accepted in scientific literature. For a detailed description of semiautomatic data selection procedures see Thatcher et al. (1987, 2003).

3. Results

3.1. Locomotor activity

Two way ANOVA of the total trajectory length showed a significant effect of the ketamine treatment ($F(2,54) = 12.648$, $p < 0.001$) and LY379268 treatment ($F(1,54) = 14.808$, $p < 0.001$), but no interaction between factors ($F(2,54) = 1.553$, $P = 0.221$). The total distance was increased by ketamine 30 mg/kg ($p < 0.05$) (*), on the contrary LY379268 3 mg/kg alone decreased the locomotion of animals ($p < 0.05$) (*). LY379268 3 mg/kg blocked ketamine 30 mg/kg induced hyperlocomotion ($p < 0.01$) (++) (Fig. 2a).

3.2. Prepulse inhibition of acoustic startle reaction

Startle reaction was significantly affected by ketamine ($F(2,53) = 11.526$, $p < 0.001$), LY379268 ($F(1,53) = 11.845$, $p = 0.001$) and an interaction of factors was also present ($F(2,53) = 4.209$, $p < 0.05$). However, post hoc analysis only showed the significant increase of startle in animals treated with LY379268 3 mg/kg compared to the vehicle ($p < 0.001$) (***) (Table 1).

PPI was significantly disrupted by both ketamine ($F(1,53) = 4.236$, $p < 0.05$) and LY379268 ($F(2,53) = 18.972$, $p < 0.001$) treatments, however no interaction of factors was present. Post hoc tests showed that both doses of ketamine and LY379268 3 mg/kg alone significantly disrupted PPI ($p < 0.05$–$p < 0.01$) (*–**). LY379268 3 mg/kg had no effect on the PPI disruption induced by ketamine, on the contrary it insignificantly potentiated the ketamine disruptive effect (PPI yielded negative values; differences from the vehicle were in the range $p < 0.01$–0.001) (**–***) (Fig. 2b).

3.3. Power spectra — epochs of behavioral inactivity

3.3.1. Comparisons to baseline using paired T-tests

Animals receiving the vehicle (saline) exhibited no major alternations in mean absolute EEG power (however a trend to increased delta was observed) and a slight increase in mean relative power in the delta band (110% of the baseline, $t = -2.33$; $p < 0.05$).

Ketamine 30 mg/kg led to a significant decrease in mean absolute power in the delta and theta bands (61% and 78% of the baseline; $t = 3.3$ and $t = 2.88$, $p < 0.01$ and $p < 0.05$), on the contrary an increase in the low gamma band (172% of the baseline; $t = -2.89$, $p < 0.05$), and an increasing trend in the high beta power were also observed (129% of the baseline; $t = -2.1$, $p = 0.057$). In the relative power spectra ketamine decreased the delta power (81% of the baseline; $t = 2.67$, $p < 0.05$) and again increased the power in the beta, high beta and low gamma bands (117%, 146% and 189% of the baseline, $t = -4.1$, -5.92 and -5.79, $p < 0.001$ for all bands). All of the above-described changes were present on almost all of the single electrodes.

LY379268 3 mg/kg induced a significant decrease in the mean beta, high beta and low gamma absolute power (72%, 61% and 61% of the baseline; $t = 7.78$, 8.01 and 7.71, $p < 0.001$ for all bands). The decrease was also observed in the relative power spectra but the significance was reached only for the high beta and low gamma bands (74% of the baseline in both cases; $t = 3.07$ and 3.22, $p < 0.05$ and $p < 0.01$). Again, all of the changes were present on almost all of the single electrodes.

Co-administration of LY379268 3 mg/kg and ketamine 30 mg/kg yielded a decrease in the absolute beta and high beta power (78% of the baseline for both bands; $t = 5$ and 5.2, $p < 0.001$ for both bands), while in relative power only the beta band was decreased (89% of the baseline, $t = 2.79$, $p < 0.05$). Again, the significant decreases were present on all of the electrodes in both hemispheres. No changes in

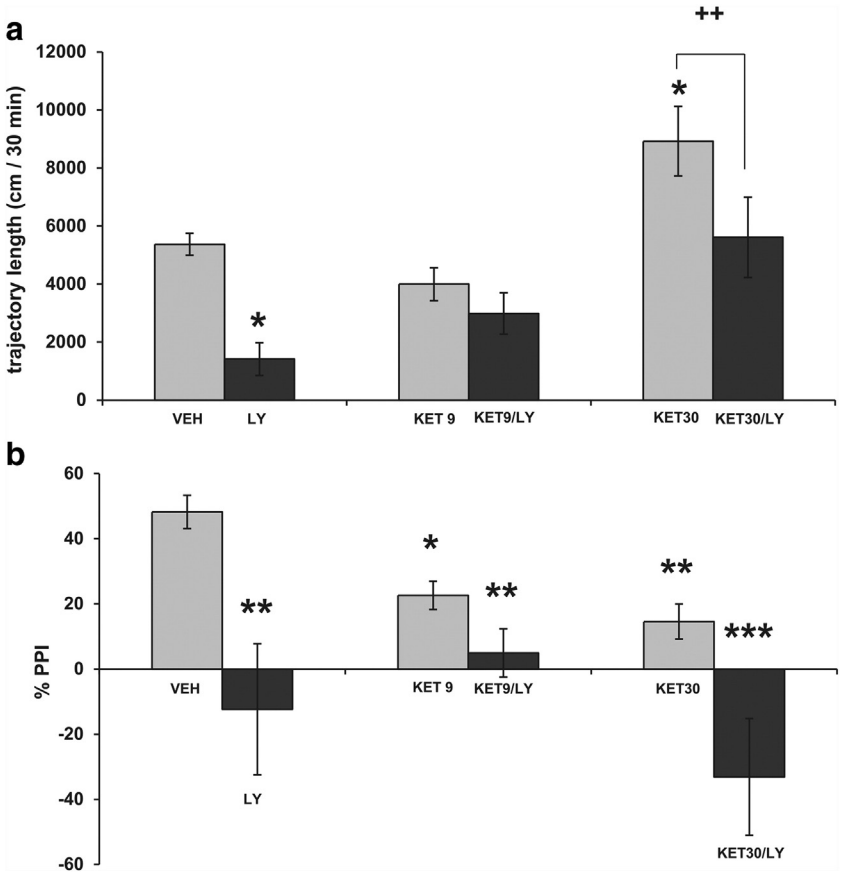

Fig. 2. (a) The effect of LY379268 on locomotor activity (as measured by trajectory length). Only ketamine 30 mg/kg significantly increased locomotion, an effect that was blocked by LY379268 pretreatment. LY379268 on its own significantly decreased locomotor activity. (b) The effect of LY379268 on prepulse inhibition (PPI). Ketamine in both doses and LY379268 alone disrupted PPI. Deficit in PPI after ketamine administration was not affected by LY 379268. Values are means ± SEM. *, **, *** P < 0.05–P < 0.001 compared to the vehicle (VEH). ++ p < 0.01 for within-group comparisons. LY379268 3 mg/kg = LY, ketamine 9 and 30 mg/kg = KET9 and KET30, ketamine 9 and 30 mg/kg + LY379268 3 mg/kg = KET9/LY and KET30/LY.

the low gamma band were observed indicating that LY379268 blocked the ketamine-induced changes in the low gamma band.

3.3.2. Comparisons within treatment groups using ANCOVA

Comparison of the absolute power spectra yielded differences between treatment groups in the beta [$F(3,39) = 6.608$; $p = 0.001$], high beta [$F(3,39) = 13.146$; $p < 0.001$] and low gamma [$F(3,39) = 12.106$; $p < 0.001$] bands. Post hoc comparisons showed a significant increase of low gamma power after ketamine treatment compared to the controls ($p < 0.001$) (***). On the contrary, LY379268 alone induced a decrease of beta, high beta and low gamma power ($p < 0.05$–0.01) (#–##). The only effect of LY379268 on the ketamine treated animals was observed in low gamma band, where the drug completely blocked the low gamma power increase ($p < 0.01$ from the ketamine group and $p = 0.57$ from the control group).

Table 1
The effect of ketamine and LY379268 on ASR (amplitude in arbitrary units). Ketamine had no influence on startle magnitude; LY379268 itself significantly increased the ASR amplitude compared to the vehicle, no other significant differences were observed ***p < 0.001 for LY 379268 versus the vehicle.

ASR amplitude in arbitrary units (±SEM)		
	Vehicle	LY379268 3 mg/kg
Vehicle	124.4 (±13.5)	266.2 (±46.9)***
Ketamine 9 mg/kg	110.6 (±8.4)	187.1 (±37)
Ketamine 30 mg/kg	98.3 (±10.3)	97.72 (±15.5)

In the relative power spectra differences between treatment groups in the delta [$F(3,39) = 3.414$; $p < 0.05$], beta [$F(3,39) = 8.172$; $p < 0.001$], high beta [$F(3,39) = 19.211$; $p < 0.001$] and low gamma [$F(3,39) = 22.468$; $p < 0.001$] bands were observed. Post hoc comparisons confirmed a significant increase of low gamma power after ketamine treatment compared to the controls ($p < 0.001$) (***) as well as a decrease in beta, high beta and low gamma power after LY379268 ($p < 0.001$ for all bands) (###). Again, the main effect of LY379268 on ketamine was in the low gamma band ($p < 0.001$ from the ketamine group and $p = 0.13$ from the control group). In this case, however, the power decrease in the beta and high beta bands remained significant even after drug combination ($p < 0.001$ from the controls for both groups) (‡‡‡). An isolated effect was observed in delta power, where comparison between ketamine and LY379268 yielded a significant difference ($p < 0.01$) (Fig. 3a, b).

3.4. EEG coherence — epochs of behavioral inactivity

Vehicle treated animals exhibited minor changes in coherence: mainly a left fronto-temporal intrahemispheric increase in the theta band and a fronto-parietal intrahemispheric increase on both hemispheres in the alpha band. Some minor decreases in coherence temporally on the right hemisphere in the low-gamma band were also observed.

The major finding after the administration of ketamine 30 mg/kg was a robust and global decrease of intra-hemispheric coherence in the delta, theta, alpha and beta bands and an inter-hemispheric

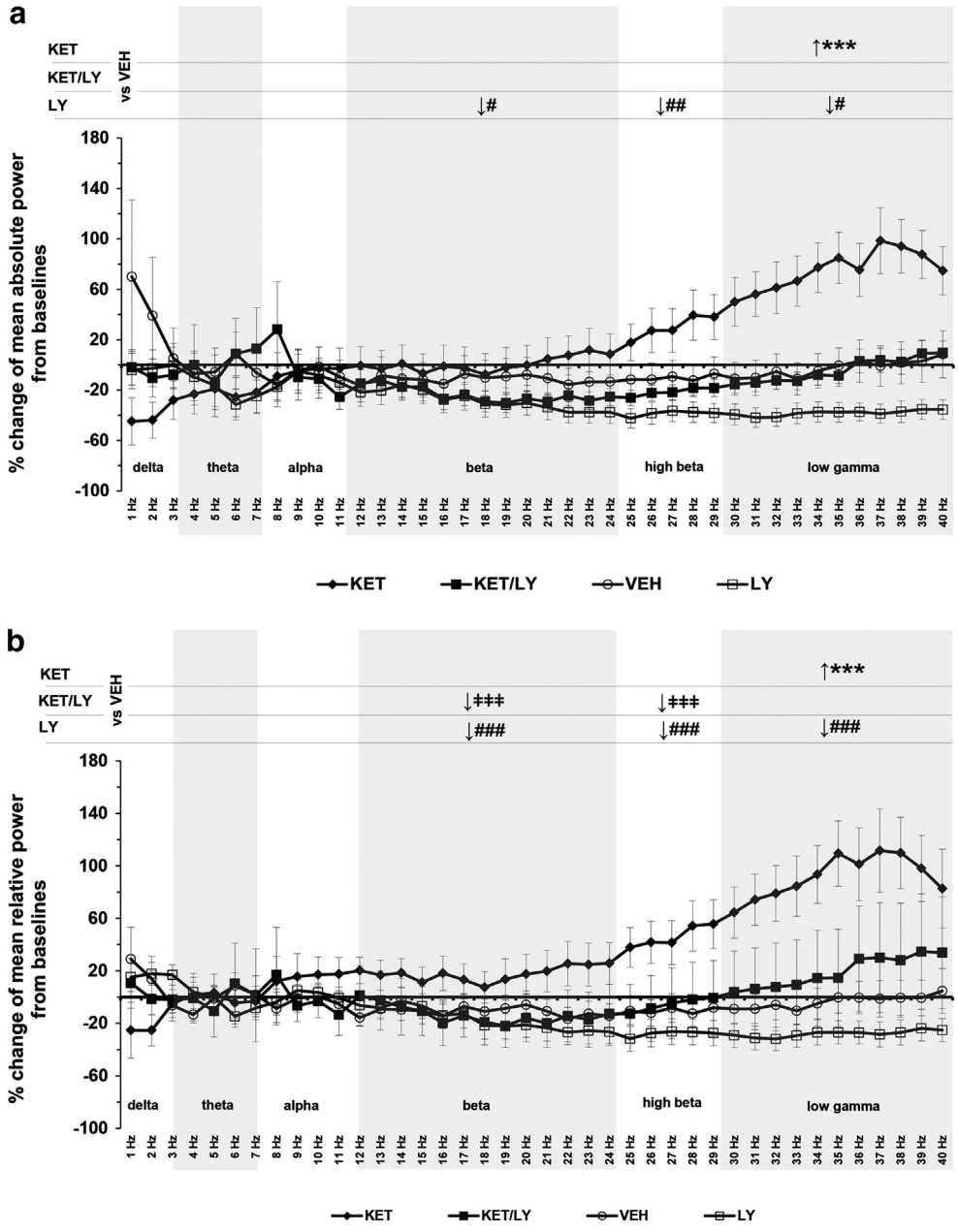

Fig. 3. Mean absolute and relative power spectra. The graphs show the effects of ketamine 30 mg/kg (KET), LY379268 3 mg/kg (LY), the vehicle (VEH) and co-administration of ketamine 30 mg/kg + LY379268 3 mg/kg (KET/LY) on the absolute (a) and relative (b) power spectra. For better graphical presentation, data are expressed per 1 Hz as the percent change of their corresponding baseline with ±SEM × 100 / mean power of the corresponding baseline. Thus, all baselines are represented by the X axis (the zero line). Significant differences of mean power within the whole spectral bands of each treatment compared to the vehicle are shown in the upper part of the figure (ANCOVA). The direction of change is indicated by arrows. The ketamine-induced increase of low-gamma and the decrease in delta and theta power were reversed by LY379268. The decrease in beta and high power in LY379268 was also observed in the ketamine + LY379268 treated animals. *** indicates $p < 0.001$ for ketamine 30 mg/kg vs the vehicle. ‡‡‡ indicates $p < 0.001$ for ketamine 30 mg/kg + LY379268 3 mg/kg vs the vehicle. #, ## and ### indicate $p < 0.05$, 0.01 and 0.001 for LY379268 3 mg/kg vs the vehicle. ↓ indicates a decrease, ↑ indicates an increase.

coherence in the beta, high beta and low-gamma bands between most of the electrodes.

The mGlu2/3 agonist LY379268 3 mg/kg mainly induced a robust coherence increase in the high beta and low-gamma bands. The increase was predominantly in the fronto-parietal and fronto-temporal electrodes within each hemisphere, although an interhemispheric increase between frontal regions also occurred. On the contrary, a decrease of coherence between the parietal and temporal regions in the delta to high beta band was also present.

The co-administration of LY379268 3 mg/kg and ketamine 30 mg/kg mostly reversed the coherence decrease induced by the ketamine except for the interhemispheric coherence in the beta, high beta and low-gamma bands. The drug also induced a fronto-parietal and fronto-temporal intrahemispheric coherence increase in the theta to low-gamma bands (Fig. 4).

3.5. The effect of behavioral activity on absolute power spectra and coherence

3.5.1. The duration of behavioral activity

Analysis of the duration of behavioral activity in animals during the EEG recording showed a significant effect of the ketamine treatment [$F(1,40) = 45.88$, $p < 0.001$] as well as LY379268 treatment [$F(1,40) = 17.51$, $p < 0.001$], but no interaction of factors. Post hoc tests showed

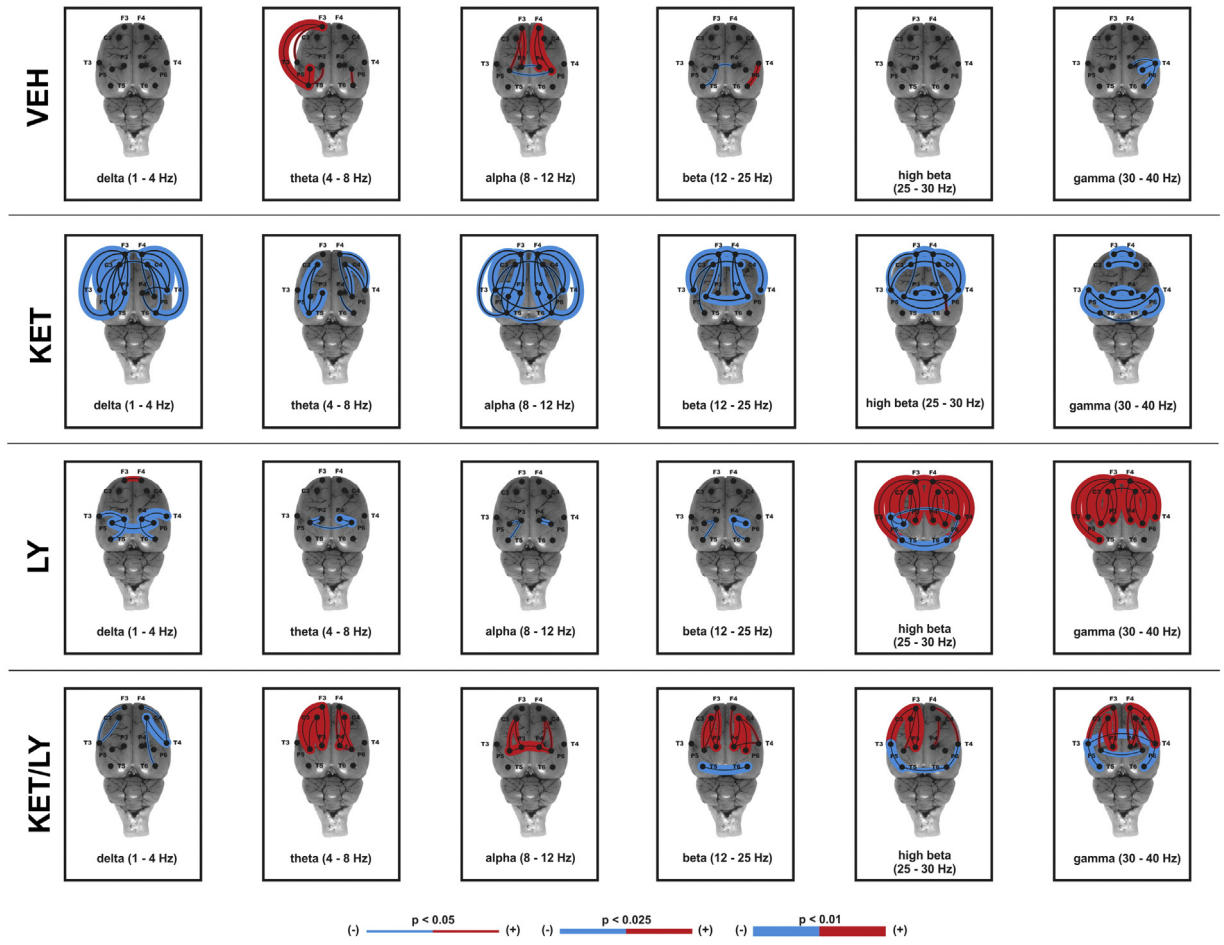

Fig. 4. Significant changes in EEG coherence — baseline compared to segments after administration of drugs. Significant changes (increase or decrease) in EEG coherence compared to baseline recordings during behavioral inactivity in the vehicle (VEH), ketamine 30 mg/kg (KET), LY379268 3 mg/kg (LY), and ketamine 30 mg/kg + LY379268 3 mg/kg (KET/LY) are represented by lines connecting the corresponding electrodes. The level of significance (p-value) is illustrated by the thickness of the lines (paired t test) according to the graphical presentation displayed below the images. Red color indicates an increase and blue color a decrease in coherence. The massive ketamine-induced decrease in coherence was partially reversed by LY379268. The latter compound itself mainly induced an increase in high beta and low-gamma coherence.

that the ketamine 30 mg/kg treated animals spent significantly more time being behaviorally active than the vehicle treated animals ($p < 0.001$) (***). LY379268 3 mg/kg blocked this hyperactivity ($p < 0.001$) (+++) but the compound itself also decreased the duration of behavioral activity ($p < 0.05$) (*) (Fig. 5a).

3.5.2. Absolute power spectra in ketamine and vehicle treated animals

Comparison of EEG traces corresponding to behavioral activity with those of inactivity in ketamine treated animals revealed increases of the absolute power spectra of 5–21% in all frequency bands. The significance for the mean absolute power was reached in the delta and theta bands with the power magnitude being 116% and 121% of the power in episodes corresponding to behavioral inactivity ($t = -2.21$ and -2.97, $p = 0.05$ and 0.01) (* and **). Similar findings were observed in the vehicle treated animals, where behavioral activity increased the mean power by 12–54% in all frequency bands. Significant differences were observed in the theta, alpha, high beta and low-gamma bands (154%, 127%, 118% and 129% of the power in episodes corresponding to behavioral inactivity; $t = -3.95$, -2.97, -3.25, and -4.1 $p < 0.05$–0.01) (+−++) (Fig. 5b).

3.5.3. Effect on EEG coherence in ketamine and vehicle treated animals

Behavioral activity increased EEG coherence compared to inactivity in both groups. In ketamine treated animals the increases were mainly in the theta and alpha bands. In the vehicle treated animals increases in the theta, alpha, beta, high beta and low-gamma bands were present (Fig. 6).

4. Discussion

The main findings of the present study are that the mGlu2/3 agonist was able to reverse the ketamine-induced changes in qEEG and also partially normalize its behavioral effects. Hyperlocomotion induced by ketamine 30 mg/kg and disrupted sensorimotor gating after both doses confirmed the behavioral validity of the model and doses used. LY379268 blocked hyperlocomotion but had no effect on PPI deficits induced by ketamine. Compared to other studies the drug alone produced significant hypolocomotion, increased startle reaction and disrupted PPI (Imre, 2007). The blockade of ketamine-induced hyperlocomotion can be interpreted as a putative antipsychotic effect, however the lack of effectiveness on PPI might also support a simple mechanistic explanation which cancels out the effects due to the opposite direction of the changes. Quantitative EEG analysis revealed increases of the EEG power in the low gamma band after ketamine administration. In addition, an increase in beta and high beta power and a slight decrease in delta and theta power were observed. EEG coherence was generally decreased. LY379268 reversed the ketamine-induced increase in EEG power and an absolutely novel finding was that it also normalized and/or reversed most of the decreases in coherence. On the other hand, the compound alone induced a decrease in mean power in the beta to low gamma bands and an increase in coherence in the high beta and low gamma

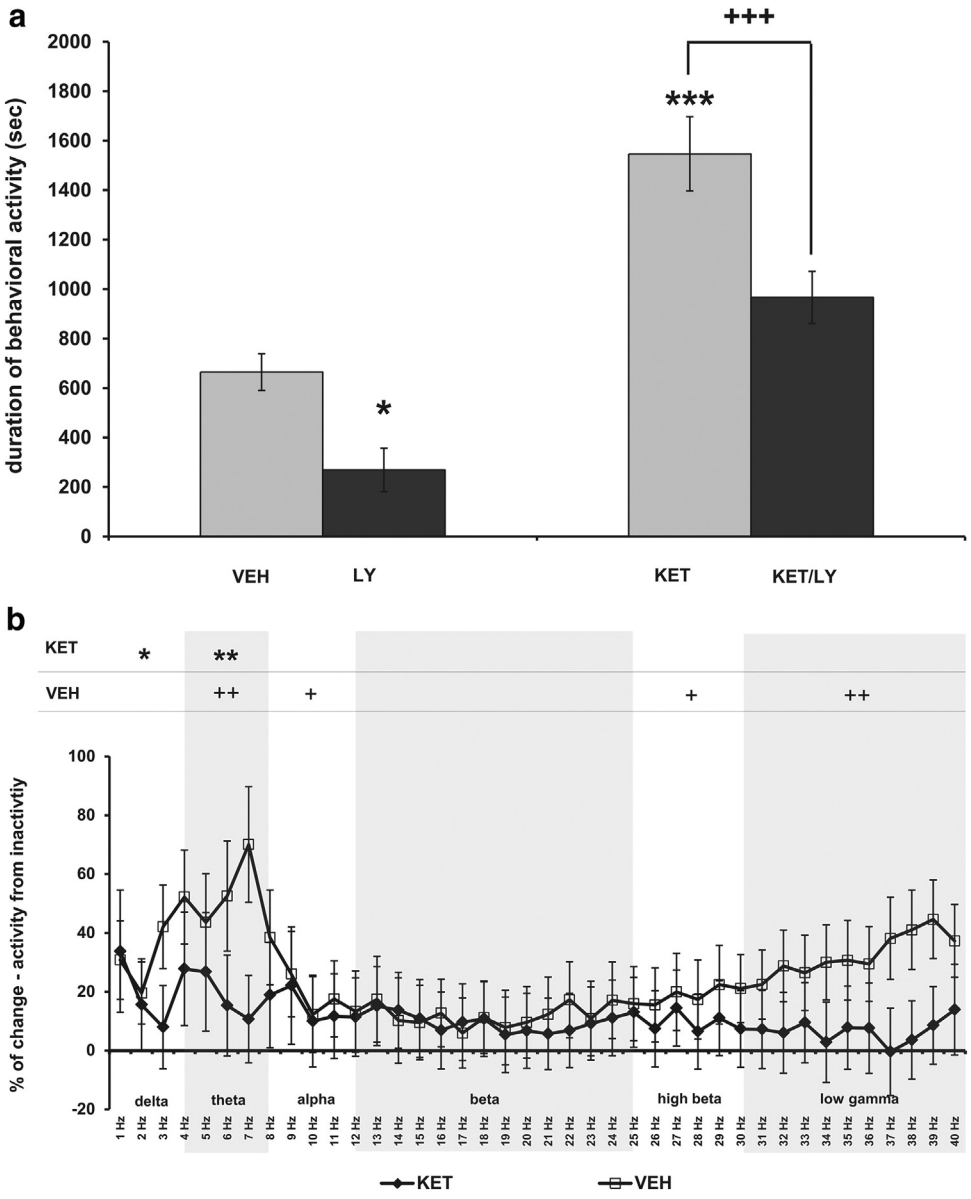

Fig. 5. Duration of behavioral activity and mean absolute power spectra of behavioral activity compared to inactivity. (a) Duration of behavioral activity in animals during the EEG recording after administration of ketamine 30 mg/kg (KET), LY379268 3 mg/kg (LY), the vehicle (VEH) and co-administration of ketamine 30 mg/kg + LY379268 3 mg/kg (KET/LY). Ketamine 30 mg/kg increased the duration of behavioral activity. LY379268 3 mg/kg shortened the period of behavioral activity itself as well as in ketamine-treated animals. * and *** indicate $p < 0.05$ and 0.001 compared to the vehicle. +++ indicates $p < 0.001$ compared to ketamine 30 mg/kg. (b) The graphs show the effects of the treatments with ketamine 30 mg/kg (KET) and the vehicle (VEH) on the absolute power spectra compared to EEG epochs corresponding to behavioral activity versus inactivity. Data are expressed per 1 Hz as a percent change of activity from inactivity (zero line) with ±SEM × 100 / mean absolute power of corresponding inactivity. Significant differences calculated for the mean power within the whole spectral bands are shown in the upper part of the figure (paired *T*-test). Behavioral activity increased the mean absolute power in the ketamine as well as vehicle treated animals. Significant increases were in the delta and theta bands for ketamine and in the theta, alpha, high beta and low-gamma bands in the vehicle treated animals. * and ** indicate $p < 0.05$–0.01 for ketamine 30 mg/kg. + and ++ indicate $p < 0.05$–0.01 for the vehicle treated animals.

bands, effects that were also partly observable in the ketamine + LY379268 treated animals. An additional comparison of the EEG epochs corresponding to behavioral activity versus inactivity in the control and ketamine treated animals showed that behavioral activity increases EEG power as well as coherence.

The current experiments compared to our previous findings with ketamine revealed different results: in our previous study ketamine significantly increased mean power and coherence in all frequency bands (Palenicek et al., 2011b). However, the EEG analysis in the previous experiments was performed independently of behavioral activity, which means it also included the EEG signal that corresponded to episodes with increased behavioral activity. The recent study clearly shows that behavior is an important confounding factor which can significantly influence the EEG findings. It is in line with Maloney et al. (1997) who found that behavioral activity is associated with theta peak and increased coherence in the gamma band (Maloney et al., 1997) and is supported by our other recent findings under various treatment conditions (behavioral activity was associated with a general increase in power and coherence with maximal changes in the theta/alpha bands) (Palenicek et al., 2011a, 2012). However, similar to e.g. Hakami et al. (2009) the observed increase in low gamma power after ketamine was present in both of our studies (Palenicek et al., 2011b), suggesting that it is specific for the drug and independent of behavioral activity. Further recent data from our laboratory with more selective NMDA antagonist dizocilpine (MK-801) showed a very similar profile of changes (increase in low gamma power and decreased coherence in episodes of inactivity), which indicates that these effects can be generalized to NMDA receptor blockade. The gamma power increase is also the most

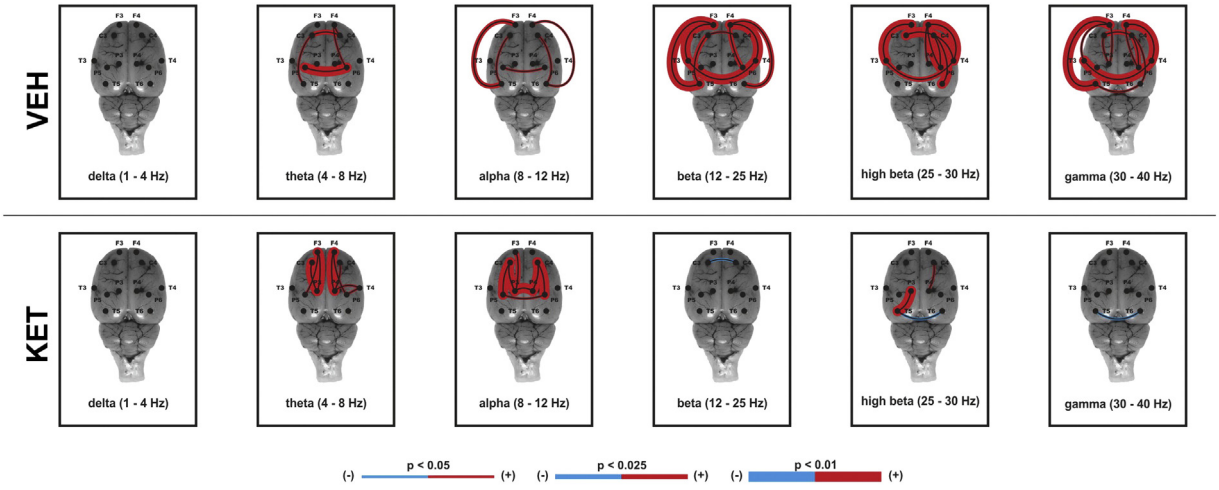

Fig. 6. Significant changes in EEG coherence — behavioral activity compared to inactivity. Comparison of epochs corresponding to behavioral activity with inactivity in the vehicle (VEH) and ketamine 30 mg/kg (KET) treated animals. Significant changes (increase or decrease) in EEG coherence are represented by lines connecting the corresponding electrodes. The level of significance (p-value) is illustrated by the thickness of the lines (paired *T*-test) according to the graphical presentation displayed below the images. Red color indicates an increase and blue color a decrease in coherence. Behavioral activity generally increased the EEG coherence.

consistent finding present in human ketamine studies with subanesthetic as well as anesthetic doses (Hong et al., 2010; Kochs et al., 1991; Maksimow et al., 2006; Oga et al., 2002). Interestingly, subanesthetic doses of ketamine in human volunteers in our recent study also showed a global decrease in coherence during resting (Horacek et al., 2011). A comparison of our data with findings in unmedicated schizophrenia patients revealed that decreased functional connectivity (mainly fronto-temporal) is also typical in schizophrenics (Ford et al., 2002; Gonzalez-Burgos et al., 2010; Lawrie et al., 2002; Spencer et al., 2003; Yeragani et al., 2006). On the other hand, findings of resting gamma activity do not bring uniform results (increases as well as decreases) (Sun et al., 2011). Inasmuch as the analysis of EEG epochs during behavioral inactivity brought much more comparable results to human findings than our previous study (Palenicek et al., 2011b), we can conclude that our recent data have strong translational validity and that our approach may serve as an animal model of "resting EEG".

There are currently not enough studies with a comparable design to enable a direct comparison of our EEG findings. A global decrease of absolute power and decrease of coherence is characteristic in serotonergic models (Fujakova et al., 2011; Palenicek et al., 2012; Tyls et al., 2011). Thus, while changes in the EEG power seem to correspond to the specific mechanism of action of the drug a common denominator in both models is decreased connectivity, expressed by decreased coherence. Since it is also a typical finding in human glutamatergic models and schizophrenia we believe that it is an epiphenomenon typical for psychotic processes.

Comparably to other studies recent experiments showed that LY379268 restored the increase in gamma oscillations after ketamine (Feinberg et al., 2005; Jones et al., 2012). This is congruent with the hypothesis that the generation of gamma oscillations induced by NMDA antagonists is related to glutamate–GABA interactions (Bubenikova-Valesova et al., 2008; Olney et al., 1999). However, a simple mechanistic explanation can also be proposed like in the case of locomotor activity. Further effects of LY379268 on EEG power (decrease in the beta and high beta bands) seem to be characteristic for the compound itself (Feinberg et al., 2005; Jones et al., 2012). Since beta oscillations and coherence are linked to sensorimotor processing, to planning motor tasks as well as to cognitive tasks related to non-attended stimuli (Brown et al., 2001; Engel and Fries, 2010), we suggest that these can underlie the hypolocomotor effect of the drug. Interestingly, both of the compounds used in our recent study, each having completely different mechanism of action, altering high frequency oscillations, but in opposite directions, congruently induced a disruption of sensorimotor processing. Knowing that these oscillations are important for informational processing (Engel and Fries, 2010; Sun et al., 2011) we postulate that their dysregulation in whatever direction is an underlying factor of the observed deficits in PPI. This is also supported by our recent findings in serotonergic models of psychosis. In these models, serotonergic hallucinogens, agonists at the 5-HT2A receptor (psilocin, lysergamide (LSD), mescaline, 2C-B (4-bromo-2,5-dimethoxyphenylethylamine) and DOB (2,5-dimethoxy-4-bromoamphetamine)) all congruently induced a deficit in prepulse inhibition as well as a significant decrease in high frequency oscillations (Fujakova et al., 2011; Palenicek et al., 2012; Tyls et al., 2011).

Finally, the beta power decreases can also reflect the similarity of LY379268 to various antipsychotic drugs (e.g. olanzapine and haloperidol) (Dimpfel, 2007; Saletu et al., 1986). In relation to this, there is an ongoing discussion of the activity of LY379268 on dopaminergic D2/D3 receptors (Fell et al., 2009; Seeman and Guan, 2008; Zysk et al., 2011) which indicates that it may have several common mechanisms of action with other antipsychotics. However, further studies will be needed to reveal this.

5. Conclusion

In conclusion, LY379268 was able to block ketamine-induced hyperlocomotion, normalize changes in high frequency oscillations and restore functional disconnection. These findings indicate that the mGlu2/3 agonism could restore some of the changes in the glutamatergic animal model of psychosis. However, LY379268 was not able to restore ketamine's disrupting effects on sensorimotor gating indicating its potential antipsychotic effects have to be confirmed by further studies.

Acknowledgments

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