Psychological Medicine (2010), **40**, 1443–1451. © Cambridge University Press 2009
doi:10.1017/S0033291709991619

ORIGINAL ARTICLE

Subanesthetic dose of ketamine decreases prefrontal theta cordance in healthy volunteers: implications for antidepressant effect

J. Horacek[1,2,3]*, M. Brunovsky[1,2], T. Novak[2], B. Tislerova[3], T. Palenicek[2,3], V. Bubenikova-Valesova[1,2], F. Spaniel[1,3], J. Koprivova[2,3], P. Mohr[1], M. Balikova[4] and C. Hoschl[1,2,3]

[1] *Prague Psychiatric Centre, Prague, Czech Republic*
[2] *Centre of Neuropsychiatric Studies, Prague, Czech Republic*
[3] *Third Medical Faculty of Charles University, Prague, Czech Republic*
[4] *Institute of Forensic Medicine and Toxicology, First Medical Faculty, Charles University, Prague, Czech Republic*

Background. Theta cordance is a novel quantitative electroencephalography (QEEG) measure that correlates with cerebral perfusion. A series of clinical studies has demonstrated that the prefrontal theta cordance value decreases after 1 week of treatment in responders to antidepressants and that this effect precedes clinical improvement. Ketamine, a non-competitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors, has a unique rapid antidepressant effect but its influence on theta cordance is unknown.

Method. In a double-blind, cross-over, placebo-controlled experiment we studied the acute effect of ketamine (0.54 mg/kg within 30 min) on theta cordance in a group of 20 healthy volunteers.

Results. Ketamine infusion induced a decrease in prefrontal theta cordance and an increase in the central region theta cordance after 10 and 30 min. The change in prefrontal theta cordance correlated with ketamine and norketamine blood levels after 10 min of ketamine infusion.

Conclusions. Our data indicate that ketamine infusion immediately induces changes similar to those that monoamineric-based antidepressants induce gradually. The reduction in theta cordance could be a marker and a predictor of the fast-acting antidepressant effect of ketamine, a hypothesis that could be tested in depressive patients treated with ketamine.

Received 27 January 2008; Revised 3 September 2009; Accepted 28 September 2009; First published online 9 December 2009

Key words: Depression, healthy volunteers, ketamine, QEEG, theta cordance.

Introduction

The traditional quantitative electroencephalography (QEEG) measures of absolute and relative power yield complementary perspectives on regional brain activity. Absolute power in a given frequency band reflects the intensity of energy at a particular brain region and is expressed in power units. Relative power reflects brain electrical activity on a proportional basis, that is as a percentage of the total power in a given channel contained within the frequency band.

Previous studies evaluating absolute and relative power in affective disorders and antidepressant treatment have had only low clinical impact because of the limited specificity and predictive validity (see review by Hunter *et al*. 2007). This problem was at least partially solved by the introduction of a new QEEG measure, cordance (Leuchter *et al*. 1994). The invention was inspired by the observation that the deafferentation of cortical areas leads to a slow-wave band of the lowest absolute brain electrical activity and simultaneously of the greatest relative power. These empirical findings resulted in an algorithm for a linear transformation that combines complementary information from absolute and relative power to yield values that have a strong association with metabolism and white matter lesions (Leuchter *et al*. 1994). The cordance of numerical expression indicates to what extent, if at all, the departure of absolute and relative power is in the same direction from a selected base value (e.g. mean values from all electrodes). Specifically, a categorical value (+/−) of cordance determines whether the departure of both powers normalized across electrode sites and frequency bands is in the same direction (plus sign for 'concordance'

* Address for correspondence: Prof. Dr J. Horacek, Ph.D., Prague Psychiatric Centre, Ustavni 91, 181 03 Prague 8, Czech Republic.
(Email: horacek@pcp.lf3.cuni.cz)

and minus sign for 'discordance'). The numerical cordance value (*Z*) calculated as the sum of both normalized powers signifies the intensity of brain activity.

The cordance values specifically in the 4–8 Hz theta frequency band (i.e. theta cordance) are correlated positively and significantly with cortical perfusion measured by positron emission tomography (PET). This correlation is stronger than that for either absolute or relative power and allows theta cordance to be interpreted in the same physiological framework as PET (Leuchter *et al*. 1999).

The clinical relevance of this measure has been established by several studies reporting that theta cordance predicts response or remission with at least 70% accuracy for different antidepressants (for reviews, see Hunter *et al*. 2007; Leuchter *et al*. 2009). In particular, replicated studies on subjects with major depression treated with various antidepressants have demonstrated a decrease in prefrontal theta cordance 1 week after the start of medication. This change preceded the clinical improvement, which did not emerge until several weeks later and predicted the response consistently with overall high accuracy (Cook *et al*. 2002, 2005; Bares *et al*. 2007, 2008). These findings support the hypothesis that early metabolic changes in the prefrontal region mediate (and precede) the response to antidepressant treatment (Mayberg, 2003). Early changes in prefrontal theta cordance were recently identified as a specific marker of antidepressants even in healthy volunteers (Leuchter *et al*. 2008).

Glutamatergic agents have been studied as novel antidepressants (Krystal *et al*. 2002; Mathew *et al*. 2005). In particular, there is substantial evidence that the *N*-methyl-D-aspartate receptor (NMDAR) antagonists have antidepressant properties, with the dissociative anesthetic drug ketamine as the model agent. Two double-blind studies have reported that ketamine infusion exerts a rapid (within hours) antidepressant effect in pharmaco-resistant depressive patients lasting up to 1 week (Berman *et al*. 2000; Zarate *et al*. 2006). A functional magnetic resonance imaging (fMRI) study found recently that ketamine decreases activity in the ventromedial frontal cortex (Deakin *et al*. 2008). Human magnetoencephalographic (MEG) studies identified this region (specifically the anterior cingulate and prefrontal medial superficial cortex) as the source of midline frontal theta rhythm (Asada *et al*. 1999; Ishii *et al*. 1999). The source of the theta frequency oscillatory field potentials was also confirmed using direct recordings in monkeys in area 32 (monkey analog of the anterior cingulate) and in the medial part of area 9 (Tsujimoto *et al*. 2006).

Based on these observations, it can be expected that the clinical effect of both ketamine and monoaminergic-based antidepressants is mediated by the inhibition of the mediorefrontal cortex. Consequently, ketamine would very early after administration decrease the prefrontal theta cordance and this effect could serve as a biomarker of its clinical antidepressant effect.

Testing the *a priori* hypothesis that a subanesthetic dose of ketamine induces a decrease in prefrontal theta cordance, we measured its effect on theta cordance in healthy volunteers. Ketamine undergoes extensive liver metabolism by CYP-450 *N*-demethylation to norketamine, which is also an NMDAR antagonist (Ebert *et al*. 1997). To determine the role and influence of both compounds on theta cordance, we analyzed the relationship between ketamine and norketamine blood levels and theta cordance.

Method

Subjects

Twenty right-handed healthy volunteers (mean age 29.9 years, S.D. = 5.69, 13 males, 7 females) were recruited by local advertisement. The main exclusion criteria were a personal history of any psychiatric or substance abuse disorder established by the Structured Clinical Interview for DSM-IV, and psychotic disorder in first- or second-degree relatives. The study was carried out in accordance with the rules of ethics for ketamine studies in volunteers (Tishler & Gordon, 1999), written informed consent was obtained, and the local ethics committee approved the study.

Experimental design and procedures

In the double-blind, cross-over, controlled study participants attended ketamine or placebo sessions in a randomized order with a minimum separation of 2 weeks. After 5 min, baseline EEG recording racemic ketamine hydrochloride (Narkamon, Spofa, Czech Republic) or placebo (0.9% saline solution) was applied into the right cubital vein using an infusion pump. Ketamine was applied in a loading dose of 0.27 mg/kg for the first 10 min, followed by a maintenance infusion of 0.27 mg/kg within 20 min. These infusion rates were calculated with respect to the pharmacokinetics of ketamine (Hetem *et al*. 2000) to: (*a*) produce the stable ketamine blood levels for EEG recordings between 10 and 30 min, (*b*) apply a total dose very close to both clinical studies in depression (Berman *et al*. 2000; Zarate *et al*. 2006), and (*c*) maximize safety by using a loading dose over 10 min. To measure ketamine and norketamine serum levels, 2 ml of vein blood was sampled from the left arm 5 min before and 10 and 30 min after the beginning of the infusion.

https://doi.org/10.1017/S0033291709991619 Published online by Cambridge University Press

Each participant was interviewed and evaluated with the Brief Psychiatric Rating Scale (BPRS, total and five subscales) at the same time points. At the end of the session, subjects rated their emotional change during the infusion by two 100-mm visual analog scales (VAS) for 'any positive' or 'any negative' emotions, with zero indicating no change and 100 mm indicating extreme change compared with baseline. One hour after the end of the experiment, clinical interview and BPRS were used to confirm the cessation of ketamine-induced symptoms.

EEG recordings

A continuous EEG, 35 min in duration, registered in the eyes-closed resting state with participants seated comfortably, was collected with a BrainScope digital amplifier (Unimedis, Czech Republic) from 21 surface electrodes placed according to the 10/20 system referenced to the Cz electrode. Data were digitized at 250 Hz, amplified, and filtered between 0.15 and 70 Hz after sampling. Three 5-min EEG segments, obtained at baseline and prior to BPRS examination 10 and 30 min after dosing, were inspected visually to exclude all obvious EEG artifacts or a decrease in alertness. In addition, split-half reliability tests were conducted on the edited EEG segments (NeuroGuide software, version 2.4.6) and 30 artifact-free 2-s epochs with $>90\%$ reliability were entered into the spectral analyses after digital filtering of 0.5 to 30 Hz.

Fast Fourier transform was used to calculate the absolute and relative power in each of four non-overlapping frequency bands (Nuwer *et al*. 1999): delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–20 Hz). QEEG cordance was calculated using the algorithm described in detail elsewhere (Cook *et al*. 1999; Bares *et al*. 2008). In brief, this algorithm normalizes power across both electrodes and frequency bands in three consecutive steps: first, absolute power values are reattributed to each individual electrode by averaging power from all bipolar electrode pairs sharing that electrode, to yield the reattributed power. Then the relative power values are calculated as the percentage of power in each band, relative to the total spectrum (here, 0.5 to 20 Hz). In the second step, the absolute and relative power values for each electrode site (s) in each frequency band (f) are z transformed to measure deviation from the mean values from all electrodes, yielding normalized absolute [$A_{\mathrm{NORM}(s,f)}$] and normalized relative [$R_{\mathrm{NORM}(s,f)}$] powers respectively. Third, the cordance values [$Z_{(s,f)}$] are computed by summing the z scores for normalized absolute and relative power [$Z_{(s,f)} = |A_{\mathrm{NORM}(s,f)}| + |R_{\mathrm{NORM}(s,f)}|$].

With respect to previous studies (Cook *et al*. 1999, 2002, 2005; Bares *et al*. 2007, 2008), we further limited the number of comparisons by averaging the values from electrodes overlying four major regions: prefrontal (Fp1, Fp2, Fpz), central (C3, C4, Cz), left temporal (T3, T5) and right temporal (T4, T6). Analyses were limited to the theta band (4–8 Hz) because it has been shown previously to be sensitive to antidepressant treatment (Cook *et al*. 1999, 2002, 2005; Leuchter *et al*. 1997; Knott *et al*. 2000; Pizzagalli *et al*. 2001; Bares *et al*. 2007, 2008).

Gas chromatography–mass spectrometry (GS-MS) for ketamine and norketamine serum levels

The G28-MS toxicological method was developed and validated according to international standards (Penders & Verstraete, 2006). For toxicological analyses the analytical standards norketamine, ketamine and deuterated ketamine (ketamine-D4) supplied as hydrochlorides from Cerilliant, USA were used. For quantitation, the internal standard method was applied using ketamine-D4. Isolation of analytes from blood serum samples was performed using SPEC-DAU discs and analyses were performed with acetyl derivatives using an HP 6890–5973 instrument (Agilent, Germany) operating in electron impact single ion monitoring (SIM) mode. The lower limit of quantification (LLOQ) for ketamine was 50 ng/ml and for norketamine 8 ng/ml. The limit of detection (LOD) for ketamine was 20 ng/ml and for norketamine 1 ng/ml.

Statistical analyses

Data are expressed as means (standard deviation) and in non-Gaussian distributed measures as medians (interquartile range) as well. Repeated-measures ANCOVA for a two-period cross-over design with baseline cordance values as covariate was used to assess the changes in theta cordance values separately in each region. Bonferroni *post-hoc* tests were used to reveal the differences between treatments at the particular time points. The influence of treatment on psychopathology (BPRS) was determined by two-way repeated-measures ANOVA, with time and treatment as the independent variables, followed by Bonferroni *post-hoc* tests (because the EEG data were missing for one patient for technical reasons at 30 min, this measurement was not included in the analysis).

Emotional response measured on the VAS was treated by the Wilcoxon signed-rank test and the McNemar test. A Pearson correlation coefficient was used to detect the relationship between theta cordance change and ketamine and norketamine serum levels. Differences between groups of reducers (decrease of theta cordance 10 and 30 min after dosing compared with baseline) and non-reducers were tested by the Mann–Whitney test and by Fisher's exact test for

https://doi.org/10.1017/S0033291709991619 Published online by Cambridge University Press

Table 1. *Changes in theta cordance, theta cordance Z score values, psychopathology and emotions during placebo and ketamine infusion*

	Placebo			Ketamine		
	Baseline	10 min	30 min	Baseline	10 min	30 min
PFC	1.57 (0.20)	1.56 (0.21)	1.74 (0.22)	2.00 (1.15)	1.26 (0.21)[a]	1.07 (0.25)[a]
CC	0.24 (0.29)	0.53 (0.32)	0.27 (0.24)	0.42 (0.14)	1.26 (0.27)[a]	1.53 (0.30)[a]
LTC	−0.57 (0.37)	−0.45 (0.32)	−0.94 (0.29)	−1.41 (0.22)	−1.25 (0.20)	−1.50 (0.26)
RTC	−0.87 (0.26)	−0.57 (0.31)	−0.84 (0.28)	−0.91 (0.41)	−1.60 (0.17)	−1.63 (0.27)
BPRS total	0.65 (0.98)	0.70 (1.30)	0.65 (1.26)	0.90 (1.16)	32.2 (14.46)[ab]	38.35 (14.82)[ab]
BPRS subscales						
Anxiety-depression	0.40 (0.68)	0.40 (0.82)	0.35 (0.67)	0.22 (0.41)	3.7 (2.36)[ab]	4.50 (2.30)[ab]
Withdrawal	0.00 (0.00)	0.15 (0.48)	0.20 (0.52)	0.10 (0.44)	10.98 (6.02)[ab]	13.00 (6.69)[ab]
Thought disturbance-hallucinations	0.05 (0.22)	0.10 (0.44)	0.10 (0.30)	0.05 (0.22)	9.85 (5.39)[ab]	11.65 (4.00)[ab]
Activation	0.25 (0.44)	0.05 (0.22)	0.00 (0.00)	0.63 (0.83)	5.26 (3.63)[ab]	6.20 (3.94)[ab]
Hostility-suspicion	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.05 (0.22)	2.55 (2.56)[ab]	3.00 (2.77)[ab]
VAS positive emotions	6.05 (17.13) [0.00 (0.00–0.00)]			62.50 (40.83) [76.50 (21.0–100.0)][a]		
VAS negative emotions	0.00 [0.00 (0.00–0.00)]			19.65 (28.49) [0.00 (0.00–43.00)][a]		

PFC, Prefrontal cordance; CC, central cordance; LTC, left temporal cordance; RTC, right temporal cordance; BPRS, Brief Psychiatric Rating Scale; VAS, visual analog scale.

Data are presented as mean (standard deviation) and because of the non-normally distributed variables in VAS, as median (interquartile range). Theta cordance decreased in prefrontal (PFC) and increased in central (CC) region after 10 and 30 min. We found no significant effect on LTC and RTC. Ketamine administration induced a significant increase of total BPRS and all its subscales after 10 and 30 min. Ketamine induced both positive and negative emotional changes in the VAS.

[a] $p \leqslant 0.05$ in comparison with corresponding values in the placebo condition.

[b] $p \leqslant 0.05$ in comparison with the baseline (*post-hoc* test for ANOVA, ANCOVA and the Wilcoxon test).

numbers of subjects reporting positive and negative emotions in the VAS. All comparisons were two-sided at a 0.05 level of significance. The statistical analyses were performed using Statistica 7.1 (StatSoft, Inc., Czech Republic, 2005).

Results

Prefrontal theta cordance decreased on ketamine infusion in comparison with placebo [ANCOVA: $F(2, 34) = 4.11$, $p = 0.03$]. The Bonferroni *post-hoc* test confirmed the difference between treatments at 10 ($p = 0.04$) and 30 min ($p = 0.02$, Table 1, Fig. 1*a*). In the central region we found the opposite course. Theta cordance increased on ketamine infusion [$F(2, 34) = 6.05$, $p = 0.006$] and differed from placebo at both time points ($p = 0.01$ and $p = 0.001$ respectively) (Table 1, Fig. 1*b*). We did not detect a significant effect of ketamine administration on cordance values in the left [$F(2, 34) = 0.29$, $p = 0.75$] and right temporal regions [$F(2, 34) = 3.09$, $p = 0.06$] [Table 1, Fig. 1(*c*, *d*)].

Two-way repeated ANOVA confirmed the significant effect of both treatment and time in total BPRS [$F(2, 72) = 80.41$, $p \leqslant 0.001$] and in all of its subscales: anxiety-depression [$F(2, 72) = 32.08$, $p \leqslant 0.001$], withdrawal [$F(2, 72) = 46.75$, $p \leqslant 0.001$], thought disturbance-hallucinations [$F(2, 72) = 84.31$, $p \leqslant 0.001$], activation [$F(2, 72) = 28.99$, $p \leqslant 0.001$] and hostility-suspicion [$F(2, 72) = 14.64$, $p \leqslant 0.001$] (Table 1). These symptoms disappeared within 1 h of post-infusion observation, and BPRS 1 h min after the infusion did not detect any residual symptoms (data not displayed). Apart from the induced psychopathology, we did not observe any other side-effects.

In the VAS, the Wilcoxon test revealed an increase in both positive ($U = 51.5$, $p \leqslant 0.001$) and negative ($U = 114{,}0$, $p \leqslant 0.001$) emotions with ketamine compared with placebo. In the ketamine session 11 subjects reported a change in positive emotions, three in negative emotions, and five in both (McNemar test, $p = 0.06$). Only two subjects reported any emotional change in the placebo session, both of which were positive (Table 1).

Neither ketamine nor its metabolite norketamine was detectable in the placebo or in the active ketamine session at baseline. In the case of ketamine infusion, the serum levels increased after 10 and 30 min for ketamine and its metabolite norketamine (Fig. 2). The decrease in prefrontal theta cordance 10 min after the infusion correlates with ketamine ($r = -0.68$, $p = 0.005$) and norketamine ($r = -0.49$, $p = 0.47$) serum levels in the corresponding time. The correlation was not

https://doi.org/10.1017/S0033291709991619 Published online by Cambridge University Press

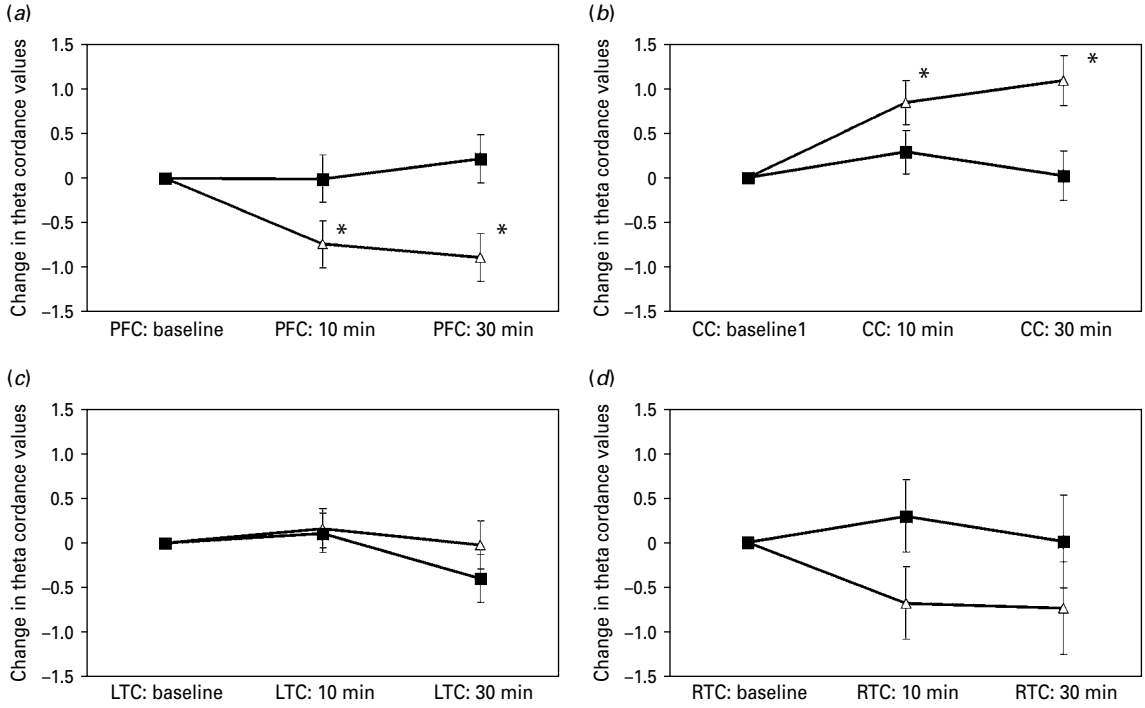

Fig. 1. Change in theta cordance values after placebo (–■–) and ketamine (–△–) infusion in the four regions of interest: (*a*) prefrontal cordance (PFC); (*b*) central cordance (CC); (*c*) left temporal cordance (LTC); and (*d*) right temporal cordance (RTC). Data are presented as mean change from baseline in theta cordance *Z* scores (standard error of the mean). * $p \leqslant 0.05$ in comparison with corresponding values in the placebo condition.

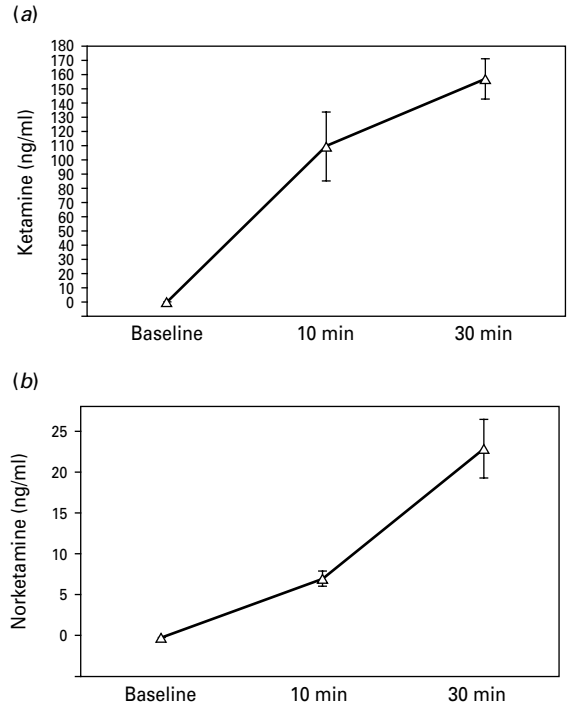

Fig. 2. Changes in (*a*) ketamine and (*b*) norketamine serum levels in the active session. Data are presented as means and standard error of the mean.

significant at 30 min for either ketamine ($r = -0.1282$, $p =$ N.S.) or norketamine ($r = -0.3531$, $p =$ N.S.). We did not find any significant association between ketamine or norketamine plasma level and theta cordance calculated for other regions.

With respect to the predictive role of theta cordance decrease in the antidepressant action, we compared the changes in BPRS and VAS in the theta cordance reducers and non-reducers after 10 and 30 min. Because of the low number of subjects in the non-reducers groups (four for the 10-min and five for 30-min time point), the generalization of these findings is limited. In brief, the groups did not differ in ketamine and norketamine serum levels. After 10 min of the infusion, non-reducers had a higher expression of total BPRS and the subscales withdrawal, thought disturbance-hallucinations and activation. On the contrary, positive emotional reactions were reported in the VAS more often in reducers than in non-reducers at both 10 and 30 min (Fisher's exact test: $p = 0.013$ and $p = 0.037$ respectively). Both groups also differed in the intensity of positive emotional reaction (VAS in mm) at 10 min (Table 2). We did not find any significant difference between reducers and non-reducers in the negative emotional reaction measured by the VAS (Table 2).

https://doi.org/10.1017/S0033291709991619 Published online by Cambridge University Press

Table 2. *Comparison in BPRS, VAS, ketamine and norketamine serum levels between reducers and non-reducers of theta cordance after ketamine infusion for 10 and 30 min*

	10 min			30 min		
	Reducers	Non-reducers	*Z*	Reducers	Non-reducers	*Z*
No.	16	4		14	5	
Ketamine (ng/ml)	82.0 (68.5–90.0)	66.0 (57.0–111.0)	0.6	163.0 (119.5–220.0)	153.0 (120.0–179.5)	0.6
Norketamine (ng/ml)	7.0 (4.0–8.0)	7.0 (5.0–9.5)	0.0	23.0 (15.5–37.5)	17.0 (1.5–31.5)	1.1
BPRS total	27.0 (17.0–35.0)	52.0[a] (42.0–57.0)	−2.7	34.5 (27.5–48.5)	38.0 (17.0–57.5)	0.13
BPRS subscales						
Anxiety-depression	3.5 (1.0–5.0)	6.0 (3.0–8.0)	−1.8	4.5 (3.0–6.5)	3.0 (3.0–4.5)	1.2
Withdrawal	7.5 (5.5–14.5)	17.0[a] (13.0–22.0)	−2.2	11.5 (6.5–18.0)	16.0 (5.0–19.5)	−0.2
Thought disturbance-hallucinations	9.0 (6.0–11.0)	17.0[a] (12.0–18.0)	−2.6	11.0 (9.0–16.0)	12.0 (6.0–13.5)	−0.0
Activation	4.9 (3.0–6.0)	9.0[a] (4.0–16.0)	−2.1	5.0 (2.5–7.5)	5.0 (2.5–15.5)	−0.5
Hostility-suspicion	2.0 (0.0–3.0)	2.5 (1.0–3.0)	−0.3	2.5 (0.5–4.5)	2.0 (0.0–5.0)	−0.6
VAS positive emotions	92.5 [15] (50.5–100.0)	0.0 [1][ab] (0.0–34.5)	2.4	86.5 [13] (39.5–100.0)	0.0 [2][b] (0.0–100.0)	0.1
VAS negative emotions	0.0 [5] (0.0–26.5)	40.0 [3] (7.5–72.5)	−1.5	0.0 [6] (0.0–57.5)	0.0 [2] (0.0–47.5)	0.09

BPRS, Brief Psychiatric Rating Scale; VAS, visual analog scale.

Data are presented as medians (interquartile range) for 10 and 30 min of infusion, VAS indicates emotional change during all 30 min of the infusion. The numbers of subjects who reported a positive or negative emotional reaction is shown in square brackets.

[a] $p \leqslant 0.05$ (Mann–Whitney test).

[b] $p \leqslant 0.05$ (Fisher's exact test).

Discussion

The main finding of our study is the decrease in prefrontal theta cordance and the increase in central theta cordance during ketamine infusion. With respect to the correlation of theta cordance with perfusion (Leuchter *et al*. 1999), the ketamine-induced theta cordance decrease in the prefrontal regions and the increase in the central regions, as found in our study, could reflect the opposite reaction of neuronal activity in the anterior and central midline regions. This interpretation is congruent with a recent fMRI study that documented ketamine-induced inhibition of the ventromedial frontal cortex (including the subgenual part of the anterior cingulate) and increased activity in the mid-posterior cingulate (Deakin *et al*. 2008).

The clinical studies documenting a reduction in prefrontal theta cordance are in accordance with data demonstrating a decrease in medioprefrontal perfusion and metabolism in antidepressant treatment (Mayberg *et al*. 1999; Kennedy *et al*. 2007). The decrease of theta cordance precedes the response to standard antidepressant treatment (Leuchter *et al*. 1997; Cook *et al*. 2002, 2005; Bares *et al*. 2007, 2008) but not to placebo (Leuchter *et al*. 2002). Our findings support the hypothesis that a decrease in activity in the prefrontal cortex (detected by theta cordance) would also mediate the antidepressant effect of ketamine.

Consistent with our observation of central theta cordance increase, elevated centrotemporal theta cordance (Cook *et al*. 1998) and increased metabolism in the dorsal anterior and posterior cingulate coupled, with a reduction in the subgenual cingulate (Mayberg *et al*. 1999), were detected previously during depression recovery.

Our study is the first to report that ketamine immediately induces the same changes in theta cordance as standard antidepressants do after 1 week in patients

https://doi.org/10.1017/S0033291709991619 Published online by Cambridge University Press

with depression. Ketamine reduced prefrontal theta cordance at 30 min by 41.3% (S.D. = 65.8). In connection with our study confirming cordance reduction as a predictor of response to antidepressant treatment, it is of interest that venlafaxine responders reduced cordance after 1 week by only 29.6% (S.D. = 19.9) (Bares *et al*. 2008).

The clinical effect of ketamine is thought to be mediated by the blocking of NMDAR followed by extracellular release of glutamate, which preferentially activates glutamatergic α-aminopropionic acid receptors (AMPARs) and induces their phosphorylation (Du *et al*. 2006). Changes in phosphorylation of AMPAR have been confirmed after acute ketamine administration in the hippocampus (Maeng *et al*. 2008) and in subchronic treatment by imipramine in the prefrontal cortex (Szabo *et al*. 2009). Taking together, the effect of both ketamine and monoaminergic-based antidepressants may be mediated by the facilitation of AMPAR but in antidepressants this effect occurs gradually after a series of downstream signaling steps (Du *et al*. 2006).

An increase in glutamate turnover with ketamine administration was demonstrated by magnetic resonance spectroscopy in the anterior cingulate (Rowland *et al*. 2005), which is, along with other ventromedial regions, the generator of frontal theta rhythm (Asada *et al*. 1999; Ishii *et al*. 1999; Tsujimoto *et al*. 2006).

Not only ketamine but also its first metabolite norketamine may contribute to the effect on theta cordance because of its substantial binding to NMDARs (Ebert *et al*. 1997). The fact that the serum levels of both ketamine and norketamine correlate with a decrease in prefrontal theta cordance at 10 min but not at 30 min supports the hypothesis that the early ketamine dose-dependent effect initiates subsequent downstream signaling steps that are not directly related to ketamine and norketamine blood levels.

Our observation that ketamine induces a wide range of psychotic symptoms detected by BPRS is consistent with previous studies of ketamine in schizophrenia modeling (reviewed by Bubenikova-Valesova *et al*. 2008). However, the unexpected finding is that psychotic symptoms were expressed more widely in prefrontal theta cordance non-reducers than in reducers. On the contrary, positive emotions measured by the VAS were more pronounced in the group of reducers. These data support the hypothesis that the opposite reaction of prefrontal theta cordance would discriminate between psychotogenic and euphoric emotional reaction.

The duration of the theta cordance decrease after a single ketamine application has not yet been studied. With respect to the antidepressant effect, the hypothesis that the AMPA-mediated effect of ketamine on synaptic potentiation lasts for up to 1 week should be tested. The predictive role of prefrontal theta cordance reduction is supported by recent findings that confirmed that the pretreatment activity of the anterior cingulate correlates negatively with the clinical antidepressant response to ketamine infusion (Salvadore *et al*. 2009). However, the predictive role of prefrontal theta cordance needs to be tested in depressive patients treated with ketamine.

Taken together, our data suggest that the decrease in prefrontal theta cordance could serve as an indicator of the fast antidepressant effect of ketamine, mediated by changes in the glutamatergic system in the medial prefrontal cortex. This assumption is partially supported by the finding that prefrontal theta cordance non-reducers did not detect a positive emotional reaction to ketamine as the majority of reducers did.

Acknowledgments

This study was supported by grant no. NR8792 from the Internal Grant Agency of the Ministry of Health, Czech Republic and by the projects 1M0517 and VZ 0021620816 from the Ministry of Education, Youth and Sports of the Czech Republic. We thank H. Fridrichova for technical assistance and subject coordination and I. Gorman for helpful comments and language correction.

Declaration of Interest

None.

References

Asada H, Fukuda Y, Tsunoda S, Yamaguchi M, Tonoike M (1999). Frontal midline theta rhythms reflect alternative activation of prefrontal cortex and anterior cingulate cortex in humans. *Neuroscience Letters* **274**, 29–32.

Bares M, Brunovsky M, Kopecek M, Novak T, Stopkova P, Kozeny J, Sos P, Krajca V, Hoschl C (2008). Early reduction in prefrontal theta QEEG cordance value predicts response to venlafaxine treatment in patients with resistant depressive disorder. *European Psychiatry* **23**, 350–355.

Bares M, Brunovsky M, Kopecek M, Stopkova P, Novak T, Kozeny J, Hoschl C (2007). Changes in QEEG prefrontal cordance as a predictor of response to antidepressants in patients with treatment resistant depressive disorder: a pilot study. *Journal of Psychiatric Research* **41**, 319–325.

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH (2000). Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry* **47**, 351–354.

https://doi.org/10.1017/S0033291709991619 Published online by Cambridge University Press

Bubenikova-Valesova V, Horacek J, Vrajova M, Hoschl C (2008). Models of schizophrenia in humans and animals based on inhibition of NMDA receptors. *Neuroscience and Biobehavioral Reviews* **32**, 1014–1023.

Cook IA, Leuchter AF, Morgan ML, Stubbeman W, Siegman B, Abrams M (2005). Changes in prefrontal activity characterize clinical response in SSRI nonresponders: a pilot study. *Journal of Psychiatric Research* **39**, 461–466.

Cook IA, Leuchter AF, Morgan M, Witte E, Stubbeman WF, Abrams M, Rosenberg S, Uijtdehaage SH (2002). Early changes in prefrontal activity characterize clinical responders to antidepressants. *Neuropsychopharmacology* **27**, 120–131.

Cook IA, Leuchter AF, Uijtdehaage SH, Osato S, Holschneider DH, Abrams M, Rosenberg-Thompson S (1998). Altered cerebral energy utilization in late life depression. *Journal of Affective Disorders* **49**, 89–99.

Cook IA, Leuchter AF, Witte E, Abrams M, Uijtdehaage SH, Stubbeman W, Rosenberg-Thompson S, Anderson-Hanley C, Dunkin JJ (1999). Neurophysiologic predictors of treatment response to fluoxetine in major depression. *Psychiatry Research* **85**, 263–273.

Deakin JF, Lees J, McKie S, Hallak JE, Williams SR, Dursun SM (2008). Glutamate and the neural basis of the subjective effects of ketamine: a pharmaco-magnetic resonance imaging study. *Archives of General Psychiatry* **65**, 154–164.

Du J, Machado-Vieira R, Maeng S, Martinowich K, Manji HK, Zarate J (2006). Enhancing AMPA to NMDA throughput as a convergent mechanism for antidepressant action. *Drug Discovery Today: Therapeutic Strategies* **3**, 519–526.

Ebert B, Mikkelsen S, Thorkildsen C, Borgbjerg FM (1997). Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. *European Journal of Pharmacology* **333**, 99–104.

Hetem LA, Danion JM, Diemunsch P, Brandt C (2000). Effect of a subanesthetic dose of ketamine on memory and conscious awareness in healthy volunteers. *Psychopharmacology* (*Berlin*) **152**, 283–288.

Hunter AM, Cook IA, Leuchter AF (2007). The promise of the quantitative electroencephalogram as a predictor of antidepressant treatment outcomes in major depressive disorder. *Psychiatric Clinics of North America* **30**, 105–124.

Ishii R, Shinosaki K, Ukai S, Inouye T, Ishihara T, Yoshimine T, Hirabuki N, Asada H, Kihara T, Robinson SE, Takeda M (1999). Medial prefrontal cortex generates frontal midline theta rhythm. *Neuroreport* **10**, 675–679.

Kennedy SH, Konarski JZ, Segal ZV, Lau MA, Bieling PJ, McIntyre RS, Mayberg HS (2007). Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. *American Journal of Psychiatry* **164**, 778–788.

Knott V, Mahoney C, Kennedy S, Evans K (2000). Pre-treatment EEG and its relationship to depression severity and paroxetine treatment outcome. *Pharmacopsychiatry* **33**, 201–205.

Krystal JH, Sanacora G, Blumberg H, Anand A, Charney DS, Marek G, Epperson CN, Goddard A, Mason GF (2002). Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. *Molecular Psychiatry* **7** (Suppl. 1), S71–S80.

Leuchter AF, Cook IA, DeBrota DJ, Hunter AM, Potter WZ, McGrouther CC, Morgan ML, Abrams M, Siegman B (2008) Changes in brain function during administration of venlafaxine or placebo to normal subjects. *Clinical EEG and Neuroscience Journal* **39**, 175–181.

Leuchter AF, Cook IA, Hunter A, Korb A (2009) Use of clinical neurophysiology for the selection of medication in the treatment of major depressive disorder: the state of the evidence. *Clinical EEG and Neuroscience* **40**, 78–83.

Leuchter AF, Cook IA, Lufkin RB, Dunkin J, Newton TF, Cummings JL, Mackey JK, Walter DO (1994). Cordance: a new method for assessment of cerebral perfusion and metabolism using quantitative electroencephalography. *NeuroImage* **1**, 208–219.

Leuchter AF, Cook IA, Uijtdehaage SH, Dunkin J, Lufkin RB, Anderson-Hanley C, Abrams M, Rosenberg-Thompson S, O'Hara R, Simon SL, Osato S, Babaie A (1997). Brain structure and function and the outcomes of treatment for depression. *Journal of Clinical Psychiatry* **58** (Suppl. 16), 22–31.

Leuchter AF, Cook IA, Witte EA, Morgan M, Abrams M (2002). Changes in brain function of depressed subjects during treatment with placebo. *American Journal of Psychiatry* **159**, 122–129.

Leuchter AF, Uijtdehaage SH, Cook IA, O'Hara R, Mandelkern M (1999). Relationship between brain electrical activity and cortical perfusion in normal subjects. *Psychiatry Research* **90**, 125–140.

Maeng S, Zarate Jr. CA, Du J, Schloesser RJ, McCammon J, Chen G, Manji HK (2008). Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. *Biological Psychiatry* **63**, 349–352.

Mathew SJ, Keegan K, Smith L (2005). Glutamate modulators as novel interventions for mood disorders. *Revista Brasileira de Psiquiatria* **27**, 243–248.

Mayberg HS (2003). Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *British Medical Bulletin* **65**, 193–207.

Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, Silva JA, Tekell JL, Martin CC, Lancaster JL, Fox PT (1999). Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *American Journal of Psychiatry* **156**, 675–682.

Nuwer MR, Lehmann D, da Silva FL, Matsuoka S, Sutherling W, Vibert JF (1999). IFCN guidelines for topographic and frequency analysis of EEGs and EPs. The International Federation of Clinical Neurophysiology. *Electroencephalography and Clinical Neurophysiology. Supplement* **52**, 15–20.

Penders J, Verstraete A (2006). Laboratory guidelines and standards in clinical and forensic toxicology. Accreditation and quality assurance. *Accreditation and Quality Assurance* **11**, 284–290.

Pizzagalli D, Pascual-Marqui RD, Nitschke JB, Oakes TR, Larson CL, Abercrombie HC, Schaefer SM, Koger JV, Benca RM, Davidson RJ (2001). Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. *American Journal of Psychiatry* **158**, 405–415.

Rowland LM, Bustillo JR, Mullins PG, Jung RE, Lenroot R, Landgraf E, Barrow R, Yeo R, Lauriello J, Brooks WM (2005). Effects of ketamine on anterior cingulate glutamate metabolism in healthy humans: a 4-T proton MRS study. *American Journal of Psychiatry* **162**, 394–396.

Salvadore G, Cornwell BR, Colon-Rosario V, Coppola R, Grillon C, Zarate Jr. CA, Manji HK (2009). Increased anterior cingulate cortical activity in response to fearful faces: a neurophysiological biomarker that predicts rapid antidepressant response to ketamine. *Biological Psychiatry* **65**, 289–295.

Szabo ST, Hado-Vieira R, Yuan P, Wang Y, Wei Y, Falke C, Cirelli C, Tononi G, Manji HK, Du J (2009). Glutamate receptors as targets of protein kinase C in the pathophysiology and treatment of animal models of mania. *Neuropharmacology* **56**, 47–55.

Tishler LC, Gordon LB (1999). Ethical parameters of challenge studies inducing psychosis with ketamine. *Ethics and Behavior* **9**, 211–217.

Tsujimoto T, Shimazu H, Isomura Y (2006). Direct recording of theta oscillations in primate prefrontal and anterior cingulate cortices. *Journal of Neurophysiology* **95**, 2987–3000.

Zarate Jr. CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK (2006). A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry* **63**, 856–864.