HOW KETAMINE CHANGES NEUROPHYSIOLOGY OF DEPRESSIVE PATIENTS BRAINS - RANDOMIZED CONTROLLED TRIAL

P. Sos¹,², M. Klirova¹,², M. Brunovsky¹,²,³, J. Horáček¹,², T. Novák¹,², B. Kohútová¹,², M. Bareš¹,², M. Kopeček¹,², V. Krajča³

¹) Prague Psychiatric Centre, Czech Republic
²) Charles University in Prague, 3rd Faculty of Medicine, Czech Republic
³) Faculty Hospital Na Bulovce, Department of Neurology, Prague, Czech Republic

OBJECTIVE
Administration of subanesthetic doses of non-competitive NMDA (N-methyl-D-aspartic acid) antagonist, ketamine hydrochloride, led in numerous studies to the rapid onset (hours), but relatively shortly detectable (days) antidepressive-like effect [1]. Maximum of mood improvement within the period from 2 hours to 3 days was significantly better on ketamine than on placebo. Functional imaging studies found out consistently abnormal type of metabolism or perfusion in dorsolateral prefrontal cortex and/or in anterior cingular cortex in depressive depression. Both structures are functional and neuroanatomically linked. Theta activity (4-8 Hz) scanned in EEG from prefrontal regions reflects both dorsolateral prefrontal cortex activity and projection of rhythms generated in anterior cingular. Increased glucose metabolism in rostral part of anterior cingular (Brodmann area 24/32) before a treatment predicate the response and hyperactivity (higher current density in theta frequency band) in the same regions is connected with the response rate in depressive patients. These findings support also QEEG (quantitative electroencephalography) cordance, measuring regional cerebral activity. QEEG cordance computing combines complementary information of absolute and relative EEG spectrum in algorithm that was developed in half nineties on UCLA (University of California, Los Angeles) by Leuchter and Cook. Cordance value correlates with regional cerebral perfusion and metabolism much better than the other QEEG indicators. Previous studies demonstrated predictive value of prefrontal QEEG cordance reduction in depressive patients treated with different antidepressants. Congruently with previous findings we hypothesised in our compressed model decrease of prefrontal QEEG theta cordance in 10 minutes of ketamine hydrochloride infusion as the prediction of antidepressant response in following day.

METHODS
14 depressive disorder patients (6 female and 8 male) diagnosed with a moderate to severe depressive episode without psychotic symptoms (F32.1, F32.2 according to ICD-10) on constant antidepressant medication were included [table 1]. All of the participants received single infusion with subanesthetic dose of ketamine hydrochloride solution (0.54mg/kg). Depressive symptoms and overall clinical state was assessed using MADRS (Montgomery-Åsberg Depression Rating Scale) and BDI (Beck Depression Inventory) [schema 1]. Response to treatment was defined as equal to or more than 50% reduction of MADRS scores. EEG measurements on the baseline, after 10 and 30 minutes of infusion were taken into account in computation of prefrontal QEEG theta cordance [schema 2].

RESULTS
There were 64.3% (9) of subjects who responded to single ketamine hydrochloride infusion following day [graph 1]. 89.9% (8) of responders decreased prefrontal QEEG theta cordance. No significance appeared in repeated measures ANOVA (F2,36; df=2,24; p<0.11), nevertheless subsequent pair comparison found significant difference in cordance values between baseline and after 10 minutes of ketamine infusion in responders (F=4.12; p<0.003) without correction for repeated measures [graph 2].

CONCLUSIONS
Preliminary results have shown the higher tendency of prefrontal QEEG cordance to decrease in ketamine responders. These results imply predictive function of prefrontal QEEG theta cordance even in the compressed model. Combination of latest QEEG method and fast-acting antidepressant-like effect of ketamine in this trial is unexampled.

LIMITATIONS
Larger sample size is needed to increased precision in estimates of cordance sensitivity and specificity.

REFERENCES

Table 1
Demographic and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>responders (N=9)</th>
<th>non-responders (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38.9 ± 7.1</td>
<td>36.3 ± 4.9</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>6/3</td>
<td>5/0</td>
</tr>
<tr>
<td>Handedness (R/L)</td>
<td>9/0</td>
<td>6/3</td>
</tr>
<tr>
<td>MADRS (baseline)</td>
<td>26.5 ± 3.7</td>
<td>26.2 ± 4.3</td>
</tr>
<tr>
<td>MDD treatment (years)</td>
<td>10 ± 7.5</td>
<td>18 ± 6.0</td>
</tr>
</tbody>
</table>

Results are reported as account or mean ± SD (standard deviation)
MADRS - Montgomery-Åsberg Depression Rating Scale
MDD - Major Depressive Disorder

Graph 1
Objective scale changes after single ketamine hydrochloride (0.54mg/kg) infusion

Graph 2
QEEG Cordance Values During Ketamine Infusion