[3,4]. Especially evening chronotypes have been related to mood and emotional dysregulation. Thus the purpose of this study was to assess the possible association between early life stress, chronobiological rhythms dysregulation in given chronotypes and emotional dysregulation in bipolars.

Method: One hundred patients (62 females mean age 48.2+12.4 years) with Bipolar disorder, depressive episode with mixed features, according to DSM-5 [5] and 21 healthy controls (16 females, mean age 47.7+12 years) were recruited. Bipolar subjects were evaluated with the Structured Clinical Interview (SCID-DSM-5), with the Morningness Eveningness Questionnaire (MEQ) to study chronotypes, Difficulties in Emotion Regulation Scale (DERS) to assess the emotional regulation, Beck Depression Inventory Scale (BDI-II) and Mania Rating Scale (MRS) to assess depressive and manic symptoms, and Early Trauma Inventory Scale-Short Form (ETISR-SF) to assess stressful events across the developmental age. An a priori power analysis was performed and correlations were studied by regression and mediation analyses.

Results: Twenty-nine bipolars (29.9%) and 3 healthy controls (15%) have shown evening chronotypes ($p<0.01$). The BDI-II and MRS scores were respectively 23.3 ± 11.1 and 9.1 ± 6.8 in bipolars, 5.2 ± 1.2 and 3.0 ± 0.1 in controls ($p<0.001$). The ETISR-SF score was 9.8 ± 04 in bipolars and 2.1 ± 1 in controls ($p<0.01$). Bipolars showed greater early life stress which significantly correlated with greater MEQ scores (coeff $= -0.49$, $p = 0.03$), with the chance to show evening type (coeff $= 0,23$ $p<0.001$) and the DERS scores (coeff $= 0.05$, $p = 0.009$). No significant correlations were found with BDI-II (coeff $= 0.04$, $p = 0.22$) and MRS (coeff $= 0.07$, $p = 0.30$) total scores. In bipolars greater early life stress independently predicted greater emotional dysregulation ($p = 0.0009$) and evening types (coeff $= 0.14$, $p = 0.04$). Evening chronotype mediates the association between early life stress and emotional dysregulation ($Z = 2.9$, $p = 0.02$).

Conclusions: These data show that early life stress are frequent in bipolars and are related to both evening chronotypes and emotional dysregulation; evening chronotype has been shown to be frequent in patients with bipolar disorder and to be related to emotional dysregulation. Particularly, evening chronotypes resulted to play a role in the relationship between early life stress and emotion dysregulation. If evening chronotypes may contribute to the association between early life stress and emotion dysregulation in bipolars, we may hypothesized early life stress having negative consequences at first on chronobiological rhythms. The evaluation and treatment of chronobiological rhythms should be useful in prevent and treat bipolar disorders.

References

[1] Palagini, L., Drake, C.L., Gehrman, P., Meerlo, P., Riemann, D., 2015. Early life origin of adult insomnia: does prenatal-early life stress play a role? Sleep Medicine. http://dx.doi.org/doi:10.1016/j.sleep.2014.10.013.

[2] Etain, B., Aas, M., Andreassen, O.A., Lorentzen, S., Dieset, I., Gard, S., Kahn, J.P., Bellivier, F., Leboyer, M., Melle, I., Henry, C., 2013. Childhood trauma is associated with severe clinical characteristics of bipolar disorders. J Clin Psychiatry 74 (10), 991–998.

[3] McClung, C.A., 2013. How might circadian rhythms control mood? Let me count the ways. Biol Psychiatry 74, 242–249.

[4] Harvey, A.G., 2011. Sleep and circadian functioning: critical mechanisms in the mood disorders? Annu Rev Clin Psychol 7, 297–319.

[5] American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders, Fifth edition (DSM-5), Arlington, VA.

doi: 10.1016/j.euroneuro.2018.11.591

P.578 Concurrent benzodiazepines undermine the antidepressant effect of ketamine

V. Andrashko*, T. Novak, J. Horacek, M. Klirova, M. Brunovsky

National Institute of Mental Health, Diagnostics and Treatment of Mental Disorders, Klecany, Czech Republic

Introduction: Rapid antidepressant effect of ketamine became a breakthrough in the research on depression. Nevertheless, nearly 30% of patients do not respond to ketamine infusion [1]. Although predictive and modulating factors of response to ketamine are broadly studied [2], little is known about optimal concurrent medication protocols. Concerning GABA being a shared target for both ketamine and benzodiazepines, we aimed to study this interference as a possible modulating factor for nonresponse.

The objective of the study was to assess the influence of BZD on the antidepressant effect of single ketamine infusion in depressed patients and to study eventual dose-dependence of this interaction.

Methods: We have analyzed the data from forty seven depressed patients (MADRS$\geq$ 20, $\geq$1 prior non-response to antidepressant treatment in current episode, on a stable dose of antidepressants minimum four weeks prior to admission) from two consecutive randomized, placebo-controlled, cross-over trials in our clinic, between 2010 and 2015. All subjects were given racemic ketamine intravenous infusion (0.54 mg/kg) as an add-on medication to previous depression treatment. The severity of depressive symptoms was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS). Ratings were obtained at baseline (before the infusion), and 24hours, 72hours and 7 days after the infusion. Response to treatment was defined as MADRS reduction of at least 50% from baseline any day during the one-week follow-up period.

Summary of results: The study included twenty males (43%) and twenty-seven females (57%) aged 31-52 years (Mean 43.0, SD 12.3). Baseline depression severity measured by MADRS was 24.0 ± 6.3. Eleven subjects (23%) were dealing with their first depression episode. The sample was divided into responders ($\geq$ 50% MADRS reduction, $n = 13$) and non-responders ($<$50% MADRS reduction, $n = 34$). Responders did not significantly differ from non-responders in age, sex, duration of depression diagnose, or dose of antidepressants. Nineteen patients (40%) were taking concomitant benzodiazepines since the enrolment in the study, though one patient discontinued BZD medication during the follow-up after the study infusion. Thirteen patients (28%) were taking

BZDs in doses higher that 10 mg diazepine equivalent pro die. We have found a significant difference in BZD dosage (after choosing a cut-off 10 mg diazepam equivalent daily) between responders and nonresponders (≥10 mg diazepam equivalent in 12 patients from the responders group vs. 1 patient in the responders group, $p = 0.07$). Logistic regression has revealed that concomitant benzodiazepine medication (daily dose 10 mg and more in diazepam equivalent) predicted nonresponse anytime during one-week follow-up after ketamine infusion (Odds ratio = 1.5; $p = 0.0445$).

Conclusions: Our study has revealed that benzodiazepines attenuate ketamine's antidepressant effect in patients with major depression in a dose-dependent manner. These findings are consistent with two previous post hoc studies [3,4] but replicate this trend on a much bigger sample. The results should be considered in future research on concomitant medication and clinical aspects of individualized ketamine application.

References

[1] Han, Y., et al., 2016. Efficacy of ketamine in the rapid treatment of major depressive disorder: a meta-analysis of randomized, double-blind, placebo-controlled studies. Neuropsychiatr Dis Treat 12, 2859–2867.

[2] Niciu, M.J., Luckenbaugh, D.A., Ionescu, F.D., Guevara, S., Machado-Vieira, R., Richards, E.M., et al., 2014. Clinical predictors of ketamine response in treatment-resistant major depression. J Clin Psychiatry 75, 417–423.

[3] Frye, M.A., Blier, P., Tye, S.J., 2015. Concomitant benzodiazepine use attenuates ketamine response: implications for large scale study design and clinical development. J Clin Psychofarmacol 35, 334–336.

[4] Albott, C.S., Shiroma, P.R., Cullen, K.R., Johns, B., Thuras, P., Wels, J., Lim, K.O., 2017. The antidepressant effect of repeat dose intravenous ketamin is delayed by concurrent benzodiazepine use. J Clin Psychiatry 78, e209–e308.

doi: 10.1016/j.euroneuro.2018.11.592

P.579 Interactions between oxytocin receptor gene methylation and callous-unemotional traits impact socioaffective brain systems in conduct-disordered youth

M. Aghajani[1,*], E. Klapwijk[2], O. Colins[3], C. Ziegler[4], K. Domschke[4], R. Vermeiren[3], N. Van der Wee[3]

[1] *Leiden University Medical Center/VU University Medical Center, Psychiatry, Leiden/Amsterdam, The Netherlands*
[2] *Leiden University, Psychology, Leiden, The Netherlands*
[3] *Leiden University Medical Center, Psychiatry, Leiden, The Netherlands*
[4] *University of Wuerzburg, psychiatry, Wuerzburg, Germany*

Objective: The developmental trajectory of psychopathy seemingly begins early in life and includes the presence of callous-unemotional (CU) traits (e.g., perturbed socioaffective reactivity and empathy, callousness) in conduct-disordered (CD) youth [1]. A biological substrate potentially relevant to CU traits and antisociality is the neuromodulatory peptide oxytocin [2], which among other things, shapes key socioaffective processes such as emotion recognition, affective resonance, and emotional learning [3]. Whereas oxytocin receptor gene methylation (OXTRMeth) and its downstream neuromodulatory effects are deemed particularly relevant to CU traits, nothing is known of how OXTRMeth interacts with CU to impact socioaffective brain systems in CD youngsters. Of particular interest is how these interactive effects might impact corticolimbic activity and amygdala subregional connections, as these neural processes are deeply influenced by oxytocinergic function, heavily involved in socioaffective behaviors, and crucially implicated in CU pathogenesis [4,5].

Methods: To address these issues, 39 severely antisocial male juvenile offenders with DSM-IV CD diagnosis (mean age = 16.87, SD = 1.35) and 27 age- and IQ-matched healthy control (HC) males (mean age = 17.04, SD = 1.15) were included in this study. All participants underwent a fMRI scanning session, wherein distressing facial expressions (i.e., angry and fearful) were presented, and participants had to either infer the emotional state from the face (proxy for emotion recognition) or feel into/empathize with the emotional face and judge their own emotional response to it (i.e., proxy for emotion resonance). Saliva samples collected on the day of scanning were used to establish OXTRMeth patterns for all participants. Whole-brain, voxelwise general linear modeling (GLM) next assessed how OXTRMeth levels interact with CU traits and diagnostic status (CD vs. HC) to impact task-related corticolimbic activity. Psychophysiological interaction (PPI) analyses, on the other hand, probed how these interactions impact task-related connectivity of basolateral (BLA) and centromedial (CMA) amygdala complexes with corticolimbic territories. Age, IQ, socioeconomic status, ethnicity, comorbidity, substance use, and OXTR genotype were corrected for, and all results adjusted for multiple comparisons via Gaussian Random Field Method ($Z > 3.1$, $p < 0.05$).

Results: Relative to HC youth, elevated OXTRMeth and CU levels in CD youth essentially interacted to predict frontoparietal hyperactivity and amygdalo-frontoparietal disconnection during task performance. Specifically, increasing OXTRMeth and CU levels in CD youth interactively predicted midcingulate hyperactivity during both emotion conditions, with insular, temporoparietal, and precuneal hyperactivity additionally emerging during emotion recognition. Interactions between high OXTRMeth and CU levels in CD youth additionally predicted centromedial amygdala decoupling from ventromedial/orbitofrontal regions during emotion recognition, along with basolateral amygdala decoupling from precuneal and temporoparietal cortices during emotion resonance.

Conclusions: In summary, elevated OXTRMeth and CU levels in CD youth interacted to predict frontoparietal hyperactivity and amygdalo-frontoparietal disconnection, when recognizing or resonating distressing socioaffective information. These results uniquely suggest that interactions between OXTRMeth and CU traits in CD youth may affect brain systems critical to decoding and integrating socioaffective information. Developmental models of CU and psychopathy could thus possibly advance by further examining OXTR epigenetic effects, which may hold promise for indicated prevention and personalized treatment by targeting oxytocinergic function.