[4], but is supportive for recent studies finding no attentional bias after remission [5]. Future work will focus on the relation to individual relapse risk and to other cognitive processes, while also adding measures such as eye-tracking.

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P.2.a.020 Investigating dose dependency of ketamine binding on the serotonin transporter with positron emission tomography

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Introduction: One of the primary set-backs of conventional antidepressant medication is the latency of efficacy. Ketamine is increasingly being utilized in clinical settings as a rapid-acting treatment for patients with depressive symptoms. The substance shows pronounced antidepressant and antisuicidal effects in clinical trials. Ketamine inhibition of NMDA-receptor function is well known. However, recent studies emphasize a possible role for serotonin (5-HT) in modulating ketamine's antidepressant effects. Among these are animal studies showing that ketamine's antidepressant effects are inhibited by prior tryptophan depletion, which implies dependency on the availability of 5-HT [1]. Furthermore, ketamine binding on the serotonin transporter (SERT) and inhibition of serotonin reuptake have been shown in-vitro [2] and in animal studies [3,4]. This is the first study to investigate the extent of ketamine's binding of the SERT in humans.

Aims: To assess ketamine's binding of the serotonin transporter (SERT) and whether the extent of binding is associated with ketamine plasma levels.

Methods: 12 healthy male subjects underwent two PET measurements (PET1, PET2) with [11C]DASB (4.7 MBq/kg) PET on a GE Advance full-ring scanner. PET1 was performed as a baseline scan, without pharmacologic intervention. Immediately prior to PET2, 0.5 mg/kg bodyweight racemic ketamine hydrochloride was applied intravenously over 40 min. [11C]DASB non-displaceable binding potential (BPND) was quantified using a multilinear reference tissue model and PMOD 3.509. SERT occupancy was quantified for 3 SERT-rich regions of interest (ROI) defined using the automated anatomic labeling atlas (ROIs: caudate, putamen, thalamus). Occupancy was quantified using the formula: occupancy (%) = (1−BPNDPET2 / BPNDPET1)x100. Blood was drawn at 5, 10, 20, 30, 40, 60, and 80 min after PET start for quantification of ketamine plasma levels. Ketamine levels were determined by gas chromatography –tandem mass spectrometry in multiple reaction monitoring (MRM). The analytical method was validated according to the EMA guideline.

Results: Occupancy was at 6.01%, 2.56%, and 1.38% for the caudate, putamen, and thalamus respectively. Ketamine plasma levels correlated positively with occupancy in the caudate (at 20 ($p = 0.032$), 30 ($p = 0.005$), and 40 ($p = 0.026$) min) and putamen (at 10 ($p = 0.028$), 20 ($p = 0.013$), 30 ($p = 0.002$*), 40 ($p = 0.011$) and 60 ($p = 0.044$) min). (*indicates p values that survive Bonferroni correction for multiple testing).

Conclusion: For the investigated ROIs, the observed occupancy is within [11C]DASB test-retest variability [5]. The positive correlation between ketamine plasma levels and occupancy, which was most significant at 30 min, points towards dose-dependent binding of the SERT by ketamine. This is underlined by the fact that animal studies demonstrating occupancy of the SERT by ketamine applied higher ketamine doses [3,4]. Thorough description of ketamine's molecular binding profile is necessary for safe and effective implementation in clinical practice. Our results underline the possibility of a role for the serotonergic system in modulation of ketamine's efficacy, which may be particularly relevant when the substance is applied at higher doses.

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P.2.a.021 Heart rate variability, autonomic tone and depressive-like behavior differences in resilient and susceptible rats to social defeat stress

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Background: Stress exposure is known as an important risk factor for psychiatric and cardiovascular disorders. Nevertheless, not every individual exposed to stress develops diseases, a difference which may be related to an individual's ability to adapt to adversity, i.e. their resilience or susceptibility to stress. After exposure of rodents to Social Defeat Stress (SDS), two phenotypes are perceived: one susceptible, that shows decreased social interaction (SI) and behavioral changes related to depression, and a resilient, that does not show these alterations [1]. However, little is known about the cardiovascular alterations related to SDS exposure in these phenotypes and its correlation to depressive-like behaviors.

Objective: The aim of this study was to evaluate the cardiovascular alterations related to heart rate variability (HRV), autonomic tone and depressive-like behavior in resilient and susceptible rats to SDS.

Methodology: Forty-eight male Wistar rats were used. They were exposed to 7 days of SDS composed of 4 aggressive encounters with a male Long Evans rat every other day. Control animals were maintained undisturbed in their home cage during this period. In the next day following the last encounter, they were evaluated in the SI test to the segregation of resilient and susceptible phenotype by k-means cluster analyses using the interaction ratio (IR). After that, animals were used to the evaluation of depressive-like behavior ($n = 26$) in the forced swim test (FST) or had their femoral artery canulated ($n = 22$) to the register of the heart rate (HR) and evaluation of the HRV and autonomic tone by power spectral analyses. Data were expressed as means ± SEM and analyzed by one-way ANOVA followed by Newman-Keuls test, considering $p < 0.05$ as significant.

Results: Susceptible rats to SDS showed social avoidance, compared to the control and resilient animals (Control = 3.0 ± 0.4; Resilient = 2.9 ± 0.2; Susceptible = 1.0 ± 0.2; $p < 0.001$) as well increased immobility time in FST (Control = 160.1 ± 20.0; Resilient = 147.7 ± 19.4; Susceptible = 212.8 ± 10.8 sec; $p < 0.05$). HR increased in susceptible animals, compared to control and resilient groups (Control = 351 ± 4; Resilient = 346 ± 6; Susceptible = 381 ± 9 bpm; $p < 0.01$). Heart rate variability increased in resilient animals and decreased in susceptible animals relative to controls (Control = 16.8 ± 2.5; Resilient = 30.9 ± 3.0; Susceptible = 8.4 ± 1.2 ms^2; $p < 0.001$). Sympathetic tone, measured by the low frequency band of the power spectrum, increased in susceptible compared to the control group (Control = 0.7 ± 0.1; Susceptible = 2.1 ± 0.6 ms^2; $p < 0.05$) and remained unchanged in resilient group (1.5 ± 0.3 ms^2; $p > 0.1$). Vagal tone, measured by the high frequency band of the power spectrum, was increased in resilient animals compared to the susceptible ones (Resilient = 4.2 ± 0.7; Susceptible = 1.9 ± 0.5 ms^2; $p < 0.05$), with no alterations found when compared to control group (3.0 ± 0.4 ms^2; $p > 0.05$).

Conclusions: Our results suggest a correlation between a depressive-like state and bad cardiovascular alterations [2] in rats classified as susceptible to SDS. The basal tachycardia found in susceptible rats might be due to the increased sympathetic tone to the heart, which in turn decreases HRV. Increased vagal tone in resilient animals probably acts as a protector factor against these alterations.

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P.2.a.022 3β Methoxypregnenolone (MAP4343), a synthetic pregnenolone derivative, promotes neuronal and synaptic plasticity in vitro

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3β Methoxypregnenolone (MAP4343) is a synthetic pregnenolone analog devoid of any hormonal activity, which displayed antidepressant-like activity in animal models of depression [1,2]. Although it does not bind to steroid receptors, it is able to interact with Microtubule-Associated-Protein 2, leading to the activation of tubulin polymerization in vitro [3]. Probably as a consequence to this effect, MAP4343 has been evidenced to increase neurite outgrowth in PC12 cells [3]. Microtubule cytoskeleton plays a critical role in neuroplasticity by regulating the dendritic spines formation. Since neuroplasticity stimulation is a part of anti-depressant effects, we hypothesized that MAP4343 may promote neuronal plasticity via its direct action on microtubule cytoskeleton, to exert this therapeutic effects. The aim of this study was to highlight MAP4343 actions on neuronal and synaptic plasticity in primary cultures of neurons.

Cortical neurons from SWISS mice embryos (E16-E17) were cultured during 3 days in vitro (DIV) and MAP4343 effects on neuronal morphology, including neurite length and branching point count, were studied using a high content screening platform analysis. Then, MAP4343 effects on synapse formation were analyzed, by measuring the expression of PSD95 protein (Post-Synaptic Density 95) at different time points (5, 7, 10, 13 DIV), by Western-blot analysis. Data were analyzed using either one-way or two-way ANOVA followed by Bonferroni post-hoc test. Finally, diolistic labelling of hippocampal neurons cultured for a longer time (17 DIV) was used to visualize density and morphology of protrusions treated or not with MAP4343. Data were analyzed using unpaired t-test.

The first set of data showed that a dose-ranging of MAP4343 (from 1 nM to 5 μM) induced a dose-dependent increase of neurite length, which was significant at 100 nM (+11%, $p < 0.05$), 1 μM (+25%, $p < 0.001$) and 5 μM (+40%, $p < 0.001$). MAP4343 5 μM also increased branching point number (+20%, $p < 0.001$). Western-blot experiments revealed a time-dependent increase of PSD95 expression in untreated neurons: +11% at 7DIV, +51% at 10 DIV and + 208% at 13DIV ($p < 0.001$) when compared to control measure at 5 DIV. When neurons were treated with MAP4343 (1 μM), PDS95 expression increased faster during the culture period than in untreated conditions: +75% vs + 11% at 7 DIV and + 188% vs + 51% at 10DIV ($p < 0.01$). in addition, MAP4343-enhanced PSD95 expression was found to be dose-dependent at 7DIV: +27% with 0.1 μM of MAP4343, +89% with 1 μM ($p < 0.05$) and + 96% with 5 μM ($p < 0.05$) when compared to untreated neurons. In hippocampal neurons,