using the BrainSeq resource. Only CPLX2 rs3892909*T has been significantly associated with the decreased CPLX2 expression, which proves the protective role of the variant in SCZ pathogenesis investigated previously in our laboratory [3]. Further, the LD analysis revealed the linkage of CPLX2 rs1366116 and rs3892909 with 15 other variants correlated with the expression levels of CPLX2. The results showed increased minor allele frequency (MAF) of rs1366116*T and decreased MAF of rs3892909*T are associated with the decreased CPLX2 expression. Interestingly, the CPLX2 expression is increased depending on age and reaches its maximum in early adulthood. The last STRING analysis showed that the protein, encoded by the genes CPLX2, CPLX4 and CRMP4 are not directly involved in the same mechanism of the synaptic plasticity regulation, but they interact on different levels with the help of the different intermediate proteins.
Conclusion: Summarizing the results of the bioinformatical analysis of the mentioned data bases, we can conclude that the studied single nucleotide variants CPLX2 rs1366116 and rs3892909, CPLX4 rs4940456 and CRMP4 rs1049171 might be indirect markers of the expression alterations of these genes and the proteins encoded by these genes are linked by intermediate proteins involved in the synaptic plasticity.

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P.799 Quantification of antidepressant and antipsychotic exposure increase caused by CYP2C19 and CYP2D6 intermediate and poor metabolizer status by meta-analysis

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Introduction: Most of the antipsychotics and antidepressants are metabolized by CYP2C19 and CYP2D6 enzymes. Both CYP2D6 and CYP2C19 genes are polymorphic and metabolic capacity of the enzymes is genotype-determined. Homozygous null allele carriers do not possess active enzyme, and they are referred to as CYP2C19 or CYP2D6 poor metabolizers (PM). Certain genotypes do not abolish the enzyme completely, but they do cause drastic reduction of metabolic capacity and carriers of such genotypes are referred to as intermediate metabolizers (IM). It is known that CYP2C19 and CYP2D6 PM and IM status cause increase in exposure of certain antidepressants and antipsychotics; however, due to small sample size of the previously published studies, the magnitude of this effect still cannot be estimated with sufficient precision. Therefore, the aim of this meta-analysis was to pool all these studies and estimate the magnitude of drug exposure increase caused by CYP2C19 and CYP2D6 PM and IM status, compared with normal metabolizers (NM) to the best possible degree.
Methods: The inclusion of the drugs used for the literature survey for meta-analysis was based on the list of new generation antidepressants [1] and antipsychotics [2]. These drugs were screened for inclusion by the PubMed search *DrugName AND (CYP2C19 OR CYP2D6). The studies were included in the meta-analysis if (1) the patients were genotyped for CYP2C19 or CYP2D6; (2) adequate sorting of patients into NM, IM, and PM was possible; (3) the study included at least three patients per subgroup; and (4) drug exposure was measured in representative way by: (a) dose normalized area under plasma level (time) curve, (b) dose normalized steady state plasma levels, or (c) apparent total clearance of the drug from plasma after oral administration (CL/F, reciprocal value represented the drug exposure). Meta-analysis for a specific drug was performed if three or more studies met the inclusion criteria. Drug exposure head-to-head comparisons were made between PM or IM subjects and the NM subject group, which served as a reference. Heterogeneity across the studies was assessed using Cochran's Q test at a given significance level and the percentage of total variability across the studies attributable to heterogeneity was quantified using I2 value. Magnitude of increase is presented as: Odds ratio (95% Confidence interval)
Results: Based on the outcome of the literature survey, it was possible to perform meta-analysis for escitalopram, venlafaxine, risperidone, and aripiprazole. Escitalopram exposure was 1.37-fold (1.30-1.44) increased in CYP2C19 IM and 2.44-fold (2.27-2.61) increased in CYP2C19 PM. Venlafaxine exposure was not significantly changed in CYP2D6 PM, 1.10 (0.99-1.22). Risperidone and aripiprazole exposure increased was similar for CYP2D6 IM and PM. Risperidone exposure was 1.42 (1.36-1.51) increased in CYP2D6 IM and PM admixed. Aripiprazole exposure was 1.52 (1.45-1.58) increased in CYP2D6 IM and PM admixed.
Conclusions: According to the results, reducing escitalopram dose by 60% in CYP2C19 PM and by 30% in CYP2C19 IM are appropriate dosing decision. Next, reducing risperidone and aripiprazole dose by 30% in CYP2D6 PM is appropriate

dosing decision. Finallytract, CYP2D6 metabolizer status is not clinically relevant in venlafaxine dosing.

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P.800 Further evidence of association between genetic variation in the glucocorticoid and mineralocorticoid receptor genes and cognition in major depressive disorder

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Background: Dysregulations in the activity of the hypothalamic-pituitary-adrenal (HPA) axis activity have been linked to the pathophysiology of stress related mental disorders, such as major depressive disorder (MDD), as well as cognitive functioning. Variations in the genes encoding for the glucocorticoid (NR3C1) and mineralocorticoid receptor (NR3C2) have been associated to altered glucocorticoid sensitivity, influencing the efficacy of stress-response mechanisms which could determine a differential vulnerability to MDD. A recent study by Keller et al [1] reported statistically significant associations between single nucleotide polymorphisms (SNPs) in these genes and cognitive performance in a sample of MDD patients.
Objective: We aimed to replicate the implication of genetic variants in NRC3C1 and NR3C2 in specific cognitive functions in an independent sample of MDD.
Methods: The sample included 89 patients (69.7% females, mean age 60.8±11.8) diagnosed following DSM-IV-TR criteria for MDD, depression severity was assessed using the Hamilton Depression Rating Scale (HDRS). Neurocognitive performance was assessed using a comprehensive neuropsychological test battery covering the following cognitive domains: verbal and visual learning, working memory, processing speed, attention/vigilance and executive functioning. Among the reported SNPs with a significant association with cognitive performance in the study conducted by Keller et al [1], data for 3 SNPs in the NR3C1 gene (rs10052957, rs41423247 and rs6198) and 1 SNP in the NR3C2 gene (rs2070951) were available in our sample. Genotyping was performed using the MassARRAYiPLEX platform. Multiple linear regression analysis was performed to explore the association between the selected SNPs and cognitive functioning while adjusting for sex, age, years of education and HDRS scores.
Results: Our results show a significant association between NR3C1 SNPs with performance in attention and processing speed tasks: rs11052957 predicted results in Trail Making Test Part A (TMT-A) (β: 0.255; p: 0.004), Trail Making Test Part B (β: 0.199; p: 0.027), Brief Assessment of Cognition in Schizophrenia–Symbol Coding (β: 0.−0.138; p: 0.037) and Continuous Performance Test–Identical Pairs (CPT-IP) (β: 0.−0.202; p: 0.047). rs6198 was associated to results in the TMT-A (β: 0.213; p: 0.018). NR3C2 SNP rs2070951 was associated to working memory and attention tasks, the Corsi Block-Tapping Test (β: −0.2; p: 0.035) and CPT-IP (β: −0.205; p: 0.036). Standardized beta coefficients are shown.
Conclusions: Our results are in accordance with those found by previous research suggesting that genetic variants in NR3C1 and NR3C2 genes contribute significantly to cognition in patients with MDD. Similarly to Keller et al, we found that NR3C1 SNPs were associated to attention and processing speed tasks which are related to prefrontal cortex activity; whereas NR3C2 seems to be more implicated in memory, which is associated to hippocampal function. Our results further illustrate the promising role of the study of these genes to advance in our understanding of the relationship between genetic variation and clinical manifestations, such as cognitive performance, in MDD.

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