Evaluation Scale (NES); the CGI-S; the PANSS; the Heinrichs’ Quality of Life Scale (QLS); the UCSD Performance-Based Skills Assessment (UPSA); the Personal and Social Performance (PSP) scale and Specific Level of Functioning (SLOF). Patients were subdivided in NSHigh (severe NSs) and NSLow (mild NSs) based on ROC curve-derived cut-off. **Results:** At the Student’s t test, NSHigh had significantly lower scores than NSLow patients on: Verbal Fluency; QLS score; PSP score; UPSA Financial, Communication, and Family Skills; UPSA total score; all SLOF areas (except Area-4). NSHigh patients had significantly higher scores than NSLow patients on CGI-S; PANSS Positive and General Psychopathology Subscale scores; and NES score. Distribution of NS patients was significantly different between TRS/ARS diagnostic groups, as NSHigh patients were significantly more frequent in the TRS group (Pearson chi square: $\chi^2=5.51, p=.001$). Notably, mean PANSS Negative Subscale scores were significantly higher in TRS compared to ARS patients (Student’s t: $t=1.48, p=.016$).

Since multiple variables found to be significantly different in NSHigh vs. NSLow patients were also significantly different between TRS and ARS patients, the question arises whether the significant differences found between diagnostic groups may depend on the higher percentage of patients with more severe NSs in the TRS group. Therefore, a two-way ANOVA was carried out with dichotomous NS and Diagnosis variables as the independent variables. Outcomes on multiple clinical variables were significantly different among groups. A NS*Diagnosis interaction effect was found for NES score ($F(1,58)=4.32, p=0.02, R^2=0.042$; Visuospatial Memory, UPSA Transportation skills, and SLOF Area-1). In all these cases, NSHigh/TRS patients performed significantly worse than the other patient groups; in the case of NES score, NSHigh/TRS patients score significantly higher than the other groups. Independent effect of either NSs or Diagnosis were also found for multiple variables, suggesting that NSs and Diagnosis may interact but their effects are not completely overlapping. To have a more deep comprehension of NS effects on diagnosis, we carried out a moderator regression analysis and an ANCOVA analysis that further confirmed the finding that NSs mediate Diagnosis effects on a number of clinical outcomes.

Given that NSs largely affect clinical variables, we asked which distinct symptom may exert the greater impact on each of these variables. Therefore, we carried out a including the seven PANSS Negative Subscale items as the independent variables. The items that explained the highest variance in clinical variables were mostly Stereotyped Thinking (N7), Passive Social Withdrawal (N4), and Difficulty in Abstract Thinking (N5). **Discussion:** These data suggest that NSs are both independent determinants and moderators of TRS/ARS diagnosis effect on multiple psychopathology, cognitive, and psychosocial factors. More impaired functions attributed to non-response to antipsychotics may depend on more severe NSs. However, only a subset of NSs appears to exert this action, possibly related to the multidimensional construct of these symptoms.

F234. TYPICAL AND ATYPICAL ANTIPSYCHOTICS’ D2R AFFINITY AND DOSES INFLUENCES POSTSYNAPTIC DENSITY BY MODULATING THE SPATIAL EXPRESSION OF HOMER1A GENE HIGHLY IMPLICATED IN SYNAPTIC PLASTICITY AND PSYCHOSIS

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**Background:** Post-synaptic density (PSD) is an ultra-specialized structure of excitatory synapses composed by a large variety of molecules (scaffold proteins, glutamate receptors, cytoskeleton proteins). PSD has been implicated in synaptic plasticity, memory formation and in the pathophysiology of psychiatric disorders by extensive GWA studies. The immediate early gene Homer1a is part of this complex molecular machinery for signaling transmission and its expression is modulated by antipsychotics (APDs). Here we show a comparative analysis of Homer1a expression data by first and second-generation APDs, in order to correlate it to their receptor profile.

**Methods:** We analyzed Homer1a expression induced by APDs at various doses in Sprague-Dawley rat forebrain, collecting data from multiple In Situ Hybridization experiments carried out in our laboratory in standard controlled conditions. Homer1a expression levels were normalized as the ratio of the corresponding mean vehicle value in each region. Normalized expression levels were quantitatively compared by ANOVA and Tukey’s post-hoc test ($p<0.05$) and grouped in four classes: no induction; light induction; moderate induction; high induction.

**Results:** In the striatum, sertindole did not induce Homer1a expression. Quetiapine and amisulpride were observed to trigger light induction of the gene. Clozapine triggered a light-moderate induction. Moderate induction was found by olanzapine and amisulpride, while high induction was found by ziprasidone, asenapine, and haloperidol, especially in caudate-putamen regions.

In the cortex, Homer1a mRNA was not induced by sertindole, 4mg/kg ziprasidone, haloperidol (0.25 and 0.5mg/kg). Haloperidol (0.8mg/kg, 15mg/kg quetiapine, 10mg/kg and 35mg/kg amisulpride triggered light induction. Moderate induction was found for 30mg/kg quetiapine, olanzapine, clozapine, 10mg/kg ziprasidone and for asenapine at all doses tested. Notably, both clozapine and 10mg/kg ziprasidone induced the highest levels of Homer1a mRNA in the insular cortex.

**Discussion:** A strong correlation with D2 receptor blockade and the extent of Homer1a expression in striatum, but not in the cortex, was found. However, other molecular mechanisms (e.g. D1 receptor activation in striatum; 5-HT2A receptor blockade in the cortex) may contribute to affect its expression levels.

F235. DIFFERENTIAL EFFECTS OF ANTIPSYCHOTICS ON NEUROINFLAMMATION AND ENERGY SENSING IN A HYPOTHALAMIC CELL LINE

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**Background:** Antipsychotics (APs) are the cornerstone of treatment for schizophrenia but cause serious metabolic side-effects. The hypothalamus is the primary brain region responsible for whole body energy regulation and disruptions in energy sensing (e.g. insulin signaling) and inflammation in this brain region have been implicated in the development of peripheral insulin resistance and obesity. Thus, it is possible that hypothalamic inflammation and disturbed energy sensing could be involved in AP-induced metabolic disturbances. Data in relation to AP-associated changes in inflammatory markers in schizophrenia has been inconsistent, owing in part to confounds of illness-related factors (e.g. diet, smoking) and secondary effects of weight gain. To our knowledge, direct effects of APs on hypothalamic cells in relation to insulin signaling and inflammation have not been examined.

**Methods:** To examine direct, molecular effects of APs in the hypothalamus, an immortalized rat hypothalamic cell line, rHypoE-19, was treated with olanzapine (dose range between 0.25–100 uM), clozapine (2.5–100 uM) or aripiprazole (5–20 uM). Western blotting was used to detect changes in the energy sensing protein AMPK, components of the insulin signaling pathway (AKT, GSK3B), and components of the mitogen activated-protein kinase (MAPK) pathway (ERK1/2, JNK, p38), the latter which are linked to inflammation. Quantitative real-time PCR was performed to determine changes in the mRNA expression of interleukin (IL)-6, IL-10 and brain derived neurotrophic factor (BDNF).
Results: Both olanzapine (100 uM) and clozapine (100 uM) significantly increased pERK1/2 and pJNK protein expression, while aripiprazole (20 uM) only increased pJNK. Clozapine (100 uM) and aripiprazole (5 and 20 uM) significantly increased AMPK phosphorylation and inhibited insulin-induced phosphorylation of AKT. Olanzapine (100 uM) treatment caused a significant increase in IL-6 while aripiprazole (20 uM) significantly decreased IL-10. Olanzapine (100 uM) and aripiprazole (20 uM) increased BDNF expression.

Discussion: All the APs studied upregulated pJNK, along with olanzapine-associated increases in IL-6, and aripiprazole-associated decreases in IL-10, together suggesting AP-mediated upregulation of pro-inflammatory pathways in rHypoE-19 neurons. Aripiprazole and clozapine (but not olanzapine) inhibited insulin-stimulated AKT, suggesting impaired hypothalamic insulin action by some, but not all, APs. Clozapine additionally increased AMPK phosphorylation (activation), an orexigenic energy sensor, which would also be expected to disrupt energy homeostasis. Conversely, olanzapine and aripiprazole increased BDNF, a factor linked to the underlying etiology of schizophrenia, suggesting BDNF upregulation may be a mechanism of therapeutic action. Taken together, our findings suggest differential and pleotropic effects of APs on neuroinflammation and energy sensing in the hypothalamus, which do not necessarily align consistently with known metabolic liability of these agents (i.e. clozapine = olanzapine > aripiprazole). Our data warrants further exploration into the mechanism of these effects, including replication of these effects in an in vivo model.

F236. CLONIDINE NORMALIZES MMN IN SCHIZOPHRENIA PATIENTS ON STABLE MEDICATION

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Background: Schizophrenia is a severe brain disorder with profound deficits in prefrontal cortical cognitive functioning. These cognitive deficits form a core feature in schizophrenia for which treatment has been proven to be clinically challenging. One of the key neurotransmitters involved in cognitive functioning is noradrenaline. Previous research has demonstrated disrupted noradrenergic activity in schizophrenia while several studies report improvements in prefrontal cognitive functioning by a selective α2-agonist. Clonidine is such a selective α2A-agonist and previous research in our lab has demonstrated that a range of single dosage(s) of clonidine normalize(s) sensory gating in chronically ill, yet stably medicated patients with schizophrenia. Currently, we investigated if clonidine also normalizes sensory gating in chronically ill patients with schizophrenia in spite of the fact that they were stable on their medical treatment. In addition, our data provide evidence that a single dose of clonidine is able to normalize MMN amplitude in these patients. Furthermore, patients could not distinguish between the placebo and the treatment conditions or reported any side effects of these low doses of clonidine. Together with our previous reports indicating normalized sensory and sensorimotor gating in these patients following administration of clonidine, our results could be of potential high clinical relevance in the treatment of schizophrenia. Future studies should therefore focus on longer trial periods to investigate if clonidine, besides normalizing MMN amplitude and sensory(motor) gating, can also ameliorate negative symptoms and cognitive functioning in schizophrenia.

F237. DOPAMINERGIC EFFECTS ON HIERARCHICAL PREDICTION ERRORS AND CONNECTIVITY DURING SOCIAL LEARNING

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Background: Persecutory delusions (PD) constitute core symptoms in psychosis that may emerge from aberrant learning and inference about others’ intentions. Computational assays that use generative models of electrophysiological data to probe this learning process and its underlying neuronal mechanisms, in particular the effects of dopamine (DA) on synaptic plasticity, could provide mechanistic insights into the emergence of PD in psychosis. More importantly, they could enable prediction of individual treatment response to DA antagonists and thus help to address an important problem of clinical management of psychosis.

Methods: We tested 137 healthy volunteers (mean age: 22 ± 3) in a double-blind, placebo-controlled, between subject pharmacological study: placebo (n = 47), DA precursor L-Dopa (n = 45), and DA receptor antagonist amisulpride (n = 45). Electroencephalography was recorded using a 128-channel Brain-Vision system. Participants performed a social learning task that required learning about an adviser’s intentions and how they changed over time. Subsequently, we modeled participants’ behavior with the hierarchical Gaussian filter (HGF), a model in which learning is driven by hierarchical prediction error (PE) updates: At the first level, positive PEs indicate that advice was better than expected (advice PE: aPE). At the second level, a positive PE signals that the adviser’s intentions were less stable (PE update: pJNK). To this end, we divided corresponding to positive and negative PEs.

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