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transcripts may indicate a more symptomatic patient requiring higher treatment doses.

O11.3. SYNAPTIC MARKER PROTEIN SV2A IS REDUCED IN SCHIZOPHRENIA IN VIVO AND UNAFFECTED BY ANTIPSYCHOTICS IN RATS

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Background: The synaptic dysfunction hypothesis of schizophrenia is supported by multiple lines of evidence. However, in vivo evidence is lacking. Moreover, it is not known if antipsychotics alter synaptic protein levels. We addressed this in a combined clinical study using [11C]UCB-J, a positron emission tomography (PET) radioligand specific for synaptic vesicle glycoprotein 2A (SV2A), and rodent study of clinically relevant antipsychotic drug exposure.

Methods: We scanned 18 subjects with schizophrenia (SCZ) and 18 healthy volunteers (HV) with [11C]UCB-J PET and T1-weighted MRI, estimating grey matter volumes of distribution (VT) and corrected grey matter volumes (GMV) for the frontal cortex (FC), anterior cingulate cortex (ACC) and hippocampus. In addition, we estimated the [11C]UCB-J distribution volume ratio (DVR) in these regions, using the centrum semiovale (CS) as a pseudoreference region. We collected clinical data including PANSS score, chlorpromazine-equivalent antipsychotic dose (CPZ) and duration of illness (DOI). In parallel, we investigated the effects of olanzapine and haloperidol administration on SV2A levels in the Sprague-Dawley rat frontal cortex using western blotting, [3H]UCB-J autoradiography and immunostaining with confocal microscopy. We used two-way analysis of variance (ANOVA) to test effects of group, ROI and group-by-ROI interaction on VT and DVR. We used planned post hoc t-tests to test group effects at each ROI, with false discovery-rate adjustment for multiple comparisons. We used two-way ANOVA with Bonferroni's post-hoc test to analyse autoradiography and SV2A immunostaining data, and the Kruskal-Wallis test, with alpha=0.05, to analyse western blot data.

Results: Clinical study: We found significant group-by-region interaction $(F2, 68=7.472, p=0.001)$, group $(F1, 34=6.170, p=0.02)$ and ROI $(F2, 68=426.0, p<0.0001)$ effects on VT, with significant reductions in mean [SEM] VT of large effect size in the SCZ group in the FC (SCZ=16.93 [0.80]; HV=19.50 [0.64]; t=2.51, df=34.0, p=0.03, Cohen's d=0.8) and ACC (SCZ=19.55 [0.75]; HV=22.49 [0.72]; t=2.83, df=34.0, p=0.02, Cohen's d=0.9), but not in the hippocampus (SCZ=14.09 [0.59]; HV=15.44 [0.50]; t=1.75, df=34.0, p=0.09, Cohen's d=0.6). Furthermore, we found significant group-by-region interaction $(F2, 68=7.97, p=0.0008)$, group $(F1, 34=8.1, p=0.007)$ and ROI $(F2, 68=510.9, p<0.0001)$ effects on DVR, with significant reductions of large effect size in the FC (SCZ=2.93 [0.17]; HV=3.48 [0.09]; t=2.89, df=34.0, p=0.01, Cohen's d=1.0), ACC (SCZ=3.39 [0.17]; HV=3.99 [0.09]; t=3.05, df=34.0, p=0.01, Cohen's d=1.0) and, additionally, hippocampus (SCZ=2.40 [0.12]; HV=2.74 [0.07]; t=2.32, df=34.0, p=0.03, Cohen's d=0.8). There were no significant relationships (p>0.05) between VT and GMV, PANSS score, DOI and CPZ.

Preclinical study: Chronic olanzapine or haloperidol exposure did not significantly affect total SV2A immunostaining intensity (p=0.97 and p=0.71 respectively) in the rat frontal cortex as compared to vehicle-exposed controls. Moreover, chronic haloperidol exposure did not significantly

affect [3H]UCB-J specific binding (p=0.27) or SV2A protein levels (relative to GAPDH, p=0.71).

Discussion: These findings provide evidence for the first time that presynaptic marker protein levels are reduced in schizophrenia in vivo and that antipsychotic drug exposure is unlikely to account for this, consistent with the synaptic dysfunction hypothesis.

O11.4. INTERACTOME OVERLAP BETWEEN SCHIZOPHRENIA AND COGNITION

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Background: Cognitive impairments constitute a core feature of schizophrenia, and a genetic overlap between schizophrenia and cognitive functioning in healthy individuals has been identified. However, due to the high polygenicity and complex genetic architecture of both traits, overlapping biological pathways have not yet been identified between schizophrenia and normal cognitive ability. Network medicine offers a framework to study biologically meaningful gene networks through protein-protein interactions among risk genes. Here, established network-based methods were used to further reveal the biological relatedness of schizophrenia and cognition.

Methods: The protein interactome was used to examine the genetic link between schizophrenia risk genes and genes associated with cognitive performance in healthy individuals. First, we used a method called network separation to examine if there is an overlap between schizophrenia and cognition in the interactome network space. Then, we used network propagation analyses to identify schizophrenia risk genes that are close to cognition-associated genes in the interactome network space. Gene ontology and pathway enrichment analysis was performed to describe the function of this gene set.

Results: Network separation analyses showed a profound interactome overlap between schizophrenia risk genes and genes associated with cognitive performance (SAB = -0.22, z-score = -6.80, p = 5.38e-12). We identified 140 schizophrenia risk genes that are close to cognition-associated genes in the interactome. Risk genes close to cognition were enriched for pathways including long-term potentiation and Alzheimer's disease, and included genes with a role in neurotransmitter systems implemented in cognition, such as glutamate and dopamine, that were not part of the direct genetic overlap. Moreover, schizophrenia risk genes close to cognition included 45 druggable genes not yet used as drug targets.

Discussion: These results pinpoint schizophrenia risk genes of particular interest for further examination in schizophrenia patient groups to reveal the genetic architecture of cognitive impairments in schizophrenia, of which some are druggable genes with potential as candidate targets for cognitive enhancing drugs.

O11.5. INCREASED INFLAMMATION AND MACROPHAGE INFILTRATION IS ASSOCIATED WITH ALTERED SUBEPENDYMAL ZONE NEUROGENESIS IN SCHIZOPHRENIA BUT NOT BIPOLAR DISORDER

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