Background: Recent Magnetic Resonance Imaging (MRI) studies on schizophrenia suggest that auditory verbal hallucinations (AVH) might be caused by alterations in connectivity of frontal and temporoparietal language-related areas, as well as in connectivity of the default mode network (DMN). Therefore, diffusion tensor imaging (DTI) of white matter fiber tracts, subserving anatomical connections between distant and proximal brain regions, could offer complementary information for understanding the anatomical underpinnings of AVH.

Methods: Tract-based spatial statistics (TBSS) allows voxel-wise analysis of multi-subject diffusion data based on fractional anisotropy (FA), assessing microstructural properties of white matter tracts. This study investigates brain white matter tracts in 85 schizophrenia patients and 111 healthy, matched controls using TBSS analysis. Patients were grouped into subgroups (hallucinating and non-hallucinating) based on the Positive and Negative Syndrome Scale (PANSS), with a cut-off PANSS P3 ≥ 3 in a 12 months period. Additionally, a comparison between the whole patient sample and controls was performed. The whole-brain analysis was performed with permutation analysis of linear models (PALM). Two-tailed t-test was used for group comparison of the patients and controls and a 2 x 2 factorial design was used for hemispheric comparison between patients and controls.

Results: TBSS results show significantly lower fractional anisotropy in the right inferior longitudinal fasciculus in schizophrenia patients in comparison to healthy controls (FDR correction p < 0.05). However, after subtracting non-hallucinating patients from the group this effect was no longer present. Hemispheric comparison between patients and healthy controls revealed wide-spread FA reduction in several white matter pathways such as: the corpus callosum (genus and body), cingulum cortex, inferior longitudinal fasciculus, superior corona radiata, anterior thalamic radiation (FDR correction p < 0.05). This effect was also present after excluding the non-hallucinating patients from the sample.

Discussion: The present findings indicate reduced white matter integrity in schizophrenia patients compared with controls in the inferior longitudinal fasciculus. However, this observation is most likely not related to hallucination proneness since it was not present when comparing the hallucinating patient subgroup with the control group. Hemispheric comparison between patients and controls in both the whole data sample as well as hallucinating groups showed significant differences in several white matter pathways. This could indicate that schizophrenia patients (with or without AVH) have altered FA differences between the hemispheres. More research is needed to further understand the implications of these findings.

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F188. THALAMIC MICROSTRUCTURE IN UNAFFECTED RELATIVES OF SCHIZOPHRENIA

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Background: Family, twin, adoption and candidate gene studies all support a genetic component for psychotic disorders. A considerable evidence suggests that the thalamus is abnormal in schizophrenia. The thalamus has a heterogeneous structure with its nucleus having distinct inputs and outputs. Disrupted thalamo-cortical connectivity, in particular, is considered as a core psychopathology in patients with schizophrenia. The disruption is also observed in subjects at clinical-high risk for psychosis. However, using the conventional magnetic resonance imaging methods, it had been difficult to investigate the subtle structural changes that may be present in the thalamus. Furthermore, despite the numerous reports of thalamic abnormalities in schizophrenia, the genetic aspect of the thalamic microstructure has not been thoroughly investigated.

Methods: To examine the microstructure of the thalamus, a total of 34 unaffected relatives of schizophrenia (UR) and 33 healthy control subjects underwent diffusion-weighted and diffusion kurtosis magnetic resonance imaging. Using the probabilistic tractography the projections from the thalamus to the lateral and medial prefrontal cortices, lateral and medial temporal cortices, occipital cortex, somatosensory cortex, parietal cortex and orbitofrontal cortex were analyzed. Then, the thalamus was segmented by the projections and the microstructures of those segmented regions were compared between the groups. The mean kurtosis values of the segmented regions were analyzed by analysis of covariance with age and sex as covariates and the results were adjusted with Bonferroni correction.

Results: There was no statistical difference in the mean kurtosis values of the left and right thalamic regions projecting to any of the investigated regions between the UR and healthy controls.

Discussion: Our findings, via diffusion kurtosis imaging, show preserved microstructural integrity of the thalamus in UR and that this imaging technique may be less well suited to detect thalamic abnormalities in them.

F189. PERSONALIZED MEDICINE: ESTIMATING THE IMPACT OF GENOTYPES ON ANTIPSYCHOTIC EFFICACY USING A QUANTITATIVE SYSTEMS PHARMACOLOGY APPROACH

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Background: CNS disorders are lagging behind other indications such as oncology in implementing genotype-dependent treatment algorithms for personalized medicine. This is due to the limited knowledge about the interaction of the relevant biology and the drug’s pharmacology.

Methods: We applied a mechanism-based computer model of a cortico-striatal-thalamocortical loop of the dorsal motor circuit that has been calibrated with clinical data on antipsychotic treatment in schizophrenia patients (Spiros, Roberts et al. 2017). The Quantitative Systems Pharmacology (QSP) model is based on the appropriate connections between basal ganglia regions and consists of 220 neurons (8 different cell types), 3500 synapses and implementations of 32 CNS active targets, based on their unique locations and coupling with intracellular pathways. COMTVal156Met, 5-HTTLPR rs2351 s/L and D2DR1a1A1 genotypes are implemented using human imaging data in non-medicated human volunteers.

Results: The dose-dependent antipsychotic effect for risperidone, aripiprazole and paliperidone is sensitive to the COMT genotype with the MM genotype having the greatest difference with the wild-type. Interestingly the 5-HTTLPR genotype interacts with the COMT genotype: this difference is positive for 5-HTTLPRsrs and negative for 5-HTTLPR LL. Olanzapine, quetiapine, clozapine and haloperidol are affected much less. The D2DR1a1A1 allele interacts in a complex way with the COMT genotype with haloperidol, aripiprazole and risperidone and with the 5-HTTLPR genotype for haloperidol, aripiprazole, risperidone and paliperidone. These effects are anticipated to be detectable in clinical settings.
F190. EFFECT OF SELECTED GENE VARIANTS ON THE RELATIONSHIP BETWEEN EARLY CANNABIS USE AND AGE OF ONSET OF PSYCHOSIS

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Background: Cannabis use, particularly regular use in adolescence, is associated with an increased risk of developing psychosis earlier. An earlier age of onset negates the protective effects of more mature psychosocial and individual variables, thus the potential for worse outcomes. Genetic variations in this relationship are important to understand as this will allow not only a better understanding of the biological interaction of cannabis and psychosis, but would inform future genetic approaches to risk identification as well. We uniquely examined the mediation of this association (gene x cannabis associations in age of onset of psychosis (AoP)) in 3 genetic variants which, while each have been examined separately, not in combination in the same population. We examined: 1) COMT Val158Met (rs4680) 2) BDNF Val66Met (rs6265) and 3) the AKT1 variant rs2494732.

Methods: 168 subjects with a diagnosis of psychosis were recruited from 2 sites in Canada, Edmonton Alberta and Halifax Nova Scotia. Cannabis use data (age at first and regular use) were collected using an electronic self-report survey (to address potential minimization of use to a researcher) and saliva samples were used for genotyping. Kaplan-Meier and Cox regression analyses were used to study the gene – cannabis effects.

Results: In those who had used cannabis, first use of cannabis prior to 20 years of age was associated with earlier AoP (p = .005). In those who used cannabis before age 20, rs4680 had a trend level association with AoP (log rank test: p=0.0617). A trend effect for an rs6265 x gender interaction (HR = 2.08, p = 0.067) on AoP, controlling for regular cannabis use was also observed. No association was observed between rs2494732 and rs6265 - rs2494732 interaction, and AoP.

Discussion: The trends in our associations are in keeping with previous studies. The result could be test that undoubtedly will be of great clinical value in treating patients and by prospectively preventing debilitating DRMD.

F191. THE GENETICS OF DRUG-RELATED MOVEMENT DISORDERS AN UMBRELLA REVIEW OF META-ANALYSES

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Background: Treatment with antipsychotics can provoke drug-related movement disorders (DRMD) (also known as extrapyramidal symptoms (EPS)), i.e. tardive dyskinesia (TD), parkinsonism, akathisia and tardive dystonia. DRMD remain a cause for concern in the treatment of patients with psychotic disorders, especially because the DRMD can become irreversible (Correll and Schenkl, 2008). There are lower percentages in younger patients (32%) (Mentzel 2017), but the prevalence is substantial in chronic patients (68%) (Bakker 2011), with around a quarter of chronic patients showing two different types of DRMD (Bakker 2011). DRMD can cause severe impairment in quality of life (Fujimaki 2012). In addition, a meta-analysis (Ballesteros 2000) and two recent studies showed a higher mortality in patients with tardive dyskinesia (Chong 2009, Dean and Thuras 2009). It is therefore important to find ways of preventing DRMD. Pharmacogenetic studies may identify genetic risk factors, which underlie individual vulnerability for DRMD in response to antipsychotics (Reynolds 2007; Ohmori 2003; Lerer 2002), in theory paving the way for individually tailored medication prescriptions (Lerer and Segman 2006). To date, many different papers have been written on the subject and they have presented inconsistent results.

The aim of this umbrella review is to provide clinicians and patients with evidence-based information regarding the genes that are thought to be associated with DRMD and to use this umbrella review on the genetics of DRMD as a basis for recommendations for future prevention programs and research.

Methods: To identify all relevant meta-analyses a Medline, Embase, and Psychinfo literature search was performed. Titles and abstract were screened using predetermined criteria by two independent authors. The methodological quality of included meta-analyses was assessed by two overview authors using ‘assessment of multiple systematic reviews’ (AMSTAR) critical appraisal checklist. Reference lists of included papers and those of reviews were cross-checked and no new publications were found.

Results: The search yielded 14 meta-analysis studies and consensus was obtained. The DR3, DR2, CYP2D6, 5-HT2A, COMT and MnSOD genes all contain variants that increase the odds ratio of TD. However meta-analyses showed diminishing significance over time and meta-analyses on the same subject were difficult to compare due to differences in patient population and methods used.

Discussion: For now it appears that TD is a complex disease with multiple genes that are involved in its phenotype and more studies (eg. Genome wide associatio studies), on a larger scale, are required to develop a genetic test kit to predict the chance of TD. To achieve this multiple research groups need to work together, a DRMD genetic database needs to be in place to overcome publication bias and results need to be stratified by patient characteristics.

The result could be test that undoubtedly will be of great clinical value in treating patients and by prospectively preventing debilitating DRMD.

F192. SYSTEMATIC META-ANALYSIS IDENTIFIES FIVE NOVEL ASSOCIATION LOCI FOR SCHIZOPHRENIA

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Background: Schizophrenia is a highly heritable psychiatric disorder. In the past 30 years, thousands of case-control and family-designed association studies have examined candidate genes for schizophrenia. To assist the field in interpreting this large volume of gene-association studies, the online SzGene database was created and included meta analyses for 287 polymorphisms at the time of its final update in 2010. However, since then more than one-thousand new gene-association studies in schizophrenia...