of microglia can be studied experimentally. This model system is based on intracerebral injection of clodronate disodium salt (CDS) into selected brain areas of interest. The behavioral and cognitive effects of temporary microglia depletion in the adolescent medial frontal cortex (mPFC) were assessed after full microglia recovery in adulthood. In addition, genome-wide transcriptional profiling was conducted during the peak of microglia depletion and after full microglia recovery in the mPFC. 

**Results:** We show that a single intracerebral injection of CDS is a suitable and efficient approach to selectively deplete microglia without affecting astrocytes and neurons in-vivo, leading to a robust (~ 80% depletion) but temporary (~ 1 week) microglia deficiency in selected brain areas of interest. Using this model, we further demonstrate that CDS injection into mPFC during late adolescence (6 weeks of age) causes numerous mPFC-related cognitive dysfunctions in adulthood, that is, when microglial cells have been fully restored again. The spectrum of cognitive deficits included impairments in social recognition memory, temporal order memory and extinction of conditioned fear responses. These deficits emerged similarly in male and female animals and were paralleled by a permanent transcriptional dysregulation of genes relevant for synaptic refinement and stability. Intriguingly, CDS injections into the mPFC during early adolescence (4 weeks of age) or adulthood (12 weeks of age) did not induce similar cognitive dysfunctions in adulthood.

**Discussion:** Taken together, the present data demonstrate that temporary prefrontal microglia deficiency during adolescence leads to permanent cognitive impairments in adulthood. Our findings further highlight that distinct adolescent stages of cortical maturation show a differing sensitivity towards the long-term cognitive effects of temporary microglia hypoactivity.

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**T180. REDUCED [3H]RO15-4513 RECEPTOR BINDING IN THE VENTRAL HIPPOCAMPUS IN THE MAM DEVELOPMENTAL DISRUPTION MODEL OF SCHizophrenia**

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**Background:** Post-mortem studies in schizophrenia patients have repeatedly found abnormalities in the γ-aminobutyric acid (GABA) inhibitory neurotransmitter system in the form of parvalbumin (PV)-expressing GABAergic interneuron reduction and aberrant glutamic acid decarboxylase mRNA expression and receptor distribution. However, these findings cannot be separated from medication effects. Evidence from the methylation-methanol acetate (MAM) animal model of schizophrenia has suggested a reduction of hippocampal PV interneurons in MAM-treated rats results in hippocampal dysfunction in the form of increased pyramidal neuron activity, which contributes to dysregulation of the stress response and concurrent disinhibition of dopaminergic neurons in the midbrain. Administration of a positive allosteric modulator of the α5 subunit-containing GABA-A receptor (α5 GABAAR) reversed dopamine neuron hyperactivation in the ventral tegmental area and attenuated schizophrenia-like behaviour in MAM-treated rats, suggesting this receptor subtype’s involvement in the development of psychosis. Conflictingly, an in vivo PET imaging study found no difference in α5 GABAAR binding compared to controls but demonstrated a negative correlation between binding in the hippocampus and negative symptoms of schizophrenia patients. However, this study included previously medicated patients. To understand the involvement of α5 GABAAR in hippocampal dysfunction without a confound of antipsychotic medication, we investigated whether these receptors are differentially expressed in MAM-treated compared to control rats using autoradiography.

**Methods:** MAM-treated (n=21) and saline (vehicle)-treated (n=22) male rats were assessed for schizophrenia- and anxiety-like phenotypes via amphetamine-induced hyperlocomotion (AIH) and the elevated plus maze assays (EPM), respectively. To quantify the density of α5 GABAAR, we used [3H]Ro15-4513, a selective radioligand binding to the benzodiazepine site of this subunit. [3H]Flumazenil, an antagonist of the benzodiazepine-binding site of α1-3,5 GABAAR, was used on adjacent brain slices of the same animals to investigate more general binding to GABAAR. Brain sections were treated with the radioligands and x-ray sensitive films were exposed to the brain sections and radioactivity standards for 4 (flumazenil) or 8 (Ro15-4513) weeks. Developed films were imaged and normalised to background, radioactive binding in images was calculated based on the standard curve using the robust regression method in Graphpad Prism 8. Subsequently, quantified images were sampled for the CA1 of the ventral hippocampus using MCID software. Independent t-tests were used to investigate group differences in time spent in open arms during the EPM, total distance moved during AIH, and receptor binding. The significance threshold was set to p=0.05.

**Results:** MAM-treatment induced a schizophrenia-like phenotype (AIH: t(39)=-3.022, p=0.004) and an anxiety-like phenotype (EPM: t(41)=2.810, p=0.008) compared to saline. We found reduced α5 GABAAR binding in the ventral hippocampus CA1 region of MAM-treated rats compared to saline-treated rats (t(41)=2.563, p=0.014), but no differences in flumazenil binding to α1-3,5 GABAAR (t(41)=1.333, p=0.190).

**Discussion:** MAM treatment induced schizophrenia- and anxiety-like phenotypes, accompanied by an α5 GABAAR density decrease in the CA1 region of the ventral hippocampus. Specific reduced binding to α5 was corroborated by the absence of any binding changes in the flumazenil treated sections. These findings reveal part of the molecular mechanisms behind hippocampal dysfunction and implicate the α5 subunit as a potential novel target for treatment of schizophrenia.

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**T181. PROTEIN ACYL-THIOESTERASE ENZYME ACTIVITY IN THE POSTMORTEM DORSOLATERAL PREFRONTAL CORTEX IN SCHizophrenia**

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**Background:** The role protein trafficking and localization is a recent target of investigation in schizophrenia pathophysiology. An important mediator of protein trafficking is S-acylation, also known as S-palmitoylation, which is the reversible attachment of long chain fatty acids to cysteine residues. S-acylation is a dynamic post-translational modification that modulates hydrophobicity of proteins, regulating their membrane association and subcellular localization. Notably, we have previously reported a proteome-wide decrease in S-acylated protein levels in the dorsolateral prefrontal cortex (DLPFC) of subjects with schizophrenia. One potential mechanism of decreased S-acylation is increased removal of acyl groups from proteins by protein acyl-thioesterase enzymes (PATs). Here we describe the optimization of an assay to measure the activity of the PAT family of enzymes in human postmortem cortical tissue and use the assay to address our hypothesis that PAT activity is increased in the DLPCF of subjects with schizophrenia.

**Methods:** To determine PAT activity, tissue homogenate was incubated with 4-methylumbelliferyl-6-thio-palmitate-[β-D-glucopyranoside (4MU-Gluc-Palm) and 1U of exogenous β-glucosidase (to hydrolyze the 4MU-Gluc reaction intermediary). Released 4MU was excited at 360 ± 40 nm and fluorescent emission was measured, per minute, at 460 ± 40 nm. To determine the relationship between initial reaction rate and amount of enzyme, the initial reaction rate using 300 µM 4MU-Gluc-Palm was measured in homogenate containing 1 – 10 µg of total protein from the DLPCF of a subject with no history of psychiatric illness. The PAT activity of DLPCF homogenate
boiled for 30 min and total protein homogenate from lymphocytes were measured as negative and positive control reactions, respectively. To estimate the maximum reaction rate (Vmax) and the concentration of 4MU-Gluc-Palm which achieved ½ Vmax (Km; a measure of enzyme-substrate affinity) the initial reaction rate was calculated in the presence of 0 – 200 μM 4MU-Gluc-Palm and the Michaelis-Menten equation was fit to plots of concentration vs. initial rate. Reactions were performed on 2.5 μg total protein homogenate from the DLPFC of 24 subjects with schizophrenia and 24 non-psychiatrically ill subjects.

**Results:** A fluorescent signal, which increases with time to a plateau upon substrate depletion, is detectable in total protein homogenate from DLPFC and lymphocytes, but not boiled DLPFC homogenate. In the DLPFC the initial reaction rate is linear with total protein amount \( r^2 = .96; p = .007 \), demonstrating that the reaction is sensitive to varying amounts of enzyme in a 10-fold range. When compared between schizophrenia and control subjects, neither Vmax \( t(46) = 0.756; p = .45 \) nor Km \( t(46) = 0.780; p = .44 \) were statistically significantly different.

**Discussion:** Here we have demonstrated that PAT activity is measurable in human cortical tissue homogenate. Additionally, we have found no difference in the Vmax or Km of the combined PAT enzyme group in schizophrenia, providing no evidence to support our hypothesis that total PAT activity is increased in subjects with schizophrenia. This suggests that the proteome-wide decrease in S-acylated proteins in schizophrenia is caused by another mechanism, possibly increased expression or function of one or more of the specific PATs, leading to substrate specific changes in S-acylation, or a decrease in activity the acyl protein transferase enzymes, which attach acyl groups to proteins.

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**T182. DIAGNOSIS INDEPENDENT SYNDROME RELATED GRAY MATTER VOLUME CHANGES IN A LARGE TRANS DiAGNOSTIC COHORT: RESULTS FROM THE FOR2107 STUDY**

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**Background:** More than a century of research on the neurobiological underpinnings of the Major Psychoses (Schizophrenia SZ, Bipolar Disorder BD, Major Depressive Disorder, Schizoaffective Disorder SZA) has been unable to identify diagnostic “markers”. An alternative approach is to study dimensional psychopathological syndromes that cut across categorical diagnoses. Brain imaging studies on the correlates of syndromes are thus far restricted to one diagnosis, however it is unclear, whether structural brain correlates of syndromes are the same across diagnoses. Previously, we have identified 7 syndromes in n=811 patients suffering from major psychoses, applying a confirmatory factor analysis, including depressed mood, negative symptoms, delusions, formal thought disorders, hallucinations, mania and increased appetite. The aim of the current study was to identify gray matter volume correlates of these syndromes across the major psychoses.

**Methods:** We tested the association of the above 7 psychopathological factors with whole brain GMV (voxel-based morphometry) in a sample of n=713 patients meeting DSM-IV criteria for MDD (n=550), BD (n=79), SZ (n=51) and SZA (n=33) (www.for2107.de). T1 weighted brain images were acquired at a 3-Tesla MRI. Images were pre-processed as implemented in the Cat12 (SPM12) toolbox. We performed multiple regression analyses for each factor separately and used the family wise error correction (FWE) to correct for multiple comparisons. Additionally, we tested if local VBM associations were driven by one diagnosis extracting the beta-volumes of the clusters and then comparing the subgroups using ANCOVA.

**Results:** The delusion factor was negatively correlated with gray matter volume in the left inferior temporal gyrus/fusiform gyrus (k=138 voxels, x/y/z=-48/-58/-15, t=5.23, p<.05 FWE peak level) and the left amygdala/hippocampus (k=23 voxels, x/y/z=-15/12/-12, t=4.84, p<.05 FWE peak level). The hallucinatory syndrome was negatively correlated with volume in the right thalamus proper (k=54 voxels, x/y/z=8/4/2, t=4.9, p<.05 FWE peak level). Extraction of the beta-volumes revealed no effect of diagnosis (delusions (F (3,708) p=.54); hallucinations (F (3,708) p=.542).

**Discussion:** Volume changes underlying psychopathological syndromes are independent of diagnosis. We could confirm previous results from much smaller studies which have restricted themselves to single diagnoses or case control designs. Our findings open a new avenue for neurobiological research of the major psychoses, using syndrome based, dimensional approaches rather than DSM or ICD diagnoses.

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**T183. LOW LEVELS OF VITAMIN D ARE ASSOCIATED WITH REDUCED CORTICAL THICKNESS AND SURFACE AREA IN FRONTAL, TEMPORAL AND OCCIPITAL REGIONS IN FIRST-E PISODE PSYCHOSIS PATIENTS**

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**Background:** Vitamin D is a neuro-steroid hormone important in brain development, maturation and function as it modulates the production of numerous brain growth factors. Indeed insufficient levels seem to compromise development and confer an increased risk of developing schizophrenia later on in life. Finally patients with first-episode psychosis tend to have lower levels of vitamin D than healthy controls. We aimed to explore: 1) The association between vitamin levels and brain structure (i.e. cortical thickness and surface area) in FEP individuals; 2) Differences in brain structure (i.e. cortical thickness and surface area) between FEP individuals with optimal and sub-optimal levels of Vitamin D.

**Methods:** Sample: 49 patients with first episode of psychosis (mean age: 27.8 SD ± 9.1 years) part of the BRC Psychosis Theme study on Genetics and Psychosis (GAP). Vitamin D: Vitamin D (serum 25-hydroxyvitamin D) levels were determined by immunoassay. Patients were considered to have sub-optimal levels if vitamin D concentration was below 20 ng/ml, with higher concentrations deemed optimal. Twenty patients had sub-optimal levels of Vitamin D whereas 29 had optimal Vitamin D concentration. Brain Structure: 3T MRI scan were used to evaluate the cortical thickness and the surface area in 49 FEP patients. FreeSurfer 5.3.0 was used to correlate Vitamin D levels with both cortical thickness and surface area in a vertex-by-vertex analysis. Afterwards differences in cortical thickness and surface area between FEP participants with both optimal and sub-optimal Vitamin D levels were examined using a vertex-by-vertex General Linear Model analysis in FreeSurfer 5.3.0. Results were corrected for multiples comparison with MonteCarlo simulation.

**Results:** Vitamin D levels positively correlated with cortical thickness in the left superior-frontal gyrus and surface area in the right peri-calcarine and right inferior-parietal gyrus (all p<0.05 FWE corrected). FEP patients with sub-optimal levels of Vitamin D (below 20 ng/ml) had reduced cortical thickness in the right medial-orbitofrontal gyrus and lingual gyrus compared to those with optimal levels of Vitamin D (all p<0.05 FWE corrected). Additionally, FEP patients with sub-optimal levels of Vitamin D had smaller surface areas in the cuneus, latero-orbitofrontal gyrus, pre- and post central gyri, superio-frontal gyrus, and inferio parietal gyrus in the right hemisphere than those with optimal levels (all p<0.05 FWE corrected).