

POSTER PRESENTATIONS

POSTER #: 1

Genome-wide association study identifies genetic loci associated with body mass index and HDL-cholesterol levels during psychopharmacological treatment

Lavinia Athanasiu, Andrew A. Brown, Astrid B. Birkenaes, Morten Mattingsdal, Ingrid Agartz, Ingrid Melle, Vidar M Steen, Ole A Andreassen, Srdjan Djurovic

Background:
Metabolic and cardiovascular side effects are serious clinical problems related to psychopharmacological treatment, but the underlying mechanisms are mostly unknown. We performed a genome-wide association study of metabolic and cardiovascular risk factors during pharmacological therapy in patients with severe mental disorders.
Objectives:
The aim of the present study was to identify genetic variants associated with psychopharmacological-induced metabolic and cardiovascular side effects, using a genome-wide cross-sectional approach in a genetically homogenous sample of Norwegian patients treated in a naturalistic setting.
Methods:
Our sample consisted of 594 patients with a severe mental disorder (schizophrenia or bipolar disorder) from the Thematically Organized Psychosis (TOP) Study and were sucsessfully genotype on Affymetric Genome-Wide Human SNP array 6.0 (Affymetrix Inc., Santa Clara, CA, USA) The patients were examined for twelve indicators of metabolic side effects (body mass index, waist circumference, total cholesterol, HDL-cholesterol, LDL-cholesterol, HDL-cholesterol/total cholesterol ratio, triglycerides, glucose, and C-reactive protein), and cardiovascular variables (blood pressure and heart rate) were measured. The patients used antipsychotics, mood stabilizers and/or antidepressants. We analyzed interactions between gene variants and three categories of psychopharmacological agents based on their reported potential for side effects and defined genome-wide significance based on false discovery rate (FDR) of 0.1. We investigated these interactions between SNP and the medication with respect to differences in the level of metabolic -and cardiovascular side effects, using linear regression models implemented in PLINK.
Results:
The analyses revealed 14 significant interactions (FDR<0.1), one where the interaction acted on HDL-C levels and 13 interactions acting on BMI. For BMI, two significantly associated loci were identified on 8q21.3, highlighted by 13 markers. There were seven markers in one 30kb region and the strongest signal was $P = 6.07 \times 10^{-8}$ (FDR= 0.051). In another locus 140 kb away, six markers were significant, and the strongest signal was $P = 1.54 \times 10^{-7}$ (FDR= 0.018).For HDL-C, a marker on 12q21 was significant ($P = 9.01 \times 10^{-8}$, FDR =0.051).
Conclusion:
The results highlight three genomic regions potentially harboring susceptibility genes for drug induced metabolic side effects. This deserves to be replicated in additional populations to provide more evidence for molecular genetic mechanisms of side effects during psychopharmacological treatment.

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POSTER #: 2

"Visualizing segmentations from FreeSurfer"

Ø. Bergmann, C. B. Hartberg, I. Agartz

Background:
FreeSurfer has become one of the de facto standards for analyzing cortical surface measurements and subcortical anatomy. Included with the FreeSurfer distribution are tools for visualizing the 3D results of cortical surface reconstruction (*tksurfer)*, and a 2D tool for editing and visualizing slices of sub-cortical intensities and segmentation (*tkmedit*).
Objectives:

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In this work we describe our implementation of an automatic 3D visualization tool that we use to generate high quality images of selected sub-cortical brain structures pre-processed in FreeSurfer. Our tool extends the 2D tools included with FreeSurfer by using volume ray-casting to project the 3D sub-cortical brain structures onto an image surface.

Methods:

The data available after the FreeSurfer pre-processing stage is 3D; each voxel contains an integer index corresponding to a named sub-cortical structure. All voxels assigned to the same segment belong to the same structure.

Frequently we are only interested in visualizing a subset of all the sub-cortical segmentations that FreeSurfer recognize. For each of the *k* segments of interest we create a binary dataset where a voxel is 1 if it belongs to that segment, and 0 otherwise. Each of these binary segments is then convolved with a 3D Gaussian kernel in order to make the segments appear smoother, and have well-defined surface normals everywhere.

The volume ray-casting then proceeds as usual by defining a virtual observer looking at the data through a 2D regular grid, and projecting a ray from the observer, through each grid pixel position onto the data. The data is sampled at discretized positions at regular intervals along the ray (at distance Δ apart) producing intensities that are transformed to color using the transfer function of the hit object. In order to sample the data at a given position we interpolate each of the *k* smoothed binary datasets at that location and consider the segments with the greatest value larger than a threshold parameter *t* as "hit". The ray is terminated after a predetermined number of steps *n*, and the colors are blended in a "back-to-front" manner in order to produce the final image pixel color using Phong shading.

Results:

We show our visualization for the *fsaverage* isometric test dataset of size 256x256x256 distributed along with FreeSurfer. We use a 7x7x7 Gaussian blurring kernel with standard deviation 1, and the following sampling parameters; Δ=1, *n*=256 and *t*=0.5.

Conclusion :

We have create a visualization framework capable of visualizing FreeSurfer segmented brain MRI.

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POSTER #: 3

Neural correlates of anticipating and avoiding negative events: An fMRI version of the CAR task

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Background:

The mesolimbic system, and the ventral striatum in particular is thought to be a central component in anticipation of motivationally salient events.. Both typical and atypical antipsychotic medications target these regions. The conditioned avoidance response (CAR) is much used and studied in animal models when validating the effect of antipsychotic medication (Wadenberg, 2010).

Objectives:

In this study a functional Magnetic Resonace Imaging (fMRI) version of the CAR task was employed in order to look at the brain activations associated with a CAR-like response in humans. Thus, the neural correlates when subjects have an opportunity to avoid aversive events were examined.

Methods:

In the MRI scanner, the 16 included subjects were presented with two types of colored circles that were associated either with an aversive or a non-aversive sound, and given the possibility to avoid the sounds by responding to a target with a button-press. A general linear model was used and the contrast of the two conditions (circle associated with aversive sound vs. circle associated with non-aversive sound) was generated. Data processing and analyses were performed in SPM5.

Results:

Behavioral analyses showed that responses on targets were significantly faster in aversive than in non-aversive trials. A whole brain analysis correcting for multiple comparisons revealed activations in: bilateral ventral striatum, right amygdala, right inferior frontal gyrus, right insular cortex, bilateral anterior and middle cingulate cortex and the left inferior parietal lobe.

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Conclusion:
The activations in the ventral striatum are in line with previous reports, and suggest that this region is involved in anticipation of future negative events. However, activations in frontal, cingular and insular regions indicate that these areas, in addition to the ventral striatum, are important for preparing to avoid danger or unpleasant events. The CAR fMRI task employed in this study is interesting in a pharmacological perspective because of its similarity to the well known animal model for antipsychotic medication, and will be used in future human pharmacological MRI studies.

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POSTER #: 4

Impulsivity in bipolar II and borderline personality disorder

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Background:
The relationship between bipolar II (BPII) and borderline personality disorder (BPD) is debated, but studies thoroughly comparing their clinical features are lacking. Impulsivity is one of the diagnostic criteria for BPD, and regarded as a core feature of the disorder. Impulsivity is also a prominent feature of bipolar spectrum disorders, and shown to be elevated across mood states. The term "impulsivity" encompasses a wide spectrum of traits. The UPPS Impulsive Behavior Scale[1], a 45 item self report questionnaire, is based on factor analysis of a number of common impulsivity measures including BIS-11, NEO-PI, TCI and others, and identify four distinct facets of impulsivity: **U**rgency, **P**remeditation, **P**erseverance and **S**ensation seeking.
Objectives:
The purpose of this study was to compare aspects of impulsivity in BIPII and BPD patients using the UPPS scale and clinical assessment.
Methods:
25 borderline patients, 21 bipolar II patients, and 40 healthy controls (HC) were investigated. All patients were euthymic to moderately depressed. The two diagnoses in question were mutual exclusion criteria. Investigations included the UPPS scale and psychiatric evaluation including assessment of eating disorders, substance abuse, ADHD, suicide attempts, self mutilation, aggressive behavior and mood state, as well as neuropsychological assessment.
Results:
Preliminary results showed that both patient groups had significantly higher levels of Urgency and (lack of) Perseverance than HC. Comparisons between patient groups showed significant higher levels of Urgency (p=.002) and (lack of) Perseverance (p=.003) in BPD (mean age 25.5; 87.5% female) compared to BIPII patients (mean age 33.0, 76.2% female). After adjusting for age, the differences remained significant for (lack of) Perseverance (p =.049), but only reached near-significance (p= .055) for Urgency. There were no between patient group differences on the other subscales.
Conclusion:
Both patient groups showed elevated levels of facets of impulsivity compared to HC. After adjusting for age, BPD had significantly higher scores than BPII on the Perseverance subscale, and near-significant higher scores on the Urgency subscale. The findings point towards possible different phenomenological impulsivity profiles. Final results including other impulsiveness-related data from the assessment will be presented.

Reference
1. Whiteside and Lynam *Personality and Individual Differences 30 669-689(2001)*

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POSTER #: 5

Immunological Variables in Depressed Outpatients during 12 weeks of Treatment.

J.Dahl , Ormstad H, Andreassen OA, Malt UF

Background:
Several studies have shown abnormal levels of cytokines in major depressive disorder (MDD), and there are indications of treatment related changes in the immune system. However, the relationship between cytokine levels and the severity and outcome of depression is still unknown.
Objectives:
The aim of this pilot -study was to investigate the feasibility of cytokine measurements during treatment of MDD, in terms of relation between cytokine levels and both severity of depressive symptoms and changes during treatment.
Methods:
A naturalistic 12 weeks follow-up study in an outpatient clinical setting of 12 patients with MDD. Depressive symptoms were assessed with Montgomery Aasberg Depression Rating Scale (MADRS) and Inventory of Depressive Symptoms (IDS) at baseline and after week 12 of therapy. At both time-points, the serum levels of the following 27 cytokines were measured using BioPlex XMap technology (Luminex): IL(interleukin) -1β , IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p70), IL-13, IL-15, IL-17, basic FGF, eotaxin, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1 (MCAF), MIP-1α, MIP-1β, PDGF-BB, RANTES, TNF-α, VEGF. We chose to examine a broad range of cytokines because of the scarcity of data on their serum levels in MDD patients.
Results:
We found detectable levels of 25 of the 27 cytokines. After 12 weeks of treatment 7 patients (58%) had a 50% reduction in IDS or MADRS, and of these, 5 patients (42% of total) had a MADRS <10 or IDS <13. The levels of GM-CSF (p=0,02), IL-4 (p=0,035), IL-8 (p=0,044), and IL-5 (p=0,028) were found to decrease significantly from baseline to 12 weeks.
Conclusion:
Our results show that a wide range of cytokines are detectable in patients with MDD. Furthermore, some cytokines may decrease during the treatment period, indicating a drop in cytokine levels as a result of treatment. Possibly, a fall in cytokine levels may correlate with severity and fall in depressive symptoms. A study of larger sample size will provide more conclusive results on these issues.

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POSTER #: 6

Secondary Hyperparathyroidism due to vitamin D deficiency in residents of a Nursing home for elderly in Norway.

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Background:
Vitamin D, 25(OH)D, deficiency is common in institutionalized elderly, especially in Europe.
Low vitamin D levels lead to Secondary Hyperparathyroidism, i.e. a state of higher concentration of plasma parathyroid hormone (P-PTH) which stimulates the production of 1,25-$(OH)_2D$. The most common causes of vitamin D deficiency in geriatric patients are insufficient sunlight exposure, decreased functional capacity of the skin to synthesize vitamin D3 under influence of UV light, diet lacking vitamin D supplements and kidney disease. Hyperparathyroidism is known to give neuropsychiatric symptoms including confusion, anxiety and depression.
Objectives:
The aim of the current study was to investigate the prevalence of previously undiagnosed Secondary Hyperparathyroidism and potential etiologies at a small Norwegian nursing home. In addition, we wanted to explore whether Hyperparathyroidism could be corrected by supplementation with vitamin D. Methods:
Of sixteen residents, eleven were investigated for Calcium regulatory biochemical tests, P-PTH and kidney function. (Ten females, one male, mean age 83 years, all had severe dementia). Five residents with very advanced dementia or bedridden, were excluded. Reference values from the Clinical laboratory at Stavanger University Hospital based on immunological testing (Sandwich principle;

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1.5-7.0 pmol/L) were used as cut-off. Residents with P-PTH over or equal to the maximum value were administered Calcium 1000 mg with vitamin D 800IE daily for a minimum period of eight weeks and the tests were repeated.
Results:
Nine of eleven residents (82%) had abnormal values of P-PTH. Eight (all females) had normal Creatinin, suggesting that the Hyperparathyroidism was due to vitamin D deficiency. After administration of Calcium/ vitamin D, for eight weeks, there was a statistically significant reduction of mean P-PTH from 9,1pmolL to 6,6pmol/L ($p=0.008$; $t=3.664$ and $df=7$; paired samples test). All eight patients had a fall in P-PTH and six of eight now had values in the normal range.
Conclusion:
It is postulated that Secondary Hyperparathyroidism due to vitamin D deficiency in Nursing home residents is grossly under-diagnosed. The condition can be easily investigated biochemically and treated. More research is needed to explore the relationship between neuropsychiatric symptoms and Secondary Hyperparathyroidism due to vitamin D deficiency in the elderly, and whether supplementation with vitamin D and Calcium can improve neuropsychiatric symptoms.

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POSTER #: 7

A Novel Device Concept Improves Delivery to the Nasal Mucosa Innervated by the Olfactory and Trigeminal Nerves: A New Avenue to treat CNS-disorders?

Per G Djupesland, Arne Skretting.

Background:
The blood-brain-barrier (BBB) is a major obstacle to drug delivery in psychiatric, neurological and neurodegenerative diseases. The proximity between the nose and brain offers a potential avenue to circumvent the BBB and deliver directly into the limbic system regulating emotions and memory. Indeed, animal studies have demonstrated rapid nose-to-brain (N2B) transport of small molecules and peptides along the olfactory and trigeminal nerves. Traditional nasal sprays are unable to reliably reach these nasal target sites; however, a new concept for nasal delivery may enable progress in this field. The breath powered drug delivery device developed by OptiNose exploits the posterior connection between the nasal passages persisting when the soft palate closes during oral exhalation. The deep nasal cavity airflow delivers medication to target sites.
Objectives:
To compare the deposition patterns of a conventional spray pump and a powder version of the novel "OptiNose" nasal drug delivery device.
Methods:
The regional deposition and clearance patterns of medication delivered by "OptiNose" device were compared to a traditional hand-actuated liquid spray pump in 7 healthy subjects by gamma camera imaging after administration of either ^{99m}Tc-labeled lactose powder or liquid ^{99m}Tc-DTPA-aerosol. The gamma camera images were aligned with sagittal MRI's to identify nasal regions. Correction for tissue attenuation was performed.
Results:
For target regions, compared to a traditional spray pump, the novel nasal powder device achieved a sevenfold larger initial deposition in the upper posterior third of the nose (Powder: 18.3%±11.5 vs. Spray:2.4%±1.8; $p<0.02$) and threefold deposition in the upper posterior 2/3 of the nose innervated mainly by the olfactory and trigeminal nerves (Powder: 53.5%±18.5 vs. Spray: 15.7%±13.9; $p<0.02$). For non-target regions conventional spray deposition was higher (in areas lined by squamous rather than respiratory or olfactory epithelium), as was deposition on the floor of the nasal cavity (Powder: 17.4%%±24.5 vs. Spray: 59.8%±18.2; $p<0.02$).
Conclusions:
Compared to a conventional spray pump, the novel "OptiNose" powder device, initially tested in clinical trials with sumatriptan, provides significantly greater deposition in the upper posterior segments of the nasal mucosa beyond the nasal valve innervated by the olfactory and

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trigeminal nerves. The results open new therapeutic drug delivery possibilities in management of CNS disorders.

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POSTER #: 8

The load of short telomeres is increased and associated with lifetime number of depressive episodes in bipolar II disorder

Elvsåshagen T, Vera E, Bøen E, Bratlie J, Andreassen OA, Josefsen D, Malt UF, Blasco MA, Boye B

Background:
In recent years, associations have been found between bipolar disorders and elevated rates of cardiovascular disease, type 2 diabetes, and other diseases of aging. The exact mechanisms underlying the increased prevalence of age-related illnesses in bipolar disorders remain to be clarified. It has recently been hypothesized that bipolar disorders are associated with accelerated aging. Telomere dysfunction, a biomarker of aging, is determined by the load of short telomeres, rather than by mean telomere length. To our knowledge, the load of short telomeres has not been reported in any psychiatric disorder.
Objectives:
The main objective of the present study was to examine the load of short telomeres and mean telomere length in peripheral blood mononuclear cells (PBMCs) in bipolar II disorder (BD-II). In addition, we aimed to examine the relationships between the two telomere measures and illness duration and lifetime number of depressive episodes.
Methods:
We examined 28 individuals with a DSM-IV diagnosis of BD-II and 28 healthy comparison subjects matched for age, sex, and education in a cross-sectional case-control study. The load of short telomeres (number of telomeres < 3 kilobases divided by total number of measured telomeres) and mean telomere length in PBMCs were measured using high-throughput quantitative fluorescence in situ hybridization.
Results:
No group differences were observed regarding sex, age, education, body mass index, smoking, or average hours of physical training per week. The load of short telomeres in PBMCs was increased in patients with BD-II relative to comparison subjects and may represent 13 years of accelerated aging. The load of short telomeres and mean telomere length in PBMCs were, after adjustment for age, body mass index, and smoking, associated with lifetime number of depressive episodes, but not with illness duration in patients.
Conclusion:
These findings suggest that BD-II is associated with an increased load of short telomeres in PBMCs. Depressive episode-related stress may accelerate telomere shortening and aging. Emerging telomere protective strategies may find a role in the treatment of BD-II

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POSTER #: 9

Early intervention augments running activity and decrease depressive-like behaviour in a genetic rat model of depression

Fischer CW, Abildgaard A, Lund S, Wegener G

Background:
Major depressive disorder is one of the most prevalent psychiatric disorders. However, initial treatment strategies often fail to fully relieve depressive symptoms when 65%–75% of the patients not achieving remission. Exercise has beneficial effects on general health, but also on psychiatric well-being. The effects of exercise alone or in combination with an antidepressant might serve as an additional template for the treatment of depressed patients.
Objective:
The aim of the study was to investigate the effect of exercise alone or in combination with an antidepressant on behaviour and brain gene expression in a genetic rat model of depression, the Flinders Sensitive/Resistant Line (FSL/FRL) rats.
Methods:

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In male FSL rats, the effect of three long-term treatments, voluntary running, imipramine or the combination of both, were evaluated on behaviour in the Forced Swim Test (FST) and Elevated Plus Maze (EPM). Gene expression levels were measured using Real-time qPCR.
Results: Exercise alone did not affect immobility, a measure of depressive-like behaviour in the FST. However, the combination of both imipramine and exercise decreased immobility compared to controls and the treatment regimes, exercise and imipramine. FSL rats did not engage in a motivated increase in running behaviour compared to the activity found after treatment with imipramine two weeks prior to having free access to running wheels. The FSL rats were associated with reduced anxiety in the elevated plus maze, but treatments did not affect the behaviour.
Conclusion:
Early intervention with imipramine seems to motivate the FSL rats to increasing running behaviour. This combined effect of imipramine and exercise leads to outcomes not seen with either treatment alone, decreasing depressive-like behaviour in the FST.
Perspectives:
The results from this study confirm that the combined effect of exercise and imipramine is more efficient in improving depressive symptoms and keeping patients motivated in physical activity than either treatment alone. This might be a way of reducing the risk of relapse and decreasing morbidity in patients with major depression, as well as having positive effect on metabolic parameters.

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POSTER #: 10

CYP2D6 genotype and risperidone steady-state serum concentrations. A study based on therapeutic drug monitoring data.

M. Hendset , Knape M, Molden E

Background: The atypical antipsychotic drug risperidone is metabolized by the polymorphic enzyme cytochrome P450 2D6 (CYP2D6).
Objectives: The aim of the present study was to investigate the impact of *CYP2D6* genotype on serum concentrations of risperidone (RIS) and the pharmacologically active metabolite 9-hydroxyrisperidone (9-OHRIS). Our main focus was on the phenotypical consequence of carrying a combination of one reduced ('red') and one non-functional ('def') *CYP2D6* variant allele.
Methods: Serum concentrations and *CYP2D6* genotypes from patients treated with oral risperidone (Risperdal™) were withdrawn from a routine therapeutic drug monitoring database at the Center for Psychopharmacology, Diakonhjemmet Hospital, Norway. The 141 patients included in the analysis were stratified into subgroups according to *CYP2D6* genotype: **1/*1* (two functional alleles, n=50), **1/red* (one functional and one reduced allele, n=21), **1/def* (one functional and one defective allele, n=44), *red/red* (two reduced alleles, n=6), *red/def* (one reduced and one defective allele, n=10) and *def/def* (two defective alleles, n=10). Dose-adjusted serum concentrations (C/D ratios) of RIS and 9-OHRIS were compared between the subgroups using the Kruskal-Wallis test with Dunn's post test.
Results: Median RIS C/D ratio in the *CYP2D6*1/*1* subgroup was 1.5 nM/mg/day (range 0.2-27). In comparison, the median RIS C/D ratio was 1.7- ($p>0.05$), 1.9- ($p>0.05$), 7.1- ($p<0.05$), 9.7- ($p<0.01$) and 10.7- fold ($p<0.001$) higher in the **1/red*, **1/def*, *red/red*, *red/def* and *def/def* subgroups, respectively. The observed C/D ratio of RIS was not significantly different between the *red/def* and the *def/def* subgroups ($p>0.05$). The median 9-OHRIS C/D ratio was significantly different between the *CYP2D6*1/*1* and the *CYP2D6def/def* subgroups ($p<0.05$).
Conclusion: Our study confirms that *CYP2D6* genotype has a major impact on the serum concentration of risperidone. Furthermore, the *red/def* genotype appears to have a comparable effect on CYP2D6 phenotype as the *def/def* genotype. Reduced variant alleles should therefore be included in pharmacogenetic screening analyses of *CYP2D6* in clinical practice.

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POSTER #: 11

Interleukin 1 receptor antagonist and tumor necrosis factor receptor 1 are associated with general severity and psychotic symptoms in schizophrenia and bipolar disorder.

Sigrun Hope, Ingrid Melle, Thor Ueland, Steinar Lorentzen , Nils Eiel Steen, Akiah O. Berg, Ingrid Dieset, Ingrid Agartz, Pål Aukrust, Ole A. Andreassen

Background:
Several lines of evidence suggest elevated activity of the Interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor (TNF)-alpha pathways in schizophrenia and bipolar disorder, and recently elevated levels of von Willebrand factor (vWf) and osteoprotegerin (OPG) was found. It is unclear how immune activation is involved in the psychopathology.
Objectives: We aimed to investigate if elevated cytokine levels were associated with disease severity (trait) or current symptom level (state), comparing psychotic with general characteristics.
Methods:
Plasma levels of soluble TNF receptor 1 (sTNF-R1), IL-1 receptor antagonist (IL-1Ra), IL-6, vWf and OPG were measured with ELISA techniques in 322 patients with schizophrenia spectrum and bipolar disorder. Current symptom level (state) was measured with Global Assessment of Functioning (GAF) and Positive and Negative Syndrome Scale (PANSS). Disease severity (trait) was measured with premorbid adjustment scale (PAS), age at onset, number of psychotic episodes and number and length of hospitalizations.
Results:
After controlling for confounders, IL-1Ra and TNF-R1 were independently associated with GAF. IL-1Ra and sTNF-R1 were significantly correlated with PANSS negative and positive, respectively. Il-1Ra was associated with PAS, and sTNF-R1 with hospitalizations and psychotic episodes. VWf was significantly correlated psychotic episodes, OPG with hospitalizations and IL-6 with history of psychosis. Linear regression analysis showed that GAF remained associated with sTNF-R1 and IL-1ra with PANSS, after controlling for the other clinical measures.
Conclusion:
This supports that IL-1Ra and sTNF-R1 are associated with disease severity, which support the role of immune activation in the pathological mechanisms of severe mental disorders.

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POSTER #: 12

Association between the ASMT gene and autism measures in a Community-based twin cohort

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Background:
Autism spectrum disorders (ASDs) are pervasive developmental disorders that include Autistic disorder, Asperger syndrome, and pervasive developmental disorder-not otherwise specified (PDD-NOS). One consistent biological finding in autism is low levels of melatonin and it has been shown that this decrease of melatonin is due to low activity of the acetylserotonin O-methyltransferase (ASMT), the last enzyme in the melatonin synthesis. In addition, genetic variants in the ASMT gene have been associated with both ASD and lowered melatonin levels. Objectives: In our study, we use a symptom-based approach to investigate the possible association between melatonin-related genes and autism. Our aim was to investigate, not only the previously associated ASMT gene, but also all other genes in the melatonin pathway, for possible association with autistic traits in the general population. Methods:
The subjects (N=1171, 9-12 years old) in this study are a subset of the "The Child and Adolescent Twin Study in Sweden" (CATSS), identified through the Swedish Twin Registry. The continuous autistic symptoms were flexibility, language and social interaction. To cover most of the genetic variability of the investigated genes, a total of 13 SNPs were genotyped in the genes encoding the melatonin synthesis enzymes (AA-NAT and ASMT) and the two receptors (MTNR1A and MTNR1B). Results:

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In girls, an intronic SNP (rs5949028) in the ASMT gene was significantly associated with the total scores of autism symptoms and with the traits flexibility and social interaction. However, no significant association was seen between this ASMT SNP and the third autistic trait, language. Carriers of the CC-genotype had significantly higher means on the continuous scale on both of the associated traits. Boys did not show significant association with any of the autism symptoms measured.
Conclusion:
The present study gives further support for the involvement of the ASMT gene in ASD. In our study, not all symptoms of autism showed similar association with the investigated genes. Hence, our investigation of common polymorphisms and autistic-like traits in the general population suggest that genetic research may benefit from taking a symptom-specific approach to finding genes associated with autism.

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POSTER #: 13

Effects of the androgen receptor on oxytocin and vasopressin-related genes

S Karlsson, Studer E, Westberg L

Background:
Sex differences in psychiatric disorders are common, both in turns of prevalence and manifestation of symptoms. These differences are probably, to a large extent, due to the different levels of sex steroids in males and females during development and in adulthood. The male sex steroid, testosterone, act via the androgen receptor (AR) which is a classic steroid receptor found in the cytoplasm. Once bound to testosterone (or its metabolite dihytrotestosterone), the AR enters the cell nucleus, where it binds to DNA and affects transcription. Testosterone can also be aromatized to estradiol which binds to the estrogen receptor (ER-α or ER-β), and thereby influence transcription similarly. Through the influence on the gene transcription, AR and ERs will consequently have effects on the expression levels of many different genes and proteins. The limited knowledge about which of these proteins are needed to increase in order to understand the origin of sex differences in psychiatric disorders. Previous data indicate that at least some of the effects of sex steroids on social behaviors are mediated by actions on the neuropeptides oxytocin and vasopressin.
Objectives:
The aim of this study is firstly to investigate if the expression levels of genes relevant for the actions of oxytocin and vasopressin are sexually dimorphic and secondly to investigate if the same genes are regulated by the androgen receptor - using AR knockout mice (nes-ARKO), lacking the receptors in the brain – but not in the periphery.
Methods:
We conducted quantitative gene expression studies, using Taqman Low Density Arrays (TLDAs) allowing us to study 48 genes simultaneously in hypothalamus and amygdala dissected from adult male (N=9), female (N=9) and nes-ARKO mice (N=12).
Results and Conclusion:
Gene expression data from amygdala and hypothalamus will be presented.

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POSTER #: 14

The dopaminergic stabilizer (-)-OSU6162 improves memory in normal and scopolamine-treated mice.

M.K.L Nilsson

Background:
Memory deficits are common in many neuropsychiatric disorders. Disruptions to the episodic memory system are for example among the earliest signs and symptoms of Alzheimer's disease. The monoaminergic transmitter systems, especially the dopaminergic, have been shown to

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have great importance for memory and executive functions. Several studies have shown that there is a narrow range of dopaminergic neurotransmission for optimal working memory, where extremely high or low dopamine activity is associated with poorer performance. Dopaminergic stabilizers are able to either stimulate or inhibit dopaminergic activity depending on dopaminergic tone. Thus, there might be a potential for this type of compounds to facilitate memory functions. This study has been performed in collaboration with Carlsson Research AB, Sweden.
Objective:
The aim of the present study was to evaluate the effect of the dopaminergic stabilizer (-)-OSU6162 on spatial episodic-like memory.
Methods:
Male NMRI mice were tested in the object location test. The test was divided into two sessions, each lasting five minutes. In the first session two novel objects were presented. In the second session one of the objects was moved into a new position. The time spent exploring the objects was scored.
Results:
In a first series of experiments the effect of (-)-OSU6162 on natural forgetting was evaluated. Mice were given an i.p injection of (-)-OSU6162 directly after the first session. With an inter trial interval of 6 hours, untreated mice were unable to identify the displaced object. However, (-)-OSU6162 up to 30 µmol/kg, dose dependently increased the interest for the displaced object. Twenty-four hours after administration, (-)-OSU6162 was still effective in facilitating object location memory. In order to evaluate the effect of (-)-OSU6162 on scopolamine-induced memory deficits, a model of Alzheimer's disease, scopolamine hydrobromide and (-)-OSU6162 were given 30 minutes before the first session which was followed by the second session 60 minutes later. During these conditions scopolamine induced a clear deficit in object location memory and this effect was reversed by (-)-OSU6162.
Conclusion:
(-)-OSU6162 prolongs object location memory in normal mice and reverses scopolamine-induced memory deficits. The favourable effect of (-)-OSU6162 on spatial episodic-like memory might be due to increased consolidation of encoded information. These data suggest that (-)-OSU6162 might be a valuable drug candidate for memory deficits and other cognitive disorders.

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POSTER #: 15

Temperament modulation of SSRI response in Wistar rats

Jacob Näslund, Studer E, Nilsson K, Westberg L, Eriksson E

Background:
The influence of acute administration of selective serotonin reuptake inhibitors (SSRIs) in humans is the subject of marked inter-individual variation in the sense that some experience enhanced anxiety upon acute intake of these drugs, whereas most people do not. The reasons for these striking differences are not known, but personality traits, as well as baseline anxiety, seem to be of importance, the enhanced susceptibility for experiencing an anxiety-provoking effect of SSRIs in panic disorder patients being particularly noteworthy. The effect of personality, or temperament, on serotonergic modulation of behaviour in commonly used rodent models of anxiety is however a largely unexplored field.
Objectives:
This study aimed to investigate the effect of baseline anxiety levels on the response to an acute challenge with the SSRI paroxetine.
Methods:
A measure of baseline anxiety levels was obtained in the elevated plus-maze. Three weeks later the animals were given injections of either paroxetine or saline and anxiety-like behaviour was assayed in the elevated plus-maze and light-dark box, with measures of locomotion obtained in photocell boxes.
Results:
Significant differences between high- and low-anxiety (HA and LA) animals were observed, with marked enhancement of different indices of anxiety in HA but not LA animals; moreover, a strong depressing effect on photocell box

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locomotion was observed in HA animals with no such tendencies in LA animals.
Conclusion:
The results may facilitate further preclinical exploration of the mechanisms underlying SSRI-induced anxiety, as well as of the reasons for the inter-individual differences characterizing this response in humans. Furthermore, our results indicate that baseline differences in temperament may be a factor

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POSTER #: 16

Combined clinical and pharmacogenetic model to predict treatment responses, adverse effects and serum levels of clozapine in patients with treatment resistant schizophrenia

Rajkumar AP, Poonkuzhali B, ; Jacob M, Jacob KS,

Background:
Despite clozapine's superior clinical efficacy in Treatment-Resistant Schizophrenia (TRS), its adverse effects, need for periodic leukocyte monitoring, higher cost and variable clinical outcomes mandate the need to predict its treatment response. Presence of therapeutic window, high inter-individual variability and of level dependent adverse effects demands estimation of serum clozapine levels. Pharmacogenetic studies on clozapine often collect limited clinical data and have achieved only limited clinical success to predict serum levels, treatment response and adverse effects of clozapine so far.
Objectives:
We aimed to investigate the associations between CYP1A2, HTR3A Single Nucleotide Polymorphisms (SNP) as well as various clinical variables and treatment response, adverse effects and serum levels of clozapine in patients with TRS.
Methods:
We evaluated four CYP1A2 (rs2069514, rs35694136, rs2069526 and rs762551), two HTR3A gene SNP (rs1062613 and rs2276302), treatment response, adverse effects and serum clozapine levels in 101 consecutive patients with TRS on stable doses of clozapine. We assessed their socio-demographic and clinical profiles, premorbid adjustment, traumatic events, cognitive functioning and disability using standard assessment schedules. We defined clinical response to clozapine, a priori, and calculated allelic odds ratios, genotypic associations and appropriate permutation statistics. We employed backward conditional multiple logistic regression to develop a combined clinical and pharmacogenetic model to predict clinical response to clozapine. We performed all multivariate analyses using Plink v1.07 and STATA 10.0.
Results:
Past catatonia (P=0.005), smoking (P=0.008) and cognitive dysfunction (P=0.007) increased the risk for non-response to clozapine. Oral dose of clozapine (P=0.001), caffeine intake (P=0.02) and valproate co-medication (P=0.02) had significant linear relationship with serum clozapine levels. Serum clozapine levels above 750 ng/ml increased the risk of seizures (P=0.03). HTR3A SNP (T allele of rs1062613 and G allele of rs2276302) were significantly associated with better clinical response to clozapine, after 100 million permutations (p=0.02). CYP1A2 SNP were not associated with clinical response, adverse effects and serum levels of clozapine. A combined clinical and HTR3A pharmacogenetic association model could explain 38% of variability in the treatment responses to clozapine (Nagelkerke R^2= 0.380).
Conclusions:
Clinical variables can predict response to clozapine and are useful to model a dosing nomogram for serum clozapine levels. We documented that combined clinical and pharmacogenetic models have better predictive values and that the results of pharmacogenetic studies depend heavily on the outcome definitions chosen. Future pharmacogenetic studies should study associated clinical variables and evaluate multiple outcome definitions to develop better predictive models

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POSTER #: 17

Cortisol metabolism as a mechanism for increased HPA axis activity in bipolar disorder and schizophrenia

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Background:
Bipolar disorder (BD) and schizophrenia (SCZ) seem to be part of a psychosis continuum with etiological and pathophysiological factors in common, including increased hypothalamic-pituitary-adrenal (HPA) axis activity. Components of the axis have been associated with cognitive, affective and psychotic symptoms. Control of the activity is complex, and dysfunctions may arise from any level. There is growing interest in cortisol metabolism in disorders associated with HPA axis alterations, however, this is not previously studied in BD and SCZ.
Objectives:
To investigate the cortisol metabolism in BD and SCZ, and present a model for increased cortisol metabolism as a potential mechanism for HPA axis alterations and symptoms in BD and SCZ.
Methods:
1) Estimate activities of cortisol metabolizing enzymes using cross-sectionally sampling of spot urine with assessments of free cortisol, cortisone and metabolites from BD (n=69), SCZ (n=87) and healthy controls (HC, n=169), and comparing groups. 2) Do SNP association tests of genes coding for cortisol metabolizing enzymes in a case-control sample of BD (n=213), SCZ (n=274) and HC (n=370), and compare enzyme activities in a subsample (BD, n=39; SCZ, n=40; HC, n=151) between genotype categories of SNPs indicated by these tests.
Results:
Elevated systemic cortisol metabolism was present in SCZ (5α-reductase, 5β-reductase, 11β-HSD2: all $p<0.001$) and BD (5α-reductase, 5β-reductase, 11β-HSD2: $p=0.016$, $p=0.001$, $p=0.007$ respectively) compared to HC. A genetic liability for increased 5α-reductase activity was indicated in SCZ from a significant association test of rs6732223 in SRD5A2 (5α-reductase) ($p=0.0043$, Bonferroni corrected $p=0.030$), and an increased 5α-reductase activity associated with the risk allele within the SCZ group ($p=0.011$). The literature supports an association between increased cortisol metabolism and increased HPA axis activity. Studies suggest that manipulation of peripheral cortisol impact central corticosteroid receptors, corticotrophin releasing hormone and arginine vasopressin, and that increased peripheral cortisol metabolism could lead to periods with increased cortisol. These factors are implicated in established models of HPA axis involvement in affective and/or psychotic symptomatology.
Conclusion:
Previous research has neglected cortisol metabolism as a modulator of HPA axis activity in BD and SCZ. We present data indicating genetically altered cortisol metabolism in BD and SCZ, and argue that the present findings could implicate cortisol metabolism as a mechanism in established hypotheses of HPA axis involvement in affective and psychotic symptomatology.

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POSTER #: 18

Influence of androgen receptors on brain serotonin turnover

Erik Studer, Näslund J, Westberg L, Eliasson E

Background:
It is well known that the presence of sex steroids is crucial for the development and maintenance of sexual and aggressive behavioral patterns in both humans and animals, but largely unknown how the genomic effects of these hormones translate into functional differences between the sexes in the neural circuits regulating behavior.
Objectives:
The aim of the current study was to investigate the influence of androgen receptors on the levels of brain monoamines and their metabolites.
Methods:
Using HPLC we measured levels of monoamine neurotransmitters and their metabolites in several discrete brain regions of male and female mice as

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well as of mice lacking functional androgen receptors (AR) in the central nervous system due to genetic manipulation (ARKO).
Results:
We found the hypothalamic quotient of 5HIAA to 5HT to be reduced in the hypothalamus when ARKO male mice or wild-type female mice were compared to wild-type male mice; trends in the same direction were found also in the amygdala and the hippocampus. In contrast, male ARKO mice, in contrast to female wild-type mice, did not differ from male wild-type mice with respect to dopamine turnover.
Conclusion:
We suggest that testosterone influences brain serotonin turnover at least partly by activating AR receptors, but that sex differences in dopamine turnover are not regulated by these receptors but, tentatively, by estrogen receptors. The relative importance of AR on serotonergic neurotransmission during development, and in the adult animal, respectively, will be discussed.

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POSTER #: 19

Neuropsychiatric assessment of major depression

Stürup, AE, Tehrani, ES, Videbech, P

Background :
Many reports have shown that depression can be caused by cerebral lesions, such as infarctions and tumors. Although these lesions are rather uncommon, they can radically alter the treatment and prognosis for the individual patient. Depression can also be caused by other somatic illnesses, such as myxoedema, and may pass unnotised in the psychiatric wards. The Neuropsychiatric Clinic at Aarhus University Hospital, Risskov was founded with the purpose to thoroughly asses psychiatric patients with MRI, blood tests, neuropsychiatric interview, neuropsychological tests and neurological examination.
Objectives:
The aim of the current study was twofold:
To review the existing literature on the findings of cerebral MRI or CT scans of depressed patients.
To investigate whether patients with late onset depression or treatment resistant depression should routinely undergo neuropsychiatric assessment as mentioned above. In the present paper, we especially wanted to focus on the usefulness of routine MRI in these patient groups
Methods:
We conducted a critical literature search of studies investigating infarctions, tumors, white matter lesions and other abnormal findings on structural MRI or CT scans of patients suffering from major depression or other psychiatric illnesses. We compared the results of the review to the preliminary results of our prospective study of neuropsychiatric assessment of 63 consecutive patients, who suffered from late-onset depression or treatment resistant depression.
Results:
The reviewed literature reported a wide range of frequencies of abnormal MRI/CT scan findings. The majority of the studies had severe methodological limitations. Furthermore preliminary results of the neuropsychiatric assessment at Aarhus University Hospital, Risskov will be presented. We will report the abnormal cerebral findings among the depressed patients and how the findings of the neuropsychiatric assessment influenced the patients' psychiatric and somatic diagnoses.
Conclusion:
The review showed the need for more thorough research of cerebral MRI/ CT scans of psychiatric (especially depressed) patients as part of a routine assessment programme. Additionally preliminary results of our consecutive assessment will be presented.

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POSTER #: 20

Association analysis of *ANK3* gene variants in Nordic bipolar disorder and schizophrenia case-control samples

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Background:
Several recent association studies have found genetic variants in ankyrin 3 (*ANK3*), a gene involved in ion channel regulation, to be associated with bipolar disorder (BD).
Objectives: We wanted to investigate the potential association between two previously identified genetic variants in *ANK3* and BD in a Nordic case-control sample. Due to evidence of genetic overlap between BD and schizophrenia (SZ), we also included SZ cases in our analyses.
Methods:
We genotyped the two *ANK3* SNPs rs10994336 and rs1938526 in a Scandinavian case-control sample (N = 854 BD cases, 1073 SZ cases and 2919 healthy control subjects). Statistical analyses in the Scandinavian sample were performed with the software PLINK, using the Cochrane-Mantel-Haenszel test to correct for population stratification.
Results:
When we combined the results from our Scandinavian sample with the results from an Icelandic case-control sample (N = 435 BD cases, 651 SZ cases and 11491 healthy controls), we found rs10994336 to be significantly associated with BD in this combined Nordic BD sample (N = 1289/14105) (P=0.024 using Fisher`s combined probability test). None of the SNPs were significantly associated with SZ in the combined Nordic SZ case-control sample (N = 1724/14410).
Conclusion:
These results give further support to the hypothesis that *ANK3* is a susceptibility
gene specific to BD and that ion channelopathy may be involved in BD pathophysiology.

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POSTER #: 21

Cellular and molecular mechanisms of naltrexone action at the mu- opioid receptor (MOP)

V Vukojević, Ming Y, Gruol D, Terenius L

Background:
Naltrexone, the antagonist at the mu-opioid receptor (MOP) and active substance in several clinically used drugs was found to reduce the relapse in heroin (opiate) abuse, alcoholism, diminish the "high" induced by amphetamine in healthy volunteers and chronic addicts, lessen the craving for food in obesity, but also decrease hedonic responses in gambling. This wide range of naltrexone activity against diverse addictive stimuli raises the question on the molecular mechanism of its action.
Objectives:
The aim of this study is to understand the mechanisms of naltrexone action at the molecular and cellular level. In particular, we are interested in understanding the mechanisms underlying the protective effect of naltrexone against ethanol.
Methods:
We have generated cell models expressing the wild type variant of MOP (MOP_{wt}) or the polymorphic (MOP_{N40D}) isoform, found clinically to improve the therapeutic response to naltrexone, fluorescently tagged with the green fluorescent protein (GFP). We use functional Fluorescence Microscopy Imaging (fFMI), a multimodal approach by fluorescence imaging and correlation spectroscopy, methods with single-molecule sensitivity and high temporal and spatial resolution, to study in live cells the effects of ethanol and naltrexone on MOP surface density, mobility and interactions in the plasma membrane. In parallel, we use electrophysiological methods to study the downstream effects of ethanol/naltrexone on MOP-mediated cellular signaling.
Results:
We observed that relevant concentrations of ethanol (20-40 mM) facilitate opioid signaling by mobilizing MOP and transiently increasing its surface density in the plasma membrane. This effect could be blocked by pre-incubation with naltrexone, which acted in the opposite way, by "stalling" MOP mobility in the plasma membrane

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and apparently reducing its surface density through MOP oligomerization and/or sorting to lipid rafts.
Conclusion:
We suggest that naltrexone neutralizes the ethanol effects by exerting an opposite effect on MOP dynamics and properties at the plasma membrane, rather than by blocking the effect of ethanol-induced excessive production of endogenous opioids.

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POSTER #: 22

Serum concentrations of antidepressants in the elderly.

R.B Waade , Hermann M, Molden E.

Background:
Due to age-related physiological changes, pharmacokinetic processes and organ function are generally diminished in older persons. Depression is one of the most common co-morbid conditions in age-related diseases, and little is known about the serum concentrations obtained of antidepressants in older versus younger patients.
Objectives:
The aim of the present study was to investigate the impact of age on the serum concentrations of antidepressants in a naturalistic setting.
Methods:
A therapeutic drug monitoring database was screened for patients who had measured serum concentrations of antidepressant drugs. Altogether, 32126 samples of SSRIs, TCAs, SNRIs and tetracyclic antidepressant drugs were included, with about 37%, 48% and 15% stratified into the age groups <40 years, 40-65 years and >65 years respectively. Dose-adjusted drug serum concentrations (i.e., nM/mg/day) were compared between the subgroups using the former (<40 years) as control.
Results:
There were no relevant differences in mean serum concentrations between patients aged 40-65 years and those younger than 40 years. Of the 14 drugs included, an approximately 2-fold higher mean serum concentration was observed for citalopram, escitalopram, fluvoxamine, nortriptyline and paroxetine in patients >65 years vs. controls. For amitriptyline, clomipramine, duloxetine, mianserin, mirtazapine, sertraline and venlafaxine about 1.5-fold higher mean serum concentrations were observed in the elderly compared to those <40 years. No significant difference in serum concentrations of fluoxetine and trimipramine was detected between older patients and controls.
Conclusion:
Our data suggest that doses of most antidepressants should be reduced by approximately 30-50% in patients >65 years to avoid concentration-dependent adverse effects.

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