hypothesis, which considers impaired synaptic plasticity a central mecha-
nisms in the pathophysiology of schizophrenia.
Methods: To probe the dichotomy between DA and ACh and to investigate
timing parameters of pwPEs, we tested 74 healthy male volunteers perform-
ing a probabilistic reward associative learning task in which the contingency
between cues and rewards changed over 160 trials between 0.8 and 0.2.
Furthermore, the current study employed pharmacological interventions
(amisulpride / biperiden / placebo) and genetic analyses (COMT and
ChAT) to probe DA and ACh modulation of these computational quanti-
ties. The study was double-blind and between-subject.
We inferred, from subject-specific behavioural data, a low-level choice PE
about the reward outcome, a high-level PE about the probability of the
outcome as well as the respective precision-weights (uncertainties) and used
them, in a trial-by-trial analysis, to explain electroencephalogram (EEG)
signals (64 channels). Behavioural data was modelled implementing three
versions of the Hierarchical Gaussian Filter (HGF), a Rescorla-Wagner
model, and a Sutton model with a dynamic learning rate. The computa-
tional trajectories of the winning model were used as regressors in singu-
lar-subject trial-by-trial GLM analyses at the sensor level. The resulting
parameter estimates were entered into 2nd-level ANOVAs. The reported
results were family-wise error corrected at the peak-level (p<0.05) across
the whole brain and time window (outcome phase: 0 - 500ms).
Results: A three-level HGF best explained the data and was used to com-
cpute the computational regressors for EEG analyses. We found a significant
interaction between pharmacology and COMT for the high-level precision-
weight (uncertainty).
Specifically:
- At 276 ms after outcome presentation the difference between Met/Met
and Val/Met was more positive for amisulpride than for biperiden over
occipital electrodes.
- At 274ms and 278 ms after outcome presentation the difference between
Met/Met and Val/Met was more negative over fronto-temporal electrodes
for amisulpride than for placebo, and for amisulpride than for biperiden,
respectively.
No significant results were detected for the other computational quantities
or for the ChAT gene.
Discussion: The differential effects of pharmacology on the processing of
high-level precision-weight (uncertainty) were modulated by the DA-related
gene COMT.
Previous results linked high-level PEs to the cholinergic basal forebrain. One
possible explanation for the current results is that high-level computational
quantities are represented in cholinergic regions, which in turn are influenced
by dopaminergic projections. In order to disentangle dopaminergic and cholin-
ergic effects on synaptic plasticity further analyses will concentrate on biophys-
ical models (e.g. DCM). This may prove useful in detecting pathophysiological
subgroups and might therefore be of high relevance in a clinical setting.
O1.4. CEREBROSPINAL FLUID FINDINGS IN
TWINS WITH PSYCHOTIC SYMPTOMS – NOVEL
FINDINGS AND FUTURE PROSPECTS
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Background: Schizophrenia and bipolar disorder are severe mental disor-
ders with unknown etiology. Our research group has studied biomarkers in the
cerebrospinal fluid (CSF) of twins with schizophrenia and bipolar
disorder to be able to determine the genetic and environmental influences.
In brain disorders, CSF is the most appropriate substrate to study as it
may reflect the brain biochemistry better than blood. In this presentation
I aim to give an overview of our findings and their relation to psychotic
disorders. I intend to present our most recent preliminary finding and to
discuss future prospects.
Methods: We studied CSF-markers from a cohort of 50 monozygotic (MZ)
and dizygotic (DZ) twins with schizophrenia or bipolar disorder. The twins
have gone through diagnostic assessments and have been extensively phe-
notyped with questionnaires, symptom scales for psychiatric symptoms
as well as neuropsychological testing. We have analyzed monoamines,
microglia-, neurodegenerative-, kyurenine-, and inflammatory markers
using immunoassays and high-performance liquid chromatography tech-
niques. We have also studied microscopic structures with scanning electron
microscopy.
Results: One of our main findings was that soluble cluster of differentiation
14 protein (sCD14) was higher in twins with schizophrenia or bipolar
disorder compared to their not affected co-twins. A later analysis showed
that the difference within the discordant twin-pairs was higher in the DZ
when twins (β=28697.1, t=3.20, p=0.024) compared with the MZ twin pairs
(β=5777.5, t=2.10, p=0.081) suggesting that genetic components along
with unique environmental effects have an influence on the higher sCD14
levels in patients with schizophrenia and bipolar disorder. We also found
that sCD14 was higher in those patients with more psychotic symptoms.
In our study on microscopic structures in CSF we found that the struc-
tures were prevalent not only in the patients with schizophrenia and bipolar
disorder but also in their not affected co-twins. The finding suggests that
genetic factors may be partly involved in the formation of the structures.
Discussion: We have analyzed inflammatory and neurodegenerative markers
in the CSF of twins with psychotic disorders to be able to study genetic
and environmental influences. Our results indicate that sCD14 may have
an influence on microglia activation in psychosis. We have continued with
analyses on the correlations between all the markers, the monoamine
metabolites and associations with symptoms and cognitive ability and the
preliminary results from these analyses will be presented.
To conclude CSF analyses for biomarkers in twins may result in extended
knowledge regarding the genetic and environmental relationships. Our
unique twin data gives us the possibility to study CSF-markers in rela-
tion to psychotic symptoms and cognitive measures. For future studies it
would be of interest to assemble twin-samples from several research groups
to be able to study research questions regarding gene and environment
interactions.
O1.5. ICAM-1 IS INCREASED IN BRAIN AND
PERIPHERAL LEVELS OF SOLUBLE ICAM-1
IS RELATED TO COGNITIVE DEFICITS IN
SCHIZOPHRENIA
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Cynthia Shannon Weickert5
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Background: Schizophrenia is a disabling and often unremitting mental ill-
ness with an unknown cause that is characterized by heterogeneity in psy-
chotic symptom presentation, cognitive deficits and treatment response.
There is accumulating evidence for the role of inflammation in the etiology
of schizophrenia. Inflammatory markers have been identified in the brains
and peripheral blood of chronically ill patients with schizophrenia and in
first episode patients and these markers have been associated with struc-
tural and functional brain abnormalities and cognitive deficits. Intercellular
adhesion molecule 1 (ICAM-1) is a transmembrane protein expressed on
endothelial cells which binds to leukocyte receptors that promotes trans-
migration of white blood cells into tissue. While peripheral inflammatory
markers are altered in people with schizophrenia relative to controls, the
extent to which ICAM-1 is elevated in the brains of people with schizo-
phrenia and peripheral levels of soluble ICAM-1 (sICAM-1) is increased in
relation to cognitive impairment in schizophrenia is unknown.
Methods: In a post-mortem cohort, 8 mRNAs relating to BBB function and
3 immune cell markers were measured by qPCR in the prefrontal cortex of
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O1.6. INCREASED COMPLEMENT FACTORS C3 AND C4 IN SCHIZOPHRENIA AND THE EARLY STAGES OF PSYCHOSIS: IMPLICATIONS FOR CLINICAL SYMPTOMATOLOGY AND CORTICAL THICKNESS

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Background: The complement system - a key component of the innate immune system, has been proposed to contribute to the pathogenesis of schizophrenia. Recently, complement C4 was associated with increased risk of schizophrenia, and in a mouse model, developmentally-timed synaptic pruning. These observations have led to proposals that abnormal activation of the complement system might contribute to the development of schizophrenia by disrupting synaptic pruning during key developmental periods. However, despite renewed interest in the complement system in schizophrenia it remains unclear whether peripheral complement levels differ in cases compared to controls, change over the course of illness and whether they are associated with current symptomatology and brain cortical thickness. This study aimed to: i) investigate whether peripheral complement protein levels are altered at different stages of illness, and ii) identify patterns among complement protein levels that predict clinical symptoms and grey matter thickness across the cortex.

Methods: Complement factors C1q, C3 and C4 were quantified in 183 participants [n=83 Healthy Controls (HC), n=10 Ultra-High Risk (UHR) for psychosis, n=40 First Episode Psychosis (FEP), n=50 Chronic schizophrenia] using Multiplex ELISA. Permutation-based t-tests were used to assess between-group differences in complement protein levels at each of the three illness stages, relative to age- and gender-matched healthy controls. Canonical correlation analysis was used to identify patterns of complement protein levels that correlated with clinical symptoms and regional thickness across the cortex.

Results: C3 and C4 were significantly increased in FEP and UHR patients, whereas only C4 was significantly increased in chronic patients. A molecular pattern of increased C4 and decreased C3 was associated with positive and negative symptom severity in the pooled patient sample. Increased C4 levels alone, or decreased C3 levels alone, did not correlate with symptom severity as strongly as the pattern of increased C4 in combination with decreased C3. Preliminary canonical correlation analyses revealed that, in healthy controls, a molecular pattern characterised by increased C3 and decreased C4 was associated with relatively thinner paracentral, inferior parietal and inferior temporal cortices, but relatively thicker insular, in the left hemisphere. In the pooled patient group, a trend for increased C3 in combination with decreased C1q was associated with relatively thinner left lateral occipital cortex and pars orbitalis but relatively thicker pars opercularis and precuneus.

Discussion: Our findings indicate that peripheral complement concentration is particularly increased early and preceding psychosis and its imbalance may be associated with symptom severity and variation in regional grey matter thickness across the cortex.

O1.7. PROTEOMIC ANALYSIS OF BLOOD BASED SAMPLES FROM THE OPTIMISE (OPTIMIZATION OF TREATMENT AND MANAGEMENT OF SCHIZOPHRENIA IN EUROPE) STUDY POINT TOWARDS COMPLEMENT PATHWAY PROTEIN CHANGES

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Background: The OPTiMiSE (Optimization of Treatment and Management of Schizophrenia in Europe) trial may help in the identification of predictors of treatment response. Medication naïve patients with first episode schizophrenia or schizoaffective disorder were enrolled in the study and treated open-label for a four-week period with amisulpride. PANSS ratings were undertaken at baseline and following the four-week treatment. 30 non-remitters (as defined by the Andreasen criteria) with the worst change in PANSS scores and the 30 remitters with the best change in PANSS scores were selected to represent good and poor outcome groups.

Methods: We compared proteomic markers in serum collected prior to treatment in 30 patients who subsequently showed a good response to amisulpride (“responders”, and 30 patients who did not show a good response (“non-responders”). Serum samples were depleted using High Performance Liquid Chromatography (HPLC) attached to a MARS column to remove the 14 most abundant plasma proteins (albumin, IgG, antitrypsin, IgA, transferrin, haptoglobin, fibrinogen, alpha2-macroglobulin, alpha1-acid glycoprotein, IgM, apolipoprotein AI, apolipoprotein AI, complement C3, and transthyretin). The groups were matched for ethnicity, gender and age.