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Biological correlates across and between diagnostic groups in the PsyCourse Study: Paving the way for biomarkers through genomics, proteomics, mitochondria and cognition

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List of abbreviations

ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorder
AUC	Area under curve
BD	Bipolar disorder
BD-PRS	Bipolar disorder polygenic risk scores
C9	Complement C9
COA8	Cytochrome C oxidase assembly factor 8
DGT-SP-BCK	Verbal digit span (Backward) test
DGT-SP-FRW	Verbal digit span (Forward) test
DG-SYM	Digit-Symbol test
DSM-IV	Diagnostic and statistical manual of mental disorders, Fourth edition
FDA	Food and drug administration
FDR	False discovery rate
FUMA	Functional mapping and annotation
GWAS	Genome-wide association study
IL	Interleukin
IL1RAP	Interleukin 1 receptor accessory protein
MAC	Membrane attack complex
MAGMA	Multi-marker analysis of genomic annotation
MDD	Major depressive disorder
mtDNA	Mitochondrial DNA
^{MT}PRS-SCZ	Mitochondrial schizophrenia polygenic risk scores
MWT-B	Multiple choice vocabulary intelligence test
nDNA	Nuclear DNA
NIH	National institutes of health
OR	Odds ratio
OXPHOS	Oxidative phosphorylation
PC1	First principal component
PCA	Principal component analysis

pQTL	Protein quantitative trait locus
PRS	Polygenic risk scores
PTSD	Posttraumatic stress disorder
ROC	Receiver operating characteristic
SCZ	Schizophrenia
SCZ-PRS	Schizophrenia polygenic risk scores
SCZ-vs-BD PRS	Schizophrenia versus bipolar disorder polygenic risk scores
SNP	Single nucleotide polymorphism
TMT-A	Trail making test (part A)
TMT-B	Trail making test (part B)
TRD	Treatment resistant depression

List of publications

- **Mojtaba Oraki Kohshour**, Vanessa F Gonçalves. **Mitochondrial genetics in mental disorders: The bioenergy viewpoint.** *European Neuropsychopharmacology* 67 (2023) 80–82.

- Anna Tkachev, Elena Stekolshchikova, Anna Vanyushkina, [...], **Mojtaba Oraki Kohshour,** [...], Thomas G Schulze, Peng Xie, Eva C Schulte, Philipp Khaitovich. **Lipid Alteration Signature in the Blood Plasma of Individuals with Schizophrenia, Depression, and Bipolar Disorder.** *JAMA Psychiatry 2023 Jan 25. doi: 10.1001.*

- **Mojtaba Oraki Kohshour**, Eva C. Schulte, Urs Heilbronner, [...], Peter Falkai, Sergi Papiol, Thomas G. Schulze. **Association between mitochondria-related genes and cognitive performance in the PsyCourse Study.** *Journal of Affective Disorders 325 (2023) 1–6*
  - **PART OF MY CUMULATIVE DISSERTATION**

- **Mojtaba Oraki Kohshour**, Nirmal R Kannaiyan, August Jernbom Falk, Sergi Papiol, [...], Moritz J. Rossner, Peter Nilsson, Thomas G. Schulze. **Comparative serum proteomic analysis of a selected protein panel in individuals with schizophrenia and bipolar disorder and the impact of genetic risk burden on serum proteomic profiles.** *Transl Psychiatry 12, 471 (2022).*
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1. My contribution to the publications

1.1 Contribution to paper I

Comparative serum proteomic analysis of a selected protein panel in individuals with schizophrenia and bipolar disorder and the impact of genetic risk burden on serum proteomic profiles. *Transl Psychiatry 12, 471 (2022).* (Original Research)

Sergi Papiol and I designed the project under the direction of Thomas G. Schulze, Moritz Roßner, and Thorsten Müller. I conducted the data analysis including data cleaning, quality control, running the different association analysis with the programs PLINK and R, plotting the outcomes, and designing the figures and tables. In addition, for all 95 proteins in the designed protein panel, I performed the pQTL analysis by running GWAS and check for the effect of genetic variations on the level of the serum proteins. I also ran post-GWAS analysis by using FUMA for all the achieved GWAS results. The serum proteomics dataset was analyzed and interpreted by Sergi Papiol and I with assistance from Nirmal R. Kannaiyan and August Jernbom Falk. I drafted the first version of the manuscript, including the discussion section, and participated in revising the text, tables, figures, and general conception as recommended and assisted by Sergi Papiol and Thomas G. Schulze based on the comments from all co-authors and the journal reviewers.

1.2 Contribution to paper II

Association between mitochondria-related genes and cognitive performance in the PsyCourse Study. *Journal of Affective Disorders 325 (2023) 1–6.* (Original Research)

I designed this study under the directions of Sergi Papiol and Thomas G. Schulze. This project's main idea was based on the presumption that mental illness can result from impairments in the brain cells' capacity to produce energy. I planned the methods for this study and performed data extraction and genotype-phenotype data analysis using the programs PLINK and R. Specifically, I studied the association between mitochondria-related SNPs (mtDNA and nDNA) and the neuropsychological tests in the PsyCourse Study. Also, I plotted the results and created the figures and tables under Sergi Papiol's guidance. I interpreted the findings with assistance of Sergi Papiol and Urs Heilbronner. I drafted the first version of the manuscript, including the discussion section, and participated in revising as recommended and assisted by Sergi Papiol and Thomas G. Schulze based on the comments from the other co-authors and the journal reviewers.

1.3 Contribution to paper III (Appendix A)

The Genetics of Response to and Side Effects of Lithium Treatment in Bipolar Disorder: Future Research Perspectives. *Front Pharmacol. 2021 Mar 25;12:638882.* (Review)

I searched the literature for ”Pharmacogenetic Studies in Bipolar Disorder” and ”Side Effects of Lithium” sections, and designed the tables with the help of Sergi Papiol. I contributed to the first draft of the manuscript and participated in revising the manuscript assisted by Fanny Senner and Sergi Papiol.

1.4 Contribution to paper IV (Appendix B)

Genomic and neuroimaging approaches to bipolar disorder. *BJPsych Open 2022 Feb 1;8(2):e36. doi: 10.1192/bjo.2021.1082.* (Review)

I conceptualized this descriptive review under the supervision of Sergi Papiol and Thomas G. Schulze. I conducted the literature search regarding different genomic approaches (GWAS; Whole Exome Sequencing; Whole Genome Sequencing) to bipolar disorder. I drafted the first version of the manuscript. I also designed the tables, created the figure and participated in revising the manuscript assisted by Sergi Papiol and Thomas G. Schulze.

1.5 Contribution to paper V (Appendix C)

Extracellular vesicle approach to major psychiatric disorders. *Eur Arch Psychiatry Clin Neurosci. 2022 Oct 27. doi: 10.1007/s00406-022-01497-3.* (Review)

I designed the review. I performed the literature search related to extracellular vesicle in major psychiatric disorders (SCZ, BD, and MDD). I created the figures. Ivana Dellale and I designed the table. I prepared the first draft of the manuscript and participated in revising the manuscript.

1.6 Contribution to paper VI (Appendix D)

Mitochondrial genetics in mental disorders: The bioenergy viewpoint. *European Neuropsychopharmacology* 67 (2023) 80–82. (Insights)

I conceptualized the insights paper, searched in the literature on the main topic, and extended the opinion. I prepared the first draft of the manuscript, created the figure, and participated in revising the manuscript based on the comments from the journal reviewers.

2. Introduction

Lack of reliable biomarkers in psychiatric disorders continues to be a major challenge. We tried to help to address this issue by designing two studies throughout this three-year-long doctoral thesis in the area of genomics and proteomics approaches in psychiatric disorders. Our two relevant original publications are:

Comparative serum proteomic analysis of a selected protein panel in individuals with schizophrenia and bipolar disorder and the impact of genetic risk burden on serum proteomic profiles. *Transl Psychiatry 12, 471 (2022). (*IF=8)

AND

Association between mitochondria-related genes and cognitive performance in the PsyCourse Study. *Journal of Affective Disorders 325 (2023) 1–6. (*IF= 6.5)

Totally from our research, we found that individuals with SCZ and those with BD had significantly different amounts of two serum proteins and one principal component. Moreover, a gene from the OXPHOS pathway revealed a strong association with short-term memory. Our findings from these two studies may shed light on a number of issues related to the hunt for useful biomarkers in psychiatric disorders.

2.1 Psychiatric Disorders

One of the most pressing concerns for human health in today's world of stress and psychological pressure is mental health issues. In the world, 970 million people are thought to be suffered from mental disorders, which usually start in early youth or adulthood and reducing quality of life (Scangos *et al.*, 2023). Psychiatric disorders were the second-most common cause of years with a disability around the globe in 2019 ('Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019.', 2022).

2.1.1 Schizophrenia and Bipolar disorder

SCZ is a complex, severe, and chronic major psychiatric disorder that impairs mental and behavioural health. This illness typically starts in early adulthood or late adolescence (Charlson *et al.*, 2018; Correll and Howes, 2021). Over 24 million people, or 1 in 300

persons (0.32%), globally suffer with SCZ (Institute of health Metrics and Evaluation (IHME), 2021). Positive and negative symptoms such as delusions, hallucinations, disordered thinking, anhedonia and cognitive impairments are the main clinical signs for a diagnosis of this mental disorder (Correll and Howes, 2021). Less than 15% of individuals with SCZ on average recover according to clinical and social recovery standards, and many suffer from repeated relapses and lifelong impairment. There is significantly increased SCZ-related mortality in all age categories (Charlson *et al.*, 2018).

BD (manic-depressive illness) is another major psychiatric disorder, which is characterized by repeated manic and depressive episodes (Delalle, 2021). The overall lifetime prevalence of bipolar spectrum disorders is 2.4%, according to a cross-sectional study (Rowland and Marwaha, 2018). BD ranks among the main global causes of disability and involves episodes of severe mood disruption, cognitive impairments, immunological and physiological abnormalities, and functioning difficulties. It is associated with high risks of early mortality from medical comorbidities and suicide (Rowland and Marwaha, 2018). Both SCZ and BD are diagnosed by the clinical evaluation of symptoms and signs. However, the similarities and overlaps between the clinical signs and symptoms of SCZ and BD might result in incorrect diagnoses, ineffective therapy strategies, and poor outcomes (Murray *et al.*, 2004; Dacquino, De Rossi and Spalletta, 2015). Across patients, these disorders can exhibit wide variations in both symptoms and courses. To enhance the accuracy of diagnosis, choice of treatment, and long-term prognosis for psychiatric disorders like SCZ and BD, discovering innovative and therapeutically useful biomarkers would be beneficial (Delalle, 2021).

2.2 Clinical need for biomarkers

The identification of a specific set of biological markers (biomarkers) for each disorder might pave the way for future successful strategies regarding early detection, patient stratification, or selection of optimal therapeutic intervention. The FDA/NIH Biomarker Working Group defines a biomarker as “a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions” (*BEST (Biomarkers, EndpointS, and other Tools) Resource*, 2016). In somatic conditions, various types of biomarkers exist including those used for diagnosis, monitoring, Pharmacodynamics /

response, prediction, prognosis, safety, and susceptibility / risk assessment (Figure 1) (Cagney *et al.*, 2018). Although the use of biomarkers in medicine is expanding, they still remain an unmet medical need in psychiatric disorders (Schwarz *et al.*, 2012). Due to the limited understanding of the biology and the multifactorial etiology of the psychiatric disorders and in particular the difficulty of accessing the brain, psychiatry is still the area of medicine that does not use routine laboratory testing for diagnostic purposes (Vargas, 2014). In the realm of biomarker discovery, in recent years studies on large samples of psychiatric patients have widely implemented multi-omics profiling approaches with the aim to uncover unique molecular fingerprints able to stratify patient subgroups, predict treatment efficacy, and develop drug discovery processes (Emanuel Schwarz and Bahn, 2008; E. Schwarz and Bahn, 2008; Budde *et al.*, 2019). According to genomic investigations, the pathophysiology of mental illness is highly polygenic and that genetic risk factors for several psychiatric disorders partially overlap. The most replicated risk genes in genomic studies on BD, are ANK3, CACNA1C, SYNE1, ODZ4, and TRANK1, which may reflect their significance in the pathophysiology of BD (Oraki Kohshour *et al.*, 2022). In the metabolomics field, panels of 25 and 15 serum extracellular vesicles-derived metabolites with good to excellent performance in differentiating individuals with SCZ and BD, respectively from healthy controls have been proposed (Du *et al.*, 2021, 2022). In the realm of miRNAomics, a study on individuals with major depression has suggested two miRNAs named let-7b and let-7c as biomarkers for MDD and also TRD (Gururajan *et al.*, 2016). By utilizing proteomics techniques in a total of 14 studies on the serum or plasma of drug-free SCZ patients, 47 proteins were found to be significantly changed (Sabherwal *et al.*, 2016).

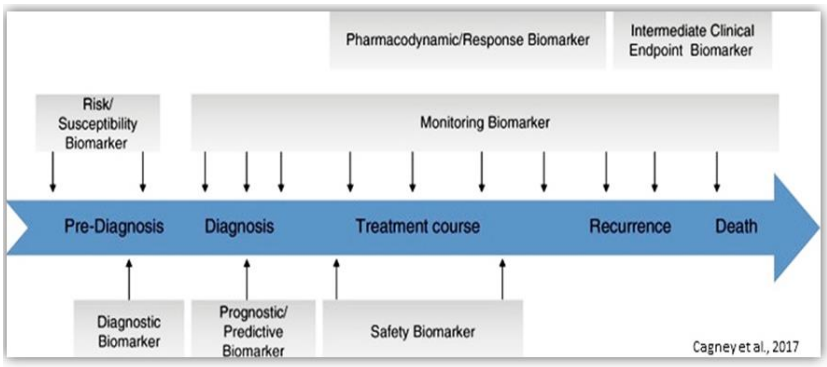

Figure 1. Biomarkers along the clinical continuum

2.2.1 Paving the way for finding biomarkers

It is still a major worry that there are no valid and reliable biomarkers for psychiatric disorders. In this vein, by designing two studies, we aimed to pave the way for finding genomic and proteomic biomarkers in samples from the PsyCourse Study. PsyCourse is a longitudinal naturalistic multi-center study conducted in Germany and Austria. The participants are patients with diagnoses from the affective-to-psychotic spectrum; mostly SCZ and BD (according to DSM-IV criteria) and healthy controls. An extensive phenotyping battery and the collection of biomaterials at four evenly spaced time points over the course of 18 months are both included in the study protocol. More information about the study is available elsewhere (Budde et al., 2019; Heilbronner Urs et al., 2021). In both of our studies here, potential genomic biomarkers (in the first study, the entire genome; in the second, the mitochondria-related genomes) have been investigated to identify some significant genetic variants that are related to serum protein levels or cognitive performance, which may help for diagnosis or prognosis purposes. In addition, to pave the way for discovering minimal-invasive blood biomarkers to enhance the efficacy of diagnostic criteria, in the first study, circulating proteins (with a focus on immune system-related proteins) were subjected to the proteomics approach. The next sections of this dissertation contain summaries of the two studies we conducted.

2.3 A study on serum proteins

Blood transports a variety of substances, including proteins, to maintain homeostasis in the body's interior environment. Serum proteins levels are frequently used in clinics to assess health. Detecting valid biomarkers in the blood as a minimally invasive and cost-effective method can greatly aid in the simple monitoring of diseases and treatment progresses (Comes *et al.*, 2018). To achieve the full potential of blood biomarkers for better diagnosis and prognosis of disorders, it is inevitable to combine well-defined cohorts with cutting-edge technologies(Comes *et al.*, 2018). Researchers may be better able to comprehend the molecular mechanisms and pathways behind diseases by employing proteomics techniques to identify a wide range of proteins (Smirnova *et al.*, 2019). In our first study, we applied high-throughput antibody-based protein profiling to serum samples of 113 individuals with SCZ, 125 individuals with BD (from the PsyCourse Study), and 44 healthy controls (from an ongoing study at the Department of Psychiatry,

University Hospital Munich). The primary goals of this study were to determine whether any profile of circulating proteins might differentiate between individuals with SCZ and BD and healthy controls, as well as to assess the influence of genetic burden on these proteomic profiles. Crosstalk between peripheral pathways and the central nervous system can control immunological and metabolic functions via neuroanatomical networks, hormonal pathways, and molecular signalling mechanisms (Schwarz *et al.*, 2012). In addition, it is conceivable that a distinctive pattern of molecules could be found in the peripheral circulation given the accumulating evidence that some psychiatric disorders exhibit anomalies in these pathways (Schwarz *et al.*, 2012). The majority of the potential proteins for our investigation were chosen based on an expanding body of literature suggesting that the immune system, in particular inflammation, has a role in the pathophysiology of mental disorders (Khandaker, Dantzer and Jones, 2017).

2.3.1 Large batch effects between cases and controls

As an unsupervised feature transformation method, PCA was applied to reduce the dimensionality of the proteomic dataset. For the proteins concentrations, between the patient and control groups, PCA discovered an outstanding batch effect that was most likely caused by differences in the methods used to collect and handle serum samples from different studies (The PsyCourse Study and an ongoing study at University Hospital Munich). Therefore, and given the impossibility to control for such a large batch effect, we decided to limit our group comparisons to the patient groups (SCZ versus BD).

2.3.2 No detectable genetic effects

2.3.2.1 PRS

In summary, our findings do not support an effect of disorder-related polygenic burden (SCZ-PRS; BD-PRS; SCZ-vs-BD-PRS) on the amount of proteins in the serum. However, it is necessary to point out that this outcome could be influenced by the small sample size of our study and further independent studies are warranted to confirm / rule out this finding (or lack thereof).

2.3.2.2 pQTLs

To check for the role of individual genetic variants on the level of the circulating proteins (pQTLs) in the serum samples, we ran GWAS analysis for all the proteins, while age, sex, duration of illness, and the first two ancestry principal components were considered as covariates. The GWAS results then were interpreted and visualized using FUMA GWAS (Watanabe *et al.*, 2017). The findings indicated no significant effect based on the strict genome-wide significance threshold ($p<5x10^{-8}$). As a result, there were no noteworthy findings from the pQTL analysis in our sample, indicating that the individual effect of genetic variants is probably not large.

2.3.3 Three significant differences in serum proteins between SCZ and BD

After Bonferroni correction for multiple testing, we found significant differences between individuals with SCZ and those with BD in two serum proteins: C9 (p-value = 0.02; OR = 0.38) and IL1RAP (p-value = 0.03; OR = 0.34); and one principal component: PC1 (p-value = 0.01; OR=1.13).

2.3.3.1 C9

C9 is a member of the complement system of innate immunity. The C9 pore-forming component is added in numerous copies to the C5b8 complex during the final step of MAC formation. The MAC, which serves to create huge pores in the target membrane, is the terminal component of the complement system (Figure 2) (Spicer *et al.*, 2018).

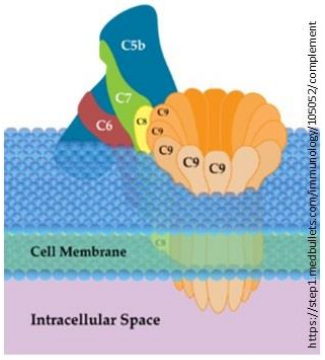

Figure 2. Complement 9

2.3.3.2 IL1RAP

IL1RAP is an essential and maybe rate-limiting component of the pro-inflammatory IL-1 signaling pathway. For this pathway to be active, the IL-1/IL-1 receptor complex needs to be bound by IL1RAP (Figure 3). Leukemia and rheumatoid arthritis (as a chronic inflammatory disease) have

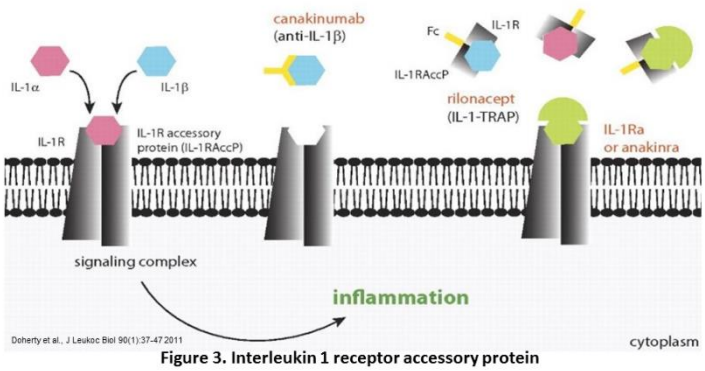

Figure 3. Interleukin 1 receptor accessory protein

been reported to respond to the therapeutic target L1RAP. IL1RAP contributed significantly to the association of immune-related pathways found by pathway analysis of a large GWAS on Alzheimer's disease (Doherty, Brydges and Hoffman, 2011; Ramanan *et al.*, 2015).

2.3.3.3 PC1

The PCA results showed that the PC1 (by explaining 39.3% of the variance in the proteomic dataset) is the only principal component that differed significantly between SCZ and BD. This finding implies that if you want to be able to effectively distinguish between SCZ and BD based on the proteins (mostly involved in specific immune response pathways); it makes more sense to employ a big number of proteins.

2.3.4 AUC-ROC

AUC-ROC analysis using C9 levels, IL1RAP levels, proteome-based PC1, and their combination as predictors and diagnostic status (SCZ/BD) as predicted variable indicated an area under the curve less than 69%. Therefore, they showed not enough predictive value in this regard. These findings suggest that in order to increase performance in prediction, investigations with more complex multivariable models and designs are required.

2.3.5 Importance of the immune system in mental illness

The immune system and particularly inflammation have been linked in a variety of ways to the risk of mental illness, and their significance in psychiatric disorders has been emphasized (Bennett and Molofsky, 2019). Our findings indicate that C9 and IL1RAP are differentially expressed in SCZ and BD, which have not been previously documented in this field of study. It is necessary to validate this finding in independent datasets that have the same characteristics as our samples and to enhance illness status prediction accuracy using more complex multivariable models. In the field of biomarker research in psychiatric disorders, due to the complexity of these disorders and the extensive interplay between genetic and environmental factors, it seems that panels of biomarkers rather than sporadic ones are more plausible and reasonable. Our PCA analysis indicates that a large number of proteins may be involved in specific pathways that aid in differentiating SCZ from BD at the proteomic level. Our study is limited by small sample size, patients'

differences in clinical condition, the sex ratio across groups, and a failure to consider the effects of medications.

2.4 A study on mitochondrial genetics

The OXPHOS-based production of cellular energy is the fundamental role of the mitochondrion, an organelle that is found in practically all eukaryotic cells (Chinnery and Hudson, 2013). Additionally, mitochondria are essential for cellular signal transduction pathways, modulating cytosolic calcium, controlling cellular metabolism, inflammation, and apoptosis (Chinnery and Hudson, 2013; Wallace, 2018). Of all the organs, the brain has the highest need for mitochondrial energy and therefore, even milder mitochondrial abnormalities are likely to have an impact on the brain energy balance (Cuperfain *et al.*, 2018; Pei and Wallace, 2018; Giménez-Palomo *et al.*, 2021). Mitochondria appear in large quantities in neuronal dendrites and synaptic terminals, having important functions in regulating neuronal activity, cellular resilience, behavioural adaptations, and sustaining synaptic plasticity, neurogenesis, and neuronal homeostasis (Giménez-Palomo *et al.*, 2021). Many studies have shown that several brain disorders are associated with abnormal mitochondrial function (Pei and Wallace, 2018). Genetic variations of the mitochondrial genome that is a bi-genomic system, determine energetic capacity. As mitochondrial genome mutations accumulate, energetics may continue to decline until it reaches the point at which disorders manifest (Wallace, 2018). In our second study, we focused on the effect of mitochondria-related genetic variations on cognitive performance, which is a common aspect of many brain diseases and often does not improve with medication (Hill *et al.*, 2010). This study sought to determine the association between variations in mitochondria-related genes (mtDNA and nDNA) related to two significant energy-related pathways, OXPHOS and Metabolism, as well as their genetic risk load with cross-sectional cognitive function in the PsyCourse Study.

2.4.1 Association of *COA8* with short-term memory

After FDR correction for multiple testing, the results showed significant association (p-value < 0.05) of 19 SNPs from OXPHOS pathway (in the *COA8* locus on chromosome 14) with short-term memory, measured by the DGT-SP-FRW test. The *COA8* gene, which is listed in MitoCarta gene-list, is an assembly factor for cytochrome c oxidase (Complex IV

in the electron transport chain in the mitochondria inner membrane) (Rath *et al.*, 2021). This effect on the cognitive performance aligns with a disorder related to *COA8*: the "mitochondrial Complex IV Deficiency, Nuclear Type 17" (MC4DN17). In this autosomal recessive neurometabolic disease with related phenotypes such as intellectual disability and ataxia, cognitive impairment is observed in some patients (Melchionda *et al.*, 2014). The DGT-SP-FRW test assesses short-term memory that is defined as the capacity to store a small amount of information in mind and keep it available for a short time (Jonides *et al.*, 2008). This is the first time, as far as we know, that variants in the *COA8* gene have been associated to a specific cognitive domain.

2.4.2 No clear effect of ^{MT}PRS on cognitive performance

We did not observe a major impact of overall load of mitochondrial SCZ-genetic risk (^{MT}PRS-SCZ) on cognitive function. Nevertheless, it should be noted that due to sample size and SNP arrays limitations, we might not have an optimal statistical power to find such associations.

2.4.3 Mitochondrial gene-sets are not significantly enriched in psychiatric traits

Gene and gene-set analyses are potentially more powerful alternatives than the typical single-SNP analyses performed in GWAS and a valuable addition to single-marker analyses (de Leeuw *et al.*, 2015). MAGMA (v1.09) was used for formal enrichment analyses with the summary statistics (https://www.med.unc.edu/pgc/download-results/) of the following psychiatric disorders: SCZ, BD, MDD, ADHD, PTSD, and ASD. MAGMA competitive gene-set analysis was used to test whether the genes in the OXPHOS, Metabolism, and All-mitochondria-related-genes gene-sets were more strongly associated with the target phenotype than other genes. The findings showed no significant gene-set enrichments for mitochondrial gene sets in any of the psychiatric traits analysed, indicating that mitochondrial gene sets were not significantly enriched in psychiatric traits in the current study (Figure 4).

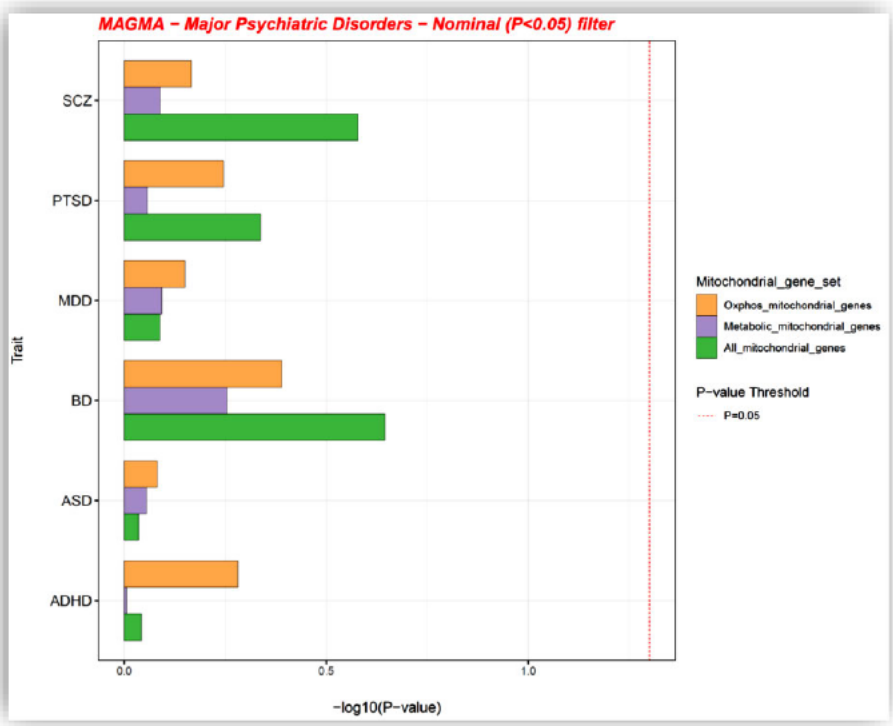

Figure 4. MAGMA analyses of mitochondrial gene sets in psychiatric traits. Uncorrected competitive test P-values on the X-axis are –log10 converted. Dashed red line indicates the nominal (uncorrected) significance threshold P = 0.05.

2.4.4 Neuronal firing and short-term memory

Short-term memory is mediated by persistent neuronal firing in the prefrontal cortex, according to studies in primates (Fuster, 1973). Considering that the cellular process of producing action potentials requires a lot of energy, polymorphisms in the mitochondria-related genes may result in decreased or altered firing patterns of neurons in brain, which would result in dysregulation of physiological and emotional processes and increased susceptibility to mental disorders (Shao *et al.*, 2021). Thus, neuropsychiatric symptoms can be brought on by abnormalities in the mitochondria and bioenergetic disturbance (Wallace, 2013). Overall, mental disorders may be at least partially caused by disrupting brain energy balance due to mitochondrial malfunction. Translating mitochondrial genetic risk using large datasets and across metabolic-psychiatric disorders may clarify some of the clinical manifestation of those disorders based on biomarker-discovery approach and open new avenues for the psychiatric genetics field (Kohshour and Gonçalves, 2023).

2.5 Conclusion

Due to the special characters of psychiatric disorders and the involvement of the brain and nervous system, which cannot be accessible non-invasively, diagnostic interferences in a variety of mental conditions are unavoidable. For this reason, the search for peripheral biomarkers in mental illnesses utilizing novel and cutting-edge methodologies is one of the primary and significant areas of research in this field. The immune system plays the defense, homeostasis, and surveillance roles by spreading its components throughout the body, including the brain. Immune system disruption and conflict caused by multiple inherited and acquired factors have different physiological and clinical effects. Several studies have suggested a connection between immune system disturbance and the etiology of brain disorders (Gibney and Drexhage, 2013). In our study, two inflammation-related proteins showed significant difference between individuals with SCZ and those with BD. The increased concentration of these inflammatory proteins in individuals with BD may indicate the existence of severe inflammatory responses in this disorder. On the biochemistry and structure of the brain, the inflammatory condition can set off a chain reaction of harmful effects; and as a result of such effects, brain plasticity may be impacted, and mood-related symptoms may appear. To fully comprehend the inflammatory profiles as diagnostic and/or therapeutic targets in BD during different episodes and totally in different psychiatric disorders, more studies are still required (Benedetti *et al.*, 2020). The immunological changes might be potent biomarker candidates that help to explain a number of psychiatric disorders features. In addition, by delving into the mechanisms involved in inflammation in the brain more thoroughly, it may be possible in the future to therapeutically target these mechanisms as well as their significant players through the use of particular anti-inflammatory agents.

The role of the mitochondrial genome in the energy generation process in the cells is complex due to the involvement of both mtDNA- and nDNA-encoded polypeptides (Chinnery and Hudson, 2013). During our investigation on mitochondria-related genes, the OXPHOS pathway showed significant association with cognitive function. Nineteen mitochondria-related genes have previously been found to be significantly associated with SCZ at the gene level by using MAGMA (Gonçalves *et al.*, 2018). Five of these genes play a part in the OXPHOS pathway. Thus, neuropsychiatric symptoms may be brought on by partial abnormalities in the mitochondrial function and bioenergetic level (Wallace,

2013); and therefore, it may be possible to improve treatment of brain disorders by concentrating on the relationship between mitochondrial mechanisms and the therapeutic advantages of some specific medications (such as lithium and N-acetylcysteine), which have direct or indirect effect on mitochondrial capacity of generating energy (Kohshour and Gonçalves, 2023). Translating mitochondrial dysfunction risk by performing genetic risk analyses in large sample size, and a deeper understanding and characterization of the mitochondrial bi-genomic system may clarify the energy-generation relevant mitochondrial pathways, which offer an opportunity in the biomarker filed as well as new insights into the etiology and treatment of mental illnesses. The last but not least point should be emphasized here is that in order to have the clearest possible picture of psychiatric disorders due to the complexity of brain physiology and function as well as the interaction of environmental inducers, we need to look for mixed panels of biomarkers from various categories, such as genomics, transcriptomics, proteomics, lipidomics, metabolomics, and so on; and while identifying a few molecules in this context may shed light on the involved processes, but they can't on their own paint a complete picture of the diagnosis, prognosis, and course of treatment. Becoming closer to the reality of psychiatric disorders may be possible by interpreting the various multi-omics data coherently and determining their relationship, particularly by looking at the key molecules and involved biochemical pathways. Overall, identification of reliable biomarkers for psychiatric disorders through the integration of multi-omics data seems promising.

3. Summary (in English)

SCZ and BD are two of the most common psychiatric disorders. The diagnostic criteria for SCZ and BD have not significantly changed over the last decades and are still based on clinical assessments of symptoms and signs, in part due to the difficulties accessing the brain tissue. Within the framework of precision and personalized medicine, many efforts have been made to identify biomarkers in blood using state-of-the-art molecular techniques for improving the specific diagnosis of these disorders. In our first publication, we designed a study by applying high-throughput antibody-based protein profiling in the serum of individuals with SCZ and BD and healthy controls with the aim of discovering potential diagnostic circulating biomarkers as well as investigating the effects of genetic risk burden on the quantitative level of the serum proteins. 113 individuals with SCZ, 125 individuals with BD belonging to the PsyCourse Study (www.PsyCourse.de) and 44 healthy controls belonging to an ongoing study at the University Hospital Munich were enrolled in this study. Analysis of a selected panel of 95 serum proteins (mostly related to the immune system) was performed using a set of 155 antibodies. The results showed two serum proteins (C9 and IL1RAP) and one principal component (PC1) differed significantly between SCZ and BD after multiple testing correction. In addition, the PRS analysis revealed SCZ-PRS, BD-PRS, and SCZ-vs-BD-PRS were not significantly associated with the levels of the individual proteins or the values of the proteome principal components after multiple testing correction, which indicates the absence of a detectable genetic effect in this regard. The immune system role and particularly inflammation in psychiatric disorders has been highlighted in different studies. Here, we found that individuals with BD have significantly higher levels of two immune system-related serum proteins than individuals with SCZ. Taken together, our primary results in this study indicate the importance of the immune system and inflammation process in differentiating SCZ and BD and lay the groundwork for large-scale studies to find more reliable diagnostic biomarkers in psychiatric disorders:

Mojtaba Oraki Kohshour, Nirmal R Kannaiyan, August Jernbom Falk, Sergi Papiol, [...], Moritz J. Rossner, Peter Nilsson, Thomas G. Schulze. **Comparative serum proteomic analysis of a selected protein panel in individuals with schizophrenia and bipolar disorder and the impact of genetic risk burden on serum proteomic profiles.** *Transl Psychiatry 12, 471 (2022).*

In our second publication, we focused on mitochondria-related genetic variants to determine the association between variations in these genes as well as their genetic risk load with cross-sectional cognitive function in the PsyCourse Study. Mitochondria are essential organelles in the cytoplasm of cells, and their dysfunction has been related to a variety of diseases. The main role of mitochondria is to produce energy through OXPHOS, and thus to be involved in metabolism. Polymorphisms in mitochondria-related genes may alter the structure and expression levels of relevant essential proteins, disrupting the energy balance, and potentially raising the risk of mental illness. We investigated the association of genetic variants of the genes belonging to two main mitochondrial pathways, OXPHOS and Metabolism, as well as All-mitochondria-related genes with cognitive performance in the PsyCourse Study. The results showed significant association of 19 SNPs from OXPHOS pathway (in *COA8* gene locus on chromosome 14) with the verbal digit span (forward) test. The forward digit-span test evaluates short-term memory capacity. Sustained neural activity in the prefrontal cortex mediates short-term memory. Since producing action potentials requires a lot of energy, polymorphisms in the mitochondria-related genes may cause decreased or altered neuronal firing patterns in the brain, which would lead to dysregulation of physiological processes and increased susceptibility to mental disorders:

Mojtaba Oraki Kohshour, Eva C. Schulte, Urs Heilbronner, Monika Budde, [...], Peter Falkai, Sergi Papiol, Thomas G. Schulze**. Association between mitochondria-related genes and cognitive performance in the PsyCourse Study.** *Journal of Affective Disorders 325 (2023) 1–6.*

4. Zusammenfassung (Deutsch)

Schizophrenie (SCZ) und Bipolare Störungen (BD) gehören zu den häufigsten psychiatrischen Störungen. Die diagnostischen Kriterien für SCZ und BD haben sich in den letzten Jahrzehnten nicht wesentlich verändert und beruhen nach wie vor auf der klinischen Bewertung von Symptomen und Anzeichen, was zum Teil auf die Schwierigkeiten beim Zugang zum Gehirn zurückzuführen ist. Im Rahmen der Präzisionsmedizin und der personalisierten Medizin wurden zahlreiche Anstrengungen unternommen, um mit Hilfe modernster molekularer Techniken Biomarker im Blut zu identifizieren und so die spezifische Diagnose dieser Erkrankungen zu verbessern. In unserer ersten Publikation haben wir eine Studie durchgeführt, in der wir ein auf Antikörpern basierendes Hochdurchsatz-Proteinprofil im Serum von Personen mit SCZ und BD sowie von gesunden Kontrollpersonen erstellten, um potenzielle diagnostische zirkulierende Biomarker zu entdecken und die Auswirkungen der genetischen Risikobelastung auf das quantitative Niveau der Serumproteine zu untersuchen. 113 Personen mit SCZ, 125 Personen mit BD aus der PsyCourse Studie (www.PsyCourse.de) und 44 gesunde Kontrollpersonen aus einer laufenden Studie am Universitätsklinikum München wurden in diese Studie einbezogen. Die Analyse eines ausgewählten Panels von 95 Serumproteinen (meist mit Bezug zum Immunsystem) wurde mit einem Satz von 155 Antikörpern durchgeführt. Die Ergebnisse zeigten, dass sich zwei Serumproteine (C9 und IL1RAP) und eine Hauptkomponente (PC1) nach Korrektur für multiples Testen signifikant zwischen SCZ und BD unterschieden. Darüber hinaus ergab die PRS-Analyse keinen signifikanten Zusammenhang zwischen SCZ-PRS, BD-PRS und SCZ-vs-BD-PRS und den Konzentrationen der einzelnen Proteine oder den Werten der Proteom-Hauptkomponenten, was auf das Fehlen eines nachweisbaren genetischen Effekts in dieser Hinsicht hinweist. Die Rolle des Immunsystems und insbesondere von Entzündungsprozessen bei psychiatrischen Störungen wurde in verschiedenen Studien hervorgehoben. Wir fanden heraus, dass Personen mit BD signifikant höhere Werte bei zwei mit dem Immunsystem verbundenen Serumproteinen aufweisen als Personen mit SCZ:

Mojtaba Oraki Kohshour, Nirmal R Kannaiyan, August Jernbom Falk, Sergi Papiol, [...], Moritz J. Rossner, Peter Nilsson, Thomas G. Schulze. **Comparative serum proteomic analysis of a selected protein panel in individuals with schizophrenia and bipolar disorder and the impact of genetic risk burden on serum proteomic profiles.** *Transl Psychiatry 12, 471 (2022).*

In unserer zweiten Veröffentlichung konzentrierten wir uns auf Varianten Mitochondrien bezogener Gene, um den Zusammenhang zwischen Variationen in diesen Genen sowie ihrer genetischen Risikobelastung mit der kognitiven Leistungsfähigkeit im Querschnitt der PsyCourse Studie zu untersuchen. Mitochondrien sind lebenswichtige Organellen im Zytoplasma der Zellen, und ihre Funktionsstörung wird mit einer Reihe von Krankheiten in Verbindung gebracht. Die Hauptaufgabe der Mitochondrien besteht darin, durch den OXPHOS Signalweg Energie zu erzeugen und somit am Stoffwechsel beteiligt zu sein. Polymorphismen in Genen, die mit den Mitochondrien zusammenhängen, können die Struktur und das Ausmaß der Expression relevanter essenzieller Proteine verändern, wodurch der Energiehaushalt gestört wird und das Risiko psychischer Erkrankungen möglicherweise steigt. Wir untersuchten in der PsyCourse Studie den Zusammenhang zwischen genetischen Varianten der Gene, die zu den beiden wichtigsten mitochondrialen Stoffwechselwegen, OXPHOS und Metabolismus, gehören, sowie aller mit den Mitochondrien verbundenen Gene und der kognitiven Leistung. Die Ergebnisse zeigten eine signifikante Assoziation von 19 SNPs aus dem OXPHOS-Pfad (im COA8-Genlocus auf Chromosom 14) mit der verbalen Gedächtnisspanne (vorwärts). Dieser Test bewertet die Kapazität des Kurzzeitgedächtnisses, und anhaltende neuronale Aktivität im präfrontalen Kortex vermittelt dieses. Da die Erzeugung von Aktionspotenzialen viel Energie erfordert, könnten Polymorphismen in den Mitochondrien bezogenen Genen zu verminderten oder veränderten neuronalen Feuermustern im Gehirn führen, was eine Dysregulation physiologischer Prozesse und eine erhöhte Anfälligkeit für psychische Störungen zur Folge hätte:

Mojtaba Oraki Kohshour, Eva C. Schulte, Urs Heilbronner, Monika Budde, [...], Peter Falkai, Sergi Papiol, Thomas G. Schulze**. Association between mitochondria-related genes and cognitive performance in the PsyCourse Study.** *Journal of Affective Disorders 325 (2023) 1–6.*

5. Paper I

Mojtaba Oraki Kohshour, Nirmal R Kannaiyan, August Jernbom Falk, Sergi Papiol, [...], Moritz J. Rossner, Peter Nilsson, Thomas G. Schulze. **Comparative serum proteomic analysis of a selected protein panel in individuals with schizophrenia and bipolar disorder and the impact of genetic risk burden on serum proteomic profiles.** *Transl Psychiatry 12, 471 (2022).*

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6. Paper II

Mojtaba Oraki Kohshour, Eva C. Schulte, Urs Heilbronner, Monika Budde, [...], Peter Falkai, Sergi Papiol, Thomas G. Schulze**. Association between mitochondria-related genes and cognitive performance in the PsyCourse Study.** *Journal of Affective Disorders 325 (2023) 1–6*

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Appendix A: Paper III

Fanny Senner*, **Mojtaba Oraki Kohshour*,** Safa Abdalla, Sergi Papiol, Thomas G Schulze. **The Genetics of Response to and Side Effects of Lithium Treatment in Bipolar Disorder: Future Research Perspectives.** *Front Pharmacol. 2021 Mar 25;12:638882. doi: 10.3389/fphar.2021.638882.*

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- **DOI**: 10.3389/fphar.2021.638882

Appendix B: Paper IV

Mojtaba Oraki Kohshour, Sergi Papiol, Christopher R K Ching , Thomas G Schulze. **Genomic and neuroimaging approaches to bipolar disorder**. *BJPsych Open 2022 Feb 1;8(2):e36. doi: 10.1192/bjo.2021.1082.*

- **PMID**: 35101157
- **DOI**: 10.1192/bjo.2021.1082

Appendix C: Paper V

Mojtaba Oraki Kohshour, Sergi Papiol, Ivana Delalle, Moritz J Rossner, Thomas G Schulze. **Extracellular vesicle approach to major psychiatric disorders.** *Eur Arch Psychiatry Clin Neurosci. 2022 Oct 27. doi: 10.1007/s00406-022-01497-3.*

- **PMID**: 36302978
- **DOI**: 10.1007/s00406-022-01497-3

Appendix D: Paper VI

Mojtaba Oraki Kohshour, Vanessa F Gonçalves. **Mitochondrial genetics in mental disorders:The bioenergy viewpoint**. *European Neuropsychopharmacology 67 (2023) 80–82.*

- **PMID**: 36640690
- **DOI**: 10.1016/j.euroneuro.2022.12.004

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