



A machine-learning framework for robust and reliable prediction of short- and long-term treatment response in initially antipsychotic-naïve schizophrenia patients based on multimodal neuropsychiatric data

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the past decade multiple studies had been launched to investigate whether anti-NMDAR antibodies were present in the sera of patients, treated with the diagnosis of schizophrenia, although results have not confirmed this hypothesis. It is possible, however, that autoimmune antibodies, which are not yet known, play a role in FEP, similarly to anti-NMDAR antibodies, therefore there is a rationale behind screening for other antibodies among these patients. The aim of our study is to screen patients with FEP for anti-NMDAR antibodies. We also would like to check whether there are any other potentially pathogenic antibodies, which are not yet known, but could be responsible for psychotic symptoms.

Methods: So far 26 patients have been recruited with FEP (with symptoms of schizophrenia), the total number of healthy controls involved in the study is currently 21. All of the patients were treated at Semmelweis University, Department of Psychiatry. Patients with affective psychosis, drug-related psychotic disorder and patients with clear signs of encephalitis had been excluded from the study.

The patients' blood samples were centrifuged, after which serum was separated from whole blood. Serum samples were then tested with EUROIMMUN immune fluorescent assays for anti-NMDAR antibodies. A different, non-specific method was also used to test anti-brain antibody activity on monkey-cerebellum and rat-hippocampus to show possibly relevant (but not yet known) antibodies. All of the immunological laboratory investigations were done at Semmelweis University, Central Laboratory and immunofluorescent slides were evaluated by an expert in this field. Further differentiation of this non-specific activity was not part of our current study. All of the samples had been frozen on -80 degrees Celsius and are stored for possible further investigations in the future. IL-6 levels will be checked in the next phase of our study.

Results: None of the samples from the 26 patients, nor any of the samples collected from healthy controls contained anti-NMDAR antibodies. However it should be noted that during the period of the study 3 patients were diagnosed with anti-NMDAR encephalitis, but as it was described earlier these cases had not been included in our study, because we focused on patients with pure psychotic symptoms.

11 of the patients' serum showed positive reaction of the neuroendothelium (6 strong, 5 moderate), whereas only 4 of the samples collected from healthy controls showed similar pattern (all of them showed moderate or mild activity). These results suggest that there is a significant difference between the groups, however we will need to increase our sample size to verify these findings. There were other non-specific reactions in both groups in low numbers.

Discussion: None of the serum samples of the 26 patients proved positive for anti-NMDAR antibodies, which is in agreement with previous studies in the literature. However, a higher proportion of samples from patients showed activity on the neuroendothelium of non-specific immune fluorescent assays compared to healthy controls. We plan to increase our sample sizes in the near future and check the serum samples for interleukins and cytokines.

S11. PLASMA LEPTIN AND ANTHRANILIC ACID IN SCHIZOPHRENIA PATIENTS: NEW BIOMARKERS OF PREDISPOSITION TO METABOLIC ABNORMALITIES

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Background: Leptin was implicated in pathophysiology of schizophrenia (Sz) and in increased risk of Sz patients for overweight and hyperlipidemia, especially in patients treated with anti-psychotic medications known to elevate plasma leptin levels. Our finding of increased plasma levels of anthranilic (ANA) and kynurenic (KYNA) acids in leptin-receptors

deficient Zucker fatty rats [Oxenkrug et al., 2016], and causative association between KYNA and major psychopathology of Sz [Erhardt et al., 2007; Schwarcz et al., 2001] warranted our further evaluation of plasma levels of leptin and tryptophan – kynurenine pathway metabolites in Sz patients.

Methods: Tryptophan (Trp), kynurenine (Kyn), ANA, KYNA, 3-hydroxykynurenine (3HK), and xanthurenic acid (XA) were evaluated by HPLC–mass spectrometry [Oxenkrug et al., 2015] in fasting plasma samples of fifty-two [19 drug-naïve first-episode and 33 previously-treated, but not medicated for, at least, 6 weeks] acutely ill Sz patients (DSM-IV) and fifty-two healthy subjects matched for age, gender, body mass index (BMI), and waist circumference [Steiner et al., 2017]. Plasma leptin levels, and other metabolic markers were previously assessed in study participants [Steiner et al., 2017]. The study was approved by the University of Magdeburg Review Board and Tufts Medical Center IRB, and written informed consent was obtained

Results: The main (and, to the best of our knowledge, original) finding of our study is the strong correlation of leptin plasma levels with ANA (but not with other studied kynurenines) in Sz patients ($r=0.44$, $p<0.006$, Spearman's rank correlations, two-tailed). There was a high tendency to such a correlation in control subjects ($r=0.26$, $p=0.06$). In patients (but not in controls) plasma levels of leptin and ANA correlated with waist circumference ($r=0.27$, $p<0.004$ and $r=0.37$, $p<0.01$, resp.) and BMI ($r=0.30$, $p<0.03$ and $r=0.34$, $p<0.01$, resp.). Plasma leptin and ANA levels did not differ between Sz patients and control subjects (Mann-Whitney U test).

Discussion: The strong positive correlation between plasma leptin and ANA (but not other kynurenines) might be explained by the shift of Kyn down-stream metabolism from formation of 3HK toward production of ANA and KYNA by adipocytes, the major source of leptin production. Notably, literature data pointed out to elevation of leptin and decrease of ANA levels after treatment with antipsychotic medications suggesting a switch from positive to negative correlation between leptin and ANA after treatment. A different regulation of ANA compared to other kynurenines in relation to leptin has previously been described in obesity: weight loss was accompanied by drop of circulating leptin levels while ANA was the only Kyn metabolite increased after weight loss [Theofylaktopoulou et al., 2013]. Our data further support the special role of ANA in leptin involvement in energy regulation in Sz patients. Evaluation of plasma leptin/ANA correlation may be useful in identification of Sz patients at increased risk for the development of metabolic abnormalities.

References

- Erhardt S, Schwieler L, Nilsson L. 2007. *Physiol Behav* 92:203
 Oxenkrug G. 2015. *Mol Neurobiol.* 52:805
 Oxenkrug G, Cornicelli J, van der Hart M, et al. 2016. *Integr Mol Med*, 3: 761
 Schwarcz, R., Rassoulpour, A., Wu, H.Q., et al. 2001. *Biol. Psychiatry* 50: 521
 Steiner J, Berger M, Guest PC, et al. 2017. *JAMA Psychiatry*, 74:968
 Theofylaktopoulou D, Midttun O, Ulvik A, et al. *Clin Exp Immunol.* 2013;173:121

S12. A MACHINE LEARNING FRAMEWORK FOR ROBUST AND RELIABLE PREDICTION OF SHORT- AND LONG-TERM CLINICAL RESPONSE IN INITIALLY ANTIPSYCHOTIC-NAÏVE SCHIZOPHRENIA PATIENTS BASED ON MULTIMODAL NEUROPSYCHIATRIC DATA

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Background: The treatment response of patients with schizophrenia is heterogeneous, and markers of clinical response are missing. Studies using machine learning approaches have provided encouraging results regarding prediction of outcomes, but replicability has been challenging. In the present study, we present a novel methodological framework for applying machine learning to clinical data. Herein, algorithm selection and other methodological choices were based on model performance on a simulated dataset, to minimize bias and avoid overfitting. We subsequently applied the best performing machine learning algorithm to a rich, multimodal neuropsychiatric dataset. We aimed to 1) classify patients from controls, 2) predict short- and long-term clinical response in a sample of initially antipsychotic-naïve first-episode schizophrenia patients, and 3) validate our methodological framework.

Methods: We included data from 138 antipsychotic-naïve, first-episode schizophrenia patients, who had undergone assessments of psychopathology, cognition, electrophysiology, structural magnetic resonance imaging (MRI). Perinatal data and long-term outcome measures were obtained from Danish registers. Baseline diagnostic classification algorithms also included data from 151 matched healthy controls.

Short-term treatment response was defined as change in psychopathology after the initial antipsychotic treatment period. Long-term treatment response (4–16 years) was based on data from Danish registers. The simulated

dataset was generated to resemble the real data with respect to dimensionality, multimodality, and pattern of missing data. Noise levels were tunable to enable approximation to the signal-to-noise ratio in the real data. Robustness of the results was ensured by running two parallel, fundamentally different machine learning pipelines, a 'single algorithm approach' and an 'ensemble approach'. Both pipelines included nested cross-validation, missing data imputation, and late integration.

Results: We significantly classified patients from controls with a balanced accuracy of 64.2% (95% CI = [51.7, 76.7]) for the single algorithm approach and 63.1% (95% CI = [50.4, 75.8]) for the ensemble approach. Post hoc analyses showed that the classification primarily was driven by the cognitive data. Neither approach predicted short- and long-term clinical response. To validate our methodological framework based on simulated data, we selected the best, a medium, and the most poorly performing algorithm on the simulated data and applied them to the real data. We found that the ranking of the algorithms was kept in the real data.

Discussion: Our rigorous modelling framework incorporating simulated data and parallel pipelines discriminated patients from controls, but our extensive, multimodal neuropsychiatric data from antipsychotic-naïve schizophrenia patients were not predictive of the clinical outcome. Nevertheless, our novel approach holds promise as an important step to obtain reliable, unbiased results with modest sample sizes when independent replication samples are not available.

S13. IMPACT OF POLYGENIC AND POLY-ENVIRONMENTAL RISK FACTORS ON A PSYCHOSIS RISK PHENOTYPE EXPLAINED THROUGH BRAIN STRUCTURE

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Background: While single (genetic and environmental) risk factors for psychosis have been studied for their impact on brain structure and function, there is little understanding of how they interact to generate psychosis liability on the neural level. Direct associations between cumulative genetic risk scores and risk phenotypes are often weak, and analyses of G×E interactions are scarce. We developed and tested a multivariate model, in which the effects of cumulative environmental and genetic risk on a dimensional phenotype are mediated by brain structural variation.

Methods: In a data set of 440 non-clinical subjects, we tested a moderated mediation model with an interaction of an environmental (ERS) and a polygenic risk score (PRS) for schizophrenia, impacting on the subclinical psychosis spectrum phenotype schizotypy. We propose this effect to be mediated by grey matter volume variation, derived from voxel-based morphometry. In addition, cognitive function (CF) was considered as a potential moderator.

Results: Firstly, in a whole-brain analysis, we detected a significant interaction effect of PRS×ERS in a cluster (k=910, x/y/z=-4/-50/33, p=0.024 FWE cluster-level corrected) including the left precuneus (Pc, 64%) and posterior cingulate gyrus (pcG, 33%). Secondly, cluster values were extracted and entered into a multivariate moderated mediation model. This model was significant, showing that Pc/pcG volume mediated the impact of a PRS×ERS interaction on positive schizotypy (R²=10.91%, p=4.9×10⁻⁵). In predicting Pc/pcG variation (R²=51.69%), neither PRS (b=0.638, p=0.830) nor ERS had a main effect on grey matter variation, but their