Association between metabolic syndrome and cognitive dysfunctions in schizophrenia

Ph.D. Thesis Booklet

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1. Introduction

1.1. Overview of the topic

Schizophrenia (SCZ) is a severe, chronic psychiatric disorder characterized by a heterogeneous constellation of positive, negative, and cognitive symptoms. Cognitive dysfunction is a central feature of SCZ and a major determinant of functional outcomes, yet the pathophysiological mechanisms underlying these impairments remain incompletely understood. In clinical practice, antipsychotic medications, which form the cornerstone of SCZ treatment, are effective in alleviating positive symptoms; however, they exert little to no therapeutic benefit on cognitive functions.

SCZ is associated with a high burden of metabolic abnormalities, including metabolic syndrome (MetS), insulin resistance (IR), and diabetes mellitus (DM). The primary aim of this thesis was to investigate the impact of metabolic dysregulation and peripheral low-grade inflammation on cognitive functions in SCZ. Addressing these multifaceted relationships requires an integrative research approach that bridges psychiatry, endocrinology,

and immunology. Prompt recognition and treatment of these comorbid conditions may, in turn, create opportunities to attenuate cognitive decline and improve functional outcomes in individuals with schizophrenia.

2. Objectives

2.1. Study I. – Glucose homeostasis and cognitive functions in schizophrenia: a systematic review and meta-analysis

The aim of this study was to systematically review the existing literature and to perform a meta-analysis to examine the impact of different stages of glucose homeostasis dysregulation -ranging from insulin resistance and prediabetes to manifest diabetes mellitus- on cognitive functions in individuals with schizophrenia

2.2. Study II. – Association between metabolic syndrome, diabetes mellitus, inflammation and cognitive dysfunctions in schizophrenia: a cross-sectional analysis

In this cross-sectional study, we aimed to comprehensively investigate the impact of metabolic

abnormalities, including metabolic syndrome and diabetes mellitus, as well as systemic inflammatory markers -specifically interleukin-6 (IL-6) and C-reactive protein (CRP)- on cognitive functions in individuals with schizophrenia. In addition to examining their overall effects on cognitive performance, we sought to identify which specific metabolic and inflammatory parameters are associated with the severity of cognitive dysfunctions across different cognitive domains.

3. Methods

3.2.1. Study I

This systematic review and meta-analysis was reported based on the recommendation of the PRISMA 2020 guideline, while we followed the guidance of the Cochrane Handbook. The protocol of the study was registered on PROSPERO (registration number CRD42023481556) and we completely adhered to it.

Eligible studies included individuals diagnosed with schizophrenia spectrum disorders presenting with diabetes mellitus or insulin resistance, who were

compared to patients without impaired glucose homeostasis. Cognitive performance was required to be evaluated using standardized and validated neuropsychological instruments. Global cognitive functioning was defined as the primary outcome measure, while domain-specific cognitive outcomes were additionally analyzed when sufficient data were available. For the review part, studies examining associations between markers of glucose metabolism and cognitive functions in schizophrenia spectrum disorders were also considered.

A comprehensive literature search was performed across five electronic databases—PubMed, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). The initial search was conducted on November 23, 2023, and subsequently updated on April 2, 2025, ensuring coverage of all eligible studies published up to that date.

The included studies were stratified into two comparison groups: individuals with SCZ with versus without DM, and patients with SCZ with versus without IR. Given the

heterogeneity of cognitive assessments employed across studies, effect sizes were primarily reported as standardized mean differences (SMDs). In addition, a subgroup analysis was performed within the SCZ with DM group, limited to studies utilizing the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), for which, outcomes were reported as mean differences (MDs).

When studies reported cognitive outcomes in quartiles only, established statistical methods described by Luo et al. and Shi et al. were applied to estimate corresponding means and standard deviations. In the study by Guo (2011), a global cognitive score was derived by calculating SMDs for individual cognitive subtests and subsequently averaging these values, employing a conservative approach for the estimation of the associated standard error.

Meta-analytic results were synthesized using random-effects models and are presented as forest plots with 95% confidence intervals (95% CI). P-values were calculated to evaluate the overall effects of diabetes mellitus and

insulin resistance on cognitive functions. All statistical analyses were conducted using R software (version 4.3.2), applying the meta package (version 6.5.0).

3.2.2. Study II.

A total of 218 patients diagnosed with schizophrenia (SCZ) were enrolled from three psychiatric institutions in Hungary: National Institute of Psychiatry, Budapest; University of Szeged, Szeged; Bács-Kiskun County Hospital, Kecskemét. Participant recruitment took place between 2012 and 2023. Inclusion criteria comprised a diagnosis of SCZ according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), age between 18 and 65 years, and a clinically stable condition under antipsychotic treatment. Exclusion criteria included a history of neurological disorders or head trauma, as well as substance misuse within the preceding six months. Comprehensive clinical documentation and complete medical histories were available for all participants.

Diagnostic assessments were conducted using the Structured Clinical Interview for DSM-5, administered by

trained psychiatrists or clinical psychologists. Symptom severity was evaluated with the Positive and Negative Syndrome Scale (PANSS), a clinician-rated instrument consisting of 30 items scored on a 7-point Likert scale.

Ethical approval was granted by the National Medical Research Council (ETT-TUKEB 18814, Budapest, Hungary), and the study was conducted in accordance with the Declaration of Helsinki. All subjects gave their written informed consent.

Metabolic status was evaluated in all participants. Sixty-two patients met the criteria for metabolic syndrome (MetS) according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). 53 patients were diagnosed with diabetes mellitus (DM), whereas the remaining patients with MetS did not meet criteria for DM. Accordingly, participants were categorized into three groups: SCZ patients without MetS or DM, SCZ with MetS without DM (SCZ+MetS), and SCZ with DM (SCZ+DM). These groups were characterized using laboratory indicators of lipid metabolism, including triglycerides (TG), high-density

lipoprotein (HDL), and low-density lipoprotein (LDL), as well as measures of glucose regulation, namely fasting blood glucose (FBG) and hemoglobin A1c (HbA1c). C-reactive protein (CRP) and interleukin-6 (IL-6) levels were also assessed.

Cognitive functions were assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

Statistical analyses were performed using Spotfire Data Science Workbench version 14.2.0 (TIBCO), JASP version 0.19.1, and the R-package.

After verifying the normality of the data distribution of all variables at the group level using the Shapiro–Wilk test, multivariate analyses of variance (MANOVA) were conducted, with group specified as the between-subjects factor (SCZ, SCZ+MetS, and SCZ+DM) and RBANS cognitive domains as the within-subjects factors (attention, immediate memory, delayed memory, visuospatial function, and language). The dependent measure comprised RBANS scores across individual cognitive domains. Effect sizes were calculated using eta

squared (η^2). For the Bayesian interpretation of p-values, Vovk–Selke p-ratios (VSRs) were calculated. (VSR > 1: evidence against the null hypothesis; VS-ratio > 10: the evidence in favor of the alternative hypothesis is strong; VS-ratio < 1: the null hypothesis is more supported). If the sphericity or homogeneity of variance was violated, Huynh-Feldt or Welch corrections were applied, respectively. Post hoc comparisons were performed using t-tests with Holm correction. Demographics, clinical scales, and laboratory parameters were entered into one-way ANOVA, followed by post-hoc tests. Where appropriate, Cohen's effect size values were also calculated.

To examine the association between cognitive dysfunctions (RBANS domain scores) and laboratory parameters (IL-6, FBG, HbA1c, TG, HDL, and LDL), multiple regression analyses were conducted, with adjustment for age, sex, education, clinical symptom severity, social functioning, chlorpromazine-equivalent antipsychotic dose, and duration of illness. We also calculated the strength and direction of the relationship

between cognitive scores and laboratory measures using Pearson's product-moment coefficients with VSR for Bayesian statistics.

4. Results

4.1. Study I.

A systematic literature search identified 11,789 records, of which 26 studies met the inclusion criteria for qualitative synthesis and 9 were eligible for meta-analysis. 7 studies examined cognitive functions in patients with SCZ and comorbid DM (n=3,214), while 3 studies investigated the effects of IR on cognition (n=552). Overall risk of bias was low to moderate, with no high-risk studies identified.

Meta-analytic results demonstrated a consistent trend toward more severe cognitive impairment in SCZ patients with DM, although the pooled effect on global cognition did not reach statistical significance (SMD = −0.26; 95% CI −0.59 to 0.08; p= 0.1087). The following results were obtained for each cognitive domain: reasoning (SMD= -0.40; 95% CI, -0.58 to -0.22; P=0.0109); working memory

(SMD=-0.17; 95% CI, -0.47 to 0.14; P=0.1824); processing speed (SMD=-0.43; 95% CI, -0.52 to -0.35; P=0.0005). Findings regarding IR were inconsistent, with no significant pooled effect on cognitive performance. Three studies on the effects of insulin resistance on cognitive functions produced conflicting findings. (SMD=-0.12; 95% CI, -0.91 to 0.68; P=0.5890)

4.2. Study II

We found no significant differences in age, education, sex, PANSS, illness duration, or general functioning. Patients with SCZ+MetS and SCZ+DM exhibited higher BMIs and WHRs than those with SCZ, but there was no significant difference between SCZ+MetS and SCZ+DM.

Patients with SCZ+MetS and SCZ+DM displayed increased TG, LDL, and lower HDL than patients with SCZ, but there was no significant difference between SCZ+MetS and SCZ+DM. In terms of FBG, the highest level was measured in SCZ+DM, followed by SCZ+MetS and SCZ. HbA1c was significantly elevated in SCZ+DM relative to SCZ+MetS and SCZ. IL-6 was significantly

elevated in SCZ+DM relative to SCZ and SCZ+MetS, with no significant difference between SCZ and SCZ+MetS. Finally, there were no significant between-group differences in CRP.

The MANOVA conducted on the RBANS domain scores indicated a significant main effect of group ($F(2,115) = 18.0, p < 0.001, \eta^2 = 0.03, VSR = 372010.54$) and RBANS domain scores ($F(3.9, 838.3) = 3.47, p < 0.05, \eta^2 = 0.01, VSR = 8.97$). The two-way interaction between the group and RBANS domain scores was also significant ($F(7.8, 838.3) = 5.80, p < 0.001, \eta^2 = 0.04, VSR = 58250.54$). Post-hoc tests revealed that patients with SCZ+DM scored lower on the attention domain than those with SCZ ($t = 6.0, SE = 2.25, p_{Holm} < 0.001, d = 1.0$) and SCZ+MetS ($t = 4.78, SE = 2.49, p_{Holm} < 0.001, d = 0.98$). However, no significant difference was observed between SCZ and SCZ+MetS ($p_{Holm} = 1, d = 0.11$). Similar results were obtained for delayed memory (SCZ+DM < SCZ, $t = 5.39, SE = 2.50, p_{Holm} < 0.001; d = 0.97$; SCZ+DM < SCZ+MetS, $t = 3.72, SE = 2.49, p_{Holm} < 0.05, d = 0.70$; SCZ = SCZ+MetS, $p_{Holm} = 1, d = 0.2$). No significant

between-group differences were observed for immediate memory, visuospatial functions, and language ($ps_{Holm} > 0.05$).

In the whole sample, multiple regression analyses identified IL-6 as the sole significant predictor of the RBANS attention score. ($\beta = -0.37$, $t = -5.34$, $p < 0.001$, $R^2 = 0.19$, $VSR = 94017.2$). For the RBANS delayed memory score, there were two predictors: IL-6 ($\beta = -0.16$, $t = -2.11$, $p < 0.05$, $R^2 = 0.08$, $VSR = 3.1$) and FBG ($\beta = -0.22$, $t = -2.58$, $p < 0.05$, $R^2 = 0.08$, $VSR = 7.6$). For the remaining RBANS domain scores (immediate memory, language, and visuospatial functions), we found no significant predictors from the laboratory measures ($ps > 0.2$).

In the entire sample, numerous significant correlations were observed between laboratory parameters and the RBANS attention scores: IL-6 ($r = -0.42$, $p < 0.001$, $VSR = 1.1 \times 10^8$), FBG ($r = -0.27$, $p < 0.001$, $VSR = 520.8$), TG ($r = -0.19$, $p < 0.05$, $VSR = 13.5$), and HDL ($r = 0.20$, $p < 0.05$, $VSR = 17.7$). However, in SCZ+MetS, the sole

significant correlation was found between RBANS attention scores and IL-6 (r = -0.45, p < 0.001, *VSR* = 207.5). This correlation was consistently significant in SCZ+DM (r = -0.42, p < 0.01, *VSR* = 31.8), but not in SCZ (r = -0.14, p = 0.15, *VSR* = 1.3).

For the RBANS delayed memory domain, several significant correlations were also observed in the overall sample, including IL-6 (r = -0.28, p < 0.001, *VSR* = 985.8) and FBG (r = -0.28, p < 0.001, *VSR* = 897.1). Significant correlation between RBANS delayed memory and IL-6 was also observed in SCZ+DM (r = -0.40, p < 0.01, *VSR* = 20.2), but not in SCZ+MetS and SCZ. (ps > 0.1)

5. Conclusions

Our findings suggest that diabetes mellitus and low-grade inflammation may play a central role in the exacerbation of cognitive dysfunctions in schizophrenia. Addressing these alterations may represent a meaningful opportunity to mitigate cognitive decline and improve functional outcomes in schizophrenia patients.

6. Bibliography

6.1. Publications related to the thesis:

Glucose homeostasis and cognitive functions in schizophrenia: a systematic review and meta-analysis.

Kancsev, A., Virág-Tulassay, E. É., Engh, M. A., Kiss-Dala, S., Horváth, A. A., Hegyi, P., Kéri, S.

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