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Major neurocognitive psychosis: a novel schizophrenia endophenotype class that is based on machine learning and resembles Kraepelin's and Bleuler's conceptions

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Abstract

The purpose of this study is to describe how to use the precision nomothetic psychiatry approach to (a) delineate the associations between schizophrenia symptom domains, including negative symptoms, psychosis, hostility, excitation, mannerism, formal thought disorders, psychomotor retardation (PHEMFP), and cognitive dysfunctions and neuroimmunotoxic and neuro-oxidative pathways and (b) create a new endophenotype class based on these features. We show that all symptom domains (negative and PHEMFP) may be used to derive a single latent trait called overall severity of schizophrenia (OSOS). In addition, neurocognitive test results may be used to extract a general cognitive decline (G-CoDe) index, based on executive function, attention, semantic and episodic memory, and delayed recall scores. According to partial least squares analysis, the impacts of adverse outcome pathways (AOPs) on OSOS are partially mediated by increasing G-CoDe severity. The AOPs include neurotoxic cytokines and chemokines, oxidative damage to proteins and lipids, IgA responses to neurotoxic tryptophan catabolites, breakdown of the vascular and paracellular pathways with translocation of Gram-negative bacteria, and insufficient protection through lowered antioxidant levels and impairments in the innate immune system. Unsupervised machine learning identified a new schizophrenia endophenotype class, named major neurocognitive psychosis (MNP), which is characterised by increased negative symptoms and PHEMFP, G-CoDe and the above-mentioned AOPs. Based on these pathways and phenome features, MNP is a distinct endophenotype class which is qualitatively different from simple psychosis (SP). It is impossible to draw any valid conclusions from research on schizophrenia that ignores the MNP and SP distinctions.

Summations

- The current gold standard approach to schizophrenia, as illustrated by DSM and ICD case criteria, is incorrect and leads to errors in scientific studies, while the label schizophrenia is stigmatising.
- One wonders how many incorrect results have been published in schizophrenia research because the new endophenotype class 'major neurocognitive psychosis (MNP)' was not taken into account.
- Clinicians and researchers must always employ the machine learning-based model of MNP rather than the flawed DSM/ICD schizophrenia diagnosis, as the endophenotype class MNP is distinguished by a unique pathophysiology, a severe generalised cognitive deficit, and a worse outcome.

Perspectives

- The endophenotype class MNP model should be cross-validated in other countries and ethnicities.
- Future precision medicine research should incorporate further pan-omics and brainome data into the immune and oxidative neurotoxicity model of MNP.

Introduction

In 2017, an estimated 1.1 million new cases of schizophrenia were reported, with a total of 20 million cases reported worldwide in 2019 (GBD, 2018; Javitt, 2014). Between 0.3% and 0.7% of all individuals are diagnosed with schizophrenia (GBD, 2018; Javitt, 2014; Jablensky, 2000). About half of them will improve significantly over time, with no more relapses, and a small percentage will recover entirely, while the other half will be disabled for the rest of their lives (Jablensky, 2000; Vita & Barlati, 2018; Maes *et al*., 2021). People with schizophrenia frequently have long-term unemployment, poverty, and homelessness, and they have a higher suicide risk and more physical health issues than the general population, resulting in a 20-year drop in life expectancy on average (Charlson *et al*., 2018; Hor & Taylor, 2010).

Dr Emil Kraepelin published the first official description of schizophrenia as a mental disorder in 1887. He coined the label 'dementia praecox' or 'early dementia' to characterise the symptoms that are now recognised as schizophrenia. The cornerstone of Kraepelin's dementia praecox was a general 'weakening' of mental processes that resulted in a 'defect' coexisting with 'productive' or 'florid' symptoms (Shepherd, 1995; Engstrom *et al*., 2006; Ebert & Bar, 2010; EBO, 2022; Berrios *et al*., 2003; Decker, 2007). In 1911, Eugen Bleuler coined the term 'schizophrenia' a combination of the Greek terms schizo (split) and phrene (mind) to describe the mental disorder and fragmented thinking that affect people with schizophrenia. Bleuler considered schizophrenia to be a psycho-organic disorder comprising two symptom clusters, namely a core with four primary symptoms, namely disordered associations, autistic behaviour and thinking, aberrant emotion, and ambivalence, and accessory symptoms including hallucinations, delusions, social disengagement, and reduced desire (Berrios, 2011; Moskowitz & Heim, 2011; Jablensky, 2010).

Kurt Schneider made the next significant advance in 1959 when he enumerated his 'first rank' characteristics of the disorder, including 'auditory hallucinations; thought withdrawal, insertion, and interruption; thought broadcasting; somatic hallucinations; delusional perception; feelings or actions as made or influenced by external agents' (Jablensky, 2010; Soares-Weiser *et al*., 2015).

The Russian school lead by A. V. Snezhnevsky was essential in the conception of negative symptoms in schizophrenia. These authors described the entire spectrum of deficiency symptoms, ranging from barely noticeable to profound deficits in mental function, including mental fatigue and diminished energy potential, a decline in intelligence and social disengagement, social withdrawal, frailty, excessive vulnerability, asthenisation of mental activity, mental marasmus, dulled affect, autism, personality regression, and dementia (Snezhnevsky, 1971; Snezhnevsky & Vartanyan, 1970). Importantly, the Russian school believed that this loss of mental capacity was caused by damage to the central nervous system (Mosolov & Yaltonskaya, 2022).

Since the 1970s, the labels 'defect' and 'productive symptoms' have mostly been replaced by the terms 'negative' and 'positive' symptoms (Jablensky, 2010). Based on this new knowledge, new diagnostic criteria were constructed, which are still used today by the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM).

Crow described a subclassification of schizophrenia depending on whether positive or negative symptoms predominate. 'Type I' (positive) schizophrenia as defined by hallucinations, delusions, and formal thought disorder (FTD), with an underlying dopaminergic dysfunction, whereas 'Type II' (negative) schizophrenia was defined by social withdrawal, loss of volition, affective flattening, and poverty of speech, all of which were presumed to be associated with structural brain abnormalities (Crow, 1980). While positive symptoms may be related to dopaminergic aberrations in the mesolimbic circuits, negative symptoms are thought to be associated with dopaminergic aberrations in the mesocortical circuits.

Kirkpatrick *et al*. (2000, 2001) suggested the definition of a subtype of schizophrenia defined by persistent 'primary' negative symptoms that cannot be attributed to other psychiatric disorders. This clinical construct which was based on Kraepelin's dementia praecox was dubbed 'deficit schizophrenia' and was speculated to represent a unique 'disease' within the schizophrenia spectrum (Kirkpatrick *et al*., 2000, 2001; Kaiser *et al*., 2011). When this negative symptom cluster is present throughout severe psychotic exacerbations and the more stable inter-episode stages of illness, it is referred to as deficit schizophrenia.

The NINH and NHS continue to categorise schizophrenia symptoms into three domains: positive and negative symptoms, as well as cognitive abnormalities (NIHM, 2019; NHS, 2019). Cognitive deficiencies associated with schizophrenia include impairments in working memory, executive functioning, fluency, list learning, attention and processing speed and those cognitive deficits contribute to lowered health-related quality of life (HR-QoL) and impairments in social functioning, including the ability to work, find work, live independently, and function normally (Maes & Kanchanatawan, 2021; Ueoka *et al*., 2011; Alptekin *et al*., 2005; Tolman & Kurtz, 2012; Mohamed *et al*., 2008; Keefe & Harvey, 2012).

Nonetheless, we discovered recently that: (a) negative and positive symptoms cannot be regarded as independent dimensions and that a latent vector underpins both positive and negative symptoms, dubbed the overall severity of schizophrenia (OSOS) latent vector; (b) a common core of cognitive deficits underpins dysfunctions in episodic, semantic, and working memory, executive functions, and attention, dubbed the generalised cognitive decline (G-CoDe); (c) the negative, positive and cognitive symptoms are strongly associated with neuroimmunotoxic pathways including increased levels of neurotoxic cytokines, chemokines, and oxidative and nitrosative stress compounds; and (d) increased severity of OSOS, G-CoDe and neuroimmunotoxic pathways shape a new endophenotype class, namely major neurocognitive psychosis (MNP), largely overlapping with deficit schizophrenia (Maes *et al*., 2020c, 2021; Kanchanatawan *et al*., 2018a, b; Al-Hakeim *et al*., 2020a, b). Such data show that the common approach of examining the correlations between positive and negative symptoms, cognitive dysfunctions and biomarkers is inadequate and that these associations should be examined using the new precision nomothetic approach combining factor analysis and multiple regression analysis in partial least squares (PLS) analysis (Maes *et al*., 2020c; Stoyanov & Maes, 2021).

Aims and methods

The present study aims to explain how to use the precision nomothetic psychiatry approach to analyse the interconnections between positive and negative symptoms, cognitive dysfunctions and biomarkers in schizophrenia. Towards this end, we review our data obtained in different study samples of patients with schizophrenia and deficit schizophrenia and using examples extracted from these studies we show how PLS path analysis should be used to examine these complex associations. We will review how

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to use machine learning to examine whether a common core underpins positive and negative symptoms and cognitive dysfunctions, to examine how biomarkers and cognitive deficits predict the symptomatome of schizophrenia, and how these data can be employed to discover new endophenotype classes.

PLS modelling

PLS modelling allows for (a) the development of causal models that link causal factors including genetic and environmental factors (dubbed the 'causome') to adverse outcome pathways (AOPs), cognitive dysfunctions (dubbed the 'cognitome') and schizophrenia symptoms (dubbed the 'symptomatome'); (b) the development and inclusion in the model of latent vectors based on unobservable variables, such as positive and negative symptom constructs; and (c) the delineation of mediation effects, such as the effects of AOPs on the symptomatome which are mediated by the cognitome. As input variables, different single indicators (age, gender, and genomic data) and latent vectors derived from a set of highly connected indicators (e.g. a set of interconnected biomarkers or cognitive test results) may be used to predict the final outcome variable, namely the symptomatome and phenomenome (Maes *et al*., 2020c; Stoyanov & Maes, 2021).

The most prominent feature of PLS (Ringle *et al*., 2014; Hair *et al*., 2022) is that linear composites or factors of observed variables are constructed which act as proxies for latent variables that are difficult to measure directly, such as the 'symptomatome'. A latent construct could be thought of as something derived from empirical data that allow for empirical testing of the underlying constructs (Ringle *et al*., 2014; Hair *et al*., 2022; Rigdon, 2012). However, the model associations among the constructed latent vectors and single indicators can only be meaningfully evaluated if the PLS model's construct validity is demonstrated. Therefore, the concept validity of the PLS model should be examined, including criterion validity, convergent validity and discriminant validity (Ringle *et al*., 2014; Hair *et al*., 2022; Henseler *et al*., 2015). Only when the model construct validity check meets predefined quality standards is a complete PLS analysis with 5000 or more bootstrap samples performed. The most critical conditions are that the model's overall quality is acceptable, as indicated by a Standardized Root Mean Squared Residual (SRMR) < 0.08, that the latent vectors demonstrate adequate reliability validity, as indicated by appropriate composite reliability > 0.8, rho $A > 0.8$, Cronbach alpha > 0.7, adequate convergence as indicated by an average variance extracted > 0.5 and high factor loadings, namely > 0.6 at $p < 0.001$, and adequate prediction performance. The latter may be evaluated using PLS_Predict and a tenfold cross-validation technique (Stoyanov & Maes, 2021; Ringle *et al*., 2014; Hair *et al*., 2022). Moreover, confirmatory tetrad analysis (CTA) should be conducted to confirm that the reflective models are not misspecified. Compositional invariance can be investigated using predicted-oriented segmentation analysis and measurement invariance assessment.

Furthermore, the produced latent vectors and indicators must have appropriate discriminant validity, which refers to how independent various latent components are different from one another. Discriminant validity assures that a construct is empirically unique and represents a reality that is not captured by other measures in the PLS model (Hair *et al*., 2022). Checking for discriminant validity is a way to assure that the model's latent vectors measure what they are supposed to measure (Henseler *et al*., 2015). Failure to disclose discriminant validity issues might lead to skewed structural parameter estimations and incorrect inferences regarding the associations between constructs. If the constructs do not have enough discriminant validity, they can be combined into a more generic construct that replaces the problematic constructs in the model, and researchers should re-evaluate the newly formed construct's discriminant validity with all opposing constructs.

The Fornell-Larcker criterion, cross-loadings and the Heterotrait-Monotrait (HTMT) ratio are three ways of determining discriminant validity (Henseler *et al*., 2015). The Fornell-Larcker criterion is used to assess the degree of shared variance between the model's latent variables by comparing a construct's AVE to its shared variance with other constructs, whereby its square root AVE (SRAVE) should exceed the correlations between the constructs. When each measured item has a poor association with every other construct except those to which it is conceptually related, discriminant validity is demonstrated (Gefen & Straub, 2005). A large correlation between items belonging to the same construct and a low correlation between items belonging to distinct constructs is necessary to demonstrate discriminant validity at the item level. Calculating cross-loadings, commonly known as 'item-level discriminant validity', is the second approach for evaluating discriminant validity. Each indicator loading should be bigger than all its cross-loadings, or the construct in question will be unable to distinguish between the construct it was designed to assess and another (Chin, 2010). Double-loaders (variables that load heavily on two different factors) are a sign of poor discrimination validity. The most accurate method for measuring discriminant validity is perhaps the HTMT ratio (Henseler *et al*., 2015) whereby an HTMT ratio >0.85 or >0.9 suggests a lack of discriminant ability (Kline, 2011; Teo, 2011).

Once the construct validity has been established, a full PLS path analysis can be performed using 5000 or more bootstrap samples, allowing for the computation of path coefficients with exact *p*-values, as well as specific indirect (or mediated), total indirect (mediated) and total (direct and indirect) effects, all of which are used to determine the significance of the (mediated) paths. As a result, PLS path modelling is an effective approach that allows the construction of novel models of a complex illness such as schizophrenia described by causal links between the causome, AOPs, cognitome, symptomatome and phenomenome (Maes *et al*., 2020c; Stoyanov & Maes, 2021). The PLS analyses we conducted on different Thai and Iraqi study samples showed that the classical concepts of negative symptoms and schizophrenia as a unitary disorder need revision.

Results

The labels 'negative and positive symptoms' are confusing

The current standard view of schizophrenia is that it is divided into positive and negative symptoms (Jablensky, 2010; Crow, 1980; NIHM, 2019; NHS, 2019). Negative symptoms like emotional flatness, avolition, alogia, and anhedonia, as well as positive symptoms like delusions, hallucinations, excitement, and disordered thinking (Andreasen, 1989), separate schizophrenia from other mental illnesses. The patient's loss of emotions (anhedonia), cognitive processes (logic thinking) and behaviours (social isolation) are classified as negative symptoms (Jablensky, 2010; Andreasen, 1989; Early Psychosis Intervention, 2022), whereas positive symptoms are assumed to be new and maladaptive mental processes and behaviours that did not exist before the onset of schizophrenia and have developed as symptoms of the illness (Maes & Anderson,

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2021; Jablensky, 2010; NIHM, 2019; NHS, 2019; Early Psychosis Intervention, 2022). Positive symptoms are changes in thoughts and feelings that are 'added on' to a person's experiences, whereas negative symptoms are 'losses' that are 'taken away' or diminished (e.g. lower motivation or reduced intensity of emotion) (e.g. paranoia or hearing voices) (Early Psychosis Intervention, 2022).

Initially, Maes et al. (Kanchanatawan *et al.*, 2018a, b, c; Noto *et al.*, 2016) distinguished between positive and negative symptoms using standard rating scales such as the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.*, 1987) and Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989) as this is the gold standard method when analysing schizophrenia data (Maes & Anderson, 2021). Nonetheless, Maes laboratories (Kanchanatawan *et al.*, 2018c) thought it would be fascinating to divide positive symptoms into their subdomains, such as psychosis (hallucinations and delusions), hostility, excitement and mannerism, just as they thought it would be fascinating to investigate the subdomains of negative symptoms, such as anhedonia, avolition and flattening. The central idea was that different symptoms may have distinct associations with biomarkers and molecular pathways. Consequently, we created composite scores expressing psychosis, hostility, excitation and mannerism (PHEM) based on all relevant z-transformed item scores of the PANSS and the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962), whilst the negative symptom categories of the SANS were deemed appropriate (Kanchanatawan *et al.*, 2018c). In addition, formal thought disorders (FTDs) and psychomotor retardation (PMR) were identified as two additional symptom domains that significantly contribute to schizophrenia symptomatology (Sirivichayakul *et al.*, 2019; Maes *et al.*, 2020a). FTD is marked by abnormalities in abstract and concrete cognition, including disorganised, illogical, and inadequate mental processes, as well as intrusions, fluid thought, and weakened connections (Sirivichayakul *et al.*, 2019). PMR is characterised by deficits in gross and fine motor function, sluggish motor responses, and slow movements (Maes *et al.*, 2019b, 2020a). The computed PMR score was based on the summed *z*-transformed PMR item scores (Maes *et al.*, 2019b, 2020a) from the PANSS, BPRS and the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Importantly, Cambridge Neuropsychological Test Automated Battery (CANTAB) assessments of the Motor Screening Task (MOT) (CANTAB, 2018), a psychomotor function index, externally confirmed this PMR score (Maes *et al.*, 2020a).

Nonetheless, a primary concern was that certain symptom domains, such as FTD and PMR, could not be properly classified as positive or negative. It is unclear, for instance, whether PMR is 'added on' to a person's normal motor behaviour (a new motor dimension) or should be considered a 'loss' (loss of movements). Similarly, the status of FTD is ambiguous: is it a novel thought process (the onset of formal cognitive disorders) or a loss of functions (loss of thought processes)? However, the same concerns can be asked regarding negative symptoms: are anhedonia and avolition, for example, really losses, or are they new 'sensations' added to human sentience experiences ('loss of feelings' is also a feeling)? And what about delusions? Do they add to the way people normally think or do they show a loss of normal human thought processes?

Schizophrenia and range restriction

A second issue is that researchers, including Maes' laboratories (Noto *et al.*, 2016), computed the associations between biomarkers and rating scale scores of positive and negative symptoms in schizophrenia study samples. Nevertheless, this study group is a restricted study sample of the population. Figure 1 (hypothetical data) shows the regression of severity of illness (the severity of the symptomatome or OSOS) on biomarker pathways (the APOs). This regression, for example, shows that around 63.6% of the variance in OSOS is explained by the severity of the AOPs when the regression is computed in controls (HC in this figure) and schizophrenia (SCZ in the figure) patients combined ($F = 44.79$, df = 2/51. $p < 0.001$). However, if this regression is calculated in the restricted study sample of patients only, the association has less impact accounting for only 29.9% of the variance ($F = 7.69$, df = 2/36, $p = 0.002$). Thus, when we restrict the range of OSOS (e.g. only patients are included), the correlation coefficient is reduced. Furthermore, if we narrow the range of OSOS even further (e.g. only patients with very high OSOS scores, SCZ2 in Fig. 1), the correlation may no longer be significant ($F = 0.23$, df = 2/18, $p = 0.796$). This is a normal phenomenon resulting from restricting the range of the data (Bland & Altman, 2011; Karsner, 2022).

By analogy, it is common practice to compute differences in the biomarkers and severity of the symptomatome between controls and patients and to compute associations between biomarkers and severity in the restricted group of patients (Maes & Anderson, 2021). In fact, this is both illogical and incorrect. Thus, the regression of severity of illness on biomarkers is computed in a restricted sample, but the regression of the biomarkers on the classification (principle of ANOVA for regression) is carried out without any range restriction. In the latter case, biomarkers are considered to be the dependent variable, whereas, in reality, biomarkers are the explanatory variables that predict the severity of illness (dependent variable) which, in turn, is used to categorise the subjects into diagnostic classes (Maes & Anderson, 2021). Thus, the diagnosis of schizophrenia is a *post hoc* man-made higher-order construct, which is the outcome variable but is frequently used incorrectly as an explanatory variable in analysis of variance or GLM analysis. It becomes even surreal when this outcome variable is employed as an explanatory variable whilst it shows very low reliability and validity, as reviewed previously (Maes & Anderson, 2021). As such, the majority, if not all, researchers use invalid higher-order constructs in incorrect statistical models (explanatory and dependent variables are switched) and use this category to range restrict when investigating covariations between features. Restricting sample variance artificially weakens existing correlations and generalisability and, consequently, correlation coefficients derived from an unrestricted sample should be corrected for range restriction using specific formulas to re-compute the actual correlation coefficient in an unrestricted sample (Karsner, 2022; Sackett & Yang, 2000). Examining these associations in schizophrenia models, we have repeatedly shown that PLS-POS, a method to disclose heterogeneity in PLS path models, did never retrieve the diagnosis as a source of heterogeneity or segmentation.

PHEMFP (PHEM, PMR, FTD) and negative symptoms do not show discriminant validity

Figure 2 illustrates an example of a PLS model in which the effects of biomarkers on negative symptoms and PHEMFP symptoms are investigated. Given that we discovered strong associations among the six PHEMFP symptom domains and the negative symptom domains of the SANS, we first investigated whether it was possible

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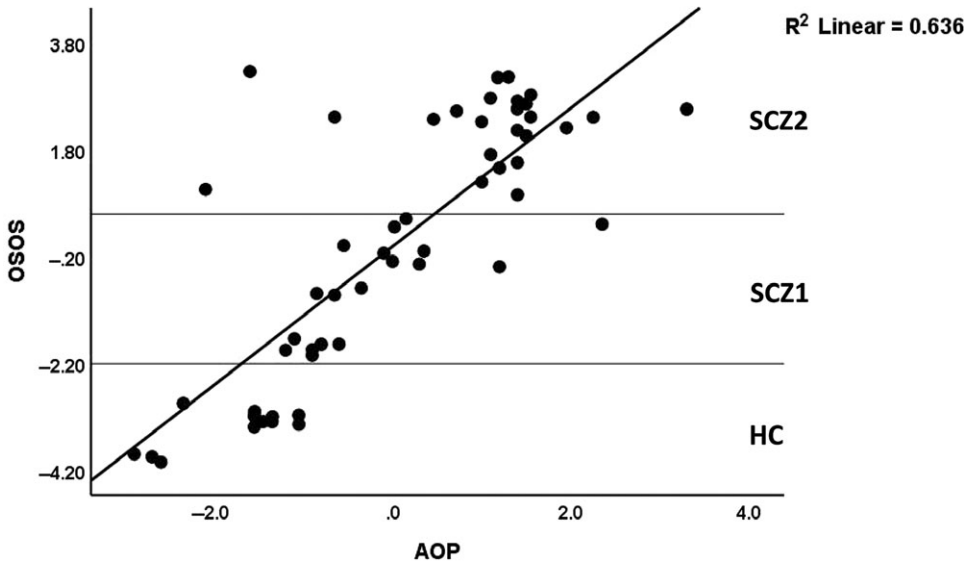

Fig. 1. Regression analysis in (range restricted) study samples including healthy controls (HC) and different schizophrenia (SCZ) endophenotype classes (SCZ1 and SCZ2).

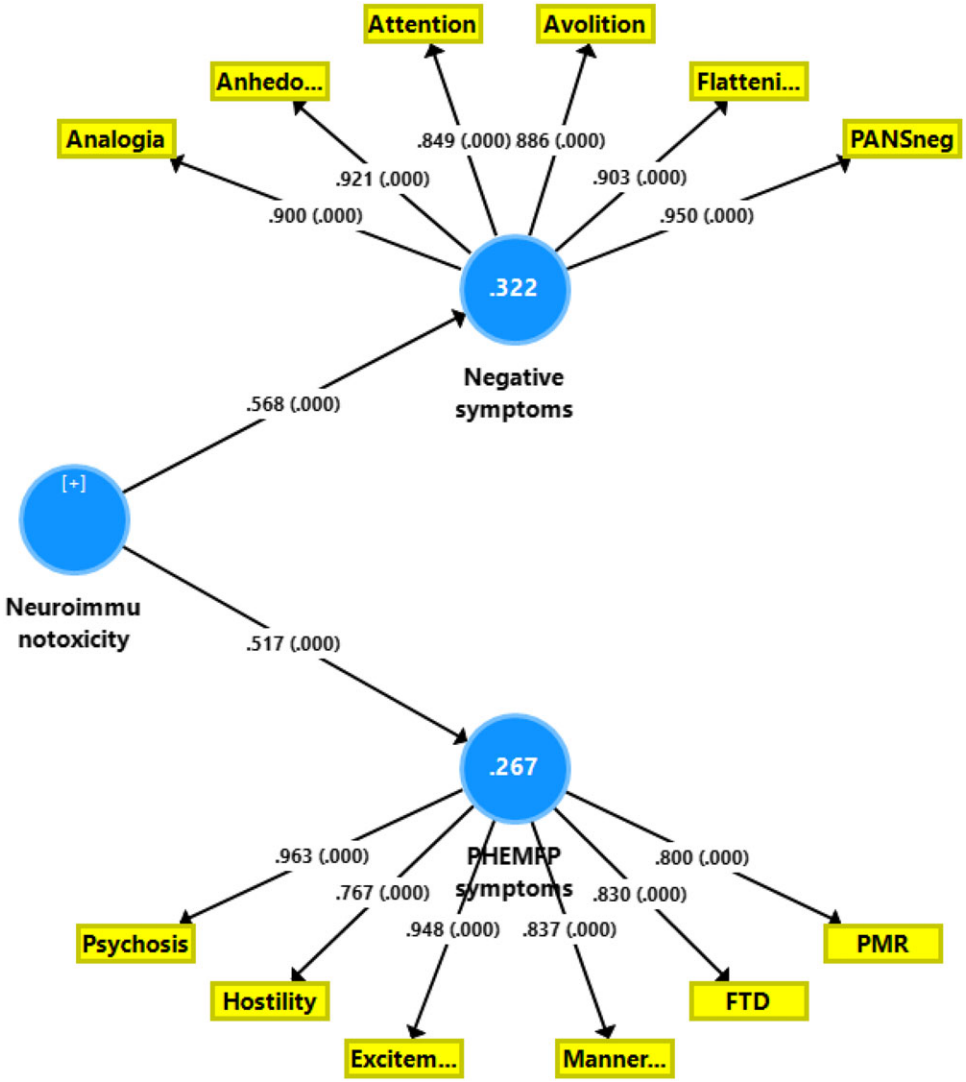

Fig. 2. Results of Partial Least Squares (PLS) analysis. The neuroimmunotoxic adverse outcome pathways predict two different latent vectors extracted from either negative symptom domains (analogia, anhedonia, avolition, attention, flattening and PANNS negative scale score) or PHEMFP (psychosis, hostility, excitation, mannerism, formal thought disorders (FTDs) and psychomotor retardation (PMR)). Shown are the loadings (with *p* values) of all indicators of the latent vectors and the path coefficients (with *p* values). Figures in the blue circles indicate explained variance. PANSneg: negative domain score of the Positive and Negative Syndrome Scale (PANNS).

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to derive reliable latent vectors from the PHEMFP and negative symptom domains. This model is based on the data presented in Maes *et al.* (2019a) and is, therefore, based on real data collected from schizophrenia patients and controls.

Firstly, the data demonstrate that we were able to extract a reliable vector with adequate construct validity that underpins the negative symptom domains because (a) the composite reliability (=0.963), rho *A* (=0.959) and Cronbach's alpha (=0.954) values are more than adequate, demonstrating accurate internal consistency or composite reliability; (b) the AVE value was 0.814 indicating sufficient convergent validity; (c) all loadings on the latent vector are significant and >0.849; and (d) CTA confirms that the vector is not misspecified as a reflective model. As a result, the six negative subdomains are manifestations of this latent vector known as the 'negative symptom domain'. In addition, the first latent vector extracted from the PHEMFP symptoms demonstrates (a) adequate composite reliability (=0.945), rho *A* (=0.946) and Cronbach's alpha (=0.929); (b) adequate convergence with AVE of 0.741 and significant loadings all greater than 0.767; and (c) CTA results confirming that this factor is not misspecified as a reflective model. Consequently, the PHEMFP symptom domains should also be viewed as manifestations of this latent single trait. In addition, PLS blindfolding revealed that the negative (0.253) and PHEMFP (0.187) latent vectors exhibit appropriate construct cross-validated redundancies, indicating that both constructs have predictive significance. Lastly, the model quality data are more than adequate, with SRMR = 0.041, whilst PLS predict demonstrates that the Q2 predict scores for all indicators are positive, indicating that they outperform the most naive benchmark and, therefore, that the model has significant predictive performance.

Based on this high-quality model data, we performed a complete PLS analysis using 5000 bootstrap samples to investigate the pathways from biomarkers to both positive and negative symptoms. To display a more parsimonious model, we entered the biomarkers as a single indicator, namely a *z* unit-based composite score computed as the sum of the z transformations of various cytokines + *z* chemokines + *z* oxidative stress biomarkers + *z* lipopolysaccharides + *z* leaky gut indicators + *z* BBB permeability indicators (Maes *et al.*, 2020b, c, 2021). The final PLS model reveals that the combined effects of neuroimmunotoxic pathways account for 32.2% of the variance in the domain of negative symptoms and 26.7% of the variance in the domain of PHEMFP.

Nonetheless, this model has significant flaws because both latent vectors lack discriminatory power. First, the Fornel-Larcker criterion (see Table 1) demonstrated that the SRAVE of the PHEMFP construct was less than its correlation with the negative symptom subdomain. Second, the cross-loadings (Table 2) demonstrate that all negative and PHEMFP domain scores have a high cross-loadings on both factors, and thus that all subdomains are double-loaders. All indicator loadings are indeed greater than their cross-loadings (except PMR), but all PHEMFP symptoms loaded highly on the negative latent vector (e.g. excitement loaded at 0.948 on the PHEM vector and 0.856 on the negative domain vector) and all negative subdomains loaded highly on the PHEMFP subdomain (e.g. avolition showed a loading of 0.886 on the negative vector and of 0.799 on the PHEMFP vector). Thirdly, the HTMT ratio between PHEMFP and the negative domain was 0.906, indicating a lack of discriminatory ability. We have rerun these tests of discriminant validity with the same six negative subdomains and the four PHEM subdomains (psychosis, hostility, excitation and mannerism). Similar results to those described in the preceding section indicate that these constructs lack sufficient discriminant validity with, for example, an HTMT ratio of 0.862. In such situations, it is recommended to reassign problematic indicators or combine problematic latent vectors. Since most of the indicators appear problematic, we looked into whether or not both vectors could be combined into a single overarching latent structure.

Table 1. Discriminant validity (Fornel-Larcker criterion) among features of schizophrenia, namely negative and PHEMFP (psychosis, hostility, excitation, mannerism, formal thought disorders and psychomotor retardation) symptom domains and neuroimmunotoxicity (NIT)

Features	NIT	Negative domains	PHEMFP domains
NIT	1.0		
Negative domains	0.568	0.902	
PHEMFP domains	0.517	0.871	0.861

Table 2. Discriminant validity (cross-loadings) among negative and PHEMFP (psychosis, hostility, excitation, mannerism, formal thought disorders and psychomotor retardation) symptom domains

Symptom domains	Negative latent vector	PHEMFP latent vector
Psychosis	0.781	0.963
Hostility	0.605	0.767
Excitation	0.856	0.948
Mannerism	0.674	0.837
Formal thought disorders	0.652	0.830
Psychomotor retardation	0.846	0.800
PANNS negative domain	0.950	0.864
Avolition (SANS)	0.886	0.799
Anhedonia (SANS)	0.921	0.806
Analogia (SANS)	0.900	0.780
Attention (SANS)	0.849	0.698
Flattening (SANS)	0.903	0.752

A common latent trait underpins all symptom domains

Figure 3 shows a new PLS model with the six negative and six PHEMFP subdomain scores combined. Surprisingly, one vector could be extracted from the 12 subdomains, and this factor showed adequate construct validity with accurate composite reliability (=0.969), rho *A* (=0.969), Cronbach's alpha (=0.964) and AVE (=0.723) values, and significant loadings (>0.707) that were all significant ($p < 0.001$). Furthermore, CTA confirmed that the vector is not misspecified as a reflective model, whilst blindfolding showed an appropriate cross-validated redundancy (0.408) indicating that this latent vector has good predictive relevance. As such, we concluded that negative and PHEM symptoms lack sufficient discriminatory power and probably do not constitute distinct constructs. All negative and PHEM(PF) subdomains are manifestations of the same common latent trait.

Almulla *et al.* (2021a) using a study sample consisting of Iraqi schizophrenia patients and controls, examined the factor structure

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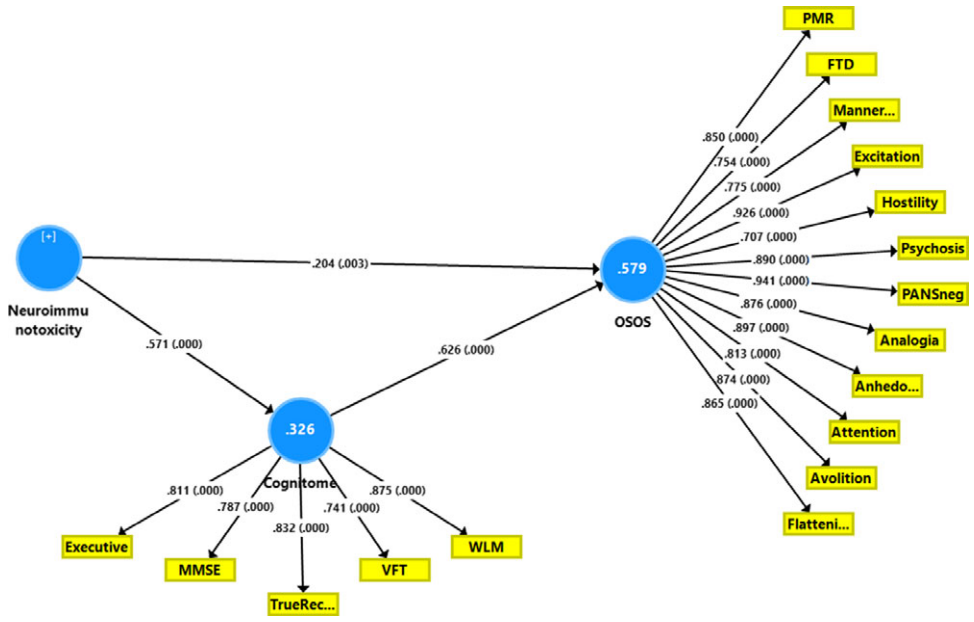

Fig. 3. Results of Partial Least Squares (PLS) analysis. The neuroimmunotoxic adverse outcome pathways and a latent vector extracted from cognitive test scores (dubbed the cognitome) predict a latent vector extracted from negative (analogia, anhedonia, avolition, attention, flattening and PANNS negative scale score) and PHEMFP (psychosis, hostility, excitation, mannerism, formal thought disorders (FTDs) and psychomotor retardation (PMR)) symptom domains. The cognitive test scores are as follows: Mini Mental State Examination (MMSE), executive functions tests, verbal fluency test (VFT), Word List Memory (WLM) and True Recall. Shown are the loadings (with *p* values) of all indicators on the latent vectors and the path coefficients (with *p* values). Figures in the blue circles indicate explained variance. P1: direct effects, P1 and P2 mediated (indirect) effects. PANSneg: negative domain score of the Positive and Negative Syndrome Scale (PANNS).

of the six PHEM symptoms, the total SANS score and the negative subscale of the PANNS using exploratory factor analysis (EFA) including dimensionality tests which allow estimating the number of factors to be retained including parallel analysis (optimal implementation), the Schwartz's Bayesian information criterion, and the Hull test (Almulla *et al.*, 2021a). Furthermore, these authors assessed closeness to unidimensionality utilising unidimensional congruence (UNICO), explained common variance (ECV) and mean of item residual absolute loadings (MIREAL), whereby the data should be treated as essentially unidimensional when UNICO > 0.95, ECV > 0.85 and MIREAL < 0.300. The EFA results indicated that all subdomains loaded highly on the first factor (all > 0.660), while the dimensionality tests showed that only one factor should be retained. The closeness to unidimensionality tests indicated that the PHEMFP and negative symptoms should be treated as essentially unidimensional. Moreover, model fit indices showed excellent model fit, good construct replicability, excellent performance across studies and good quality of the factor score estimates.

All in all, the above results of different studies (Maes *et al.*, 2020b; Almulla *et al.*, 2021a) show that a single latent trait, which is essentially unidimensional, underpins the six PHEMFP and negative symptoms of schizophrenia and, therefore, that the latent variable score of these subdomains may serve as a validated and reproducible index of OSOS (Maes *et al.*, 2019b; Almulla *et al.*, 2021a). Our results indicate that OSOS can be reflectively quantified using PHEMFP and negative subdomain scores, and that this reflective latent construct serves as the common denominator for the manifestations that are largely determined by OSOS. It follows that studies reporting on differential correlations between biomarkers and positive and negative symptoms are not very relevant, especially not when computed in the restricted study group of schizophrenia patients.

A bifactoral model

In our studies described above, we also performed PLS or EFA using the same variables in the restricted study group of schizophrenia patients (Maes *et al.*, 2019b; Almulla *et al.*, 2021a). These results showed again that one factor albeit less significant may be extracted from the PHEMPF subdomain and negative PANSS and SANS scores, indicating that even in a restricted study sample, the same latent trait could be established. These findings again show that selecting only schizophrenia to compute correlations between OSOS and biomarkers restricts the range, and thus may artificially weaken existing correlations, thereby hampering generalisability.

Nevertheless, we also analysed our data using bifactorial direct hierarchical EFA, which allows us to define a first generalised factor and additionally one or more single-group factors (SGFs) (Maes *et al.*, 2019b). A bifactor model differs considerably from classical factor analysis with rotated solutions, because a bifactor model method defines a general factor (GF) and subordinate or SGFs. The former is a broader factor which is the source of common variance running through all items in the EFA and the SGF reflects the coherency among a subgroup of items not accounted for by the GF. Maes *et al.* (2019b) detected that the PHEMFP and total SANS and PANSS negative symptom scores were best modelled by employing a bidimensional oblique solution consisting of (a) a GF reflecting OSOS; and (b) a SGF reflecting negative symptoms and PMR combined. Importantly, the same bifactorial exploratory solution with a GF reflecting OSOS and a SGF reflecting a subordinated factor of negative symptoms and PMR was detected in the restricted sample of schizophrenia patients. Moreover, the general and SGF scores were differentially associated with biomarkers pathways indicating that both constructs are mediated by different albeit partially overlapping pathways. This shows that it is also important to compute the associations between biomarkers, OSOS and putative SGFs in the restricted study group of schizophrenia patients.

Concluding remarks on the symptomatome

All in all, computing the associations between dependent symptomatome (e.g. OSOS and the SGF) and independent (causome, environmentome, AOPs, cognitome and connectome) variables in the unrestricted study group of controls and schizophrenia patients combined allows defining the covariation between those

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components all over the spectrum from controls to the schizophrenia spectrum including from mild to the most severe phenotypes. This approach should be complemented by the computation of the regression between the features in the restricted sample of schizophrenia patients to delineate schizophrenia-specific covariations among those variables.

Our findings that a unidimensional or bifactorial model is the best way to explain the symptomatome of schizophrenia contradicts the conventional gold standard, which holds that a two-dimensional construct consisting of positive and negative symptoms is the gold standard. Figure 4 shows the covariation between OSOS and AOPs all over the spectrum from controls to schizophrenia patients and the more severe phenotypes as well as the association between the SGF and AOPs which together shape a distinct more severe phenotype characterised by increased OSOS and SGF scores and more severe AOPs (see below).

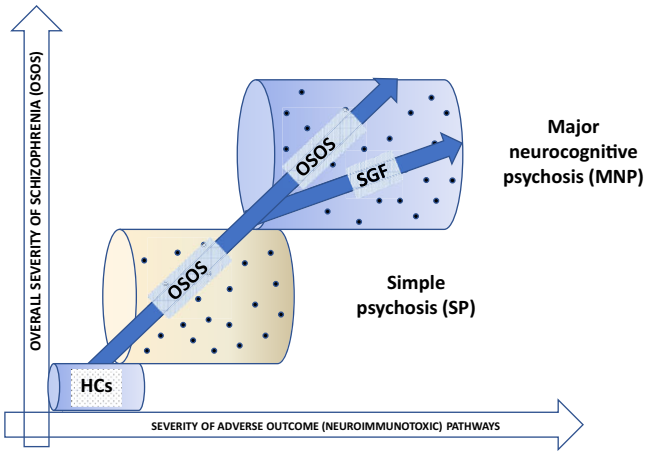

Fig. 4. Position of patients belonging to qualitatively distinct schizophrenia endophenotype classes in a spectrum of increasing adverse outcome pathways and overall severity of schizophrenia from healthy controls (HCs) to simple neurocognitive psychosis (SNP) and the more severe endophenotype class MNP. SGF: single-group factor consisting of negative symptom and psychomotor retardation. Adapted from Maes *et al.* (2019b).

The G-CoDe

We and others have previously discussed how deficits in executive functions, learning and working memory, as well as semantic and episodic memory, can result in the formation and recall of false memories and thus may partially explain FTDs, disorganised thought processes, paranoia, and other schizophrenia symptoms (Maes & Kanchanatawan, 2021; Keefe & Harvey, 2012; Orellana & Slachevsky, 2013; Corlett *et al.*, 2007). Cognitive impairments that reflect central neurocircuitry dysfunctions frequently precede the onset of acute psychotic episodes, suggesting that cognitive abnormalities contribute to the schizophrenia symptomatology (Maes & Kanchanatawan, 2021; Keefe & Harvey, 2012). For ultra-high-risk individuals, verbal memory deficits and attentional deficits, for example, are predictive of psychotic symptoms (Brewer *et al.*, 2005; Hawkins *et al.*, 2004).

Given that cognitive impairments may precede and explain at least a part of the schizophrenia symptomatology, we have incorporated cognitive impairments into our PLS models as shown in Fig. 3 and allowed cognitive impairments to predict the symptomatome and AOPs to predict cognitive deficits and the symptomatome. As a result, a mediation model is developed in which cognitive deficits fully or partially mediate the effects of AOPs on the symptomatome. In our initial attempts to investigate such mediated effects, we separately analysed cognitive disorders as measured by different probes of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Fillenbaum *et al.*, 2008) and the CANTAB (2018).

Nevertheless, when examining the highly significant intercorrelations and cross-loadings between the cognitive test scores of CERAD and CANTAB, we combined different executive CANTAB test scores (spatial working memory, one-touch stockings of Cambridge and intra-extra dimensional set-shift) with the CERAD tests' scores (verbal fluency, word list memory, recall and the Mini-Mental State Examination (MMSE) scores) in factor analyses. Figure 3 demonstrates that we were able to extract one latent vector from those multiple cognitive test scores that showed adequate psychometric properties, namely: (a) adequate internal consistency with composite reliability of 0.905, rho *A* of 0.875 and Cronbach's alpha of 0.869; (b) adequate convergent validity with AVE = 0.657 and all loadings on the latent vector are >0.741 at $p < 0.001$; (c) adequate construct cross-validated redundancy of 0.207; and (d) confirmation that the vector is not misspecified as a reflective model. Impairments in semantic and episodic memory, recall, MMSE, and executive functions are thus all manifestations of a single trait that is the cause of these cognitive dysfunctions. As a result, we coined this latent cognitive vector 'generalized decline' (G-CoDe), because the severity scores indicate gradual and more generalised deterioration of cognitive functions (Maes & Kanchanatawan, 2021). Importantly, those neurocognitive deficits in schizophrenia reflect dysfunctions in brain circuits, including 'the prefronto-parietal, prefronto-temporal, prefronto-striato-thalamic, and dorsolateral prefrontal cortex, amygdala, and hippocampus' (Maes & Kanchanatawan, 2021; Orellana & Slachevsky, 2013).

Figure 3 depicts the final PLS model, which has more than adequate model quality, with an SRMR of 0.043. We found that 57.9% of the variance in the symptomatome was explained by the regression on the G-CoDe and the AOPs, while 32.6% of the variance in the cognitome was explained by the regression on the AOPs. This PLS graph depicts the path coefficients (with exact *p*-value) of the causal relationships between the various indicators. This figure also displays the direct effects of AOPs on the symptomatome (P1), the indirect (or mediated) effects of AOPs on the symptomatome through the cognitome (P2. P3) and the total effect, namely P1 + (P2. P3). Significant specific indirect effects ($t = 5.70$, $p < 0.001$) of the AOPs on the symptomatome were mediated by the cognitome, which serves as a successful partial mediator (partly because there are also direct effects of the AOPs on the symptomatome). The total effects of the AOPs on OSOS are highly significant ($t = 8.55$, $p < 0.001$). As a result, a simple mediator model is constructed, indicating that the AOPs have both direct and indirect (or mediating) effects on the symptomatome. This is an example of complementary mediation in which the direct and indirect effects are complementary because they are both significant and point in the same direction. In addition, this is a distal-mediated model because the path from the cognitome to the symptomatome is greater than the path from the AOPs to the cognitome.

Importantly, such results demonstrate that neuroimmunotoxic AOPs cause aberrations in prefronto-parietal, prefronto-temporal, prefronto-striato-thalamic, and dorsolateral prefrontal cortical, amygdaloid, and hippocampal circuits, and that these circuits partially determine OSOS. In addition, the direct effects of AOPs on

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the symptomatome demonstrate that other pathways unrelated to the cognitome are also involved in the AOPs' effects on OSOS. It should be emphasised that the Fornell-Larcker criterion revealed that the cognitome and OSOS have sufficient discriminant validity, although the HTMT was 0.850, indicating that discriminant validity may not be achieved. Nonetheless, the cross-loadings showed that each cognitome indicator loaded highly on OSOS and that each of the 12 OSOS indicators loaded highly on the cognitome factor. Therefore, we deemed it essential to determine whether a single latent trait could be extracted from the 5 cognitome and 12 OSOS domains.

Figure 5 demonstrates that one latent trait could be extracted from these 17 indicators with sufficient construct validity (all loadings > 0.610 at $p < 0.001$, AVE = 0.632, composite reliability = 0.966, rho_A = 0.967 and Cronbach's alpha = 0.962, construct cross-validated redundancy = 0.215). In addition, CTA demonstrated that this construct was not incorrectly specified as a reflective model. This demonstrates that a single common core underlies the cognitive deficits, PHEMFP and negative symptoms of schizophrenia, indicating that objective neurocognitive deficits and the symptomatome are strongly intertwined indicators of the core of schizophrenia. Since the neurocognitive impairments measured in schizophrenia reflect aberrations in cortico-amygdala-hippocampal circuits, it follows that also OSOS is largely mediated by dysfunctions in these circuits. Moreover, PLS path analysis revealed that the regression on the AOPs explained 35.8% of the variance in this common core. Inferentially, the neuroimmunotoxic AOPs contribute to aberrations in the cortico-thalamo-hippocampal circuits leading to the cognitome and OSOS, whereby the pathway from AOPs to cognitome and OSOS is a key component of schizophrenia.

The new endophenotype class MNP

Construction of MNP, a new endophenotype class

The results of the aforementioned PLS analyses are crucial for understanding the phenome of the newly discovered endophenotype classes of schizophrenia, namely 'Major Neurocognitive Psychosis' and 'Simple Psychosis' (SP) (Kanchanatawan *et al.*, 2018a; Almulla *et al.*, 2021a; Al-Hakeim *et al.*, 2020b). Using unsupervised learning (cluster analysis) on Thai and Iraqi study groups with clinical, cognitive and AOP data as input variables, a two-cluster solution was discovered with the separation of stable-phase schizophrenia into two clinically and biologically meaningful clusters (Kanchanatawan *et al.*, 2018a).

Using conventional statistical tests, we determined that MNP is distinguished from SP and healthy controls not only by increased negative and PHEMFP subdomain scores but also by increased affective symptoms, more cognitive deficits and aberrations in a multitude of AOPs (Kanchanatawan *et al.*, 2018c; Almulla *et al.*, 2021b; Al-Hakeim *et al.*, 2020a). In addition, MNP is accompanied by highly specific abnormalities in protective AOPs (dubbed the 'protectome') including natural IgM-mediated autoimmune responses, antioxidant gene variants and diminished antioxidant defences, which are absent in SP and thus are distinguishing features of MNP (Maes *et al.*, 2019a). Therefore, MNP is a clinically and biologically distinct group that can be differentiated from SP (see below). Furthermore, using a specific supervised learning technique that allows for the examination of whether a class is qualitatively distinct, namely soft independent modelling of class analogy (SIMCA), we were able to confirm that MNP is qualitatively distinct from SP based on negative, PHEMFP and neurocognitive scores and AOPs as well (Kanchanatawan *et al.*, 2018a; Almulla *et al.*, 2021a; Al-Hakeim *et al.*, 2020b), indicating that MNP is validated as a distinct phenotype in the schizophrenia spectrum. Figure 4 depicts the position of MNP versus SP patients in the schizophrenia spectrum.

Intriguingly, the machine learning-derived cluster MNP resembles Kraepelin's dementia praecox and Snezhnevsky's deficit model because this phenotype is characterised by a 'defect' or deficit (which we have quantified by the G-CoDe and negative symptom scores) coexisting with 'productive' or 'florid' symptoms (which we have quantified by PHEMFP scores). The MNP phenotype is also reminiscent of the case definition of Eugen Bleuler and Snezhnevsky who both conceptualised 'schizophrenia' as a psycho-organic disorder (which we have delineated as a neurological disease caused by neuroimmunotoxicity) characterised by primary symptoms (which we have quantified by computing the negative symptom and G-CoDe scores) and accessory symptoms (which we have quantified as psychotic domain scores), such as hallucinations and delusions. Even so, the classification of MNP and SP based on machine learning does not match Crow's theory. This is because our machine learning shows that positive (Type I) or negative ('Type II') symptoms belong to a common core called OSOS and cannot be regarded as separate entities.

MNP and deficit schizophrenia

MNP versus deficit schizophrenia

Deficit schizophrenia was conceptualised by Kirkpatrick *et al.* (2000, 2001) as a subtype of schizophrenia defined by persistent 'primary' negative symptoms. The diagnostic criteria required the presence of schizophrenia and at least two negative symptoms from a list of six (restricted affect, diminished emotional range, sense of purpose and social drive, poverty of speech, and repression of interests) during clinically stable periods within the previous year. In addition, the negative symptoms must be idiopathic and unrelated to other conditions such as anxiety, depression, drug effects, suspicion, mental retardation or psychotic symptoms.

The distinct category of MNP has a very ambiguous relationship with 'deficit schizophrenia'. On the one hand, we derived the model of MNP using the diagnostic criteria of deficit schizophrenia, with which it exhibits a substantial overlap (Kanchanatawan *et al.*, 2018a, b), but on the other hand, the machine learning model of MNP differs significantly from the clinical concept of deficit schizophrenia. While the diagnostic criteria of deficit schizophrenia are solely based on negative symptoms, MNP is characterised by more pronounced PHEMFP symptoms, OSOS and SGF, the G-CoDe, and more severe neuroimmunotoxic and neuro-oxidative pathways as compared with SP (see below, section 'A full description of all MNP features') (Kanchanatawan *et al.*, 2018a; Maes *et al.*, 2019b; Almulla *et al.*, 2021a; Al-Hakeim *et al.*, 2020a). Moreover, there are significant issues with the diagnosis of deficit schizophrenia as reviewed in the next section.

Major concerns with Kirkpatrick's deficit schizophrenia

First, previous reports have concluded that it may be more accurate to view negative symptoms and thus deficit schizophrenia as a dimension rather than a separate disease (Roy & DeVriendt, 1994). Additionally, negative and positive dimensions may coexist in the same individual, and there is also disagreement regarding whether negative symptoms intensify from a healthy state to

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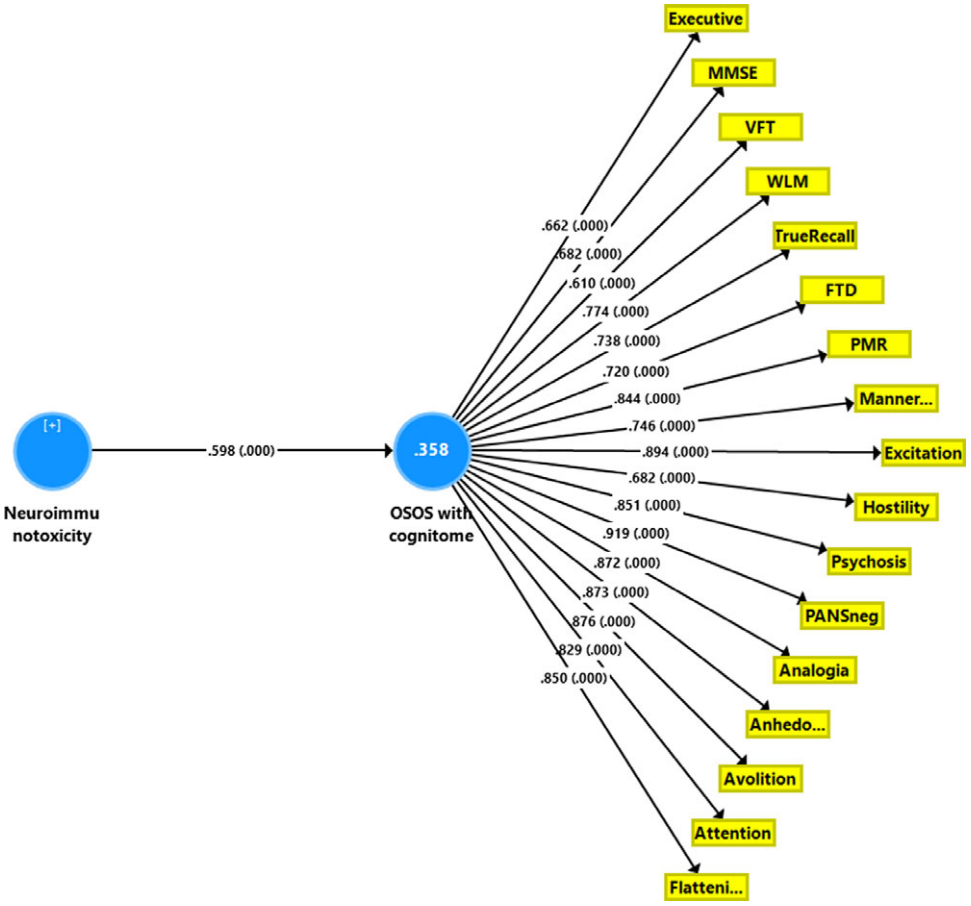

Fig. 5. Results of Partial Least Squares (PLS) analysis. The neuroimmunotoxic adverse outcome pathways predict a latent vector extracted from cognitive test scores (Mini Mental State Examination (MMSE), executive functions tests, verbal fluency test (VFT), Word List Memory (WLM) and True Recall), negative symptom domains (analogia, anhedonia, avolition, attention, flattening and PANNS negative scale score) and PHEMFP symptom domains (psychosis, hostility, excitation, mannerism, formal thought disorders (FTDs) and psychomotor retardation (PMR)). Shown are the loadings (with *p* values) of all indicators of the latent vector and the path coefficient (with *p* values). Figures in the blue circles indicate explained variance. PANSneg: negative domain score of the Positive and Negative Syndrome Scale (PANNS).

schizophrenia with a 'fully formed illness' (dimensional theory) or whether type II or deficit schizophrenia is a distinct nosological category (categorical theory) (Kanchanatawan *et al.*, 2018b; Takahashi, 2013).

Second, as described in the previous sections, negative and PHEMFP symptoms not only coexist and covary during the stable phase of schizophrenia but also share a common core that underlies those subdomains. Furthermore, in the stable phase of schizophrenia, negative and PHEMFP symptoms correlate strongly with anxiety and depression to the extent that they all appear to belong to the same latent construct (Almulla *et al.*, 2021b). All of these symptom domains are, therefore, strongly interconnected manifestations of the illness's symptomatome core, indicating that negative symptoms are not the result of psychosis, depression or anxiety, but rather are manifestations of the single-trait OSOS. Moreover, as indicated by our PLS models, neuroimmunotoxic AOPs explain a large part of the variance in the cognitome and OSOS, as well as the strong covariation between these strongly related components, despite their distinct presentation. Inference shows that negative symptoms should be thought of as a sign of OSOS that is partially determined by AOPs.

Third, Kirkpatrick's exclusion criteria that negative symptoms may not be caused by depression, anxiety or psychotic symptoms are nonetheless remarkable. How could one decide whether the negative symptoms which occur in schizophrenia are idiopathic and not the consequence (or cause for that matter) of psychosis, depression or anxiety, which are other features of schizophrenia? Excluding features of an illness to define that interrelated features of the same illness are idiopathic is at least a subjective method. Such subjective criteria have no place in the precision psychiatry approach.

Fourth, both 'schizophrenia' and 'deficit' are utterly stigmatising labels and the label 'deficit schizophrenia' does not even describe the disease's AOP, neurocognitive and symptomatome features (Kanchanatawan *et al.*, 2018a). Additionally, our machine learning-derived model is conceptually quite different from the clinical case definition of deficit schizophrenia and, therefore, we labelled the new endophenotype class MNP (Kanchanatawan *et al.*, 2018a). In fact, the 'neurocognitive psychosis' label describes the results of our machine learning results that both negative and PHEMFP symptoms are psychotic symptoms that to a large extent are explained by neuroimmune aberrations and cognitive impairments, while the label 'major' is used to denote that MNP is the full-fledged, qualitatively distinct phenotype as opposed to SP, which is a less severe phenotype.

A full description of all MNP features

Biomarkers of MNP

Table 3 shows the biomarker, clinical, cognitive and phenomenome features of MNP versus SP and controls as determined in our studies. First, MNP is characterised by significantly activated neuroimmunotoxic pathways including neurotoxic cytokines particularly tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6/IL-23/Thelper (Th)-17 signalling, and neurotoxic chemokines (particularly eotaxin), increased oxidative damage to proteins and lipids, damage to paracellular pathways including tight

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Table 3. Key features of major neurocognitive psychosis (MNP) versus simple psychosis (SP) and healthy controls

Neuroimmune and neuro-oxidative stress features of MNP	MNP	Comparisons
Tumour necrosis factor (TNF)-α	↑↑↑	SP and HC
Soluble TNF receptors	↑	HC
Interleukin (IL)-1β and soluble IL-1 receptor antagonist	↑	HC
IL-6/IL-23/Th-17 axis	↑↑↑	HC
CCL2 and CCL-11 or eotaxin	↑↑	SP and HC
IgA responses to noxious TRYCATs	↑↑	SP and HC
Damage to the paracellular pathways and tight and adherens junctions	↑↑	SP and HC
IgA to Gram negative bacteria (K pneumoniae and H. Alvei)	↑	SP and HC
Indicants of breakdown of the blood-brain-barrier	↑↑	SP and HC
Neuroimmunotoxicity	↑↑↑	SP and HC
Malondialdehyde	↑	SP + HC
Advanced oxidation protein products	↑↑	SP and HC
Sulfhydryl groups	↓↓	SP and HC
Total radical antioxidant trapping parameter (of plasma)	↓↓	SP + HC
Paraoxonase 1 (PON1) activity	↓↓↓	SP and HC
Q192R PON1QQ genotype and Q allele	↑↑	SP and HC
Ratio oxidative toxicity/antioxidant defences	↑↑↑	SP and HC
IgM responses to noxious TRYCATs	↓↓↓	SP and HC
IgM responses to oxidatively modified epitopes	↓↓↓	SP and HC
Ratio MITOTOX/PRORES (antioxidant + innate immune protection)	↑↑↑	SP and HC
Cognitive features of MNP (cognitive test results)		
Verbal fluency test	↓↓	SP and HC
Delayed memory savings	↓	SP
Word list memory	↓↓	SP and HC
Word recognition (correct)	↓↓	SP and HC
True Recall	↓↓	SP and HC
False recall	↑	SP and HC
Word recognition	↓↓	SP and HC
Episodic memory	↓↓↓↓	SP and HC
Paired association learning	↓↓	SP and HC
Rapid visual information processing	↓↓	SP and HC
Spatial working memory, strategy use	↓↓	HC
One-touch stockings of Cambridge	↓↓	HC
Emotional Recognition Test	↓↓	PS and HC
Executive functions	↓↓↓	SP and HC
Intra/extradimensional set shifting	↓↓	HC
Mini Mental State Examination	↓↓	SP and HC
Generalised cognitive decline (G-CoDe)	↓↓↓	SP and HC
Symptomatic features of MNP		
Hallucinations – delusions	↑↑↑	SP and HC
Excitation	↑↑↑	SP and HC
Hostility	↑↑↑	SP and HC
Mannerism	↑↑↑	SP and HC
Psychomotor retardation	↑↑↑	SP and HC
Formal thought disorders	↑↑↑	SP and HC
Analogia	↑↑↑	SP and HC
Anhedonia	↑↑↑	SP and HC
Avolition	↑↑↑	SP and HC
Flattening and blunted affect	↑↑↑	SP and HC
Poor rapport	↑↑↑	SP and HC
Passive/apathetic social withdrawal	↑↑↑	SP and HC
Depression	↑↑	SP and HC
Anxiety	↑↑	SP and HC
Physiosomatic symptoms	↑	HC
Chronic fatigue	↑↑	HC
Overall severity of schizophrenia (OSOS)	↑↑↑	SP and HC
Other features of MNP		
Health-Related Quality of life (HR-QoL), physical domain	↓↓	SP and HC
HR-QoL, psychological domain	↓↓	SP and HC
HR-QoL, social domain	↓↓	SP and HC
HR-QoL, environmental domain	↓↓	SP and HC
Overall HR-QoL	↓↓↓	SP and HC
Problems with usual activities	↑↑	SP and HC
Self-care problems	↑	HC
Worsening index (based on cognitive deficits + symptoms + HR-QoL)	↑↑↑	SP and HC

MITOTOX/PRORES: ratio of multiple immune and oxidative toxicities (MITOTOX) on protective resilience against neuroimmune, neuro-oxidative and bacterial stress (PRORES).
MITOTOX is computed as a *z* unit-based composite score based on key oxidative stress biomarkers + key cytokines + IgA to tryptophan catabolites + lipopolysaccharides. PRORES is computed as a *z* unit-based composite score based on paraoxonase 1 activity + sulfhydryl groups + total radical antioxidant trapping parameter + IgM directed to oxidative-specific epitopes.

and adherens junctions with increased translocation of Gram-negative bacteria and, therefore, increased lipopolysaccharides (LPS) load, and breakdown of the blood–brain barrier (Maes & Anderson, 2021; Kanchanatawan *et al.*, 2018a, b, c; Al-Hakeim *et al.*, 2020a, b; Sirivichayakul *et al.*, 2019; Maes *et al.*, 2019a, 2020a, b, c, 2021). In addition, MNP is characterised by diminished antioxidant defences, particularly diminished sufhydryl (-SH) groups and paraoxonase1 (PON1) activity, which results in a highly substantial rise in the oxidative stress toxicity/antioxidant ratio (Maes *et al.*, 2020b). Significantly, MNP is associated with changed frequencies of the Q192R PON 1 genotope, with a higher frequency of the QQ genotype and Q allele in MNP compared to

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SP and controls (Maes *et al.*, 2020b). PLS analysis demonstrates that the QQ genotype increases MNP risk via mediated effects on PON1 activity. In addition, MNP is distinguished by diminished IgM responses to a number of oxidation-specific epitopes, such as malondialdehyde, azelaic acid, and TRYCAT-adducts (Maes *et al.*, 2019a). These results demonstrate that MNP, but not SP, is associated with a malfunction in IgM production by B1 cells, which is an essential component of the innate immune system that protects against microbial infections, oxidative stress, and inflammation and strives to preserve homoeostasis (Maes *et al.*, 2019a). Computing the ratio of the multiple immune and oxidative toxicities (MITOTOX, namely neuroimmune + neuro-oxidative + bacterial translocation + damage to the paracellular pathway + increased neurotoxic levels) on the protective resilience biomarkers (PRORES, namely antioxidant levels and IgM-mediated natural immunity) reveals that an increased MITOTOX/PRORES ratio is a defining feature of MNP (Maes *et al.*, 2019a, 2020b).

Neurocognitive features of MNP

Second, MNP is characterised by multiple dysfunctions in neurocognitive functions including verbal fluency, word list memory, recognition and delayed recall, delayed memory savings, visual sustained attention, attentional set-shifting, spatial planning, strategy use, rule acquisition, emotional recognition, and a more generalised impairment as measured with the MMSE (Maes & Anderson, 2021; Maes & Kanchanatawan, 2021; Kanchanatawan *et al.*, 2018a, b; Maes *et al.*, 2020a, b, 2021; Sirivichayakul *et al.*, 2019; Almulla *et al.*, 2021b). This suggests that MNP is associated with a generalised deficit in the major cognitive domains of perception, recognition, attention, learning, semantic and episodic memory, decision-making, thought consciousness, and sensory input. In contrast to SP, MNP is accompanied by neurocognitive deficits that are more severe than those observed in mild cognitive impairment but significantly less severe than in Alzheimer's disease (Kanchanatawan *et al.*, 2018d). Consequently, the findings of our studies support earlier theories that schizophrenia is characterised by a generalised 'defect' or 'scar' that previously was mistakenly referred to as 'dementia' (Jablensky, 2000; EBO, 2022; Decker, 2007; Berrios, 2011; Moskowitz & Heim, 2011). Moreover, there is now evidence that the neuroanatomical basis of such neurocognitive impairments may be ascribed to dysfunctions in neuronal circuits including 'prefronto-striato-thalamic, prefronto-temporal, prefronto-parietal, amygdala and hippocampal circuits' (Maes & Kanchanatawan, 2021; Orellana & Slachevsky, 2013).

Moreover, as explained above a common factor, the G-CoDe, may be extracted from these multiple cognitive functions and a large part in its variance is explained by the oxidative toxicity/antioxidant and MITOTOX/PRORES ratios. Since the decreased antioxidant and innate immune system protection and increased neuroimmunotoxic and neuro-oxidative toxicity in MNP are major predictors of the G-CoDe (Maes & Kanchanatawan, 2021; Maes *et al.*, 2021), it is obvious that these neurotoxic pathways have affected the function of the neuroanatomical circuits underpinning the G-CoDe.

The symptomatome of MNP

Third, as reviewed above and shown in Table 3, diverse negative symptom domains (including blunting, alogia, avolition and anhedonia), PHEMFP symptoms as well as depressive and anxiety symptoms and the latent vector extracted from these symptoms scores (OSOS) are significantly greater in MNP than in SP and in controls (Maes & Anderson, 2021; Maes *et al.*, 2020c, 2021; Kanchanatawan *et al.*, 2018c; Almulla *et al.*, 2021b; Sirivichayakul *et al.*, 2019). Since increasing G-CODE can lead to false memories and recall, FTD and paranoia and frequently precedes the onset of acute psychotic episodes, it is safe to conclude that the severity of cognitive impairments contributes to the symptomatology on MNP.

Furthermore, we were able to extract one latent vector from the cognitive test results and the symptom domains (Maes *et al.*, 2021; Almulla *et al.*, 2021a), demonstrating that both domains are driven by a common core and, thus, that a shared substrate is the root cause of all cognitive and symptom manifestations established in MNP. Therefore, the same neuronal circuits that underpin the cognitome (namely prefronto-striato-thalamic, prefronto-temporal, prefronto-parietal, amygdala and hippocampal circuits) also underpin at least in part MNP.

Health-Related Quality of Life in MNP

Fourth, when compared to SP patients and controls, MNP patients have significantly lower scores on four different domains of HR-QoL, including physical, psychological, social and environmental scores, as well as on the overall decline in HR-QoL (Maes *et al.*, 2021; Kanchanatawan *et al.*, 2018a; Al-Musawi *et al.*, 2022). Furthermore, MNP patients have more difficulties with daily activities than SP patients and controls, as well as more difficulties with self-care than normal controls (Kanchanatawan *et al.*, 2018a). In various studies, we discovered that neuroimmunotoxic pathways (e.g. neurotoxic TRYCATs and the IL-6/IL-23/Th-17 axis) were strongly associated with lower HR-QoL, and that these effects were mediated via the AOPs, the cognitome and symptomatome (Al-Musawi *et al.*, 2022).

Most importantly, by extracting a latent vector from OSOS (based on all symptom domains), G-CoDe (based on all neurocognitive test scores) and HR-QoL (based on all four domains), we were able to compute a new comprehensive index reflecting 'behavioral-cognitive-physical-psychosocial' (BCPS) worsening (Maes *et al.*, 2020c, 2021). This BCPS-worsening index is much higher in MNP than in SP and is, therefore, another hallmark that MNP is a qualitatively distinct class. Interestingly, in first-episode schizophrenia (FES), the BCPS-worsening index is explained to a large extent by increased breakdown of the paracellular and vascular pathways, bacterial load, complement system alterations (namely increased IgA to circulating C1q immune complexes) and lowered PON1 activity (Maes *et al.*, 2021), whereas in multiple-episode schizophrenia (MES), the BCPS-worsening score is largely predicted by increased TNF-α, oxidative toxicty and number of psychotic episodes. According to our results, patients with MES and FES with very high BCPS-worsening indices also experience MNP. This demonstrates that MNP can be present from the first psychotic episode or develop because of the cumulative effects of multiple episodes and that different neurotoxic pathways may contribute to its development.

While there is some evidence that the AOPs, cognitome, symptomatome, HR-QoL and BCPS-worsening features may be considered to be on a continuum from controls to SP to MNP, as shown in Fig. 4, these features may group together to form a new class with increasing severity of the pathways, G-CoDe, OSOS, HR-QoL and the BCPS-worsening index (Kanchanatawan *et al.*, 2018a, b). As a result, quantitative differences may become qualitative, forming

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the new endophenotype class MNP. Furthermore, as shown in Table 3, some of the pathways and biomarkers, particularly those related to resilience and the protectome, differ qualitatively between MNP and SP/controls, namely (a) decreased IgM responses to oxidative-specific epitopes and TRYCAT adducts are a feature of MNP, whereas there is a trend towards increased IgM levels in SP; (b) PON1 activity is significantly reduced in MNP but not in SP; and (c) the QQ genotype is associated with MNP but not SP. These qualitative differences in the protectome coupled with increasing BCPS-worsening shape MNP as a discrete endophenotype class that is qualitatively different from SP as assessed by machine learning techniques like SIMCA (Kanchanatawan *et al*., 2018a, b).

As a consequence, failure to use these new endophenotype classes (MNP and SP) may result in false-positive outcomes (a pathway specific to only one phenotype is generalised to schizophrenia) and false-negative outcomes (existing phenotype-specific pathways for MNO or SP are not detected at all) (Maes & Anderson, 2021). One wonders how many erroneous results in schizophrenia research, including genetic research, have been published because the MNP and SP endophenotype classes were not taken into account. Future research should always include MNP and SP as key endophenotype classes, and clinicians should use these labels instead of schizophrenia because they are less stigmatising. Moreover, future research should enlarge our MNP and SP models with additional pan-omics data as well as brainome data including structural and functional (connectome) brain neuroimaging assessments in order to improve the diagnosis of MNP and SP (Stoyanov, 2020; Stoyanov *et al*., 2021).

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Ethics approval and consent to participate. The PLS analyses performed in this paper are based on previously published data. Approval was obtained from the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (No 298/57). All participants, as well as the guardians of patients (parents or other close family members), provided written informed consent to take part in the study.

References

Al-Hakeim HK, Almulla AF, Al-Dujaili AH and Maes M (2020a) Construction of a neuro-immune-cognitive pathway-phenotype underpinning the phenome of deficit schizophrenia. *Current Topics in Medicinal Chemistry* **20**(9), 747–758. doi: 10.2174/1568026620666200128143948.

Al-Hakeim HK, Almulla AF and Maes M (2020b) The neuroimmune and neurotoxic fingerprint of major neurocognitive psychosis or deficit schizophrenia: a supervised machine learning study. *Neurotoxicity Research* **37**(3), 753–771. doi: 10.1007/s12640-019-00112-z.

Almulla AF, Al-Hakeim HK and Maes M (2021a) Schizophrenia phenomenology revisited: positive and negative symptoms are strongly related reflective manifestations of an underlying single trait indicating overall severity of schizophrenia. *CNS Spectrums* **26**(4), 368–377. doi: 10.1017/S1092852920001182.

Almulla AF, Al-Rawi KF, Maes M and Al-Hakeim HK (2021b) In schizophrenia, immune-inflammatory pathways are strongly associated with depressive and anxiety symptoms, which are part of a latent trait which comprises neurocognitive impairments and schizophrenia symptoms. *Journal of Affective Disorders* **287**, 316–326. doi: 10.1016/j.jad.2021.03.062.

Al-Musawi AF, Al-Hakeim HK, Al-Khfaji ZA, Al-Haboby IH, Almulla AF and Maes M (2022) In schizophrenia, the effects of the IL-6/IL-23/Th17 axis on health-related quality of life and disabilities are partly mediated by generalized cognitive decline and the symptomatome. *International Journal of Environmental Research and Public Health* **19**, 1–18.

Alptekin K, Akvardar Y, Kivircik Akdede BB, Dumlu K, Işik D, Pirinçci F, Yahssin S and Kitiş A (2005) Is quality of life associated with cognitive impairment in schizophrenia? *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **29**(2), 239–244. doi: 10.1016/j.pnpbp.2004.11.006.

Andreasen NC (1989) The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. *British Journal of Psychiatry* **155**(Suppl. 7), 49–58.

Berrios GE (2011) Eugen Bleuler's place in the history of psychiatry. *Schizophrenia Bulletin* **37**(6), 1095–1098. doi: 10.1093/schbul/sbr132.

Berrios GE, Luque R and Villagrán JM (2003) Schizophrenia: a conceptual history. *International Journal of Psychology and Psychological Therapy* **3**(2), 111–140.

Bland JM and Altman DG (2011) Correlation in restricted ranges of data. *BMJ* **11**, d556. doi: 10.1136/bmj.d556.

Brewer WJ, Francey SM, Wood SJ, Jackson HJ, Pantelis C, Phillips LJ, Yung AR, Anderson VA and McGorry PD (2005) Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. *American Journal of Psychiatry* **162**(1), 71–78. doi: 10.1176/appi.ajp.162.1.71.

CANTAB (2018) The Most Validated Cognitive Research Software. Available at http://www.cambridgecognition.com/cantab/ (accessed 1 October 2018).

Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, McGrath JJ and Whiteford HA (2018) Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. *Schizophrenia Bulletin* **44**(6), 1195–1203. doi: 10.1093/schbul/sby058.

Chin WW (2010) How to write up and report PLS analyses. In Esposito Vinzi V, Chin WW, Henseler J and Wang H (eds), Handbook of Partial Least Squares: Concepts, Methods and Applications in Marketing and Related Fields. Berlin: Springer, pp. 655–690.

Corlett PR, Honey GD and Fletcher PC (2007) From prediction error to psychosis: ketamine as a pharmacological model of delusions. *Journal of Psychopharmacology* **21**(3), 238–252. doi: 10.1177/0269881107077716.

Crow TJ (1980) Positive and negative schizophrenic symptoms and the role of dopamine. *British Journal of Psychiatry* **137**(4), 383–386.

Decker HS (2007) How Kraepelinian was Kraepelin? How Kraepelinian are the neo-Kraepelinians?–from Emil Kraepelin to DSM-III. *History of Psychiatry* **18**(71 Pt 3), 337–360. doi: 10.1177/0957154X07078976.

Early Psychosis Intervention (2022) Symptoms of Psychosis. Vancouver, BC: Early Psychosis Intervention.

Ebert A and Bar K (2010) Emil Kraepelin: a pioneer of scientific understanding of psychiatry and psychopharmacology. *Indian Journal of Psychiatry* **52**(2), 191–192. doi: 10.4103/0019-5545.64591.

Encyclopedia Britannica Online (2022) Kraepelin E (n.d.). Available at http://www.britannica.com/EBchecked/topic/323108/Emil-Kraepelin

Engstrom EJ, Weber MM and Burgmair W (2006) Emil Wilhelm Magnus Georg Kraepelin (1856–1926). *American Journal of Psychiatry* **163**(10), 1710. doi: 10.1176/ajp.2006.163.10.1710.

Fillenbaum GG, van Belle G, Morris JC, Mohs RC, Mirra SS, Davis PC, Tariot PN, Silverman JM, Clark CM, Welsh-Bohmer KA and Heyman A (2008) Consortium to Establish a Registry for Alzheimer's Disease (CERAD): the first twenty years. *Alzheimers & Dementia* **4**(2), 96–109. doi: 10.1016/j.jalz.2007.08.005.

GBD (2018) Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* **392**(10159), 1789–1858. doi: 10.1016/S0140-6736(18)32279-7. Erratum in: Lancet. 2019 Jun 22;393(10190):e44.

Gefen D and Straub D (2005) A practical guide to factorial validity using PLS-Graph: tutorial and annotated example. *Communications of the AIS* **16**, 91–109.

Hair JF, Hult GTM, Ringle CM and Sarstedt M (2022) A Primer on Partial Least Squares Structural Equation Modeling (PLS-SEM), 3rd edn. Thousand Oakes, CA: Sage.

Hamilton M (1960) A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry* **23**(1), 56–62. doi: 10.1136/jnnp.23.1.56.

Hawkins KA, Addington J, Keefe RS, Christensen B, Perkins DO, Zipurksy R, Woods SW, Miller TJ, Marquez E, Breier A and McGlashan TH (2004) Neuropsychological status of subjects at high risk for a first episode of psychosis. *Schizophrenia Research* **67**(2-3), 115–122. doi: 10.1016/j.schres.2003.08.007.

Henseler J, Ringle CM and Sarstedt M (2015) A new criterion for assessing discriminant validity in variance-based structural equation modeling. *Journal of the Academy of Marketing Science* **43**(1), 115–135. doi: 10.1007/s11747-014-0403-8.

Hor K and Taylor M (2010) Suicide and schizophrenia: a systematic review of rates and risk factors. *Journal of Psychopharmacology* **24**(4 Suppl), 81–90. doi: 10.1177/1359786810385490.

Kaiser S, Heekeren K and Simon JJ (2011) The negative symptoms of schizophrenia: category or continuum? *Psychopathology* **44**(6), 345–353. doi: 10.1159/000325912.

Kanchanatawan B, Sriswasdi S, Thika S, Stoyanov D, Sirivichayakul S, Carvalho AF, Geffard M and Maes M (2018a) Towards a new classification of stable phase schizophrenia into major and simple neuro-cognitive psychosis: results of unsupervised machine learning analysis. *Journal of Evaluation in Clinical Practice* **24**(4), 879–891. doi: 10.1111/jep.12945.

Kanchanatawan B, Sriswasdi S, Thika S, Sirivichayakul S, Carvalho AF, Geffard M, Kubera M and Maes M (2018b) Deficit schizophrenia is a discrete diagnostic category defined by neuro-immune and neurocognitive features: results of supervised machine learning. *Metabolic Brain Disease* **33**(4), 1053–1067. doi: 10.1007/s11011-018-0208-4.

Kanchanatawan B, Thika S, Sirivichayakul S, Carvalho AF, Geffard M and Maes M (2018c) In schizophrenia, depression, anxiety, and physiosomatic symptoms are strongly related to pPsychotic symptoms and excitation, impairments in episodic memory, and increased production of neurotoxic tryptophan catabolites: a multivariate and machine learning study. *Neurotoxicity Research* **33**(3), 641–655. doi: 10.1007/s12640-018-9868-4.

Kanchanatawan B, Tangwongchai S, Supasitthumrong T, Sriswasdi S and Maes M (2018d) Episodic memory and delayed recall are significantly more impaired in younger patients with deficit schizophrenia than in elderly patients with amnestic mild cognitive impairment. *PLoS One* **13**(5), e0197004. doi: 10.1371/journal.pone.0197004.

Karsner D (2022) Restriction of Range: Definition & Examples. Study.com. Restriction of Range: Definition & Examples - Video & Lesson Transcript. Study.com (accessed 26 May 2022).

Kay SR, Fiszbein A and Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**(2), 261–276. doi: 10.1093/schbul/13.2.261.

Keefe RS and Harvey PD (2012) Cognitive impairment in schizophrenia. *Handbook of Experimental Pharmacology* **213**, 11–37. doi: 10.1007/978-3-642-25758-2_2.

Kirkpatrick B, Castle D, Murray RM and Carpenter WT Jr (2000) Risk factors for the deficit syndrome of schizophrenia. *Schizophrenia Bulletin* **26**(1), 233–242. doi: 10.1093/oxfordjournals.schbul.a033443.

Kirkpatrick B, Buchanan RW, Ross DE and Carpenter WT Jr (2001) A separate disease within the syndrome of schizophrenia. *Archives of General Psychiatry* **58**(2), 165–171. doi: 10.1001/archpsyc.58.2.165.

Kline RB (2011) Principles and Practice of Structural Equation Modeling. New York: Guilford Press.

Jablensky A (2000) Epidemiology of schizophrenia: the global burden of disease and disability. *European Archives of Psychiatry and Clinical Neuroscience* **250**(6), 274–285. doi: 10.1007/s004060070002.

Jablensky A (2010) The diagnostic concept of schizophrenia: its history, evolution, and future prospects. *Dialogues in Clinical Neuroscience* **12**(3), 271–287.

Javitt DC (2014) Balancing therapeutic safety and efficacy to improve clinical and economic outcomes in schizophrenia: a clinical overview. *American Journal of Managed Care* **20**(8 Suppl), S160–S165.

Maes M and Anderson G (2021) False dogmas in schizophrenia research: toward the reification of pathway phenotypes and pathway classes. *Frontiers in Psychiatry* **12**, 663985. doi: 10.3389/fpsyt.2021.663985.

Maes M and Kanchanatawan B (2021) In (deficit) schizophrenia, a general cognitive decline partly mediates the effects of neuro-immune and neuro-oxidative toxicity on the symptomatome and quality of life. *CNS Spectrums* **12**, 1–10. doi: 10.1017/S1092852921000419.

Maes M, Kanchanatawan B, Sirivichayakul S and Carvalho AF (2019a) In schizophrenia, deficits in natural IgM isotype antibodies including those directed to malondialdehyde and azelaic acid strongly predict negative symptoms, neurocognitive impairments, and the deficit syndrome. *Molecular Neurobiology* **56**(7), 5122–5135. doi: 10.1007/s12035-018-1437-6.

Maes M, Vojdani A, Geffard M, Moreira EG, Barbosa DS, Michelin AP, Semeão LO, Sirivichayakul S and Kanchanatawan B (2019b) Schizophrenia phenomenology comprises a bifactorial general severity and a single-group factor, which are differently associated with neurotoxic immune and immune-regulatory pathways. *Biomolecular Concepts* **10**(1), 209–225. doi: 10.1515/bmc-2019-0023.

Maes M, Sirivichayakul S, Kanchanatawan B and Carvalho AF (2020a) In schizophrenia, psychomotor retardation is associated with executive and memory impairments, negative and psychotic symptoms, neurotoxic immune products and lower natural IgM to malondialdehyde. *The World Journal of Biological Psychiatry* **21**(5), 383–401. doi: 10.1080/15622975.2019.1701203.

Maes M, Sirivichayakul S, Matsumoto AK, Michelin AP, de Oliveira Semeão L, de Lima Pedrão JV, Moreira EG, Barbosa DS, Carvalho AF, Solmi M and Kanchanatawan B (2020b) Lowered antioxidant defenses and increased oxidative toxicity are hallmarks of deficit schizophrenia: a nomothetic network psychiatry approach. *Molecular Neurobiology* **57**(11), 4578–4597. doi: 10.1007/s12035-020-02047-5.

Maes M, Vojdani A, Galecki P and Kanchanatawan B (2020c) How to construct a bottom-up nomothetic network model and disclose novel nosological classes by integrating risk resilience and adverse outcome pathways with the phenome of schizophrenia. *Brain Science* **10**(9), 645. doi: 10.3390/brainsci10090645.

Maes M, Vojdani A, Sirivichayakul S, Barbosa DS and Kanchanatawan B (2021) Inflammatory and oxidative pathways are new drug targets in multiple episode schizophrenia and leaky gut, Klebsiella pneumoniae, and C1q immune complexes are additional drug targets in first episode schizophrenia. *Molecular Neurobiology* **58**(7), 3319–3334. doi: 10.1007/s12035-021-02343-8.

Mohamed S, Rosenheck R, Swartz M, Stroup S, Lieberman JA and Keefe RS (2008) Relationship of cognition and psychopathology to functional impairment in schizophrenia. *The American Journal of Psychiatry* **165**(8), 978–987. doi: 10.1176/appi.ajp.2008.07111713.

Moskowitz A and Heim G (2011) Eugen Bleuler's Dementia praecox or the group of schizophrenias (1911): a centenary appreciation and reconsideration. *Schizophrenia Bulletin* **37**(3), 471–479. doi: 10.1093/schbul/sbr016.

Mosolov SN and Yaltonskaya PA (2022) Primary and secondary negative symptoms in schizophrenia. *Frontiers in Psychiatry* **12**, 766692. doi: 10.3389/fpsyt.2021.766692.

NHS (2019) Symptoms - Schizophrenia. Available at https://www.nhs.uk/conditions/schizophrenia/symptoms/ (accessed 14 June 2019).

NIHM (2019) Schizophrenia. Available at https://www.nimh.nih.gov/health/topics/schizophrenia/index.shtml 14 June 2019.

Noto C, Ota VK, Santoro ML, Gouvea ES, Silva PN, Spindola LM, Cordeiro Q, Bressan RA, Gadelha A, Brietzke E, Belangero SI and Maes M (2016) Depression, cytokine, and cytokine by treatment interactions modulate gene expression in antipsychotic naïve first episode psychosis. *Molecular Neurobiology* **53**(8), 5701–5709. doi: 10.1007/s12035-015-9489-3.

Orellana G and Slachevsky A (2013) Executive functioning in schizophrenia. *Front Psychiatry* **4**, 35. doi: 10.3389/fpsyt.2013.00035.

Overall JE and Gorham DR (1962) The brief psychiatric rating scale. *Psychological Reports* **10**(3), 799–812.

Rigdon EE (2012) Rethinking partial least squares path modeling: in praise of simple methods. *Long Range Planning* **45**(5-6), 341–358.

Ringle CM, da Silva D and Bido D (2014) Structural equation modeling with the SmartPLS. *Brazilian Journal of Marketing - BJM Revista Brasileira de Marketing – ReMark Edição Especial* **13**, n2.

Roy MA and DeVriendt X (1994) Symptômes positifs et négatifs de la schizophrénie: une mise à jour [Positive and negative symptoms in

https://doi.org/10.1017/neu.2022.32 Published online by Cambridge University Press

schizophrenia: a current overview]. *Canadian Journal of Psychiatry* **39**(7), 407–414. doi: 10.1177/070674379403900704.

Sackett PR and Yang H (2000) Correction for range restriction: an expanded typology. *Journal of Applied Psychology* **85**(1), 112–118. doi: 10.1037/0021-9010.85.1.112.

Shepherd M (1995) Two faces of Emil Kraepelin. *British Journal of Psychiatry* **167**(2), 174–183. doi: 10.1192/bjp.167.2.174.

Sirivichayakul S, Kanchanatawan B, Thika S, Carvalho AF and Maes M (2019) Eotaxin, an endogenous cognitive deteriorating chemokine (ECDC), is a major contributor to cognitive decline in normal people and to executive, memory, and sustained attention deficits, formal thought disorders, and psychopathology in schizophrenia patients. *Neurotoxicity Research* **35**(1), 122–138. doi: 10.1007/s12640-018-9937-8.

Snezhnevsky AV (1971) The symptomatology, clinical forms and nosology of schizophrenia. In Howells JG (ed), Modern Perspectives in World Psychiatry. New York: Brunner/Mazel, pp. 425–447.

Snezhnevsky AV and Vartanyan M (1970) The forms of schizophrenia and their biological correlates. In Himwich HE (ed), Biochemistry, Schizophrenia, and Affective Illness. Baltimore: William & Wilkins Co, pp. 1–28.

Soares-Weiser K, Maayan N, Bergman H, Davenport C, Kirkham AJ, Grabowski S and Adams CE (2015) First rank symptoms for schizophrenia. *Cochrane Database of Systematic Reviews* **1**(1), CD010653. doi: 10.1002/14651858.CD010653.pub2.

Stoyanov D (2020) The reification of diagnosis in psychiatry. *Neurotoxicity Research* **37**(3), 772–774.

Stoyanov D and Maes MH (2021) How to construct neuroscience-informed psychiatric classification? Towards nomothetic networks psychiatry. *World Journal of Psychiatry* **11**(1), 1–12. doi: 10.5498/wjp.v11.i1.1.

Stoyanov D, Aryutova K, Kandilarova S, Paunova R, Arabadzhiev Z, Todeva-Radneva A, Kostianev S and Borgwardt S (2021) Diagnostic task specific activations in functional MRI and aberrant connectivity of insula with middle frontal gyrus can inform the differential diagnosis of psychosis. *Diagnostics (Basel)* **11**(1), 95. doi: 10.3390/diagnostics11010095.

Takahashi S (2013) Heterogeneity of schizophrenia: genetic and symptomatic factors. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* **162B**(7), 648–652.

Teo T (2011) Factors influencing teachers' intention to use technology: model development and test. *Computers & Education* **57**(4), 2432–2440.

Tolman AW and Kurtz MM (2012) Neurocognitive predictors of objective and subjective quality of life in individuals with schizophrenia: a meta-analytic investigation. *Schizophrenia Bulletin* **38**(2), 304–315. doi: 10.1093/schbul/sbq077.

Ueoka Y, Tomotake M, Tanaka T, Kaneda Y, Taniguchi K, Nakataki M, Numata S, Tayoshi S, Yamauchi K, Sumitani S, Ohmori T, Ueno S and Ohmori T (2011) Quality of life and cognitive dysfunction in people with schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **5**(1), 53–59. doi: 10.1016/j.pnpbp.2010.08.018.

Vita A and Barlati S (2018) Recovery from schizophrenia: is it possible? *Current Opinion in Psychiatry* **31**(3), 246–255. doi: 10.1097/YCO.0000000000000407.

https://doi.org/10.1017/neu.2022.32 Published online by Cambridge University Press