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ORIGINAL ARTICLE

In Schizophrenia, Depression, Anxiety, and Physiosomatic Symptoms Are Strongly Related to Psychotic Symptoms and Excitation, Impairments in Episodic Memory, and Increased Production of Neurotoxic Tryptophan Catabolites: a Multivariate and Machine Learning Study

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Abstract

The depression, anxiety and physiosomatic symptoms (DAPS) of schizophrenia are associated with negative symptoms and changes in tryptophan catabolite (TRYCAT) patterning. The aim of this study is to delineate the associations between DAPS and psychosis, hostility, excitation, and mannerism (PHEM) symptoms, cognitive tests as measured using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) and IgA/IgM responses to TRYCATs. We included 40 healthy controls and 80 participants with schizophrenia. Depression and anxiety symptoms were measured with The Hamilton Depression (HAM-D) and Anxiety (HAM-A) Rating Scales, respectively. Physiosomatic symptoms were assessed with the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale (FF). Negative symptoms as well as CERAD tests, including Verbal Fluency Test (VFT), Mini-Mental State Examination (MMSE), Word List Memory (WLM), and WL Delayed Recall were measured, while ratios of IgA responses to noxious/protective TRYCATs (IgA NOX_PRO) were computed. Schizophrenia symptoms consisted of two dimensions, a first comprising PHEM and negative symptoms, and a second DAPS symptoms. A large part of the variance in DAPS was explained by psychotic symptoms and WLM. Of the variance in HAM-D, 58.9% was explained by the regression on excitement, IgA NOX_PRO ratio, WLM, and VFT; 29.9% of the variance in HAM-A by psychotic symptoms and IgA NOX/PRO; and 45.5% of the variance in FF score by psychotic symptoms, IgA NOX/PRO, and WLM. Neural network modeling shows that PHEM, IgA NOX_PRO, WLM, and MMSE are the dominant variables predicting DAPS. DAPS appear to be driven by PHEM and negative symptoms coupled with impairments in episodic memory, especially false memory creation, while all symptom dimension and cognitive impairments may be driven by an increased production of noxious TRYCATs, including picolinic, quinolinic, and xanthurenic acid.

Keywords Schizophrenia · Immune · Inflammation · Tryptophan catabolites · Depression · Anxiety

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Introduction

Schizophrenia is a complex disorder characterized by several symptom dimensions including (a) positive symptoms (such as hallucinations, delusions, aggression, hostility,

disorganized thinking) and (b) negative symptoms (such as apathy, anhedonia, alogia, flat affect, social inhibition) (Mellor 1991; Marneros et al. 1991; Cuesta and Peralta 1995). Positive symptoms were conceptualized as new behaviors and mental processes, which the individual has acquired due to the disorder, while negative symptoms are conceptualized as behaviors and mental processes that the patient has lost due to the disorder (Burton 2012). Accordingly, patients with schizophrenia were divided into type 1, namely patients with positive symptoms, and type 2, namely those with negative symptoms (Crow 1985). A comparable two-syndrome concept was developed by Bleuler who separated basic symptoms (such as withdrawal from reality and loosening of associations) and accessory symptoms (including delusions and hallucinations) (Jablensky 2010). Recently, we found that in stable-phase schizophrenia, psychotic symptoms, hostility-aggression, excitation-grandiosity as well as mannerism (PHEM) and negative symptoms are intertwined symptomatic dimensions (Kanchanatawan et al. submitted). This suggests that the two-syndrome framework differentiating "positive from negative symptoms" is not adequate because PHEM and negative symptoms may be strongly related.

Cognitive symptoms, either subjective cognitive complaints (SCCs) or objective cognitive deficits, comprise another symptom dimension of schizophrenia. Using a diversity of neuropsychological batteries, deficits in decision-making, working memory, visual memory, attention, and planning were detected in schizophrenia (Reichenberg 2010; Yu et al. 2015; Keefe and Harvey 2012; Seidman et al. 2003; Grillon et al. 2010). The Cambridge Neuropsychological Test Automated Battery (CANTAB) and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) tests show that schizophrenia is characterized by impairments in sustained attention, working, semantic and episodic memory, and emotional recognition (Kanchanatawan et al. 2017a; submitted). Moreover, these cognitive deficits are strongly associated with negative symptoms of schizophrenia (Kanchanatawan et al. 2017a).

A meaningful subset of individuals with schizophrenia present affective symptoms, including depression and anxiety symptoms (Emsley et al. 1999; Kanchanatawan et al. 2018b). Those affective symptoms of schizophrenia appear to be associated with neurocognitive deficits and with positive and negative symptoms (Kanchanatawan et al. 2017a). Previous research suggests that affective symptoms are more associated with positive than with negative symptoms, although findings have not been consistent across studies (Emsley et al. 1999; Kirschner et al. 2017). Recently, we reported that more than 50% of schizophrenia patients exhibit physiosomatic symptoms, including chronic fatigue, muscle pain, muscle tension, autonomic symptoms, and a flu-like malaise, and that these symptoms are strongly associated with affective symptoms and objective cognitive impairments as measured with CANTAB, but not with negative or positive symptoms (Kanchanatawan et al. 2017a). Nevertheless, no research has examined whether PHEM, negative, affective, physiosomatic, and cognitive symptoms are intercorrelated phenomena that may perhaps shape one or two major symptomatic dimensions. Moreover, there are no data to indicate whether affective and physiosomatic symptoms are associated with measurements of semantic and episodic memory as assessed with the CERAD.

Finally, we have reported that all abovementioned symptom dimensions are associated with specific changes in IgA and IgM responses to tryptophan catabolites (TRYCATs), including increased IgA responses to more noxious TRYCATs such as 3-OH-kynurenine (3-HK), picolinic acid (PA), xanthurenic acid (XA), and quinolinic acid (QA), and lowered IgM responses to the same TRYCATs (Kanchanatawan et al. 2017a, b, 2018a). These findings indicate increased production of those four noxious TRYCATs coupled with lowered regulation of the same TRYCATs (Kanchanatawan et al. 2017a, b, 2018a). As a consequence, different symptom dimensions in schizophrenia may be driven by TRYCAT patterning of IgA/IgM responses or their antecedents (namely immune activation and increased oxidative stress) or their consequences (namely increased neurotoxicity and excitotoxicity and detrimental effects of inflammatory, oxidative, and nitrosative stress pathways) (Kanchanatawan et al. 2017a).

Thus, the aims of this study are to examine (a) whether affective and physiosomatic symptoms are associated with CERAD measurements of semantic and episodic memory; (b) whether PHEM symptoms rather than negative symptoms are associated with affective and physiosomatic symptoms; and (c) whether PHEM, negative symptoms, changes in TRYCAT patterning, and cognitive impairments would independently predict affective and physiosomatic symptoms.

Participants and Methods

Participants

In this case-control study, we recruited Thai adults of both sexes and aged 18 to 65 years. We assessed socio-demographic, clinical, cognitive, psychopathological, and biomarker data. Eighty consecutively admitted patients with schizophrenia who fulfilled DSM-IV-TR diagnostic criteria of schizophrenia and who were in a stable phase of illness were enrolled. We recruited patients at the Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, and included 40 participants with nondeficit schizophrenia and 40 with deficit schizophrenia, as defined with the Schedule for Deficit Syndrome (SDS) criteria (Kirkpatrick et al. 1989). We also included 40 healthy volunteers recruited from the same catchment population, province Bangkok, Thailand. We

employed the following exclusion criteria for patients: acute psychotic episodes for at least 1 year prior to admission; axis I disorders other than schizophrenia, including schizoaffective disorder, bipolar disorder, depression, substance use disorders, and psycho-organic disorders; neurodegenerative/neuroinflammatory disorders, including Parkinson's disease, stroke, and multiple sclerosis; (auto)immune-inflammatory disorders, including chronic obstructive pulmonary disease, diabetes (type 1 and 2), psoriasis, rheumatoid arthritis, and inflammatory bowel disease. We excluded volunteers with lifetime and current DSM-IV-TR axis I mental disorders as well as those with a family history of psychotic disorders. Moreover, participants from either group who were currently using immunomodulatory drugs, antioxidant supplements, or ω3-polyunsaturated fatty acids were excluded.

All participants as well as the guardians of patients (parents or other close family members) provided written informed consent prior to participation in this study. The study was conducted according to Thai and International ethics and privacy laws. Approval for the study was obtained from the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, which is in compliance with the International Guideline for Human Research protection as required by the Declaration of Helsinki, The Belmont Report, CIOMS Guideline, and International Conference on Harmonization in Good Clinical Practice (ICH-GCP).

Methods

Clinical Assessments

In all participants, a senior research psychiatrist (BK) made the axis I diagnoses of mental disorders using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Kittirathanapaiboon and Khamwongpin 2005), considering DSM-IV-TR criteria (APA 2000). The diagnosis of primary deficit schizophrenia was made using SDS criteria (Kirkpatrick et al. 1989). Moreover, the same senior psychiatrist conducted semi-structured interviews in all participants to collect socio-demographic data, family history of psychosis, medical history, and different rating scales measuring severity of illness. Depression and anxiety symptoms were assessed with the Hamilton Depression (HAM-D) and Anxiety (HAM-A) Rating Scale, respectively (Hamilton 1959, 1960). Physiosomatic symptoms were measured using the 12-item Fibromyalgia and Chronic Fatigue Syndrome Rating scale (FF) (Zachrisson et al. 2002). Negative symptoms were measured using the SDS (Kirkpatrick et al. 1989). We used the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) to assess severity of negative (PANSS-) and positive (PANSS+) symptoms. Psychopathological manifestations of schizophrenia were further assessed with the Brief Psychiatric Rating Scale (Overall and Gorham 1962). Some BPRS items together with PANSS+ items were used to compute severity of the 4 PHEM dimensions using *z*-unit weighted composite scores. Severity of psychotic symptoms was computed as: *z* score PANSS P1 (delusion) (zP1) + zP3 (hallucinations) + zP6 (suspiciousness) + zBPRS11 (suspiciousness) + zBPRS12 (hallucinatory behavior) + BPRS15 (unusual thought content). Severity of hostility was computed as zP7 (hostility) + zPANSS general14 (zG14, poor impulse control) + zBPRS10 (hostility) + zBPRS14 (uncooperativeness). Severity of the excitement-grandiosity dimension was computed as zP14 (excitement) + zP5 (grandiosity) + zBPRS8 (grandiosity) + zBPRS17 (excitement). Severity of mannerism-posturing was computed as zG5 + zBPRS7 (both mannerism and posturing).

On the same day as the semi-structured interview, a trained clinical research assistant (ST), a master in mental health, performed the CERAD measurements. The CERAD comprises neuropsychological tests assessing several domains including semantic and episodic memory, and general neuropsychological functioning (CERAD 1986; Beeri et al. 2006; Welsh et al. 1994). Here, we used the following CERAD tests (Kanchanatawan et al. 2017a): Verbal Fluency Test (VFT), to probe semantic memory, fluency, language, cognitive flexibility, and verbal productivity; Modified Boston Naming Test (BNT) to measure confrontational word retrieval, visual naming, word finding, and visual perception; Mini-Mental State Examination (MMSE), to measure orientation, concentration, constructional praxis, naming, and memory; Word List Memory (WLM) to measure working memory and learning ability for new verbal information or verbal episodic memory; Word List Recall, true recall (WLR True), to measure the ability to recall and verbal episodic memory-recall; Word List Recall, false recall (WLR False), to measure intrusion errors or false memory creation; and Word List Recognition (WLRecog) to measure verbal learning recall recognition or verbal episodic memory-discriminability. As described previously (Kanchanatawan et al. 2017a), we used two indices reflecting episodic and semantic memory, namely the first two oblimin-rotated principal components (PCs) subtracted from the CERAD tests (explaining 68.3% of the total variance in the data set). The first PC loaded highly on VFT, BNT, MMSE, and Constructive Praxis and is named PC Semantic memory (reflecting impairments in semantic memory and a more general neuropsychological dysfunction) and the second PC loaded highly on WLM, WLR True, WLR False, and WLRecog and was called PC episodic memory. The diagnosis of nicotine dependence or tobacco use disorder (TUD) was made using DSM-IV-TR criteria. The same day as the clinical interviews, we also measured body mass index (BMI) as body weight (kg)/length (m^2).

Biomarker Assays

The same day as the neurocognitive tests and clinical interviews, blood was sampled around 8.00 a.m. for the assay of

TRYCATs. Serum was frozen at − 80 °C until thawed for assay of IgA and IgM responses to TRYCATs, namely the noxious (NOX) TRYCATs QA, 3HK, PA, and XA, and more protective (PRO) TRYCATs, namely kynurenic acid (KA) and anthranilic acid (AA). The methods were described in detail somewhere else (Duleu et al. 2010; Kanchanatawan et al. 2017a) and we describe the methods in supplementary file 1. We used the *z*-transformed scores of the IgA and IgM levels to the 6 TYCATs to compute three *z*-unit weighted composite scores:

$$zIgA\ \text{NOX\_PRO} = \text{sum}\ of\ \text{z}\ scores\ of\ \text{QA(zQA)} + \text{zPA} + \text{zXA–zAA–zKA}(index\ of\ increased\ noxious\ potential);$$
$$\Delta\text{NOX\_PRO} = zIgA(\text{zQA} + \text{zPA} + \text{zXA} + \text{z3HK–zAA–zKA}) – zIgM(\text{zQA} + \text{zPA} + \text{zXA} + \text{3HK–zAA–zKA})$$
$$(\text{a}\ more\ comprehensive\ index\ of\ increased\ noxious\ potential);$$
$$zIgM\ \text{KA\_3HK} = zIgM\ \text{KA–z3HK}(index\ of\ lowered\ regulation\ of\ \text{KA}\ versus\ \text{3HK}).$$

Statistics

We employed analyses of variance (ANOVAs) or the Kruskal-Wallis tests to assess differences in scale variables among diagnostic groups and analyses of contingence tables (χ^2 tests) to assess associations between sets of nominal variables. Pearson's product moment correlation coefficients were used to compute bivariate correlations between scale variables. Hierarchical stepwise regression analyses were employed to define the significant explanatory variables (TRYCATs, PHEM dimension, SDS, CERAD variables) predicting HAM-D, HAM-A, and FF scores (the dependent variables). Regression analyses were checked for multicollinearity and were additionally bootstrapped (1000 bootstraps). Statistical analyses were performed using IBM SPSS windows version 22. Tests were two-tailed and a p value of 0.05 was used for statistical significance. Exploratory factor analysis was performed using SPSS 22 and FACTOR, windows version 10.5.03 (Ferrando and Lorenzo-Seva 2013, 2017). Adequacy of the correlation matrix was assessed using the Kaiser-Meyer-Olkin (KMO) test and Bartlett's statistic. Closeness to unidimensionality was checked with unidimensional congruence (UNICO), explained common variance (ECV) and mean of item residual absolute loadings (MIREAL). The number of factors was based on eigenvalues > 1. In order to interpret the results, we employed loadings > 0.300 on oblimin-rotated factors. We employed multilayer perceptron (MLP) and radial basis function

Table 1 Socio-demographic and clinical data in normal controls and schizophrenia (SCZ) patients divided into two groups divided according to lower and higher scores on a composite score of depression, anxiety, and physiosomatic (DAPS) symptoms

Variables	Normal controls [a]	SCZ-DAPS[b]	SCZ + DAPS[c]	F/X^2	df	p
Age (years)	37.4 (12.8)	41.1 (11.0)	40.9 (11.3)	1.27	2/116	0.285
Gender (M/F)	10 / 30[b]	26/14[a]	17/22	12.98	2	0.002
Education (years)	14.2 (4.9)[c]	12.9 (3.5)	11.6 (4.7)[a]	3.56	2/116	0.032
Employed (N/Y)	4/36[b,c]	19/21[a]	26/13[a]	27.17	2	< 0.001
TUD (N/Y)	38/2	35/5	39/0	$\Psi = 0.218$	–	0.059
Duration of illness (years)	–	14.5 (9.3)	14.7 (11.4)	0.00	1/71	0.954
Number of psychotic episodes	–	2.7 (2.0)	3.8 (3.3)	3.50	1/72	0.065
BMI (kg/m^2)	24.0 (4.3)	24.7 (4.8)	24.4 (5.5)	0.20	2/111	0.818
Nondeficit/deficit SCZ	–	25/15	15/24	4.57	1	0.033
HAM-D total	0.6 (2.0)[b,c]	3.3 (2.4)[a,c]	11.5 (4.9)[a,b]	KW	–	< 0.001
HAM-A total	2.6 (5.4)[c]	4.6 (3.0)[c]	18.2 (8.3)[a,b]	KW	–	< 0.001
FF total	1.4 (3.4)[b,c]	7.2 (4.9)[a,c]	18.0 (7.0)[a,b]	KW	–	< 0.001
SDS total	0.0 (0.0)[b,c]	4.7 (4.3)[a,c]	8.9 (6.5)[a,b]	KW	–	< 0.001

Results are shown as mean (± SD). *F*: results of ANOVA; X^2 : results of analyses of contingency tables

[a,b,c] post-hoc differences between controls (a), and schizophrenia patients with (c) and without (b) DAPS

TUD tobacco use disorder, *BMI* body mass index, *HAM-D/HAM-A* Hamilton Depression and Anxiety Rating Scales, *FF* Fibromyalgia and Chronic Fatigue Syndrome Rating Scale, *SDS* Schedule for Deficit Schizophrenia

(RBF) Neural Network analyses (SPSS 22) to discover the more complex nonlinear relationships among input variables, which are determined during learning processes predicting the HAM-D, HAM-A, and FF scores. The relative number of cases assigned to the training (to estimate the network parameters), testing (to prevent overtraining), and holdout (to evaluate the final network) sets were 7, 3, and 5 respectively. As a stopping rule, we employed one consecutive step with no further decrease in the error term. The input layer of the feedforward architecture model contained symptoms, CERAD tests results and TRYCAT ratios (with or without age, sex, and education), while the output layer contained HAM-D, HAM-A, and FF score values. We considered one or two hidden layers with a variable number of nodes (2–6). Error and relative error are computed as well as the (relative) importance of each of the input variables in sensitivity analyses.

Results

Socio-demographic Data

Table 1 lists the socio-demographic and clinical data in the study groups of controls and schizophrenia patients divided into these with and without significant depression + anxiety + physiosomatic symptoms. Since HAM-D and HAM-A and FF scores are highly intercorrelated (see Table 2) and since they load on one factor (see Table 3), we have computed a *z*-unit weighted composite score reflecting the sum of these three dimensions (DAPS), namely zDAPS = *z* score of HAM-D (zHAM-D) + zHAM-A score + zFF score. Consequently, schizophrenia patients were divided into two groups (median split) according to the zDAPS values, yielding three study groups, namely normal controls and SCZ patients with low and higher zDAPS scores. After FDR p-correction, the differences among the groups in education ($p = 0.0536$) and deficit schizophrenia ($p = 0.0536$) were no longer significant. There were also no significant differences in age, TUD, and BMI between the three groups. There were somewhat more males in the schizophrenia group with lower zDAPS values as compared with controls. There were more schizophrenia patients unemployed than normal controls. There were no significant differences in duration of illness or number of depressive episodes between both schizophrenia subgroups. There were highly significant differences in HAM-D and FF scores among the study groups, both increasing from controls to schizophrenia patients with

Table 2 Intercorrelation matrix between scores on the Hamilton Depression (HAM-D) and Anxiety (HAM-A) Rating Scales, the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale (FF), on the one hand, and four symptomatic dimensions, the total score on the Schedule for Deficit Schizophrenia (SDS), Consortium to Establish a Registry for Alzheimer's Disease (CERAD) tests, age, and education, on the other

	HAM-D	HAM-A	FF
HAM-A	0.705 ($p < 0.001$) $n = 120$	–	–
FF	0.851 (< 0.001) $n = 119$	0.716 (< 0.001) $n = 119$	–
Psychotic dimension	0.676 (< 0.001) $n = 119$	0.504 (< 0.001) $n = 119$	0.617 (< 0.001) $n = 119$
Hostility dimension	0.479 (< 0.009) $n = 119$	0.290 (0.001) $n = 119$	0.432 (< 0.001) $n = 119$
Excitation dimension	0.696 (< 0.001) $n = 120$	0.503 (< 0.001) $n = 120$	0.570 (< 0.001) $n = 119$
Mannerism dimension	0.516 (< 0.001) $n = 119$	0.339 (< 0.001) $n = 119$	0.499 (< 0.001) $n = 119$
SDS total	0.658 (< 0.001) $n = 118$	0.424 (< 0.001) $n = 118$	0.521 (< 0.001) $n = 118$
Boston Naming Test	− 0.223 (0.015) $n = 119$	− 0.092 (0.322) $n = 119$	− 0.252 (0.006) $n = 118$
Word List Memory	− 0.593 (< 0.001) $n = 120$	− 0.427 (< 0.001) $n = 120$	− 0.505 (< 0.001) n = 119
Verbal Fluency Test	− 0.517 (< 0.001) $n = 120$	− 0.284 (0.002) $n = 120$	− 0.381 (< 0.001) $n = 119$
Mini-Mental State Examination	− 0.458 (< 0.001) $n = 120$	− 0.357 (< 0.001) $n = 120$	− 0.402 (< 0.001) $n = 119$
Word List True Recall	− 0.533 (< 0.001) $n = 120$	− 0.372 (< 0.001) $n = 120$	− 0.422 (< 0.001) $n = 119$
Word List False Recall	0.538 (< 0.001) $n = 120$	0.367 (< 0.001) $n = 120$	0.409 (< 0.001) $n = 119$
Word List Recognition	− 0.285 (0.002) $n = 118$	− 0.234 (< 0.001) $n = 118$	− 0.204 (0.028) $n = 118$
PC episodic memory	0.567 (< 0.001) $n = 118$	0.410 (< 0.001) $n = 118$	0.436 (< 0.001) $n = 117$
PC semantic memory	0.375 (< 0.001) $n = 118$	0.255 (0.005) $n = 118$	0.345 (< 0.001) $n = 117$
Age	0.180 (0.049) $n = 120$	0.074 (0.424) $n = 120$	0.222 (0.015) $n = 119$
Education	− 0.299 (0.001) $n = 120$	− 0.122 (0.184) $n = 120$	− 0.290 (0.001) $n = 119$

PC episodic memory first principal component subtracted from episodic memory CERAD tests, *PC semantic memory* first principal component subtracted from the semantic memory CERAD tests

Table 3 Results of four different factor analyses (FA) performed on the symptomatic dimensions of schizophrenia and also when combined with indices of episodic and semantic memory

Features	FA#1	FA#2	FA#3 oblimin rotation		FA#4 oblimin rotation	
			Rotated F1		Rotated F1	
			Rotated F2		Rotated F2	
Psychotic symptoms	*0.950*	*0.882*	*0.936*	0.052	*0.936*	0.045
Hostility	*0.807*	*0.657*	*0.809*	− 0.079	*0.806*	− 0.081
Excitation	*0.980*	*0.926*	*0.890*	0.081	*0.893*	0.079
Mannerism	*0.888*	*0.771*	*0.856*	− 0.054	*0.861*	− 0.069
SDS total	*0.753*	*0.666*	*0.607*	0.228	*0.594*	0.246
HAM-D	–	*0.331*	− 0.035	*0.791*	0.051	*0.791*
HAM-A	–	*0.762*	0.108	*0.868*	0.057	*0.916*
FF	–	*0.609*	0.001	*0.905*	− 0.015	*0.899*
PC semantic memory	–	–	–	–	0.178	0.277
PC episodic memory	–	–	–	–	*0.386*	*0.316*
KMO	0.807	0.850	0.852		0.845	
% variance	81.5%	60.2%	74.9%		71.5%	
UNICO	0.982	0.879				
ECV	0.912	0.756				
MIREAL	0.213	0.377				

SDS Schedule for Deficit Schizophrenia, *HAM-D/HAM-A* Hamilton Depression and Anxiety Rating Scales, *FF* the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale, *PC semantic memory* first principal component subtracted from the semantic memory and more general neuropsychological functions tests of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), *PC episodic memory* first principal component subtracted from episodic memory CERAD tests. Significant loadings (>0.300) are shown in italics.

lower zDAPS scores and to those with higher zDAPS scores. The HAM-A score was significantly higher in patients with higher zDAPS scores as compared with the two other groups. Supplementary file 2, figure 1,

Table 4 Results of hierarchical regression analyses with the Hamilton Depression (HAM-D) and Anxiety (HAM-A) Rating Scales and the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale (FF) as dependent variables, and the Consortium to Establish a Registry for Alzheimer's Disease, symptom dimensions and/or tryptophan catabolite (TRYCAT) ratios as explanatory variables

Dependent variables	*F* model	df	*p*	*R* squared	Explanatory variables	*t*	*p*
#1. HAM-D	40.06	2/113	< 0.001	0.415	WLM	− 5.31	< 0.001
					VFT	− 3.63	< 0.001
#2. HAM-A	25.73	1/114	< 0.001	0.184	WLM	− 5.07	< 0.001
#3. FF	40.25	1/113	< 0.001	0.263	WLM	− 6.34	< 0.001
#4. HAM-D	62.67	2/115	< 0.001	0.522	SDS total	+ 3.96	< 0.001
					Psychotic	+ 4.61	< 0.001
#5. HAM-A	39.70	1/116	< 0.001	0.255	Psychotic	+ 6.30	< 0.001
#6. FF	39.28	2/115	< 0.001	0.406	Psychotic	+ 8.29	< 0.001
					Age	+ 2.24	0.027
#7. HAM-D	38.69	4/108	< 0.001	0.589	Excitement	+ 5.01	< 0.001
					VFT	− 2.41	0.018
					IgA NOX_PRO	+ 2.67	0.009
					WLM	− 2.58	0.011
#8. HAM-A	24.30	2/114	< 0.001	0.299	Psychotic	+ 5.32	< 0.001
					IgA NOX_PRO	+ 2.59	0.011
#9. FF	30.21	3/109	< 0.001	0.454	Psychotic	+ 4.79	< 0.001
					IgA NOX_PRO	+ 2.56	0.012
					WLM	− 2.47	0.015

WLM Word List Memory, *VFT* Verbal Fluency test, *SDS* Schedule for Deficit Schizophrenia, *IgA NOX_PRO* ratio of IgA responses to noxious tryptophan catabolites (TRYCATs)/protective TRYCATs

Table 5 Multilayer Perceptron Neural Network (NN) Models with Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A) and the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale (FF) scores as output variables and DAPS (depression, anxiety, and FF) symptom dimensions, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), and/or tryptophan catabolite (TRYCAT) ratios as explanatory variables

NN models	Model	NN#1	NN#2	NN#3	NN#4	NN#5
	Output variables	zDAPS	zDAPS	HAM-D	HAM-A	FF
	Input variables	Symptoms + TRYCATs + CERAD	TRYCATs + CERAD	TRYCATs + CERAD	TRYCATs + CERAD	TRYCATs + CERAD
Training	Sum of squares error	7.847	15.005	16.373	16.815	7.670
	Relative error	0.374	0.667	0.682	0.716	0.760
Testing	Sum of squares error	4.691	7.293	6.889	10.363	3.681
	Relative error	0.483	0.579	0.437	0.651	0.757
Holdout	Relative error	0.387	0.657	0.533	0.792	0.690
Correlation	Dependent variable and predicted value	0.778	0.622	0.675	0.504	0.523

shows the zHAM-D, zHAM-A, and zFF as well as zDAPS scores in the three study groups.

Supplementary file 2, figure 2, shows the PHEM dimension scores as well as the zSDS score in the three groups. Multivariate GLM analysis showed a highly significant effect of the three diagnostic groups on these five dimensions ($F = 8.40$, df = 10/216, $p < 0.001$, partial eta squared = 0.280). Tests for between-subject effects showed significant differences in all five scores among the groups (all $p < 0.0001$) with the strongest effects on psychotic symptoms (partial eta squared 0.415), excitation (partial eta squared 0.399), and negative symptoms (partial eta squared 0.361) and less on mannerism (partial eta squared 0.274) and hostility (partial eta squared 0.147).

Supplementary file 2, figure 3, shows the z scores of the seven CERAD tests, PC semantic memory, and PC episodic memory in the three subgroups. There was a highly significant effect of diagnosis on the nine CERAD values ($F = 4.53$, df = 18/200, $p < 0.001$, partial eta squared 0.289). Tests for between-subject effects showed differences among the study groups in all nine test results, except BNT ($p = 0.443$) and WordRecognition ($p = 0.308$). PC episodic memory is significantly greater in patients with higher zDAPS scores as compared with the other schizophrenia patients and controls. PC semantic memory is significantly increased in both schizophrenia groups as compared with controls. PC episodic memory ($p = 0.003$), MMSE ($p = 0.002$), WLM ($p = 0.001$), and WLR true ($p = 0.001$) and WLR false ($p = 0.001$) were significantly lower in those with higher zDAPs scores as compared with those with lower DAPS values, while there were no significant differences in PC semantic memory ($p = 0.191$) and VFT (0.914).

Supplementary file 2, figure 4, shows the three TRYCAT ratios in the three study groups. Multivariate GLM analysis showed a significant impact of diagnosis ($F = 6.95$, df = 6/220, $p = < 0.001$, partial eta squared 0.159). Between-subject effects showed that the three ratios were significantly higher in both schizophrenia groups than in controls, while there were no significant differences between both schizophrenia subgroups. The impact of diagnosis on the IgA NOX/PRO ratio (partial eta squared 0.257) was much greater than that on the Δ NOX/PRO ratio (partial eta squared 0.090) and Δ KA_3HK (partial eta squared 0.078).

Intercorrelation Matrix

Table 2 shows the intercorrelation matrices among HAM-D, HAM-A, and FF, on the one hand, and other symptom dimensions and CERAD tests results on the other. HAM-D score

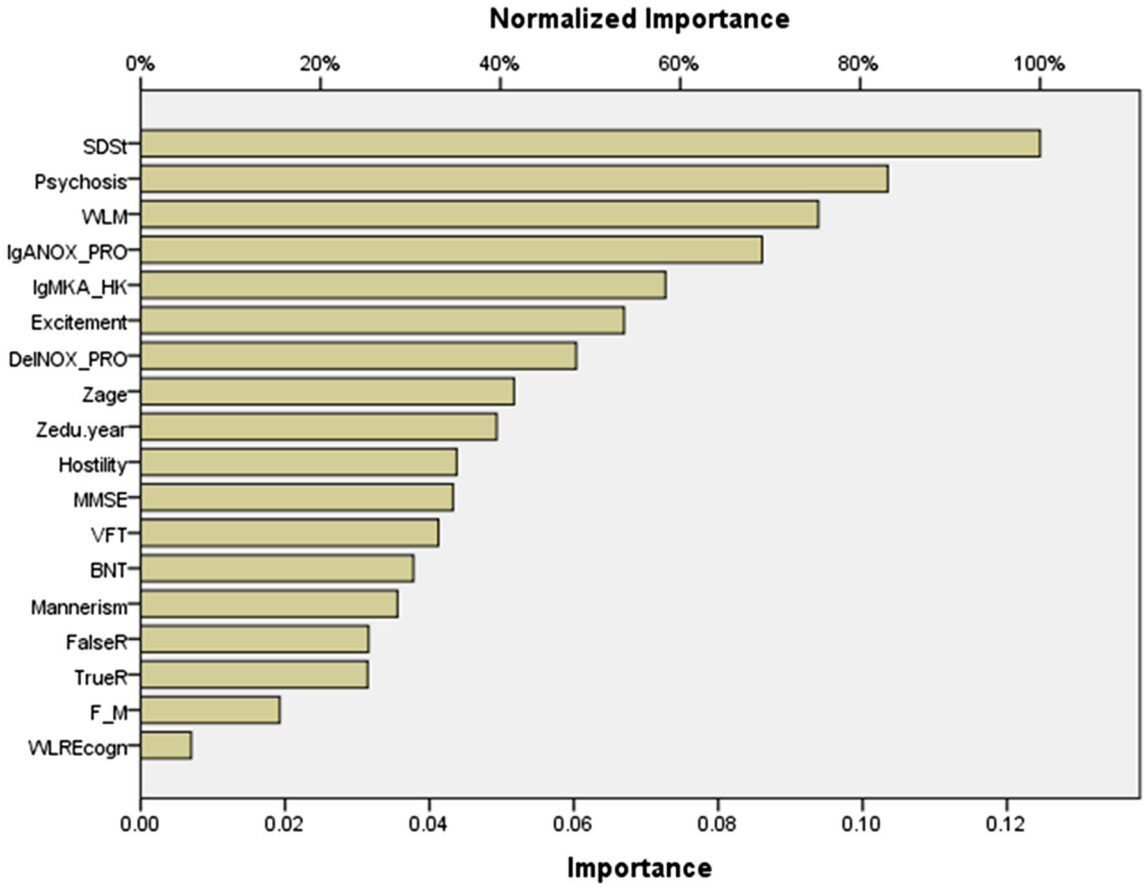

Fig. 1 Neural network importance chart with the normalized and relative importance of the input variables (including symptom dimensions) predicting the *z*-unit weighted composite score of depression, anxiety, and physiosomatic symptoms (zDAPS). SDSt: total Schedule for Deficit schizophrenia score. Psychosis, excitement, hostility, and mannerism: different symptoms dimensions of schizophrenia. WLM Word List Memory, MMSE Mini-Mental State Examination, VFT Verbal Fluency Test, BNT Boston Naming Test, FalseR Word List False Recall, TrueR Word List True Recall, WLREcogn Word List Recognition. F_M: sex (entered as dummy variable). Zage and Zedu.year: *z* scores of age and education (in years), respectively. IgANOX_PRO: computed as sum of *z* scores of QA (zQA) + zPA + zXA − zAA − zKA (index of increased noxious potential); IgMKA_HK: computed as zIgM KA − z3HK (index of lowered regulation of KA versus 3HK); DelNOX_PRO: computed as IgA (zQA + zPA + zXA + z3HK − zAA − zKA) − zIgM (zQA + zPA + zXA + 3HK − zAA − zKA) (a more comprehensive index of increased noxious potential) (QA quinolinic acid, PA picolinic acid, XA xanthurenic acid, AA anthranilic acid, KA kynurenic acid, 3HK 3-hydroxy-kynurenine)

was significantly associated with HAM-A and FF scores, all 4 PHEM and negative symptom dimensions, all CERAD test results, and age and education. The HAM-A total score was significantly associated with the FF score, all 4 PHEM dimensions and negative symptoms, and all CERAD tests results, except BNT score. The FF score was significantly correlated with all 4 PHEM dimensional scores, negative symptoms, and all CERAD tests scores as well as age and education.

Results of Factor Analysis

Table 3 shows the results of four different factor analyses. Firstly, we have examined the factor structure of the 4 PHEM and negative symptoms. Toward this end, we performed exploratory factor analysis using a polychoric correlation matrix. We found (FA#1) that the factoriability of the correlation matrix was accurate as indicated by KMO statistic (0.807). The UNICO (> 0.95), ECV (> 0.85), and I-REAL (< 0.300) values indicate that the 4 PHEM and SDS data should be treated as essentially unidimensional. In addition, only one eigenvalue was > 1.0, while the first factor explained 81.5% of the variance and all five variables loaded very highly on this factor. Consequently, we have investigated whether the data structure of the 4 PHEM and SDS data together with HAM-D, HAM-A, and FF data would be unidimensional. Therefore, we have added HAM-D, HAM-A, and FF scores to FA#1 and ran a second factor analysis. Table 3 (FA#2) shows that the factoriability of the correlation matrix was adequate (KMO statistic: 0.850). Nevertheless, the UNICO (0.879) and ECV (0.756) values were low, while the ECV value was rather high (> 0.300) indicating

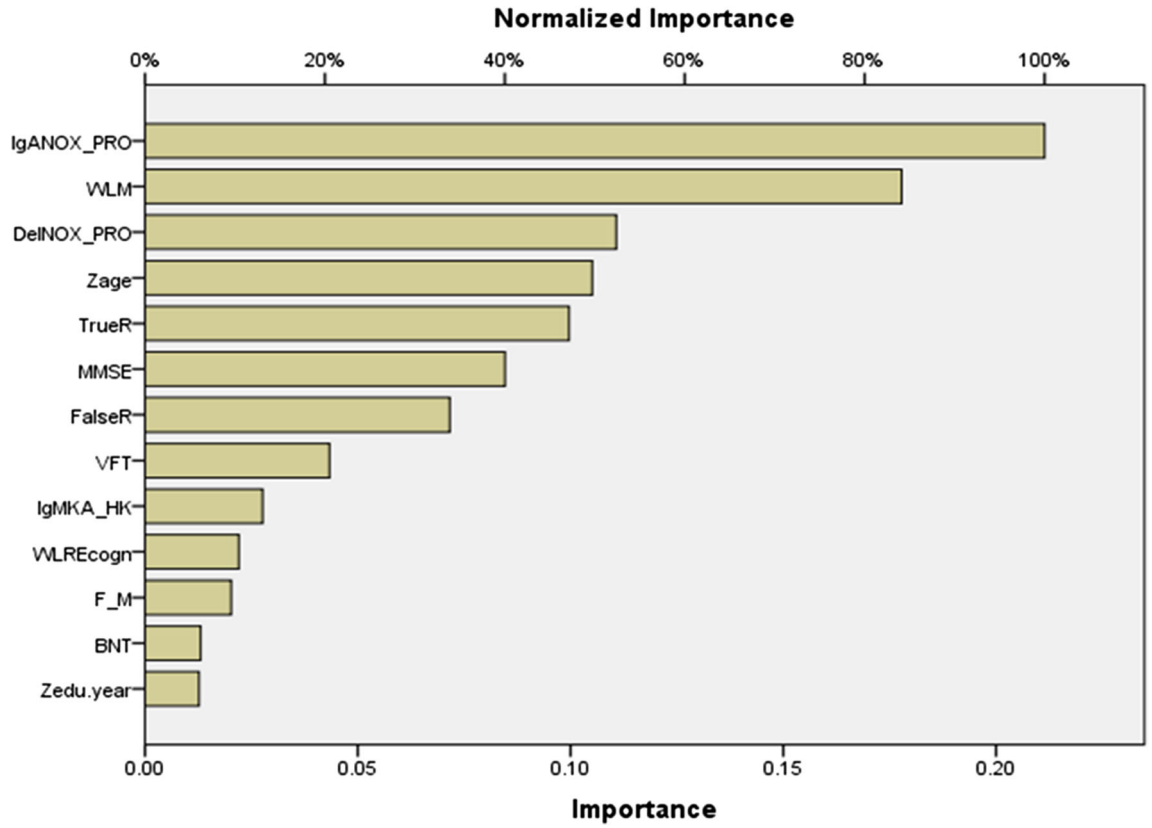

Fig. 2 Neural network importance chart with the normalized and relative importance of the input variables predicting the *z*-unit weighted composite score of depression, anxiety, and physiosomatic symptoms (zDAPS). WLM Word List Memory, MMSE Mini-Mental State Examination, VFT Verbal Fluency Test, BNT Boston Naming Test, FalseR Word List False Recall, TrueR Word List True Recall, WLREcogn Word List Recognition. F_M: sex (entered as dummy variable). Zage and Zedu.year: *z* scores of age and education (in years), respectively. IgANOX_PRO: computed as sum of *z* scores of QA (zQA) + zPA + zXA − zAA − zKA (index of increased noxious potential); IgMKA_HK: computed as zIgM KA − z3HK (index of lowered regulation of KA versus 3HK); DelNOX_PRO: computed as IgA (zQA + zPA + zXA + z3HK − zAA − zKA) − zIgM (zQA + zPA + zXA + 3HK − zAA − zKA) (a more comprehensive index of increased noxious potential) (QA quinolinic acid, PA picolinic acid, XA xanthurenic acid, AA anthranilic acid, KA kynurenic acid, 3HK 3-hydroxy-kynurenine)

that the data cannot be treated as unidimensional. In addition, two eigenvalues had values > 1.0 and consequently, we performed oblimin rotation on the first two factors. FA#3 shows the results of oblimin rotation performed on these eight variables. This model shows a good factoriability of the correlation matrix and shows that 74.9% of the variance was explained by the first two factors. The first factor loaded highly on the 4 PHEM dimensions and SDS, while the second factor loaded highly on HAM-D, HAM-A, and FF scores. Finally, we have examined the factor structure of the 4 PHEM dimension, SDS score, the 3 DAPS scores, and PC1 (episodic) and PC2 (semantic). We found that the FA#4 model shows good factoriability of the correlation matrix and that the first two factors explained 71.5% of the variance in the data. PC2 episodic memory loaded on factor 1 together with the 4 PHEM dimensions and SDS, and on factor 2 together with HAM-D, HAM-A, and FF. PC1 semantic memory did not load significantly on any of the factors.

Prediction of DAPS by CERAD Tests, Symptom Dimensions, and TRYCATs

In order to examine the associations between the DAPS scores and the CERAD tests we performed stepwise regression analyses with the HAM-D, HAM-A, or FF scores as dependent variables and CERAD scores as explanatory variables, while also entering age, sex, and education as additional explanatory variables. We found that 41.5% of the variance in HAM-D (regression #1) is explained by WLM and VFT combined. WLM explained 18.4% of the variance in HAM-A values (regression #2), while 26.3% of the variance in the FF score was explained by the regression on WLM (regression #3).

Consequently, we have examined the associations between the DAPS scores and the 4 PHEM dimensions and SDS score. Table 4, regression #4, shows that 52.2% of the variance in HAM-D is explained by the regression on SDS and psychotic symptoms. Of the variance in HAM-A, 25.5% is explained by the regression on psychotic symptoms (regression #5). Up to

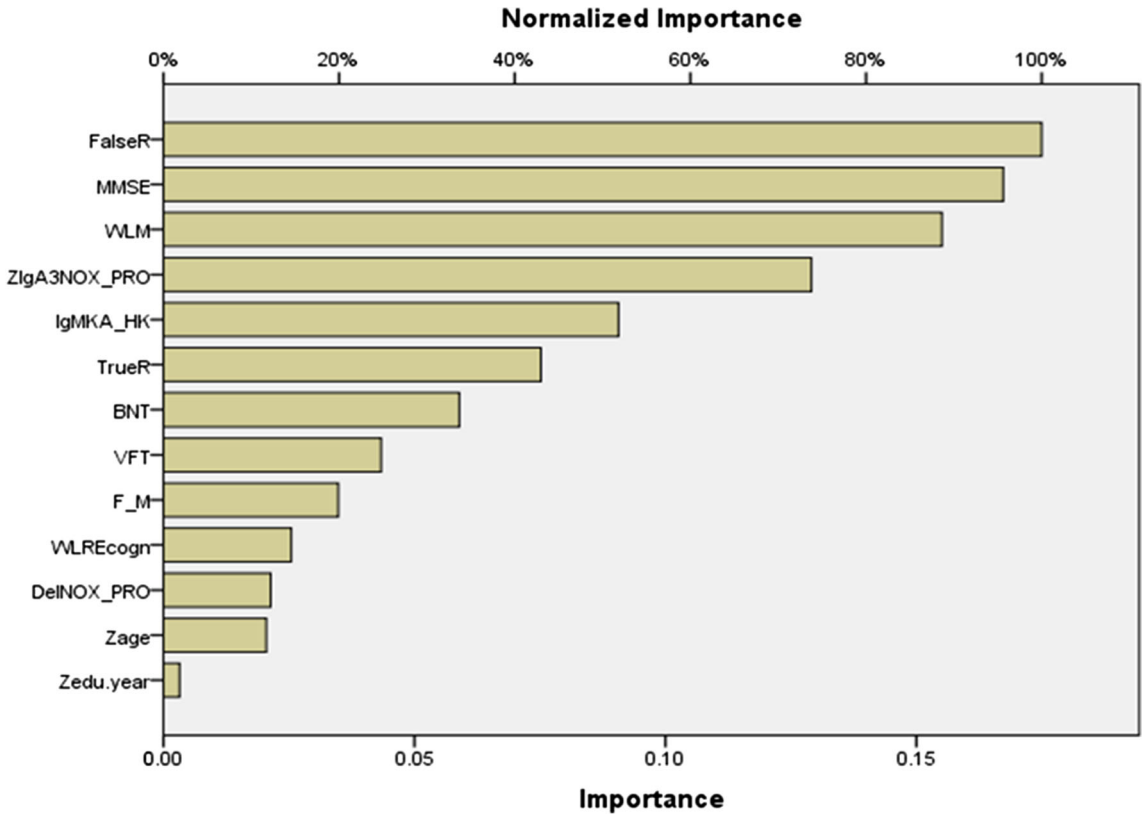

Fig. 3 Neural network importance chart with the normalized and relative importance of the input variables predicting the Hamilton Depression Rating Scale score (see legends to Fig. 2 for explanation of the input variables)

40.6% of the variance in the FF score was explained by the regression on psychotic symptoms and age (regression #6).

Finally, we have examined the associations between the three DAPS scores and CERAD tests scores, PHEM and negative symptoms and TRYCAT ratios. Therefore, the latter were used as explanatory variables in regression analyses. We found that (regression #7) 58.9% of the variance in HAM-D values was explained by the regression on excitement, VFT, IgA NOX_PRO, and WLM. Of the variance in HAM-A values, 29.9% was explained by psychotic symptoms and the IgA NOX_PRO ratio (regression #8). Regression #9 shows that 45.4% of the variance in the FF score could be explained by the regression on psychotic symptoms, IgA NOX_PRO ratio, and WLM.

Results of Neural Network Procedures

Firstly, using MLP, we predicted zDAPS values (output or target variable) using the 4 PHEM dimensions and SDS, three TRYCAT ratios, seven CERAD tests, age, sex, and education as input variables. We trained the network using two hidden layers with each 2 units, with hyperbolic tangent as activation function in hidden layer 1, and identity in hidden layer 2. Table 5, NN#1, shows the training results of the MLP network in the holdout sample. The relative errors are relatively constant among the training, testing, and holdout samples. Figure 1 shows the relative importance of the different independent (input) variables. Negative symptoms and psychosis are the most important predictors of zDAPs followed at a distance by WLM and IgA NOX_PRO ratio.

In Table 5, NN#2, we trained the network using the same input variables and architecture but now with three TRYCAT ratios, seven CERAD tests, age, sex, and education as input variables and the zDAPS score as dependent variable. Table 5, NN#2, shows that the error terms are relatively stable across the three samples. Figure 2 shows that the results of this importance chart are dominated by IgA NOX_PRO and WLM followed at a distance by ΔNOX_PRO.

In Table 5, NN#3, we trained the network using the same input variables and architecture but now with HAM-D as target variable. Figure 3 shows that the importance chart is dominated by false recall, MMSE, and WLM, while IgA NOX_PRO follows at a distance. Table 5, NN#4 and NN#5, shows the outcome of two other MLP network training with HAM-A and FF score as dependent variables. Figure 4 shows the relative importance of the input variables, namely WLM, false recall, and IgA NOX_PRO, are the most important predictors of the HAM-A score. Figure 5 shows that the FF score is best predicted by false recall and IgA NOX_PRO, followed at a distance by WLM and VFT.

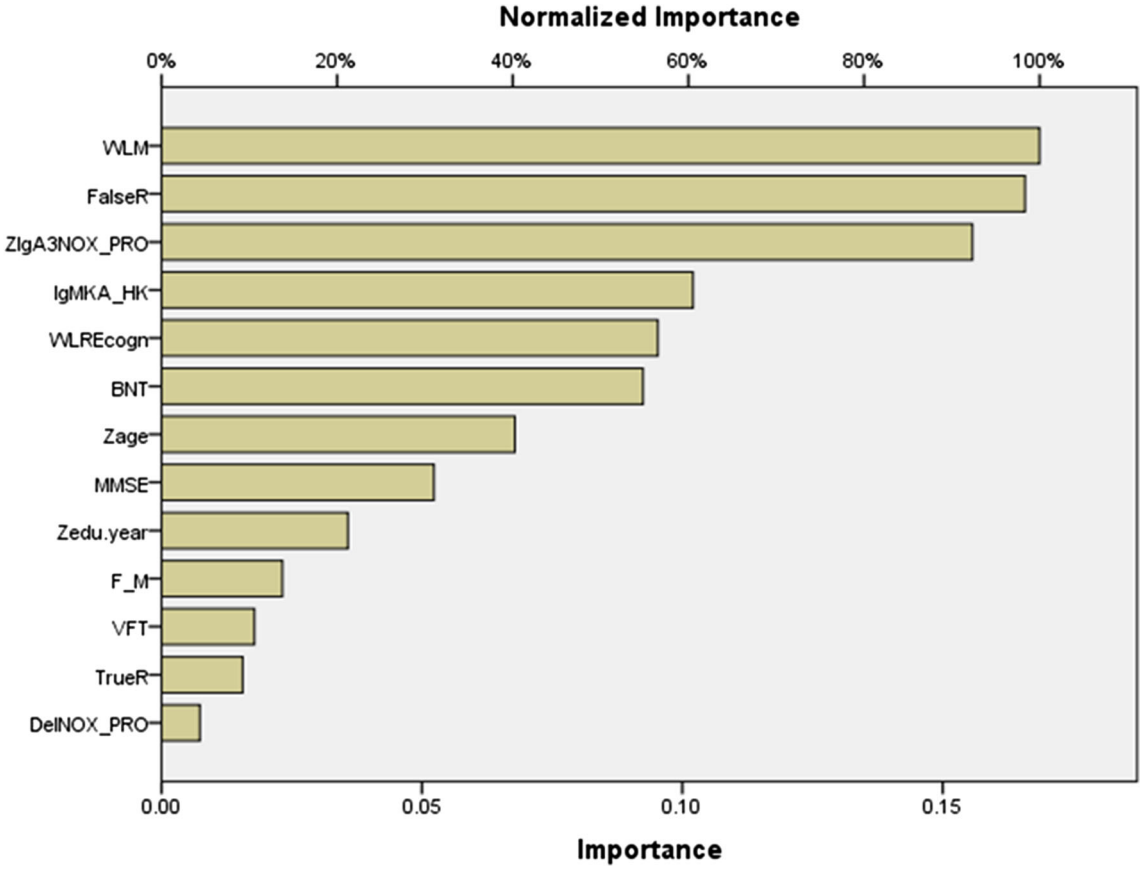

Fig. 4 Neural network importance chart with the normalized and relative importance of the input variables predicting the Hamilton Anxiety Rating Scale score (see legends to Fig. 2 for explanation of the input variables)

Discussion

The first major finding of this study is that negative and PHEM symptoms are the most dominant predictors of affective and physiosomatic symptoms in schizophrenia. Previous work suggests that both negative and positive symptoms may contribute to the emergence of anxiety and depression (Emsley et al. 1999; Kirschner et al. 2017). Nevertheless, our results show that when positive symptoms are differentiated into relevant dimensions, psychosis appears to be the most important predictor followed by excitation. We reviewed previously that schizophrenia patients are primed to develop affective symptoms in part via activated immune-inflammatory and oxidative and nitrosative processes, including increased activity of the TRYCAT pathway (Anderson et al. 2013). The affective and physiosomatic symptoms as well as negative and PHEM symptoms are strongly associated with changes in IgA/IgM TRYCAT pathway patterning indicating increased production and altered regulation of noxious TRYCATs (Kanchanatawan et al. 2017a, b, 2018a). The current findings show that not only depression but also anxiety and physiosomatic symptoms may be driven by negative, psychotic, and excitation symptoms, which in turn are associated with increased activity of the TRYCAT pathway or its antecedents and consequences (see "Introduction") (Kanchanatawan et al. 2017a).

A second major finding is that schizophrenia phenomenology comprises two main dimensions, the first being PHEM and negative symptoms, and the second dimension being affective and physiosomatic symptoms. PHEM and negative symptoms are strongly intercorrelated to the extent that they shape the main symptomatic dimension in schizophrenia phenomenology. These results indicate that prior distinctions in "type 1" (positive) and "type 2" (negative) symptoms (Crow 1985) are not adequate as "positive" symptoms are a conglomerate of different interrelated symptomatic dimensions which additionally are strongly associated with negative symptoms. Also, the differentiation of schizophrenia according to Bleuler (Jablensky 2010) into basic (loosening of associations and withdrawal from reality) and accessory symptoms (hallucinations and delusions) is not very helpful as those symptoms belong to a unitary dimension.

Previously, we have shown that there are strong associations between severity of depression and anxiety, for example, in unipolar depression and bipolar disorder (Maes et al. 1994; Cavicchioli et al. 2017). In addition, depression, anxiety, and physiosomatic symptoms, including fatigue and pain, shape a symptomatic dimension in individuals with multiple sclerosis and female breast carcinoma patients (Amtmann et al. 2015; So et al. 2009). Patients with chronic fatigue syndrome (CFS),

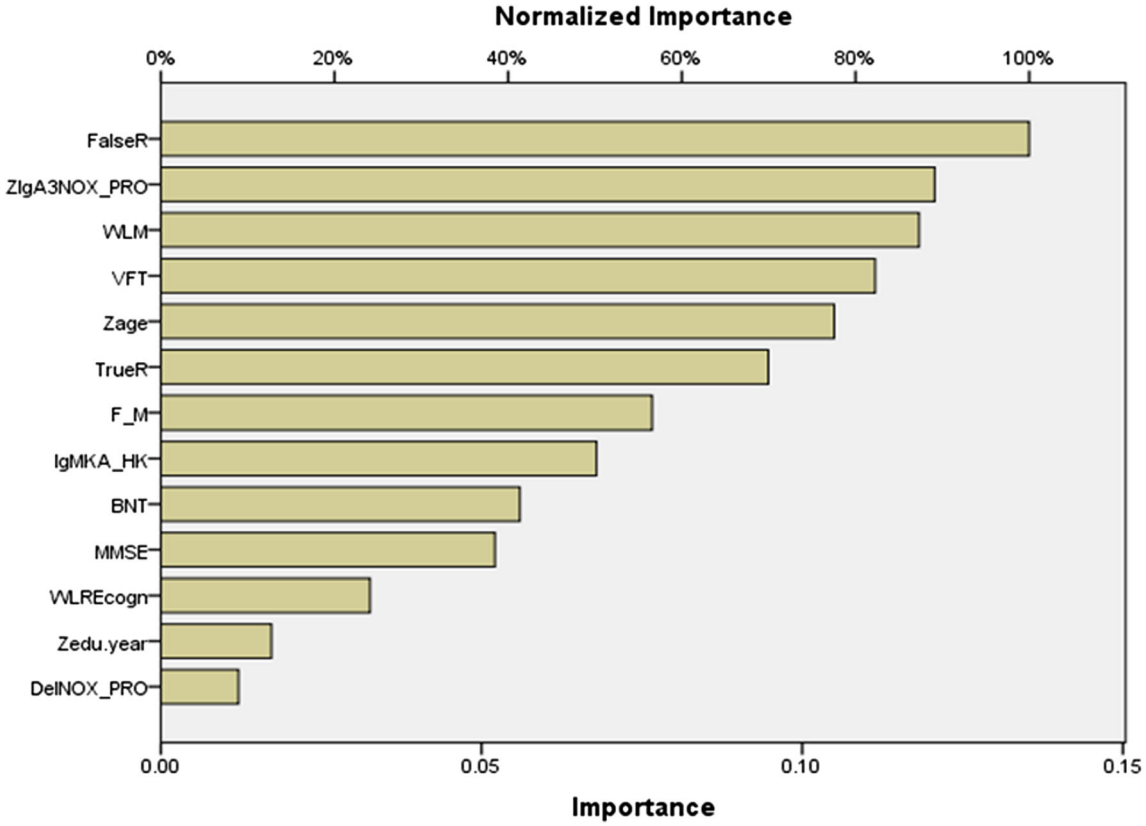

Fig. 5 Neural network importance chart with the normalized and relative importance of the input variables predicting the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale (FF) (see legends to Fig. 2 for explanation of the input variables)

which is characterized by physiosomatic symptoms, show significantly more mood and anxiety disorders than individuals without CFS (Janssens et al. 2015). Depression is also accompanied by increased levels of physiosomatic symptoms (Maes 2009, 2011), while these symptoms may have a similar neuro-immune pathophysiology as depressive symptoms (Maes et al. 2012a, b). Thus, it is not surprising that the affective and physiosomatic symptoms of schizophrenia belong to a same dimension that is associated with neuro-immune pathways.

A third major finding of our study is that affective and physiosomatic symptoms are strongly correlated with cognitive impairments indicating deficits in episodic memory, especially false memory creation and a general neuropsychological deficit. Moreover, factor analysis showed that impairments in episodic, but not semantic, memory are associated with both the affective/physiosomatic and PHEM/negative symptom dimensions. Previously, it was reported that depression, anxiety, and physiosomatic symptoms in schizophrenia are strongly associated with cognitive deficits (Kanchanatawan et al. 2017b, 2018b; Möser et al. 2006; Lysaker et al. 2005). In breast cancer patients, fatigue and anxiety are associated with perceived cognitive impairments (Li et al. 2015). Negative and PHEM symptoms are strongly

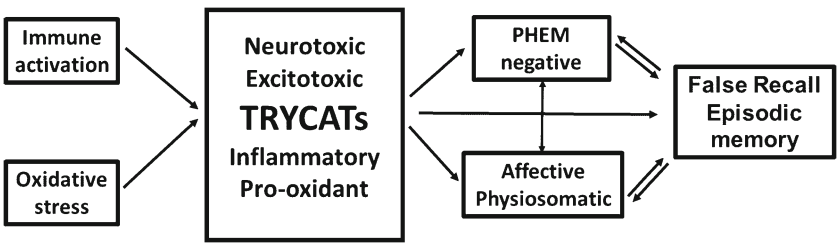

Fig. 6 Associations between the tryptophan catabolite (TRYCAT) pathway and the phenomenology of schizophrenia. Immune activation and oxidative stress may activate the TRYCAT pathway thereby exerting detrimental effects which may be causally associated with the negative, PHEM (psychosis, hostility, excitation and mannerism), affective (depression and anxiety), and physiosomatic symptoms as well as cognitive impairments in episodic memory and increased false memory creation. The latter may increase vulnerability to develop PHEM and maybe depressive symptoms

correlated with CERAD test results, including WLM and MMSE (Kanchanatawan et al. 2017a). All in all, deficits in episodic memory and lowered MMSE appear to be important determinants of negative, PHEM, affective, and physiosomatic symptoms.

Harvey et al. (2006) considered two models explaining the associations among negative symptoms and cognitive impairments. A first model considered that cognitive deficits and negative symptoms are identical features of schizophrenia. Nevertheless, our results show that deficits in episodic memory are strongly associated with the PHEM/negative and affective/physiosomatic dimensions. Harvey's second model considered that cognitive deficits and negative symptoms are distinct dimensions with a different pathophysiology. Nevertheless, also this model is not adequate as deficits in episodic memory are associated not only with negative symptoms, but also with PHEM and affective/physiosomatic symptoms, and because all dimensions are associated with changes in TRYCAT patterning.

Our results indicate that the associations between cognitive impairments and the different symptom dimensions are more complex than described by Harvey et al. (2006). Firstly, objective cognitive deficits in schizophrenia are in part a consequence of specific affective/physiosomatic symptoms, including agitation, retardation, fatigue, and autonomic symptoms (Kanchanatawan et al. 2018b). Moreover, depression coupled with anxiety may have adverse effects on immediate recall, acquisition amount and retrieval of newly learned information (Kizilbash et al. 2002). Secondly, SCCs, which are prominent symptoms of the depressive and physiosomatic dimensions, are strongly associated with objective measures of cognitive impairment (Kanchanatawan et al. 2017b). In this respect, it is thought that depressive processes may explain the SCCs associated with depression (Hubbard et al. 2016). Thirdly, cognitive deficits may increase risk to develop negative and affective symptoms in schizophrenia. Thus, "compromised cerebral functions," which often precede psychotic symptoms, may cause cognitive impairments (Harvey et al. 2006; Tamminga et al. 1998). Moreover, attentional impairments and abnormal learning processes may generate false memories and psychosis (Corlett et al. 2007). Depression may increase false memories containing negative information, while false memory creation may be present prior to depression and thus could constitute a vulnerability factor for depression (Myhre 2015).

Fourthly and most importantly, changes in TRYCAT patterning are associated with PHEM, negative, affective, and physiosomatic symptoms and with impairments in episodic memory, false recall, and MMSE (Kanchanatawan et al. 2017a, b, 2018a). We reviewed the translational evidence that TRYCATs, including 3-HK, QA, PA, and XA, via their neurotoxic, cytotoxic, excitotoxic, pro-inflammatory, and pro-oxidative effects, may generate these dimensions (Kanchanatawan et al. 2017a, b, 2018a). Moreover, also the antecedents of TRYCAT pathway activation, namely Thelper-1 and M1 macrophagic activation and neuro-oxidative stress, may generate the clinical dimensions of schizophrenia (Anderson and Maes 2013; Anderson et al. 2013; Davis et al. 2016). Therefore, it is most plausible that (a) there are reciprocal effects between the two main symptomatic dimensions of schizophrenia and cognitive deficits; and (b) multiple neuro-immune and neuro-oxidative pathways underpin PHEM, negative, cognitive, affective, and physiosomatic dimensions.

The current results should be interpreted with respect to the limitations of the study. Firstly, we performed a case-control study and consequently no causal models may be derived. Secondly, we only included patients in a stabilized phase and thus our results cannot be extrapolated to acute psychotic episodes. Strengths of the current study are the assessment of different symptomatic dimensions in association with cognitive CERAD tests using machine learning and a multivariate approach while controlling for possible confounders.

Figure 6 summarizes the findings of this study. Two main dimensions are detected in schizophrenia symptomatology, namely a first comprising psychotic, hostility, excitation, mannerism, and negative symptoms, and a second comprising affective and physiosomatic symptoms. Both dimensions are strongly associated with each other and with deficits in episodic memory including false recall. Both symptom dimensions and cognitive deficits may be driven by neuro-immune and neuro-oxidative pathways explaining their strong associations. In addition, there may be reciprocal associations between episodic memory and PHEM/negative and affective/physiosomatic symptom dimensions whereby impairments in episodic memory (including false memory creation) may increase the vulnerability to those symptom dimensions.

Author's Contributions All the contributing authors have participated in the manuscript. MM and BK designed the study. BK recruited patients and completed diagnostic interviews and rating scale measurements. MM carried out the statistical analyses. ST carried out the cognitive tests. SS and MG performed the TRYCAT assays. All authors (BK, ST, SS, AC, MG, AC, and MM) contributed to the interpretation of the data and writing of the manuscript. All authors approved the final version of the manuscript.

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Compliance with Ethical Standards All participants as well as the guardians of patients (parents or other close family members) provided written informed consent prior to participation in this study. The study was conducted according to Thai and International ethics and privacy laws. Approval for the study was obtained from the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok,

Thailand, which is in compliance with the International Guideline for Human Research protection as required by the Declaration of Helsinki, The Belmont Report, CIOMS Guideline, and International Conference on Harmonization in Good Clinical Practice (ICH-GCP).

Conflict of Interest The authors declare that they have no conflict of interest.

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