Revista de Psiquiatría
y Salud Mental

REVIEW ARTICLE

Differential blood-based biomarkers of psychopathological dimensions of schizophrenia[☆]

Leticia Garcia-Alvarez [a,b,c,*], Maria Paz Garcia-Portilla [a,b,c,d],
Leticia Gonzalez-Blanco [c,d], Pilar Alejandra Saiz Martinez [a,b,c,d],
Lorena de la Fuente-Tomas [c], Isabel Menendez-Miranda [c,d],
Celso Iglesias [c,d], Julio Bobes [a,b,c,d]

[a] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Oviedo, Asturias, Spain
[b] Instituto de Neurociencias del Principado de Asturias (INEUROPA), Asturias, Spain
[c] Área de Psiquiatría, Universidad de Oviedo, Asturias, Spain
[d] Servicio de Salud del Principado de Asturias (SESPA), Asturias, Spain

Abstract   Symptomatology of schizophrenia is heterogeneous, there is not any pathognomonic symptom. Moreover, the diagnosis is difficult, since it is based on subjective information, instead of markers. The purpose of this study is to provide a review of the current status of blood-based biomarkers of psychopathological dimensions of schizophrenia. Inflammatory, hormonal or metabolic dysfunctions have been identified in patients with schizophrenia and it has attempted to establish biomarkers responsible for these dysfunctions. The identification of these biomarkers could contribute to the diagnosis and treatment of schizophrenia.
© 2016 SEP y SEPB. Published by Elsevier España, S.L.U. All rights reserved.

Biomarcadores sanguíneos diferenciales de las dimensiones psicopatológicas de la esquizofrenia

Resumen   La sintomatología de la esquizofrenia es heterogénea, no existiendo ningún síntoma patognomónico de la misma. Además, su diagnóstico presenta dificultades, ya que se basa en información subjetiva en lugar de en marcadores. El propósito de este estudio es ofrecer una revisión del estado actual de los biomarcadores sanguíneos de las dimensiones psicopatológicas

de la esquizofrenia. En pacientes con esquizofrenia se han observado disfunciones inflamatorias, hormonales o metabólicas y se ha intentado establecer los biomarcadores responsables de esas disfunciones. La identificación de estos podría contribuir al diagnóstico y tratamiento de la esquizofrenia.

Introduction

Schizophrenia is a severe, complex and multifactor mental disorder that is characterised by its broad phenotypic variation, heterogeneous aetiology and fluctuating evolution. It commences in late adolescence or early adulthood and includes symptoms that are positive, negative, affective and cognitive. It affects at least 0.7% of the population.[1,2]

The symptoms of schizophrenia are heterogeneous, and it has no pathognomic symptom. It is also hard to diagnose, given that this is based on subjective information supplied by the patients themselves, or on the skill of the clinician in drawing inferences, rather than on markers such as laboratory tests or neuroimaging techniques. Due to this, current research centres on seeking markers which would make it possible to evaluate results in a more sensitive and precise way. Biological as well as neurophysiological markers were therefore studied, together with the psychiatric phenotype. Chan et al. reviewed a selection of studies of blood biomarkers in schizophrenia, bipolar disorder and major depression patients, to emphasise the importance of implementing valid biomarkers that not only make diagnosis and effective treatment possible, but which also improve the prognosis for patients.[3] The National Institute of Mental Health, in turn, has commenced the Research Domain Criteria Project,[4] the aim of which is to increase knowledge about the brain–behaviour relationship and to introduce this information about neural dysfunction in clinical practice, so that more effective treatments can be developed.

This study reviews the current status of blood biomarkers in the psychopathological dimensions of schizophrenia.

The positive dimension

There are no problems respecting the positive dimension of schizophrenia, as the instruments traditionally used measure it sufficiently well. The 2 most widely used scales in research as well as clinical practice are the Scale for the Assessment of Positive Symptoms[5] and the Positive and Negative Syndrome Scale for Schizophrenia (PANSS).[6–8]

Respecting the biomarkers for the positive dimension, a significant relationship has been detected between triglyceride levels in serum and the positive symptoms evaluated using the positive scale of the PANSS.[9] Additionally, a statistically significant inverse relationship has been detected between the plasma glucose levels and the positive symptoms evaluated using the PANSS, showing that an altered glucose metabolism may be associated with the pathogenesis and symptoms of schizophrenia in the early stages of the disease.[10] These authors conclude that the factors which best predict glucose levels in schizophrenia patients are insulin resistance, insulin and the positive symptom score in the PANSS.[10] Weight gain during antipsychotic treatment, in turn, predicts an improvement in the psychotic syndrome and positive symptoms.[11]

Alterations have also been detected in several inflammatory parameters: the levels of interleukin (IL)-1β seem to increase during acute phases[12] and the initial stages of the disease,[13] while levels of TGF-β and IL-6 also increase during acute phases.[12] Increased positive symptoms (hallucinations and deliria) seem to be associated with interleukin expression in schizophrenia patients;[14] thus for example, Dimitrov et al.[15] found a positive association between IL-6 levels and the positive symptoms evaluated using the PANSS. Tumour necrosis factor (TNF)-α has also been associated with the severity of the positive dimension,[16] as well as the number of hospitalisations and episodes of imbalance that reflect greater severity,[17] indicating the possibility that it may be a specific biomarker for this dimension. All of these data show the existence of state-specific markers, i.e., during the first psychotic episodes and acute relapses a series of inflammatory and associated immune processes arise.[12,18] Likewise, a positive relationship has been detected between peripheral levels of PCR and the severity of positive symptoms.[19]

Finally, the endocannabinoid system has been described as an endogenous anti-inflammatory neuroprotector system, and certain markers of this system, such as raised levels of anandamide, have been associated with positive symptoms.[20]

The negative dimension

The negative dimension of schizophrenia has traditionally been measured using the Brief Psychiatric Rating Scale,[21] the Scale for the Assessment of Negative Symptoms[22] and the PANSS.[6,22] Additionally, Marder et al. established the negative factor of the PANSS by means of factorial analysis. Nevertheless, the PANSS and even the negative factor obtained by Marder et al.[23] have important conceptual and psychometric limitations.[24,25]

This negative dimension has become of greater interest in recent years due to the diagnostic and therapeutic challenge it involves, together with the great impact of its cognitive symptoms on the functioning of individuals with schizophrenia.[24] Negative symptoms show minimum response to antipsychotic medication, and they are

therefore an attractive target for the development of new treatments. However, no antipsychotic drug used to date has proven effective in the treatment of the said symptoms.[26] Moreover, these symptoms are recognised, evaluated and recorded to a lesser extent than the positive symptoms, in spite of their persistence and impact. This is partially due to the limitations of evaluation tools. However, thanks to the National Institute of Mental Health initiative,[27–29] psychometric evaluation is developing swiftly, together with methodological refinement[24] thanks to the creation of new scales such as the Clinical Assessment Interview for Negative Symptoms[30] and the Brief Negative Symptom Scale.[31]

Regarding negative dimension biomarkers, post mortem studies of the brain and cerebrospinal fluid of patients with schizophrenia with negative symptoms have found a reduction in dopaminergic, noradrenergic and serotoninergic activity.[32] Ventricular widening is associated with the severity of negative symptoms, low monoamine activity and reduced cerebral glucose metabolism activity.[32] Additionally, an improvement in glutamatergic transmission has been associated with a reduction in negative symptoms.[32] Stradiol, the most powerful female hormone, influences not only primary and secondary sexual characteristics, but also embryonic and foetal growth and the development of brain aminergic networks which are involved in schizophrenia. Stradiol would have neuroprotector properties that may be relevant in the course of schizophrenia, and they could explain the gender differences that exist in terms of progression, negative symptoms and the therapeutic response of patients with schizophrenia.[32] According to Kaneda and Ohmori, stradiol concentrations would be a possible biomarker for negative symptoms in men.[33] The levels of S100B (a protein produced by the astroglias that regulates the balance between the proliferation and differentiation of neurons and glial cells) in serum have also been mentioned as a possible biomarkers of negative symptoms in schizophrenia.[34]

Arachidonic acid, a polyunsaturated omega-6 PUFA fatty acid, and docosahexaenoic acid, a polyunsaturated omega-3 PUFA fatty acid, are inversely correlated with the negative syndrome in schizophrenia patients, and treatment with antipsychotic drugs seems to increase these levels.[35] According to Chen et al.[36] triglycerides and HDL cholesterol are possibly the 2 main lipid components involved in the development of schizophrenia and the negative syndrome. They found a negative relationship between negative symptoms and triglycerides, and a positive relationship between them and HDL cholesterol[36] (Table 1). Another study found that high levels of triglycerides and total cholesterol are associated with a reduction in negative symptoms.[37] Additionally, negative symptoms correlate negatively with the BMI.[36] Likewise, a higher prevalence of metabolic syndrome was observed in patients with schizophrenia with negative symptoms.[38]

Some studies have observed other metabolic anomalies, such as diabetes, in patients with schizophrenia. The increased risk of this seems to be independent of the use of antipsychotic drugs[39,40] or poor health habits, and an increased risk is also even observed in the family members of these patients.[40] Nevertheless, a recent study found a comparable glucemic state in patients with schizophrenia untreated by antipsychotic drugs and healthy controls,

and subsequently antipsychotic drug treatment was associated with a glucose regulation alteration.[41] A study that compared 3 groups: patients with non-affective psychosis with deficit syndrome, i.e., with primary negative symptoms and a lack of discomfort or dysphoria; patients with psychosis without this syndrome, both recently diagnosed and therefore untreated by antipsychotic drugs; and control subjects, found significantly higher concentration of glucose in patients with psychosis and without deficit syndrome in comparison with patients with deficit syndrome. The latter in turn had significantly higher levels than the control subjects. Nevertheless, as these authors conclude, the results are not consistent with an interpretation according to which the group with deficit syndrome would have a more severe version of the same dysfunction, i.e., anomalous glucose metabolism. However, they did show that the differences between deficit syndrome and no deficit syndrome go beyond psychopathology.[42] On the other hand, it has been suggested that the PPARγ gene is involved in the alteration of glucose levels. Nevertheless, it is not known whether this gene is able to modify the risk of metabolic anomalies or psychosis, or whether it causes metabolic anomalies which lead to psychosis.[43]

Prolactin levels in patients con schizophrenia have also been associated with increased negative symptoms,[44–46] although they have not been associated with positive symptoms or the psychopathology in general.[45]

Respecting the immuno-inflammatory parameters, IL-1, IL-6 and TNF-α have been linked to negative symptoms.[47] Additionally, higher levels of PCR in patients with schizophrenia[48,49] have been associated with greater psychopathological severity as shown by the total score in the PANSS,[50,51] in the negative scub-scale[50,51] and in the general sub-scale.[50] Nevertheless, this has not been observed with the positive sub-scale in some studies,[50,51] although this is not so in all of them.[19]

The depressive dimension

Respecting the affective dimension of schizophrenia, depressive symptoms are common and form a central part of the disease.[52] They are also associated with a high rate of relapse, suicidal ideas, increased mortality, less social adjustment and a poor quality of life.[53–55] The level of depression has been evaluated using specific scales for this population, such as Calgary's Depression Scale,[56] as well as general scales used for patients with depressive disorders such as Hamilton's Scale for Depression.[57]

According to Chiappelli et al.[58] although there is no biomarker for depression in schizophrenia they suggest a lower concentration of myo-inositol in the brain as one of the potential neurochemical biomarkers. The neurotrophic factor deriving from the brain has, in turn, been positively associated with the symptoms of depression in schizophrenia.[59]

Low levels of cholesterol have also been associated with depression and affective disorders, as they may reduce the expression of serotoninergic receptors and cause a reduction in serotoninergic activity.[60] Nevertheless, in recent years this relationship has been called into question, given that some authors observed no relationship between cholesterol

Table 1 The most significant empirical studies.

Dimensions	Studies	Biomarkers
Positive	Solberg et al., 2015	Significant positive relationship with triglycerides
	Zhang et al., 2015	Significant negative relationship with glucose
	Meltzer et al., 2003	Weight gain during antipsychotic treatment predicts improved positive symptoms
	Miller et al., 2011	Increase in IL-1β, TGFβ, IL-6 in acute episodes
	Dimitrov et al., 2013	A significant positive relationship with IaIL-6
	Erbagci et al., 2001	An increase in TNF-α in acute episodes
	Hope et al., 2013	
	Fernandes et al., 2015	A significant positive relationship with PCR
	Guiffrida et al., 2004	Raised levels of anandamide in acute states of schizophrenia
Negative	Rao and Kolsch, 2003	Ventricular widening, fall in DA, NA and 5TH activity and brain glucose metabolism
	Kaneda and Ohmori, 2005	Significant negative relationship with stradiol
	Rothermundt et al., 2004	Significant positive relationship with serum levels of S100B
	Sethomet et al., 2005	Significant negative relationship with arachidonic acid (AA) and docosahexaenoic acid (DHA)
	Chen et al., 2014	Significant negative relationship with triglycerides and BMI
	Procyshyn et al., 2007	Significant positive relationship with HDL cholesterol
	Sicras-Mainar et al., 2015	Significant negative relationship with triglycerides and total cholesterol
	Kirkpatrick et al., 2009	Significant positive relationship with metabolic syndrome
	Akhondzadeh et al., 2006	Lower glucose concentrations in patients with psychosis and deficit syndrome
	Jose et al., 2015	
	Newcomer et al., 1992	Significant positive relationship with prolactin
	Meyer et al., 2011	
	Fan et al., 2007	Significant positive relationship with IL-1, IL-6 and TNF-α
	Fawzi et al., 2011	Significant positive relationship with PCR
Depressive	Chiapelli et al., 2015	Lower brain concentration of myo-inositol
	Noto et al., 2011	Significant positive relationship with BDNF
	Suttajit and Pilakanta, 2013	Significant positive relationship with metabolic syndrome
	Kawzi, 2011	Significant positive relationship with PCR
	Bioque et al., 2013	Negative relationship with fatty acid hydrolase amide
Cognitive	Rao and Kolsch, 2003	Lower serotoninergic activity in patients with cognitive function damage
	Tregellas et al., 2013	Increased hippocampus activity associated with cognitive dysfunction
	Krakowski and Czobor, 2011	Positive relationship between cholesterol levels and cognition
	Leung et al., 2014	Lower glucose levels have a facilitating effect on cognitive self-control tasks
	Ribeiro Santos et al., 2014	Association between the presence of inflammation and poorer cognitive performance
	Martinez-Cengotitabengoa et al., 2012	The relationship between oxidative stress and cognitive deficits
	Levine et al., 206	MCP-1 levels are negatively associated with learning and memory (verbal and working) while nitrite levels are negatively associated with the executive function
	Moustata et al., 2014	High levels of homocysteine may contribute to cognitive damage
	Meyer et al., 2011	
	Muller et al., 2005	IL-1, IL-6 and TNF-α have been associated with cognitive deterioration
	Zhang et al., 2013	Pharmacological inhibition of COX-2 has a positive effect on conceptual and abstract thinking
	Cabrera et al.	The relationship between IL-18 and the visual–spatial/constructive index
	Dickerson et al., 2007	15d-PGJ2 is associated with sustained attention
	Fan et al., 2007	
	Schwarz et al., 2012	High levels of PCR in serum have been associated with the severity of cognitive damage
	Schwarz et al., 2010	

level and psychiatric disorders.[61] The metabolic syndrome has been linked with depression in schizophrenia, more specifically with depressed mood, moderate insomnia and delay or inhibition.[62]

In connection with the immuno-inflammatory markers, higher levels of PCR have been linked with depression non-psychotic patients[63] as well as in patients with schizophrenia.[51]. Wen et al.[64] observed low levels of uric acid, a potential anti-oxidant, in depression but not in other disorders such as schizophrenia; however, no studies centre on evaluating these levels in patients with schizophrenia and predominantly depressive symptoms.

Finally, hydrolase fatty acid expression, an endocannabinoid system marker, has been shown to have a negative relationship with depressive symptoms in FEP.[65]

The cognitive dimension

Finally, neurocognitive faults have also been widely documented and are considered to be a core characteristic of schizophrenia.[66–70] These faults would be relatively independent of psychotic symptoms[71,72] and detectable before any sign of the disease.[73,74] Moreover, the cognitive deterioration shown by patients during a psychotic episode is similar to that which is observed in the same patients when the symptoms are under control.[75] This is why the correlations between the severity of psychotic symptoms and cognitive evaluation measurements are usually zero.[76,77] On the other hand, a sub-group of first degree schizophrenia patient family members without psychotic symptoms have displayed a pattern of cognitive alterations similar to those found in patients with schizophrenia.[78,79] This shows that certain cognitive alterations may be components of a genetic vulnerability for schizophrenia.

The most common cognitive faults include attention deficit, memory deficit (episodic and working), visual-spatial coordination and executive functions.[80–85] The data show a strong connection between these faults and the degree of functioning in patients with schizophrenia.[69,86] The presence and severity of cognitive symptoms must therefore be considered an important factor to determine the evolution of the disease,[87,88] as they are associated with a more severe course of the disease and frequent use of psychiatric departments.[89]

Increasing knowledge about neurocognitive faults and their impact on functioning has led to greater interest in possible interventions that could relieve these deficits, as well as in the creation of standardised batteries that would make it possible to measure neurocognition. Due to this the National Institute of Mental Health created the initiative Measurement and Treatment Research to Improve Cognition in Schizophrenia or MATRICS. One of the objectives of this is to create a cognitive battery by consensus that would make it possible to evaluate the said dimension in clinical trials for schizophrenia.[90] Other neuropsychological tests are also available for schizophrenia and other psychoses, such as the Brief Assessment of Cognition in Schizophrenia[91] or the Screen for Cognitive Impairment in Psychiatry.[92]

Post-mortem studies of the brand and cerebrospinal fluid in patients with schizophrenia have shown that serotoninergic activity seems to be reduced, not only in those patients with negative symptoms, but also in those with damage to the cognitive function.[32] Increased activity of the hippocampus is a characteristic of schizophrenia that has been found to be broadly associated with cognitive dysfunction, so that it has been suggested as a candidate biomarker for therapeutic development.[93]

Respecting analytical determinations, Krakowski and Czobor[94] found a positive relationship between cholesterol levels and cognition in patients with schizophrenia. This associated was especially marked for verbal memory. Additionally, they observed no interaction between medication in the different groups of patients (clozapine, olanzapine or haloperidol) and cholesterol level. I.e., the positive relationship was independent of medication. Some of the explanations which have been offered for these findings include the hypothesis that serum concentrations of cholesterol may influence serotoninergic and cholinergic neurotransmission, or that they correlate with polyunsaturated fatty acids.[94,95] Cholesterol may be a marker for polyunsaturated fatty acids, which are involved in the composition of the neuronal membrane and in the synthesis of cholinergic and serotoninergic neurotransmissors. However, in patients with euthymic bipolar disorders those who are obese were found to function less well cognitively than those with bipolar disorder and healthy controls of normal weight.[96] These authors suggest that there are several factors which may moderate the association between obesity and cognition in bipolar disorder, such as anthropometric data and lipidometry, as these may mediate the impact of the distribution of body fat in cognition.[96]

In connection with glucose, reduced levels of the same have been found to have a facilitating effect in patients with schizophrenia during cognitive self-control tasks, but not during physical self-control tasks.[97]

Inflammation markers have recently been associated with the cognitive function in schizophrenia, showing an association between the presence of inflammation and worse cognitive performance.[98] In FEP a connection has also been found between cognitive deficits and oxidative stress.[99] Patients with FEP have lower levels of antioxidants, catalase and peroxidase glutation in comparison with healthy controls. Levels of MCP-1 are negatively associated with learning and memory (verbal and working), while nitrite levels are negatively associated with executive function. Finally, glutation levels are associated positively with the executive function.[99] Homocysteine, another oxidative marker that is raised in patients with schizophrenia[100,101] seems to play an important role in cognitive processes, as has been found in studies that measure levels of homocysteine in elderly healthy subjects.[102,103] Based on these data, it has been suggested that high levels of homocysteine may contribute to the cognitive damage observed in patients with schizophrenia.[104,105] Nevertheless, in some studies with FEP no association was found between homocysteine levels and cognition, showing that levels of homocysteine may vary with clinical state, with higher levels in more advanced stages of the disease.[106,107]

Cytosines may play a central role in complex functions of the CNS such as cognition. Thus IL-1, IL-6 and TNF-α have been linked to cognitive deterioration.[47] The pro-inflammatory role of cytosines is mediated by prostaglandins and COX-2. It has been suggested that COX-2 is involved in cognitive function, as in animal models it was found to play an inhibitory role in the strength of synaptic connectivity, which is critical for learning and the consolidation of memory.[108] Moreover, Muller et al.[109] observed a positive effect on conceptual and abstract thought after pharmacological inhibition of COX-2, showing that COX2 inhibition probably influences different aspects of cognition, more specifically those associated with the prefrontal cortex. Zhang et al.[110] found a relationship between the visuospatial/constructional index and IL-18. Animal models show the neuroprotector role of prostaglandins in the CNS.[111] A recent study with FEP found a relationship between

sustained attention and 15d-PGJ2 after controlling possible confusion factors (age, sex, years of education, BMI, cannabis, tobacco and antipsychotic drug level); better performance in sustained attention tasks was associated with higher levels of anti-inflammatory expression (15d-PGJ2), leading the suggestion of considering this to be a protective factor for cognition.[107] Finally, high levels of PCR in serum have been associated with the severity of cognitive damage in patients with schizophrenia[50,112–114] and in patients with bipolar disorder.[115] Additionally, a recent study found an association between raised levels of PCR and sensory alterations (altered P50 suppression) in patients with schizophrenia.[116]

To conclude, different elements within the endocannabinoid system have been associated with different cognitive dominions in PEP.[117]

Conclusions

Current research into schizophrenia centres on the search for biomarkers that make it possible to evaluate the disease and make a less subjective diagnosis. Biomarkers have therefore been studied in connection not only with schizophrenia in general, but also with each one of its dimensions.

The positive dimension has been positively associated with triglycerides and negatively associated with glucose and weight gain. Immuno-inflammatory parameters (IL-1β, TGF-β, IL-6, TNF-α and PCR) have also been found to be positively associated with acute phases.

The negative dimension has been positively associated with ventricular widening, levels of S100B in serum, HDL cholesterol, metabolic syndrome, prolactin and immuno-inflammatory parameters (IL-1, IL-6, TNF-α and PCR). It has been associated negatively with dopamine activity, noradrenalin, serotonin, stradiol, arachidonic acid, docosahexaenoic acid, triglycerides, BMI, total cholesterol and glucose.

The depressive dimension has been linked positively to brain derived neurotrophic factor, the metabolic syndrome and PCR, and it has been negatively linked to the concentration in the brain of myo-inositol.

Finally, the cognitive dimension has been positively associated with cholesterol. On the other hand, reduced serotoninergic activity, increased hippocampus activity and immuno-inflammatory parameters (homocysteine, IL-1, IL-6, TNF-α and PCR) have been linked to cognitive deterioration. Some biomarkers have also been associated with specific cognitive tasks.

Nevertheless, in spite of all these studies, to date none of the biomarkers studied has achieved levels of precision that would allow it to be used in the diagnosis and treatment of individuals with schizophrenia.

Conflict of interests

The authors have no conflict of interests to declare.

References

1. Van Os J, Kapur S. Schizophrenia. Lancet. 2009;374:635–45.

2. Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jonsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. 2011;21:655–79.

3. Chan MK, Gottschalk MG, Haenisch F, Tomasik J, Ruland T, Rahmoune H, et al. Applications of blood-based protein biomarker strategies in the study of psychiatric disorders. Progr Neurobiol. 2014;122:45–72.

4. Insel TR. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. Am J Psychiatry. 2014;171:395–7.

5. Andreasen NC. Scale for the Assessment of Positive Symptoms. Iowa City, IA: University of Iowa; 1984.

6. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261–76.

7. Peralta V, Cuesta MJ. Psychometric properties of the Positive and Negative Syndrome Scale (PANSS) in schizophrenia. Psychiatry Res. 1994;53:31–40.

8. Peralta V, Cuesta MJ. Validación de la Escala de los Síndromes Positivo y Negativo (PANSS) en una muestra de esquizofrénicos españoles. Actas Luso Esp Neurol Psiquiatr. 1994;22:171–7.

9. Solberg DK, Bentsen H, Refsum H, Andreassen OA. Association between serum lipids and membrane fatty acids and clinical characteristics in patients with schizophrenia. Acta Psychiatr Scand. 2015;132:293–300.

10. Zhang XY, Chen DC, Tan YL, An HM, Zunta-Soares GB, Huang XF, et al. Glucose disturbances in first-episode drug-naive schizophrenia: relationship to psychopathology. Psychoneuroendocrinology. 2015;62:376–80.

11. Meltzer HY, Perry E, Jayathilake K. Clozapine-induced weight gain predicts improvement in psychopathology. Schizophr Res. 2003;59:19–27.

12. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry. 2011;70:663–71.

13. Drexhage RC, van der Heul-Nieuwenhuijsen L, Padmos RC, van Beveren N, Cohen D, Versnel MA, et al. Inflammatory gene expression in monocytes of patients with schizophrenia: overlap and difference with bipolar disorder. A study in naturalistically treated patients. Int J Neuropsychopharmacol. 2010;13:1369–81.

14. Kurian SM, Le-Niculescu H, Patel SD, Bertram D, Davis J, Dike C, et al. Identification of blood biomarkers for psychosis using convergent functional genomics. Mol Psychiatry. 2011;16:37–58.

15. Dimitrov DH, Lee S, Yantis J, Valdez C, Paredes RM, Braida N, et al. Differential correlations between inflammatory cytokines and psychopathology in veterans with schizophrenia: potential role for IL-17 pathway. Schizophr Res. 2013;151:29–35.

16. Erbagci AB, Herken H, Koyluoglu O, Yilmaz N, Tarakcioglu M. Serum IL-1beta, sIL-2R, IL-6, IL-8 and TNF-alpha in schizophrenic patients, relation with symptomatology and responsiveness to risperidone treatment. Mediators Inflamm. 2001;10:109–15.

17. Hope S, Ueland T, Steen NE, Dieset I, Lorentzen S, Berg AO, et al. Interleukin 1 receptor antagonist and soluble tumor necrosis factor receptor 1 are associated with general severity and psychotic symptoms in schizophrenia and bipolar disorder. Schizophr Res. 2013;145:36–42.

18. Takahashi M, Hayashi H, Watanabe Y, Sawamura K, Fukui N, Watanabe J, et al. Diagnostic classification of schizophrenia by neural network analysis of blood-based gene expression signatures. Schizophr Res. 2010;119:210–8.

19. Fernandes BS, Steiner J, Bernstein HG, Dodd S, Pasco JA, Dean OM, et al. C-reactive protein is increased in schizophrenia but

is not altered by antipsychotics: meta-analysis and implications. Mol Psychiatry. 2016;21:554–64.

20. Giuffrida A, Leweke FM, Gerth CW, Schreiber D, Koethe D, Faulhaber J, et al. Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. Neuropsychopharmacology. 2004;29:2108–14.

21. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep. 1962;10:790–812.

22. Andreasen NC. Scale for the Assessment of Negative Symptoms. Iowa City, IA: University of Iowa; 1983.

23. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry. 1997;58:538–46.

24. García-Portilla MP, Bobes J. The new challenge in identifying the negative syndrome of schizophrenia. Rev Psiquiatr Salud Ment. 2013;6:141–3.

25. Garcia-Portilla MP, Garcia L, Saiz PA, Al-Halabi S, Bobes-Bascaran T, Bascaran MT, et al. Psychometric evaluation of the negative syndrome of schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2015;265:559–66.

26. Rabinowitz J, Werbeloff N, Caers I, Mandel FS, Stauffer V, Menard F, et al. Negative symptoms in schizophrenia—the remarkable impact of inclusion definitions in clinical trials and their consequences. Schizophr Res. 2013;150:334–8.

27. Kirkpatrick B, Fenton W, Carpenter W, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull. 2006;32:296–303.

28. Gard DE, Kring AM, Germans GM, Horan WP, Green MF. Anhedonia in schizophrenia: distinction between anticipatory and consummatory pleasure. Schizophr Res. 2007;93:253–60.

29. Foussias G, Remington G. Negative symptoms in schizophrenia: Avolition and Occam's razor. Schizophr Bull. 2010;36:359–69.

30. Kring AM, Gur RE, Blanchard JJ, Horan WP, Reise SP. The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. Am J Psychiatry. 2013;170:165–72.

31. Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, et al. The Brief Negative Symptom Scale: psychometric properties. Schizophr Bull. 2011;37:300–5.

32. Rao ML, Kolsch H. Effects of estrogen on brain development and neuroprotection—implications for negative symptoms in schizophrenia. Psychoneuroendocrinology. 2003;28 Suppl 2:83–96.

33. Kaneda Y, Ohmori T. Relation between estradiol and negative symptoms in men with schizophrenia. J Neuropsychiatry Clin Neurosci. 2005;17:239–42.

34. Rothermundt M, Ponath G, Glaser T, Hetzel G, Arolt V. S100B serum levels and long-term improvement of negative symptoms in patients with schizophrenia. Neuropsychopharmacology. 2004;29:1004–11.

35. Sethom MM, Fares S, Bouaziz N, Melki W, Jemaa R, Feki M, et al. Polyunsaturated fatty acids deficits are associated with psychotic state and negative symptoms in patients with schizophrenia. Prostaglandins Leukot Essent Fatty Acids. 2010;83:131–6.

36. Chen SF, Hu TM, Lan TH, Chiu HJ, Sheen LY, Loh EW. Severity of psychosis syndrome and change of metabolic abnormality in chronic schizophrenia patients: severe negative syndrome may be related to a distinct lipid pathophysiology. Eur Psychiatry. 2014;29:167–71.

37. Procyshyn RM, Wasan KM, Thornton AE, Barr AM, Chen EY, Pomarol-Clotet E, et al. Changes in serum lipids, independent of weight, are associated with changes in symptoms during long-term clozapine treatment. J Psychiatry Neurosci. 2007;32:331–8.

38. Sicras-Mainar A, Maurino J, Ruiz-Beato E, Navarro-Artieda R. Prevalence of metabolic syndrome according to the presence of negative symptoms in patients with schizophrenia. Neuropsychiatr Dis Treat. 2015;11:51–7.

39. Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. Am J Psychiatry. 2003;160:284–9.

40. Spelman LM, Walsh PI, Sharifi N, Collins P, Thakore JH. Impaired glucose tolerance in first-episode drug-naive patients with schizophrenia. Diabet Med. 2007;24:481–5.

41. Wani RA, Dar MA, Margoob MA, Rather YH, Haq I, Shah MS. Diabetes mellitus and impaired glucose tolerance in patients with schizophrenia, before and after antipsychotic treatment. J Neurosci Rural Pract. 2015;6:17–22.

42. Kirkpatrick B, Fernandez-Egea E, Garcia-Rizo C, Bernardo M. Differences in glucose tolerance between deficit and nondeficit schizophrenia. Schizophr Res. 2009;107:122–7.

43. Liu YR, Hu TM, Lan TH, Chiu HJ, Chang YH, Chen SF, et al. Association of the PPAR-gamma gene with altered glucose levels and psychosis profile in schizophrenia patients exposed to antipsychotics. Psychiatry Investig. 2014;11:179–85.

44. Newcomer JW, Riney SJ, Vinogradov S, Csernansky JG. Plasma prolactin and homovanillic acid as markers for psychopathology and abnormal movements during maintenance haloperidol treatment in male patients with schizophrenia. Psychiatry Res. 1992;41:191–202.

45. Jose J, Nandeesha H, Kattimani S, Meiyappan K, Sarkar S, Sivasankar D. Association between prolactin and thyroid hormones with severity of psychopathology and suicide risk in drug free male schizophrenia. Clin Chim Acta. 2015;444:78–80.

46. Akhondzadeh S, Rezaei F, Larijani B, Nejatisafa AA, Kashani L, Abbasi SH. Correlation between testosterone, gonadotropins and prolactin and severity of negative symptoms in male patients with chronic schizophrenia. Schizophr Res. 2006;84:405–10.

47. Meyer U, Schwarz MJ, Müller N. Inflammatory processes in schizophrenia: a promising neuroimmunological target for the treatment of negative/cognitive symptoms and beyond. Pharmacol Ther. 2011;132:96–110.

48. Miller BJ, Culpepper N, Rapaport MH. C-reactive protein levels in schizophrenia: a review and meta-analysis. Clin Schizophr Relat Psychoses. 2014;7:223–30.

49. Singh B, Chaudhuri TK. Role of C-reactive protein in schizophrenia: an overview. Psychiatry Res. 2014;216:277–85.

50. Fan X, Pristach C, Liu EY, Freudenreich O, Henderson DC, Goff DC. Elevated serum levels of C-reactive protein are associated with more severe psychopathology in a subgroup of patients with schizophrenia. Psychiatry Res. 2007;149:267–71.

51. Fawzi MH, Fawzi MM, Said NS. C-reactive protein serum level in drug-free male Egyptian patients with schizophrenia. Psychiatry Res. 2011;190:91–7.

52. Zisook S, Nyer M, Kasckow J, Golshan S, Lehman D, Montross L. Depressive symptom patterns in patients with chronic schizophrenia and subsyndromal depression. Schizophr Res. 2006;86:226–33.

53. Rocca P, Bellino S, Calvarese P, Marchiaro L, Patria L, Rasetti R, et al. Depressive and negative symptoms in schizophrenia: different effects on clinical features. Compr Psychiatry. 2005;46:304–10.

54. Jones JS, Stein DJ, Stanley B, Guido JR, Winchel R, Stanley M. Negative and depressive symptoms in suicidal schizophrenics. Acta Psychiatr Scand. 1994;89:81–7.

55. Fialko L, Freeman D, Bebbington PE, Kuipers E, Garety PA, Dunn G, et al. Understanding suicidal ideation in psychosis: findings from the Psychological Prevention of Relapse in Psychosis (PRP) trial. Acta Psychiatr Scand. 2006;114:177–86.

56. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. Schizophr Res. 1990;3:247–51.

57. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–62.

58. Chiappelli J, Rowland LM, Wijtenburg SA, Muellerklein F, Tagamets M, McMahon RP, et al. Evaluation of myo-inositol as a potential biomarker for depression in schizophrenia. Neuropsychopharmacology. 2015;40:2157–64.

59. Noto CS, Gadelha A, Belangero SI, Smith MA, de Aguiar BW, Panizzuti B, et al. Association of biomarkers and depressive symptoms in schizophrenia. Neurosci Lett. 2011;505: 282–5.

60. Shrivastava S, Pucadyil TJ, Paila YD, Ganguly S, Chattopadhyay A. Chronic cholesterol depletion using statin impairs the function and dynamics of human serotonin (1A) receptors. Biochemistry. 2010;49:5426–35.

61. Ergün UG, Uguz S, Bozdemir N, Güzel R, Burgut R, Saatçi E, et al. The relationship between cholesterol levels and depression in the elderly. Int J Geriatr Psychiatry. 2004;19:291–6.

62. Suttajit S, Pilakanta S. Prevalence of metabolic syndrome and its association with depression in patients with schizophrenia. Neuropsychiatr Dis Treat. 2013;9:941–6.

63. Ford DE, Erlinger TP. Depression and C-reactive protein in US adults: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2004;164:1010–4.

64. Wen S, Cheng M, Wang H, Yue J, Li G, Zheng L, et al. Serum uric acid levels and the clinical characteristics of depression. Clin Biochem. 2012;45:49–53.

65. Bioque M, Garcia-Bueno B, Macdowell KS, Meseguer A, Saiz PA, Parellada M, et al. Peripheral endocannabinoid system dysregulation in first-episode psychosis. Neuropsychopharmacology. 2013;38:2568–77.

66. Elvevag B, Goldberg TE. Cognitive impairment in schizophrenia is the core of the disorder. Crit Rev Neurobiol. 2000;14: 1–21.

67. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the right stuff? Schizophr Bull. 2000;26:119–36.

68. Dickinson D, Iannone VN, Wilk CM, Gold JM. General and specific cognitive deficits in schizophrenia. Biol Psychiatry. 2004;55:826–33.

69. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr Res. 2004;72:41–51.

70. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology. 1998;12:426–45.

71. Lewis R. Should cognitive deficit be a diagnostic criterion for schizophrenia? J Psychiatry Neurosci. 2004;29:102–13.

72. Rund BR, Melle I, Friis S, Johannessen JO, Larsen TK, Midboe LJ, et al. The course of neurocognitive functioning in first-episode psychosis and its relation to premorbid adjustment, duration of untreated psychosis, and relapse. Schizophr Res. 2007;91:132–40.

73. Cornblatt BA, Lenzenweger MF, Dworkin RH, Erlenmeyer-Kimling L. Childhood attentional dysfunctions predict social deficits in unaffected adults at risk for schizophrenia. Br J Psychiatry. 1992;161 Suppl 18:59–64.

74. Harvey PD. When does cognitive decline occur in the period prior to the first episode of schizophrenia? Psychiatry (Edgmont). 2009;6:12–4.

75. Finkelstein JR, Cannon TD, Gur RE, Gur RC, Moberg P. Attentional dysfunctions in neuroleptic-naive and neuroleptic-withdrawn schizophrenic patients and their siblings. J Abnorm Psychol. 1997;106:203–12.

76. Bilder RM, Goldman RS, Robinson D, Reiter G, Bell L, Bates JA, et al. Neuropsychology of first-episode schizophrenia: initial

characterization and clinical correlates. Am J Psychiatry. 2000;157:549–59.

77. Goldberg TE, Gold JM, Greenberg R, Griffin S, Schulz SC, Pickar D, et al. Contrasts between patients with affective disorders and patients with schizophrenia on a neuropsychological test battery. Am J Psychiatry. 1993;150:1355–62.

78. Asarnow RF, Nuechterlein KH, Subotnik KL, Fogelson DL, Torquato RD, Payne DL, et al. Neurocognitive impairments in nonpsychotic parents of children with schizophrenia and attention-deficit/hyperactivity disorder: the University of California, Los Angeles Family Study. Arch Gen Psychiatry. 2002;59:1053–60.

79. Cannon TD, Zorrilla LE, Shtasel D, Gur RE, Gur RC, Marco EJ, et al. Neuropsychological functioning in siblings discordant for schizophrenia and healthy volunteers. Arch Gen Psychiatry. 1994;51:651–61.

80. Fioravanti M, Carlone O, Vitale B, Cinti ME, Clare L. A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. Neuropsychol Rev. 2005;15:73–95.

81. Achim AM, Lepage M. Episodic memory-related activation in schizophrenia: meta-analysis. Br J Psychiatry. 2005;187:500–9.

82. Ranganath C, Minzenberg MJ, Ragland JD. The cognitive neuroscience of memory function and dysfunction in schizophrenia. Biol Psychiatry. 2008;64:18–25.

83. Laws KR. A meta-analytic review of Wisconsin Card Sort studies in schizophrenia: general intellectual deficit in disguise? Cogn Neuropsychiatry. 1999;4:1–30.

84. Lee J, Park S. Working memory impairments in schizophrenia: a meta-analysis. J Abnorm Psychol. 2005;114: 599–611.

85. Barch DM, Smith E. The cognitive neuroscience of working memory: relevance to CNTRICS and schizophrenia. Biol Psychiatry. 2008;64:11–7.

86. Keefe RS, Fenton WS. How should DSM-V criteria for schizophrenia include cognitive impairment? Schizophr Bull. 2007;33:912–20.

87. Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, ''just the facts'' what we know in 2008. 2. Epidemiology and etiology. Schizophr Res. 2008;102:1–18.

88. Fogelson DL, Nuechterlein KH, Asarnow RF, Payne DL, Subotnik KL. Validity of the family history method for diagnosing schizophrenia, schizophrenia-related psychoses, and schizophrenia-spectrum personality disorders in first-degree relatives of schizophrenia probands. Schizophr Res. 2004;68:309–17.

89. Harvey PD, Sharma T. Understanding and treating cognition in schizophrenia. A clinician's handbook. London: Martin Dunitz; 2002.

90. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, et al. The MATRICS Consensus Cognitive Battery, part 1: Test selection, reliability, and validity. Am J Psychiatry. 2008;165:203–13.

91. Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res. 2004;68:283–97.

92. Purdon SE. The Screen for Cognitive Impairment in Psychiatry (SCIP): instructions and three alternate forms. Edmonton, Alberta: PNL Inc.; 2005.

93. Tregellas JR, Smucny J, Harris JG, Olincy A, Maharajh K, Kronberg E, et al. Intrinsic hippocampal activity as a biomarker for cognition and symptoms in schizophrenia. Am J Psychiatry. 2014;171:549–56.

94. Krakowski M, Czobor P. Cholesterol and cognition in schizophrenia: a double-blind study of patients randomized

to clozapine, olanzapine and haloperidol. Schizophr Res. 2011;130:27–33.

95. Hibbeln JR, Umhau JC, George DT, Shoaf SE, Linnoila M, Salem N. Plasma total cholesterol do not predicts CSF neurotransmitter metabolites. Am J Clin Nutr. 2000;71 Suppl 1:331–8.

96. Lackner N, Bengesser SA, Birner A, Painold A, Fellendorf FT, Platzer M, et al. Abdominal obesity is associated with impaired cognitive function in euthymic bipolar individuals. World J Biol Psychiatry. 2015:1–12.

97. Leung CM, Stone WS, Lee EH, Seidman LJ, Chen EY. Impaired facilitation of self-control cognition by glucose in patients with schizophrenia: a randomized controlled study. Schizophr Res. 2014;156:38–45.

98. Ribeiro-Santos A, Lucio Teixeira A, Salgado JV. Evidence for an immune role on cognition in schizophrenia: a systematic review. Curr Neuropharmacol. 2014;12:273–80.

99. Martínez-Cengotitabengoa M, Mac-Dowell KS, Leza JC, Micó JA, Fernandez M, Echevarría E, et al. Cognitive impairment is related to oxidative stress and chemokine levels in first psychotic episodes. Schizophr Res. 2012;137:66–72.

100. Nishi A, Numata S, Tajima A, Kinoshita M, Kikuchi K, Shimodera S, et al. Meta-analyses of blood homocysteine levels for gender and genetic association studies of the MTHFR C677T polymorphism in schizophrenia. Schizophr Bull. 2014;40:1154–63.

101. Muntjewerff JW, Kahn RS, Blom HJ, den Heijer M. Homocysteine, methylenetetrahydrofolate reductase and risk of schizophrenia: a meta-analysis. Mol Psychiatry. 2006;11:143–9.

102. Prins ND, Den Heijer T, Hofman A, Koudstaal PJ, Jolles J, Clarke R, et al. Homocysteine and cognitive function in the elderly: the Rotterdam Scan Study. Neurology. 2002;59:1375–80.

103. Hooshmand B, Solomon A, Kareholt I, Rusanen M, Hanninen T, Leiviska J, et al. Associations between serum homocysteine, holotranscobalamin, folate and cognition in the elderly: a longitudinal study. J Intern Med. 2012;271:204–12.

104. Moustafa AA, Hewedi DH, Eissa AM, Frydecka D, Misiak B. Homocysteine levels in schizophrenia and affective disorders—focus on cognition. Front Behav Neurosci. 2014;8:343.

105. Levine J, Stahl Z, Sela BA, Ruderman V, Shumaico O, Babushkin I, et al. Homocysteine-reducing strategies improve symptoms in chronic schizophrenic patients with hyperhomocysteinemia. Biol Psychiatry. 2006;60:265–9.

106. Ayesa-Arriola R, Pérez-Iglesias R, Rodríguez-Sánchez JM, Mata I, Gómez-Ruiz E, García-Unzueta M, et al. Homocysteine and cognition in first-episode psychosis patients. Eur Arch Psychiatry Clin Neurosci. 2012;262:557–64.

107. Cabrera B, Bioque M, Penadés R, González-Pinto A, Parellada M, Bobes J, et al. Cognition and psychopathology in first-episode of psychosis: are they related to inflammation? Psychol Med. 2016:1–12.

108. Murray HJ, O'Connor JJ. A role for COX-2 and p38 mitogen activated protein kinase in long-term depression in the rat dentate gyrus in vitro. Neuropharmacology. 2003;44:374–80.

109. Muller N, Riedel M, Schwarz MJ, Engel RR. Clinical effects of COX-2 inhibitors on cognition in schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2005;255:149–51.

110. Zhang XY, Chen da C, Xiu MH, Tang W, Zhang F, Liu L, et al. Plasma total antioxidant status and cognitive impairments in schizophrenia. Schizophr Res. 2012;139:66–72.

111. Toyomoto M, Ohta M, Okumura K, Yano H, Matsumoto K, Inoue S, et al. Prostaglandins are powerful inducers of NGF and BDNF production in mouse astrocyte cultures. FEBS Lett. 2004;562:211–5.

112. Schwarz E, Guest PC, Rahmoune H, Harris LW, Wang L, Leweke FM, et al. Identification of a biological signature for schizophrenia in serum. Mol Psychiatry. 2012;17:494–502.

113. Schwarz E, Izmailov R, Spain M, Barnes A, Mapes JP, Guest PC, et al. Validation of a blood-based laboratory test to aid in the confirmation of a diagnosis of schizophrenia. Biomark Insights. 2010;5:39–47.

114. Dickerson F, Stallings C, Origoni A, Boronow J, Yolken R. C-reactive protein is associated with the severity of cognitive impairment but not of psychiatric symptoms in individuals with schizophrenia. Schizophr Res. 2007;93:261–5.

115. Dickerson F, Stallings C, Origoni A, Vaughan C, Khushalani S, Yolken R. Elevated C-reactive protein and cognitive deficits in individuals with bipolar disorder. J Affect Disord. 2013;150:456–9.

116. Micoulaud-Franchi JA, Faugere M, Boyer L, Fond G, Richieri R, Faget C, et al. Elevated C-reactive protein is associated with sensory gating deficit in schizophrenia. Schizophr Res. 2015;165:94–6.

117. Bioque M, Cabrera B, García-Bueno B, Mac-Dowell KS, Torrent C, Saiz PA, et al. Dysregulated peripheral endocannabinoid system signaling is associated with cognitive deficits in first-episode psychosis. J Psychiatr Res. 2016;75:14–21.