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Letter to the Editor

Plasma metabolites in first episode psychoses

Dears Editors,

Accumulating evidence has implicated alterations in membrane phospholipid composition and metabolism including increased Phospholipase A_2 (PLA_2) activity (Gattaz et al., 1987; Schaeffer et al., 2012) in both schizophrenia (SCZ) (Smesny et al., 2015) and bipolar disorder (BD) (Ribeiro et al., 2017). This increased membrane phospholipid degradation increases membrane fluidity and disrupt neuronal function (Eckert et al., 2011). Recent reports on lipid profiles suggest that fatty acids, lipid peroxidation metabolites, steroids, and phospholipids are putative candidate biomarkers for neuropsychiatric diseases (Davison et al., 2017). These metabolites represent the final interaction products between genetic, physiological, and environmental factors (Quinones and Kaddurah-Daouk, 2009).

In the present study, we quantify the plasmatic metabolites of patients with SCZ and BD compared to healthy controls (HC) and attempt to define a set of metabolites that may aid in this differentiation, since it is unlikely that a single metabolite will have this ability.

This open-label-study was conducted at the Institute of Psychiatry, University of Sao Paulo, Brazil. The sample consisted of 55 drug-naïve patients (28 SCZ and 27 BD) and 30 HC. All participants were <60 years old and were middle-income, community-dwelling subjects from the hospital catchment area. The study was approved by the Local Ethics Committee (No. 943.883) and performed in accordance with the Helsinki declaration. All subjects provided written informed consent prior to inclusion in the study. The SCZ and BD diagnoses were established according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and SCID-I/P-Structured Clinical Interview Disorders Axis I for DSM–IV version 2.0. SCZ patients were assessed using the Positive and Negative Symptoms Scale (PANSS). Depressive and manic symptoms were assessed for BD patients by the Hamilton Depression Rating Scale (HAM-D) and Young's Mania Rating Scale (YMRS). Subjects with other psychiatric or neurological disorders were excluded.

All results were controlled for years of education and gender because of statistical differences among groups (sociodemographic characteristics are summarized in Supplementary Table 1).

Blood samples were collected in EDTA-coated tubes (Vacuntainer, Bencton Dickison) for plasma metabolite determination after 8 h of fasting. Samples were centrifuged at 20 °C and 1800 *g* for 15 min and stored at −80 °C until analysis. We analyzed endogenous metabolites with an AbsoluteIDQ® p180 Kit (BIOCRATES Life Science AG, Innsbruck, Austria), and performed a targeted quantitative and quality controlled assay using flow injection analysis (FIA), followed by mass spectrometry (MS/MS). This analysis was performed on a triple-quadrupole mass spectrometer (Xevo TQ-S, Waters Corporation, USA), and the plasma samples were processed according manufacturer instructions. MetIDQ software (BIOCRATES) was used to calculate the concentrations of metabolites.

Statistical analyses were performed with the R Program (http://www.r-project.org/) and SPSS (Statistical Package for Social Sciences, v.18, Chicago, IL). We used a Chi-square test or Fisher's exact test for comparisons of nominal parameters and Student *t*-test or ANOVA for quantitative variables. We used the Classification and Regression Tree (CART) method for group classification.

Lysophosphatidylcholines (LPC) and phosphatidylcholines (PC) levels were higher in patients with SCZ and BD compared to HC. Patients with BD also presented higher LPC and PC levels than patients with SCZ, while sphingolipid concentrations were higher in patients with BD and lower in patients with SCZ compared to HC. Acylcarnitine (AC) levels differed according to isoform and there was a mismatch in the data for this class (Supplementary Table 2).

We reached an 87.1% accuracy in differentiating patients with SCZ, BD, and HC using the CART method. According to these results, levels of PCaaC26:0 were higher than 1.35 nmol/L in node 9 characterized BD patients with a predictive value of 84.4%. In node 5, a combination of PCaaC26:0 (<1.35 nmol/L), PCaaC38:4 (>92.65 nmol/L), and PCaaC34:3 (<8.275 nmol/L), classified participants as HC with predictive value of 83.3%. In node 8, a combination of PCaaC26:0 (<1.35 nmol/L), PCaaC34:3 (>8.275 nmol/L), and C16-OH (<0.049 nmol/L) differentiated SCZ patients with predictive value of 100% (Fig. 1).

Given the complexity and heterogeneity of psychiatric disorders, a combination of multiple biomarkers may better reflect etiology and provide improved insights into the underlying biological processes (Boksa, 2013). The CART method indicated that BD patients present increased concentrations of PCaaC26:0, a saturated phosphatidylcholine that increases membrane rigidity, reflecting the pathogenic process. However, unsaturated phosphatidylcholines (PCaaC38:4 and PCaaC34:3) with an intermediate degree of saturation are associated with normal plasma membrane function and HCs. The determination of patients with SCZ requires the combination of PCs and ACs. The decrease in C16-OH seen in patients with schizophrenia is associated with cell toxicity and symptom onset (Cuturic et al., 2016).

We report that plasma levels of PC and AC may be useful in the differentiation of patients with SCZ and BD. In addition to the importance of distinguishing HC from affected individuals, the capacity to accurately distinguish between patients with SCZ and BD in first episode psychosis is relevant, considering the high rates of misdiagnosis between both diseases at this initial stage. Early diagnosis in the first onset is important for the management of psychosis. The inclusion of a HC group in this study emphasizes the applicability of the model and the inclusion of drug-naive patients represents a strength of the study since antipsychotics have been shown to affect membrane phospholipid levels (Schmitt et al., 2001).

This is the first study to identify metabolomic signatures capable of distinguishing patients with SCZ or BD in first onset psychosis. The small sample size from each diagnostic group is an important limitation of the study, therefore the results should be replicated in an independent and larger sample to reinforce these findings. The small sample size from each diagnostic group is an important limitation of the

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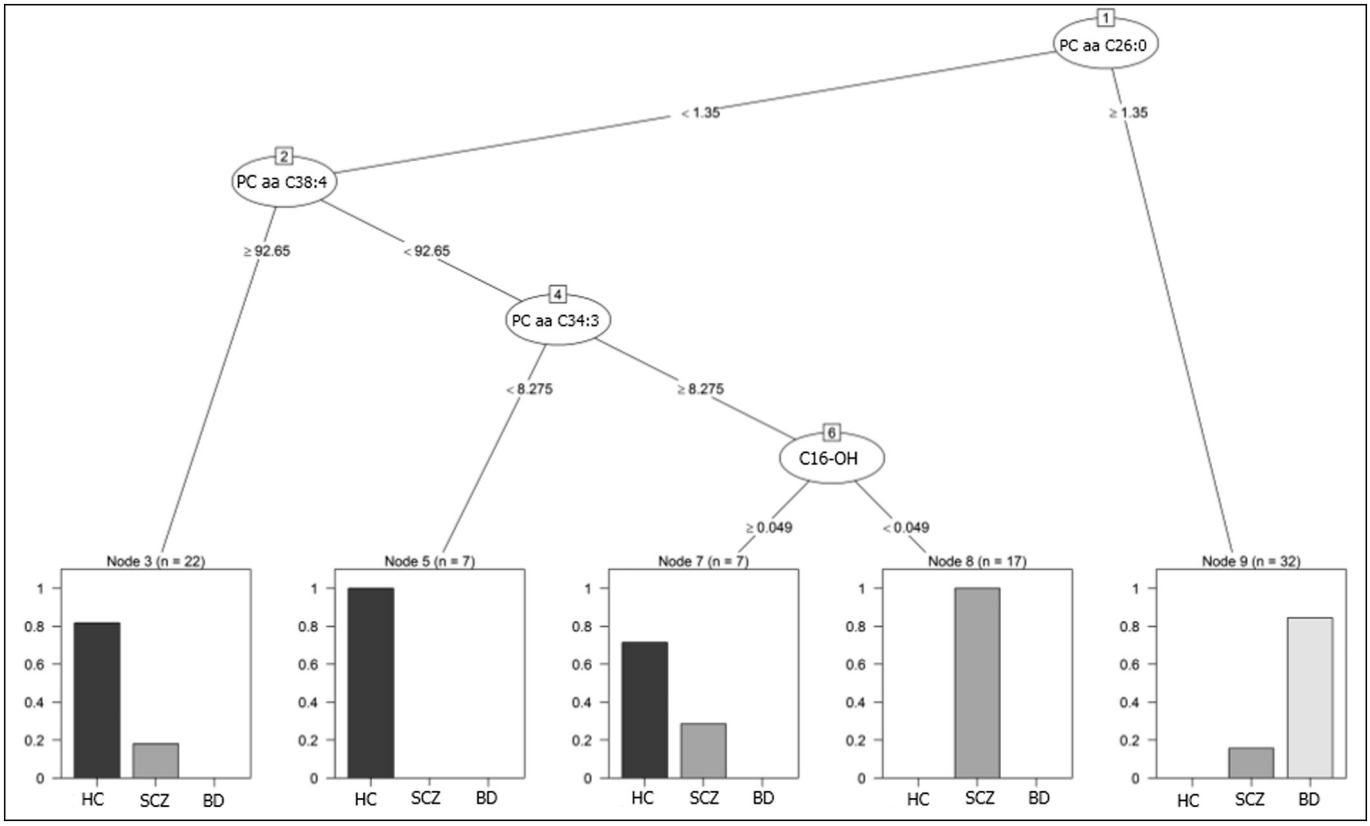

Fig. 1. Metabolite predictors of first episode psychosis using the Classification and Regression Tree model. Each predictive value is written within the line and each node is based on the data available for each of the predictive variables presented. SCZ = schizophrenia; BD = bipolar disorder; HC = healthy controls; PC = phosphatidylcholine.

study, therefore the results need replication in an independent and larger sample.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.11.010.

Author disclosure

The authors have no conflict of interest to declare.

CRediT authorship contribution statement

Alana C. Costa: Data curation, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Helena P.G. Joaquim:** Data curation, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Leda L. Talib:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Maurício H. Serpa:** Data curation, Writing - original draft, Writing - review & editing. **Marcus V. Zanetti:** Data curation, Writing - original draft, Writing - review & editing. **Wagner F. Gattaz:** Conceptualization, Writing - original draft, Writing - review & editing.

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