INTRODUCTION

Severe mental disorders (SMD) is a group of conditions that include schizophrenia (SZ), bipolar disorder (BD), and other psychotic disorders. SZ and BD exhibit genetic overlap in their pathogenesis and share certain symptoms. Neurocognitive impairment has been recognized as one of the important common symptoms, not only been a core symptom of SZ, but also persistently demonstrated during remission in BD. These cognitive deficits significantly contribute to functional disability in both SZ and BD. Overall, cognitive impairments are considered as core feature of SMD and have shown predictive value for clinical and functional outcomes.

Current research on biomarkers of cognitive impairment has revealed an association between prolactin (PRL) and cognitive performance. A study conducted in young healthy pregnant women showed a negative linear association between PRL levels and executive function scores, suggesting that higher PRL levels have a detrimental effect on executive function abilities. Furthermore, another study indicated elevated PRL levels in patients with Alzheimer’s disease, particularly in those with severe dementia. In patients with prolactinomas, hyperprolactinemia may induce cognitive toxicity by affecting the prefrontal cortex of the brain.
METHODS

Subjects

Data were drawn from the Shanghai Mental Health Center (SMHC) Key Laboratory Precision Medicine Project, which aimed to study SMD through the integration of genetic, imaging, and clinical features. Patients were recruited from multiple institutions including SMHC, Shanghai Civil Affairs First Mental Health Center, Cixi Mental Health Center, Quzhou Third People’s Hospital, and Huzhou Third People’s Hospital between January 2017 and January 2020. All patients who met the diagnosis of SZ and BD were included, and the diagnosis was made by experienced psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Healthy controls (HC) were recruited from the local community through advertisements, and screened to exclude individuals with a personal or family history of psychiatric disorders. Both patients and HC were interviewed by trained raters using the Mini-International Neuropsychiatric Interview to confirm the clinical diagnosis or to screen whether the controls have any major Axis I disorder diagnosis.

Exclusion criteria were cerebral vascular disease, central nervous system diseases, severe physical diseases, substance abuse/dependence, pregnancy, or lactation.

Of all participants screened, 491 met the predefined inclusion criteria. Subsequently, samples were categorized into two distinct populations: 1) SMD (n=195), including 83 SZ patients and 112 BD patients (the proportions of type 1 and type 2 bipolar patients as 73 and 39, respectively), 2) HC (n=294).

The protocol was reviewed and approved by the ethics committee at SMHC (IRB No. 2019-35R). Written informed consent was obtained from all subjects before the study.

Cognitive assessment

The cognitive function of participants was assessed at each center using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Form A). This battery comprises 12 subtests that are utilized to calculate five age-adjusted index scores and a total index score. A total scale score is calculated in accordance with the instructions provided in the stimulus booklet appendix. The test indices include immediate memory (comprised of list learning and story memory tasks), visuospatial/constructional (comprised of figure copy and line orientation tasks), language (comprised of picture naming and semantic fluency tasks), attention (comprised of digit span and coding tasks), and delayed memory (comprised of list recall, story recall, figure recall, and list recognition tasks). The inter-rater correlation coefficient for assessments was greater than 0.8.

PRL measurements

PRL measurements were conducted using immunoassays with standardized protocols at each center. The same standard samples were tested and the results obtained from multiple centers were standardized in order to minimize systematic errors. The participants were instructed to refrain from experiencing stress, engaging in physical activity, stimulating their breasts, and smoking within the 12 hours preceding blood sampling. Blood sample were collected between 8 and 10 AM after overnight fast and 30 min of rest by technicians who were blind to the diagnostic status of subjects.

Other variables

Clinical variables related to psychosis (including sex, age, education level, use of antipsychotics, and other medications) were collected using the self-designed questionnaire. All data were recorded by the same researcher.

Psychopharmacological treatments

Psychopharmacological treatments were documented during the neuropsychological assessment. Several antipsychotics, including risperidone, paliperidone, amisulpride, aripiprazole, and benzamide have been reported in existing studies to potentially impact PRL levels in blood. Among all individuals diagnosed with SMD, 38 were prescribed these specific antipsychotic medications.
Statistical analysis

The Shapiro–Wilk test was utilized to assess normality. Sociodemographic differences were analyzed using Student’s t-tests or the Mann–Whitney test, while PRL levels and RBANS scores were compared between controls and SMD patients using the Mann–Whitney test. Linear regression models were performed to explore the relationship between PRL and cognitive function, with original RBANS scores and log-transformed PRL values. The residual plots were utilized to assess whether the residuals conform to the assumptions of normality and homoscedasticity. All analyses were adjusted for covariates including age and education levels.

All data were analyzed using the R environment for statistical computing (R studio, 4.2.2; R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). Statistical significance was determined at a threshold of p<0.05 (two-tailed).

RESULTS

Univariate analysis

Clinical characteristics, RBANS total and index scores of the sample by groups (195 with SMD and 294 HC) are presented in Table 1. Additional information about the patients are provided in Supplementary Table 1.

There were no significant age differences observed between the HC and SMD groups. However, it is noteworthy that PRL levels were significantly higher in SMD subjects compared to HC subjects (479.4 mIU/L vs. 323.8 mIU/L, p<0.001). As expected, SMD patients scored lower on RBANS total and every index scores. A notable discrepancy was observed in both RBANS total index scores (435.0 vs. 493.0, p<0.001) and total scale score (82.0 vs. 97.0, p<0.001) among the groups. Large differences were also evident in immediate memory, visuospatial, language, attention and delayed memory scores between individuals with SMD and controls. These findings suggest that SMD patients exhibited poorer performance in cognitive tasks.

Correlation of PRL and cognitive tasks

Linear regression analyses investigating the association between PRL and RBANS total and index scores are presented in Table 2. Among individuals with SMD, a negative correlation was found between PRL levels and RBANS total index score (β=-23.21, p=0.0231). Additionally, elevated PRL levels were associated with poorer attention (β=-8.12, p=0.0057) and delayed memory performance (β=-6.01, p=0.0386) among SMD patients. However, no significant associations were observed between PRL levels and RBANS scores in HC, including total score, immediate memory, visuospatial ability, language skills or delayed memory. Attention was positively correlated with PRL levels (β=9.55, p=0.0056). These findings provide valuable insights into the relationships between PRL levels and cognitive performance across different population.

Sensitivity analysis

Considering that individuals with SMD included in this study had a documented history of stable medication use, we investigated the relationship between PRL levels and cognitive function in patients who were not taking medications that

Table 1. Clinical variables and RBANS scores by diagnostic groups

<table>
<thead>
<tr>
<th></th>
<th>SMD (N=195)</th>
<th>HC (N=294)</th>
<th>t/W</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>32.9±10.9</td>
<td>33.0±10.2</td>
<td>0.2499</td>
<td>0.884</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Junior high school and below</td>
<td>57 (28.9)</td>
<td>36 (12.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>62 (31.5)</td>
<td>36 (12.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bachelor degree and above</td>
<td>78 (39.6)</td>
<td>222 (75.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin (mIU/L)</td>
<td>479.4 (257.1–992.0)</td>
<td>323.8 (232.9–465.8)</td>
<td>21,409</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RBANS</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Immediate memory</td>
<td>78.0 (61.0–90.0)</td>
<td>85.0 (76.0–94.0)</td>
<td>35,604</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>92.0 (75.0–105.0)</td>
<td>102.0 (92.0–105.0)</td>
<td>35,377</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Language</td>
<td>80.0 (68.0–96.0)</td>
<td>94.0 (83.0–101.0)</td>
<td>37,805</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Attention</td>
<td>100.0 (88.0–110.5)</td>
<td>115.0 (109.0–125.0)</td>
<td>43,465</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delayed memory</td>
<td>83.0 (58.0–97.0)</td>
<td>97.0 (91.0–101.0)</td>
<td>40,509</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total index score</td>
<td>435.0 (375.0–490.0)</td>
<td>493.0 (452.0–523.8)</td>
<td>41,176</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total scale score</td>
<td>82.0 (68.0–96.5)</td>
<td>97.0 (86.0–105.0)</td>
<td>41,011</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean±standard deviation, number (%) or median (IQR). RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SMD, severe mental disorders; HC, healthy controls; t/W; t-statistic and W-statistic; IQR, interquartile range

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may affect serum PRL level. Out of the 195 SMD patients with reliable medication records prior to PRL measurements, 157 were naïve for the intake of those antipsychotic medication (as described in the methods).

Linear regression analyses revealed a sustained association between PRL and cognitive function in SMD patients. Specifically, higher serum PRL levels were found to be negatively correlated with RBANS score (RBANS total scale score: β=-6.01, p=0.0266; RBANS total index score: β=-29.67, p=0.0126; attention: β=-10.02, p=0.0035), indicating that higher PRL levels were related with worse cognitive performance (Table 3). This finding supports the notion that the association between PRL levels and cognitive function in patients with SMD may be independent of medication presence. We further conducted an analysis based on diagnostic groups (SZ vs. BD), as depicted in Figure 1. In both SZ and BD groups, the total scale score of RBANS decreased with the increase of PRL levels, which was consistent with the results obtained in SMD. The above findings provide additional validation for our observation of a negative correlation between PRL levels and cognition function in SMD patients.

**DISCUSSION**

Our study suggests that increased PRL levels are associated with impaired cognition function, independent of the use of antipsychotic drugs in patients with SMD. These patients exhibit poorer cognitive function and higher PRL levels compared to the general population. After adjusting for age and education, we observed a significant negative correlation between PRL levels and cognitive function. Importantly, this correlation remained robust even after excluding patients who were taking medications known to potentially influence PRL levels. To the best of our knowledge, this is the first study to highlight the significance of PRL as a crucial factor contributing to cognitive impairment in Chinese females with SMD.

In terms of cognitive function, our results are consistent with previous studies suggesting that there is a gradient of cognitive impairment from BD to SZ, which may represent a symptom dimension that crosses traditional diagnostic boundaries. These deficits, considered as fundamental characteristics of SMD, are believed to precede the onset of psychiatric illnesses and have predictive value for functional outcomes. Furthermore, our study revealed inferior performance across all cognitive domains in patients with SMD.

Traditionally, hyperprolactinemia in patients with mental disorder has been regarded as an adverse effect of antipsychotic drugs. However, elevated PRL levels or hyperprolactinemia has also been observed in patients with first-episode psychosis without antipsychotic medication or those at high risk. Our findings suggest that increased PRL levels may be an independent predictor of cognitive impairment in SMD patients.
risk for psychosis, particularly among women.\textsuperscript{21,22} In our study, PRL elevation also found in SMD. This finding aligns with the hypothesis of hyperprolactinemia in SZ suggesting that stress can trigger the outbreak of psychosis through a feedback mechanism involving enhanced PRL leading to increase dopamine release.\textsuperscript{22}

In patients who were not taking medications known to affect PRL levels in body, a significant association was observed between higher PRL levels and poorer cognitive function. These results are consistent with previous studies conducted in early psychosis.\textsuperscript{11} The propensity of antipsychotics to induce hyperprolactinemia varies due to differences in D2 receptor binding activity and duration within brain.\textsuperscript{23} Additionally, multivariate analyses indicate an independent effect of PRL on cognitive function, as all analyses were adjusted for age and education level.

The relationship between PRL and SMD may be explained by hypothalamic-pituitary-gonadal axis hypothesis. According to this hypothesis, stress causes an increase in PRL, which enhances dopamine release (i.e., prolactin inhibiting factor) in a feedback mechanism. Increased dopamine triggers psychotic symptoms in people who are prone to psychosis.\textsuperscript{24} Although the mechanisms linking higher levels of PRL to poorer cognitive performance are unknown, recent research showed that patients with prolactinomas demonstrated a decrease in gray matter volumes (GMV) in the left hippocampus, left orbitofrontal cortex, right middle frontal cortex (MFC), and right inferior frontal cortex (IFC). In addition, patients performed worse than controls on tests for verbal memory and executive function, and this was significantly related to the GMV of the left hippocampus and right MFC, respectively. Moreover, serum PRL levels were negatively related with the GMV of the left hippocampus and right IFC, suggesting a potential “neurotoxic” effect of PRL to brain.\textsuperscript{25} The reduction in PRL levels via treatment was followed by improvements in processing speed, working memory, visual learning and reasoning and problem-solving in patients with prolactinomas.\textsuperscript{26}

Although no proof-of-concept trial was conducted in SMD patients, it is plausible to speculate that the negative association of PRL with cognitive function might rely on the direct effect of PRL on brain, as PRL plays important roles as a neuropeptide and regulates neurogenesis in both the subventricular zone and the dentate gyrus of the hippocampal formation,\textsuperscript{27} suggesting a potential role of PRL in the brain in aspects other than reproductive function, including cognitive abilities. Further studies are needed to better understand the relation between PRL, SMD, and cognitive performance.

The main limitation of our study is the cross-sectional design that does not allow us to infer causality. Future prospective studies are necessary to ascertain whether persistent hyperprolactinemia is a risk factor for impaired cognition in people with SMD by repeatedly assessing PRL levels and cognitive function over time. The majority of the patients in our study were taking antipsychotics and had a long course of disease, which may affect PRL level and cognitive performance. Thus, our finding needs to be validated in patients with first episode of SMD. Moreover, our subjects were all Chinese women. This study is needed to be confirmed in other ethnicities and with a larger sample size in the future.

In conclusion, our study suggests that increased PRL levels are negatively associated with cognitive function in Chinese female patients with SMD. Our study suggests that PRL may be considered as a potential biomarker for cognitive impairment in individuals with SMD. This finding highlights the significance of monitoring PRL levels in female SMD patients to prevent cognitive deterioration.

**Supplementary Materials**

The Supplement is available with this article at https://doi.org/10.30773/pi.2024.0008.

**Availability of Data and Material**

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

**Conflicts of Interest**

The authors have no potential conflicts of interest to disclose.

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**Funding Statement**

This research was supported by grants from the National Key R&D Program of China (No: 2017YFC0909200) and the National Natural Science Foundation of China (No: 82271544) for Donghong Cui; the grant from Shanghai Mental Health Center (2021-QH-02) for Shun Yao.

**Acknowledgments**

We are grateful to Donghong Cui, Shun Yao for designing the study and proofreading the manuscript.
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