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## Review Article

### **Development of a Method for Differentiating Schizophrenia and Bipolar Disorder Based on Polygenic Risk Score, Hippocampal Volume, and Cognitive Function: Differentiation between Schizophrenia and Bipolar Disorder**

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## Abstract

Schizophrenia (SZ) and bipolar disorder (BD) are common and complex psychiatric disorders that have a lifetime prevalence of approximately 1%. Disorder-specific genetic factors as well as common genetic factors contribute to the pathogenesis of both disorders. To reduce the clinical and genetic heterogeneity between the two disorders and to differentiate between them, we considered hippocampal volume and cognitive function as promising intermediate phenotypes. Hippocampal volume and cognitive function are related to genetic factors and are more strongly impaired in SZ than BD. We are continuing research to develop a method to differentiate SZ and BD by polygenic risk score (PRS), hippocampal volume, and cognitive function using machine learning. To achieve this goal, we examined (i) subcortical volume changes between SZ and BD; (ii) causal relationships among SZ, BD, and intellectual impairments; and (iii) associations with genetic factors and intellectual function. We found that (i) hippocampal volumes were decreased in both patients with SZ and BD, whereas amygdala volumes were decreased only in patients with SZ; (ii) there was a bidirectional causal relationship between SZ and intellectual impairments, but not between BD and intellectual impairments; and (iii) genetic factors for differentiating SZ from BD were negatively correlated with intellectual function. These results suggest that amygdala volume is more

useful for differentiating SZ from BD than hippocampal volume, and that cognitive impairments are also useful in terms of causal and genetic associations. We plan to develop a method to differentiate SZ from BD by combining PRS, amygdala volume, and cognitive function, and by applying machine learning.

**Keywords:** schizophrenia, bipolar disorder, polygenic risk score, subcortical volume, cognitive function

## Introduction

Schizophrenia (SZ) and bipolar disorder (BD) are complex and “common” mental disorders, with both showing a lifetime prevalence of approximately 1% of the population. Both disorders exhibit familial aggregation,<sup>4)5)</sup> with a high heritability of approximately 80% and multifactorial genetic pattern. Furthermore, they are mental disorders that demonstrate genetic and clinical heterogeneity.<sup>9)22)25)26)</sup> As a potential clue to reducing the genetic and clinical heterogeneity of SZ and BD, intermediate phenotypes such as brain structures and cognitive functions, which are considered core components of the disorders, are gaining attention rather than diagnoses (phenotypes).<sup>1)7)27)</sup> Such intermediate phenotypes are also observed in non-affected relatives of patients, indicating familial aggregation.<sup>8)11)13)</sup> Additionally, heritability is reportedly 30–80%, suggesting that genetic factors are involved, being similar in SZ and BD.

Furthermore, it has been suggested that SZ, BD, and intermediate phenotypes may share a common genetic basis.<sup>12)15)</sup>

In the previous edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), BD was classified as a mood disorder, distinct from depression. However, recent epidemiological evidence, combined with genetic evidence from the authors' studies, demonstrated epidemiological similarities and genetic commonalities between SZ and BD.<sup>10)14)</sup> As a result, in the latest diagnostic criteria, DSM-5, SZ, BD, and depression are classified as separate disease groups. Thus, elucidating common genetic bases may be useful for determining diagnostic criteria for some mental disorders. However, there are also intermediate phenotypes that lead to more severe impairments in SZ than BD, such as cognitive dysfunction,<sup>19)</sup> suggesting the involvement of disease-specific genetic bases.<sup>17)</sup> The use of disease-specific genetic markers or clinical indicators

such as intermediate phenotypes may be useful for distinguishing between SZ and BD.

Thus, the pathophysiologies of SZ and BD suggest the involvement of not only common but also disease-specific genetic factors.<sup>10)12)14)15)</sup> Additionally, intermediate phenotypes that may reduce clinical and genetic heterogeneity between the two disorders and aid in distinguishing them include the hippocampal volume and cognitive function. These phenotypes are influenced by genetic factors in both disorders but are particularly impaired in SZ compared with BD.<sup>16)19)</sup> These are considered useful intermediate phenotypes. Currently, diagnostic criteria for mental disorders, such as DSM and the International Statistical Classification of Diseases and Related Health Problems (ICD), primarily rely on clinical interviews based on symptoms assessed by psychiatrists. There is a growing need for the introduction of objective diagnostic tools, such as blood tests, brain imaging, and neuropsychological tests.

The authors are continuing research aimed at developing a machine-learning-based method for distinguishing between SZ and BD using polygenic risk scores (PRS) calculated from numerous genetic polymorphisms (single nucleotide

polymorphisms: SNPs) across the entire genome as well as hippocampal volume and cognitive function. To achieve this goal, the following three points were examined. This paper reports the results of these investigations.

(i) Changes in subcortical volume in SZ and BD based on Japanese data.<sup>20)</sup>

(ii) Causal relationships among SZ, BD, and intellectual disability based on European and American data.<sup>18)</sup>

(iii) Association between genetic factors distinguishing BD from SZ and intellectual function based on Japanese and European/American data.<sup>17)21)</sup>

## **I. Subcortical volume changes in SZ and BD**

Based on previous evidence indicating that SZ shares genetic commonalities with the hippocampal volume, while BD does not, the authors considered the hippocampal volume to be useful for distinguishing between the two disorders. However, it remained unclear whether disease-specific differences in the subcortical volume exist between SZ and BD.

Therefore, the authors conducted a comparative analysis of subcortical volumes in participants recruited from two of their ongoing projects: “SNARP: Schizophrenia Non-Affective Relative research Project,” a comprehensive intermediate phenotype analysis study targeting Japanese patients with SZ,

their unaffected first-degree relatives, and healthy controls; and “B-SNIP-J: Bipolar & Schizophrenia Network for Intermediate Phenotypes in JAPAN,” a comprehensive intermediate phenotype analysis study targeting patients with BD and SZ. Specifically, 157 SZ patients, 51 BD patients, and 205 healthy controls underwent 3T T1-weighted head MRI, and subcortical volumes in seven regions: the thalamus, caudate nucleus, putamen, globus pallidus, hippocampus, amygdala, and nucleus accumbens, which were compared using Freesurfer v.6.0 analysis software.<sup>20)</sup> (Figure 1)

Among the seven subcortical regions, SZ patients showed significantly reduced volumes in the left thalamus, bilateral hippocampi, and left amygdala compared with healthy controls. In contrast, BD patients exhibited reduced volumes in the bilateral hippocampi only compared with healthy controls. Furthermore, SZ patients showed significantly reduced volumes in the bilateral amygdala compared with BD patients. A smaller left amygdala volume was significantly correlated with a younger age at onset in SZ patients only.

These results suggest that, since the hippocampal volume is reduced in the presence of both SZ and BD, the amygdala volume, which is specifically reduced in SZ, may be a useful

biomarker for distinguishing between the two clinically and genetically similar disorders.

## II. Causal relationships among SZ, BD, and intellectual disability

Intellectual function shows a negative correlation with the risk of developing SZ and BD, but it remains unclear whether low intellectual function is a cause of onset or consequence of the disease. To investigate the causal relationships among SZ, BD, and intellectual dysfunction, we utilized summary datasets from five large-scale genome-wide association studies (GWAS) targeting Western populations, comparing intellectual function<sup>24)</sup>: SZ vs. healthy controls,<sup>23)</sup> BD vs. healthy controls,<sup>23)</sup> SZ + BD vs. healthy controls,<sup>23)</sup> and SZ vs. BD (SZ-specific),<sup>23)</sup> and conducted Mendelian randomization analysis to examine the causal relationships between intellectual dysfunction and SZ risk, BD risk, common risk factors for SZ and BD, and SZ-specific risk factors.<sup>18)</sup> (Figure 2)

A bidirectional causal relationship was identified between SZ onset risk and intellectual dysfunction, but the strength of the relationship (odds ratio: OR) indicated that the causal relationship between intellectual dysfunction and the SZ onset risk was stronger than that of SZ onset and intellectual dysfunction. Furthermore,

intellectual impairment was associated with both shared SZ and BD onset risks and SZ-specific onset risks. However, among the shared SZ and BD onset risks and SZ-specific onset risks, only the shared SZ and BD onset risks were correlated with intellectual impairment, and this was weak. However, no significant causal correlation was noted between the BD onset risk and intellectual function in either direction.

These findings support previous observational studies reporting that SZ patients exhibit impaired intellectual function before onset and further decline after onset.<sup>13)</sup> Moreover, while risk factors shared by SZ and BD patients may contribute to both pre-onset dysfunction and post-onset decline, lower intellectual function prior to onset may be more closely linked to SZ-specific risk than BD. The strength of the causal relationship between SZ and intellectual dysfunction, including both pre- and post-onset declines, also suggests that intellectual function may be useful for differentiating SZ from BD.

### **III. Genetic factors distinguishing SZ from BD and their association with intellectual function**

Despite clinical and genetic similarities between SZ and BD, intellectual impairment is more marked in SZ than BD patients.<sup>18)19)</sup> To date, genetic factors that can be used to

distinguish SZ from BD (i.e., SZ-specific genetic factors) have been identified in Western populations.<sup>23)</sup> The authors previously demonstrated that the polygenic risk score (PRS) specific to SZ, compared with BD, is higher in SZ patients than in healthy Japanese controls.<sup>14)</sup> However, the effects of these SZ-specific genetic factors on intellectual function have not been fully elucidated.

Therefore, we investigated whether SZ-specific genetic factors are associated with intellectual dysfunction in SZ patients and healthy controls.<sup>17)</sup> To calculate PRS for SZ-specific genetic factors and intellectual function in child- and adulthood, we utilized large-scale genome-wide association study (GWAS) data from European populations (sample size: 12,441–282,014) related to SZ vs. BD,<sup>23)</sup> childhood intellectual function,<sup>2)</sup> and adult intellectual function.<sup>6)</sup> PRS was calculated for 130 Japanese SZ patients and 146 healthy controls. Additionally, we measured the severity of pre-illness estimated intellectual function (JART), current intellectual function (WAIS-III), and intellectual function decline (WAIS-III–JART) in SZ patients and healthy controls, and examined the correlation between PRS and intellectual function.<sup>17)</sup> (Figure 3a)

SZ-specific PRS was higher in both SZ patients and healthy controls when pre-

illness estimated intellectual function was lower. However, SZ-specific PRS did not show a significant correlation with current intellectual function or intellectual functioning decline. Furthermore, PRS attributable to childhood intellectual function was lower in SZ patients than healthy controls; however, PRS did not show a significant correlation with pre-illness estimated intellectual function, current intellectual function, intellectual functioning decline, or SZ-specific PRS.

Furthermore, we examined whether SZ-specific genetic factors were genetically associated with cognitive function (general cognitive function, childhood intellectual function, and educational attainment) in Western populations using LD score regression analysis.<sup>21)</sup> (Figure 3b) The results showed that SZ-specific genetic factors were negatively correlated with general cognitive function, childhood intellectual function, and educational attainment in Western populations. Impaired cognitive function was correlated with SZ-specific risk.

These results suggest that genetic factors distinguishable between SZ and BD patients may contribute to differences in their pathophysiology, not only through the pathophysiology of SZ but also through impaired estimated intelligence prior to disorder onset. Additionally, genetic factors associated

with childhood intellectual function may be involved in the pathophysiology of SZ, regardless of the degree of intellectual function in adulthood. These findings suggest that disease-specific genetic factors such as intellectual function may be useful as intermediate phenotypes for distinguishing SZ from BD.

#### IV. Future prospects

SZ and BD are both common mental disorders with a lifetime prevalence of approximately 1%, but clinical differentiation between the two can be difficult because the manic symptoms of BD are similar to the positive symptoms of SZ, and the depressive symptoms are similar to negative symptoms. Current psychiatric clinical practice (at least in university hospitals) routinely includes blood tests, head MR imaging, and cognitive assessments.

There are millions of SNPs in the human genome; brain images, one type of intermediate phenotype, can be divided into many regions, and cognitive functions span multiple domains, resulting in an enormous amount of genetic and clinical information. Therefore, manually identifying useful indicators for distinguishing between the two disorders from this vast amount of information may result in the omission of useful indicators. Artificial

intelligence (AI) technologies such as machine learning, which are currently revolutionizing many medical fields, may be useful in addressing these challenges. To date, the use of machine learning in the field of psychiatry has been limited to distinguishing between disease and healthy groups using intermediate phenotypes such as brain images and cognitive function.<sup>3)</sup> However, in clinical practice, nearly all subjects belong to one of the disease groups, and developing technology to distinguish between SZ and BD within these groups remains a challenge. Going forward, the authors aim to combine intermediate phenotypes such as amygdala volume and intellectual function, which they have identified, with PRS, and leverage machine learning to enable not only linear analysis but also various nonlinear analyses, thereby attempting to develop a diagnostic method for SZ and BD. Furthermore, by integrating large-scale genomic data, head MRI, intermediate phenotype data such as cognitive function and personality traits, and clinical information such as age at onset and duration of illness from individuals with SZ, BD, and healthy controls, and by utilizing machine learning, it may be possible to achieve more detailed and accurate predictions and identify genetic and clinical indicators capable of

accurately distinguishing SZ and BD. (Figure 4)

If useful indicators for distinguishing between the two disorders can be developed, it will be possible to select more appropriate medications. Among the antipsychotics and mood stabilizers currently used as the mainstay of pharmacotherapy, antipsychotics are effective for both disorders. However, mood stabilizers such as lithium and lamotrigine are ineffective for SZ, effective only for BD, and often associated with adverse effects. Therefore, the development of useful indicators could help avoid unnecessary medication for SZ and ensure appropriate medication for BD.

### Conclusion

The authors' results suggest that, in distinguishing SZ from BD, amygdala volume is more informative than hippocampal volume among subcortical structures, and that intellectual function is a valuable indicator from both causal and genetic perspectives. Moving forward, we aim to develop diagnostic methods for differentiating SZ and BD by integrating various intermediate phenotypes, including intellectual function, amygdala volume, cortical structure and function, and personality traits, with large-scale genetic data such as PRS, DNA methylation (epigenetics), and copy

number variations (CNVs), using machine-learning techniques.

There are no conflicts of interest to disclose in relation to this paper.

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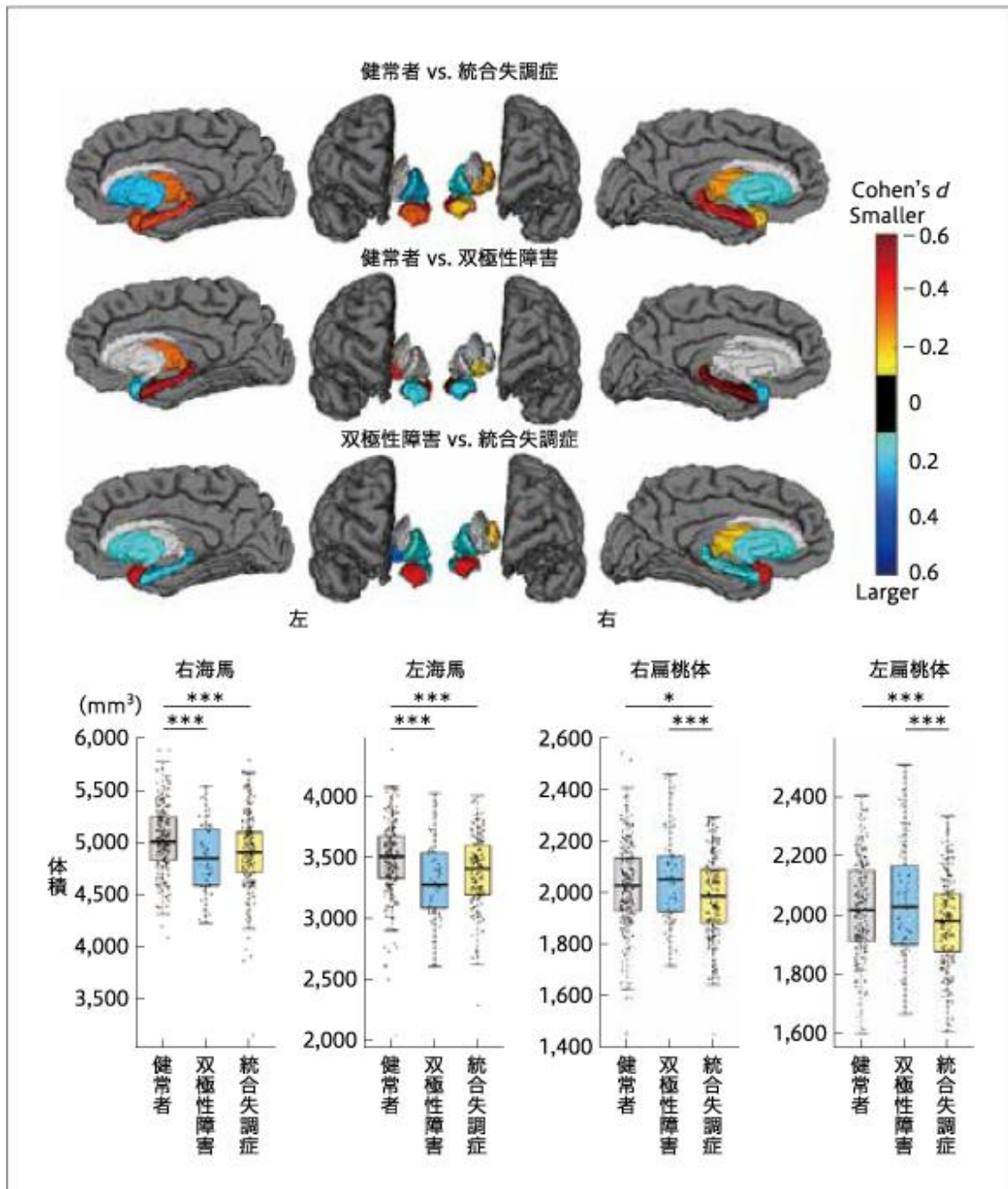


図1 統合失調症，双極性障害，健常者間における脳皮質下体積変化

健常者 vs. 統合失調症，健常者 vs. 双極性障害，双極性障害 vs. 統合失調症の比較においてそれぞれ統合失調症，双極性障害，統合失調症の体積減少領域を赤，体積増大領域を青で示した (Cohen's *d*). \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 7.14 \times 10^{-3}$

(文献 20 より和訳し改変して引用)

Figure 1: Subcortical volume changes in schizophrenia patients, bipolar disorder patients, and healthy controls

In comparisons between healthy controls vs. schizophrenia patients, healthy controls vs. bipolar disorder patients, and bipolar disorder vs. schizophrenia patients,

respective areas of volume reduction in schizophrenia, bipolar disorder, and schizophrenia are shown in red, and those of volume increase are shown in blue (Cohen's d).

\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 7.14 \times 10^{-3}$ .

(Translated and modified from Reference 20)

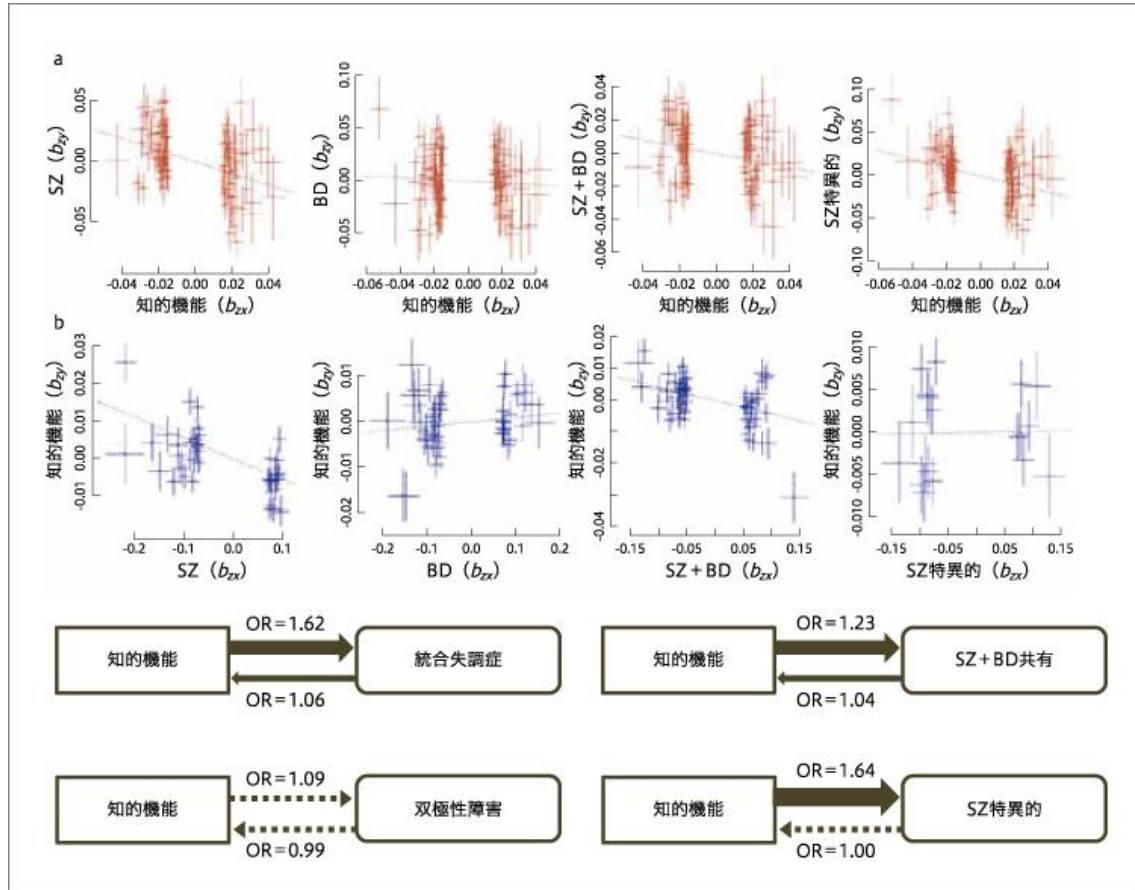


図2 メンデルランダム化解析を用いた統合失調症、双極性障害のリスクと知的機能障害間の因果関係  
(a, b)  $b_{zx}$  が  $b_{zy}$  に及ぼす影響は点線の傾きが急峻であるほど、 $b_{zx}$  が  $b_{zy}$  に及ぼす因果関係があると判断できる。  
(文献 18 より和訳し改変して引用)

Figure 2: Causal relationships among schizophrenia, bipolar disorder, and intellectual disability using Mendelian randomization analysis

(a, b) The steeper the slope of the dotted line, the stronger the causal relationship between  $b_{zx}$  and  $b_{zy}$ .

(Translated and modified from Reference 18)

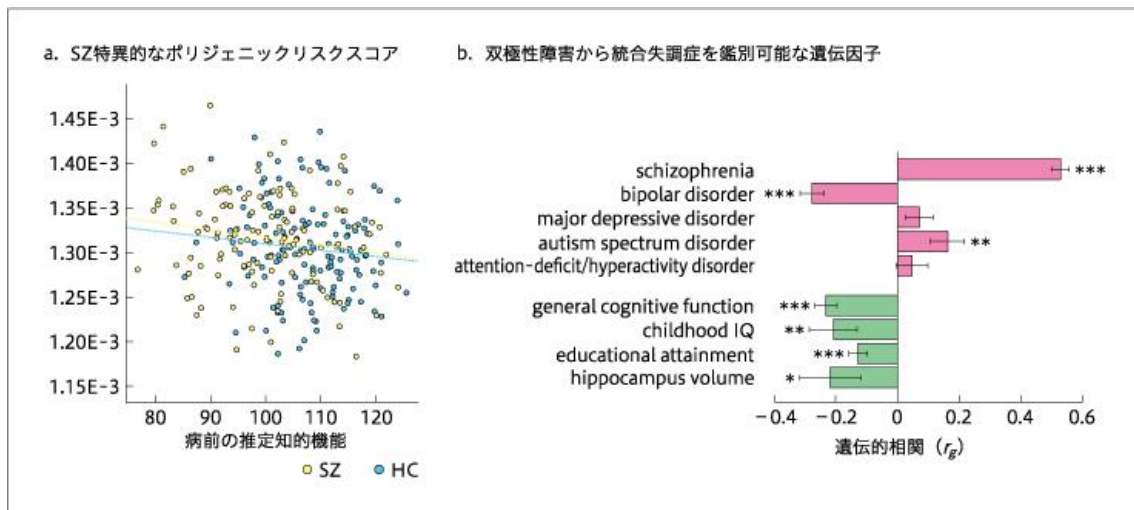


図3 双極性障害から統合失調症を区分できる遺伝因子と知的機能の関連  
(文献 17, 21 より和訳し改変して引用)

Figure 3: Genetic factors distinguishing bipolar disorder from schizophrenia and their association with intellectual function  
(Translated and modified from References 17 and 21)

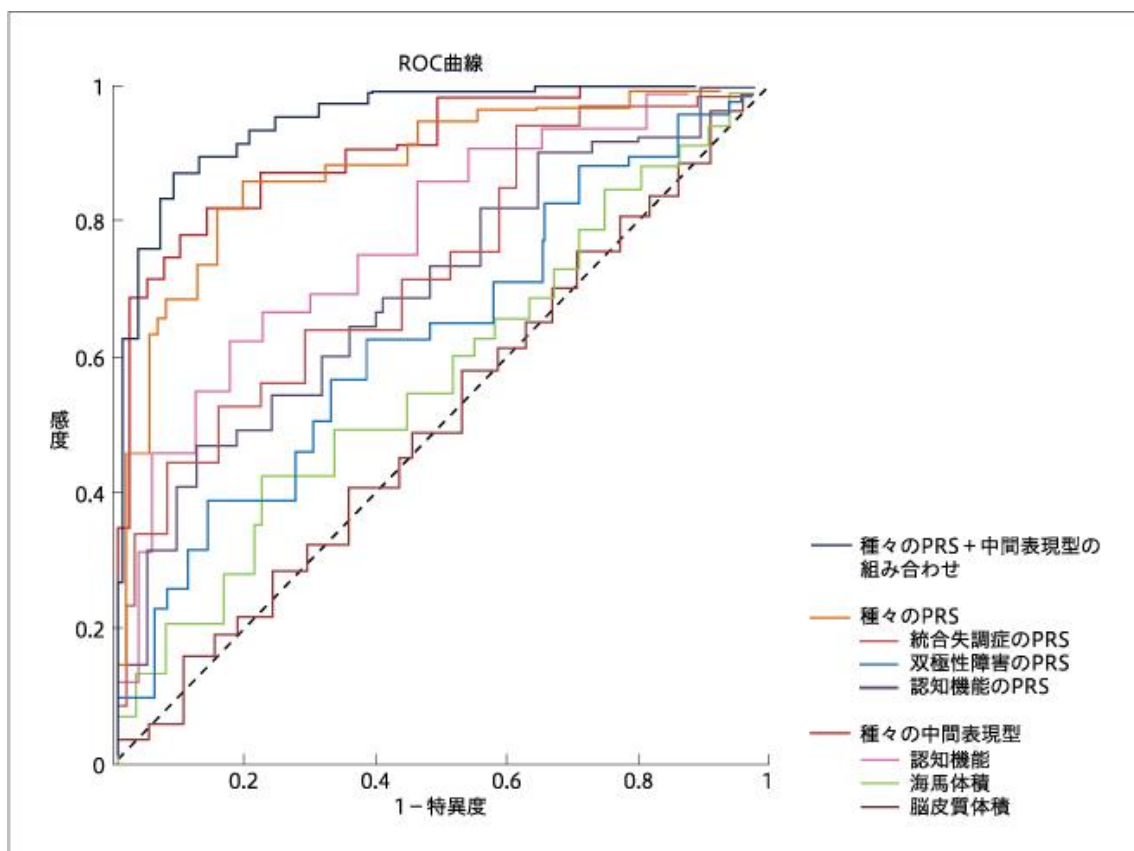


図4 種々の PRS や中間表現型の組み合わせによる疾患判別精度向上の予測 ROC 曲線

Figure 4: Predicted ROC curves for improving disease classification accuracy using various combinations of PRS and intermediate phenotypes