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The heterogeneity of neuropsychiatric disorders

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The heterogeneity of neuropsychiatric disorders

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Editorial: The heterogeneity of neuropsychiatric disorders

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Editorial on the Research Topic
The heterogeneity of neuropsychiatric disorders

Introduction

Neuropsychiatric disorders, such as attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), obsessive-compulsive disorder (OCD), and schizophrenia (SCZ), are highly heterogeneous. The heterogeneity in psychiatric disorders has still not been fully investigated (1). The current topic, therefore, aims to further illustrate the heterogeneity and explore potential strategies to reduce heterogeneity in neuropsychiatric disorders.

Heterogeneity within the same diagnostic category

Some of the patients within the same diagnostic category, though not all of them, show some personality traits that might affect their clinical presentation and prognosis (2, 3). For instance, some patients with bipolar disorder (BD) show elevated impulsivity. Zakowicz et al. assessed impulsivity levels in BD patients who had attempted suicide and those who had not. They found impulsivity to be a weak predictor of suicidal risk.

Overlapping symptoms and cognitive profile

Most neuropsychiatric disorders have overlapping symptoms. Cui et al. used the Child Behavior Checklist (CBCL) to access the clinical profiles of children and adolescents with Tourette syndrome (TS) and compared them to individuals with MDD, ADHD, and OCD. Their results established that TS has a similar emotional and clinical profile to MDD but not ADHD or OCD.

In another example with BD, it is defined as having two phases, depression and hypomania, so its symptoms overlap with those of unipolar depression (UD) during the depression phases. Some patients with depression show soft bipolar signs or bipolarity, e.g., a family history of BD or hyperthymic personality (4). Lu et al. investigated the neuropsychological characteristics of individuals with BD, UD, and depression disorder with bipolarity (UDB). They found that the cognitive dysfunction pattern in patients with UDB is different from that of individuals with

UD but similar to that of individuals with BD. Likewise, the aberrant perceptual experience and impaired social communication in ASD and SCZ are probably due to their shared impairment in audiovisual temporal integration (5).

Shared and distinct neural and genetic correlates

Overlapping symptoms in different diagnostic categories are assumed to have shared underlying mechanisms. The obsessive symptoms in OCD and delusion in SCZ have some overlapping features, such as intrusive and unwanted thoughts. Zhang Y et al. explored the neural correlates of SCZ and OCD using resting-state brain functional imaging techniques. They detected brain activity abnormalities in the right hippocampus and the left posterior cingulate cortex in both SCZ and OCD groups. Liu et al. performed a meta-analysis and found decreased gray matter volume (GMV) in children and adolescents with SCZ and increased GMV in the prefrontal cortex (PFC) in those with OCD. SCZ and MDD also have overlapping symptoms. Ma, Zhang, Zhang, Yan et al. found impaired processing speed and reduced gray matter volume in the medial superior frontal cortex were shared by SCZ and MDD.

In addition to brain morphology and function, genetic characterization of psychiatric disorders has also been shown to transcend diagnostic boundaries. For instance, OCD is often comorbid with other psychiatric disorders, and previous studies have found significant genetic correlations among OCD, MDD ($r = 0.21$) (6), and ADHD ($r = -0.17$) (7). Strom et al. explored the genetic correlations with other somatic and mental illnesses and genetic correlates of OCD in the context of comorbid MDD, ASD, or ADHD. The authors applied multiple approaches to publicly available genome-wide association studies summary statistics and unpublished imputed genotyping data to estimate the genetic relationships among multiple phenotypes robustly. The genetic correlations among the comorbid groups and other somatic and mental illnesses differed from their relationships with OCD-only group and these correlations were affected by comorbidities.

Diverse etiological factors

Although patients with the same diagnosis often share some core symptoms, they can differ in many ways, e.g., different genetic backgrounds or childhood adverse events. Ma, Zhang, Zhang, Su et al. explored the effects of childhood maltreatment on brain function in patients with major depressive disorder (MDD). Zhang H et al. investigated how the DRD4 −521 C/T SNP affects local brain activity and functional connectivity (FC) in children with ADHD. Both studies identified abnormal brain activation and/or FC that was affected by either environmental factors (e.g., childhood maltreatment) or genetic polymorphism. These results indicated that different etiological factors might be involved in developing psychiatric disorders in different individuals.

Exploration of novel nosology

Traditional nosology systems define disorders as distinct phenotypes. ADHD is conceptualized three different ways in the Diagnostic and Statistical Manual (DSM-5), the International Classification of Diseases-10 (ICD-10), and the Hierarchical Taxonomy of Psychopathology (HiTOP). To further elucidate the latent structure of ADHD symptoms, Gomez et al. used confirmatory factor analysis (CFA), the exploratory structure equation model (ESEM), and bi-factor S-1 ("asymmetrical") models in parent and teacher rating scales. Their findings showed that the optimum structure of ADHD symptoms contains only the inattention-specific factor and the g-factor (reflecting impulsivity), consistent with the HiTOP conceptualization of ADHD. Barron et al. proposed in their conceptual analysis article that digital technology, which quantifies human behaviors, may benefit psychiatry in clinical settings.

Conclusions

The current work explores the multilevel heterogeneity of various psychiatric disorders. These results support the Research Domain Criteria (RDoC) and HiTOP frameworks, which might help promote the classification of psychiatric phenotypes and accelerate progress in studies of psychiatric disorders. More studies based on RDoC and HiTOP would be valuable. "Bottom-up" pathophysiology is of great importance in creating novel nosology and in guiding treatment decisions.

Author contributions

Z-MW and B-RY developed the article concept. Z-MW wrote the draft of the manuscript. B-RY provided revision suggestions. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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ORIGINAL RESEARCH
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Unraveling the Optimum Latent Structure of Attention-Deficit/Hyperactivity Disorder: Evidence Supporting ICD and HiTOP Frameworks

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Attention Deficit/hyperactivity disorder (ADHD) is conceptualized differently in the Diagnostic and Statistical Manual (DSM-5), the International Classification of Diseases-10 (ICD-10), and the Hierarchical Taxonomy of Psychopathology (HiTOP) frameworks. This study applied independent cluster confirmatory factor analysis (ICM-CFA), exploratory structure equation model with target rotation (ESEM), and the S-1 bi-factor CFA approaches to evaluate seven ADHD models yielded by different combinations of these taxonomic frameworks. Parents and teachers of a community sample of children (between 6 and 12 years of age) completed the Disruptive Behavior Rating Scale (for ADHD symptoms) and the Strengths and Difficulties Questionnaire (for validation). Our findings for both parent and teacher ratings provided the most support for the S-1 bi-factor CFA model comprised of (i) a g-factor based on ICD-10 impulsivity symptoms as the reference indicators and (ii) inattention and hyperactivity as specific factors. However, the hyperactivity-specific factor lacked clarity and reliability. Thus, our findings indicate that ADHD is best viewed as a disorder primarily reflecting impulsivity, though with a separable inattention (but no hyperactivity) component, i.e., "ADID (attention deficit/impulsivity disorder)." This model aligns with the HiTOP proposals.

Keywords: children, ADHD, CFA models, ESEM model, S-1 bi-factor CFA models, DSM- 4, ICD-10, HiTOP

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INTRODUCTION

For Attention Deficit/Hyperactivity Disorder (ADHD), the latest fifth edition of the Diagnostic and Statistical Manual [DSM-5; (1)] has retained the same comparable nine inattention (IA), six hyperactivity (HY), and three impulsivity (IM) symptoms as in previous editions [DSM-IV; (2, 3)]. As in previous editions, the HY and IM symptoms are conceptualized as a single dimension

(HY/IM). In the International Classification of Diseases-10 [ICD-10; (4)], ADHD is referred to as Hyperkinetic Disorder (HD). Although DSM-5 and ICD-10 have the same sets of symptoms for ADHD/HD, they are grouped differently. Unlike DSM-5, the HY and IM symptoms in ICD-10 are considered as distinct groups. Additionally, the "talkative" symptom (classified as a HY symptom in the DSM-5) is designated as an IM symptom in ICD-10; these HY and IM symptom groups in ICD-10 have been referred to as "motoric HY/IM" and "verbal HY/IM," respectively (5).

Recently, a dimensional model of psychopathology called the Hierarchical Taxonomy of Psychopathology [HiTOP; (6, 7) has been proposed. HiTOP is a data-driven hierarchical, dimensional classification system (HiTOP) that continues to be refined. In the current version of HiTOP, several broad dimensional super spectra (for example, internalizing and externalizing) are at the highest level. Below this are six spectra (somatoform, internalizing, thought disorder, disinhibited externalizing, antagonistic externalizing, and detachment). At the level below the spectra are subfactors, and below this are the syndromes and disorders. These syndromes and disorders do not correspond to the broad disorder composites (for instance ADHD) listed in the more traditional classification systems (for instance, DSM-5 and ICD-10) but represent specific dimensions (such as IA, HY, and IMP) that may be relevant to the broad disorder (in this case ADHD). Below the subfactor level are symptom components and maladaptive traits, which are then followed by signs and symptoms (6). At this point in its development, there is little information in terms of signs and symptoms for the various syndromes and disorders. Overall, therefore, researchers interested in the HiTOP are not necessarily seeking to classify broad disorder composites but specific dimensions that may have relevance to the broad disorder composites. An individual's psychopathology is conceptualized along the relevant dimensions with varying degrees of severity, and not in terms of distinct categories (6). Since its proposal, emerging empirical data is providing increasing support for the HiTOP approach.

Within HiTOP, ADHD is listed in the antisocial subfactor (which is a blend of the disinhibited externalizing and antagonistic externalizing spectra). Other disorders in this subfactor include antisocial personality disorder, oppositional defiant disorder, conduct disorder, and intermittent explosive disorder. The maladaptive traits for these disorders (primarily related to the disinhibited externalizing spectra) are problematic impulsivity, irresponsibility, theft, distractibility, risk taking, low rigid perfectionism, low ruminative deliberation, and low conscientiousness (6). As problematic impulsivity and distractibility can be seen as corresponding to DSM and ICD ADHD symptom groups for IA and IMP, respectively, it can be extrapolated at this stage that HiTOP defines ADHD only in terms of IA and IMP symptom groups, with the HY not included. Indeed, the motor overactivity that corresponds to the HY symptoms is completely absent in the HiTOP model. Also, as the current HiTOP model does not specify the signs and symptoms for problematic impulsivity and distractibility, the specific symptoms proposed for ADHD IA and ADHD IM in the HiTOP model remain underexplored. Notwithstanding this, ADHD is conceived as an impulsivity disorder with inattention, instead of inattention, hyperactivity, and impulsivity. Overall, there are major differences across HiTOP, DSM, and ICD conceptualizations of the latent structure of ADHD (**Supplementary Table 1**).

Since the introduction of the DSM-IV, numerous studies have examined the factor structure of ADHD symptoms using different measurement models. The vast majority of earlier studies have used the independent cluster confirmatory factor analysis (ICM-CFA) model and, to a lesser degree, the bi-factor CFA model. More recently, researchers have begun to use more advance approaches, in particular, exploratory structural equation modeling with targeted rotation (ESEM) and S-1 bi-factor CFA modeling. In the S-1 model, the items in one of the group factors are selected (based generally on theory) as reference indicators for the g-factor: that is, the selected group of reference items load only on the g-factor and do not have their own specific factor. So far, no study has evaluated ADHD symptom structure—simultaneously in the same sample—against these seemingly irreconcilable structural constructs, as proposed by DSM, ICD, and HiTOP frameworks. This study aimed to fill this gap. To this end, we will first review and appraise the measurement models in the ADHD literature, in particular their strengths, weaknesses, and limitations, in order to select the best set of candidate models to probe the optimum structure.

The ICM-CFA model is an a priori oblique model in which items load only on their designated factors, i.e., no cross-loadings. Thus, each factor captures the shared variances of its designated items (8). Corresponding to DSM symptom grouping, past studies (involving children and adolescents) have supported ADHD models with separate factors for IA and HY/IM (9–11). The findings have also found support for three-factor models, reflecting both DSM-5 and ICD-10 symptom configurations. However, most researchers have argued in favor of the two-factor model as there was little difference in global fit between the two- and three-factor models, and the two-factor model was more parsimonious (9, 12, 13); moreover, the derived correlations between the HY and IM factors (generally >0.80) were high and deemed lacking adequate discriminant validity between these factors.

Over the last 10 years, studies have increasingly used the bi-factor CFA models to examine the structure of the ADHD symptoms. In general, the bi-factor CFA ADHD model (14, 15) comprises one general ADHD factor (g-factor) and either two (IA and HY/IM) or three (DSM-5-based or ICD-10-based) specific factors. In this model, all the ADHD symptoms load on the g-factor, and the symptoms for each group factor (e.g., IA symptoms) load only onto their own specific factor. The g-factor and specific factors are uncorrelated. As such, the g-factor captures the common variances of all items in the measure, whereas each specific factor captures the unique variances for its own set of symptoms unaccounted by the g-factor. Thus, the specific factors are conceptually and statistically different from "primary factors" in the first-order factor model.

In general, the bi-factor CFA model has demonstrated better fit for the ADHD symptoms than first-order CFA models (see 16). Additionally, studies involving adults have shown better

fit for models with three specific factors (IA, HY, IM; or IA, motoric-HY, verbal HY/IM) than with two specific factors (IA and HY/IM; 5, 17, 18). Also for adults, the three-factor model corresponding to ICD-10 configuration has shown better fit than DSM-5 configuration (5, 16, 17).

The IC-CFA and the bi-factor CFA are not without serious limitations. Constraining cross-loadings to zero in ICM-CFA models has been considered excessively restrictive as items in reality are rarely pure indicators of their latent factors, and therefore some degree of construct-relevant association with non-target but conceptually related factors is expected (18). Thus, as pointed out by Marsh et al. (19), the ICM-CFA approach does not generally express the reality of the data set, and yields artifacts of false poor fit. This shortcoming is particularly relevant for the ADHD symptoms given that exploratory factor analysis (EFA) studies have consistently demonstrated cross-loadings for the ADHD symptoms [e.g., (20–22)].

Regarding the bi-factor CFA approach, it has been suggested that such models are prone to yield statistically better-accommodated but non-sense response patterns in the data (8). As such, they will tend to yield a misleadingly better statistical fit than the corresponding first-order factor model, even when this is not actually the case; therefore, the superior fit noted for symmetrical bi-factor ADHD models may reflect a methodological artifact. Moreover, bi-factor CFA models often yield inadmissible solutions, with suboptimal parameters, such as low or even negative loadings of symptoms on designated factors. According to Burns et al. (14) and others (15), the anomalies (i.e., poorly defined factors with poor reliabilities and validities) in symmetrical bi-factor CFA can be explained in terms of improper parameterization of such a model. The bi-factor CFA model assumes that all group factors in the model are interchangeable. That is, they contribute equally toward the g-factor (thus referred as "symmetrical"). However, the findings in virtually all previous bi-factor CFA studies on ADHD have shown that this assumption does not hold (14), as the g-factor is disproportionally loaded with more variances from the HY/IM group of symptoms. To overcome the aforementioned shortcomings of these approaches, two modeling techniques have recently been proposed.

First, Asparouhov and Muthén (23) have developed the exploratory structure equation model (ESEM) with target rotation to overcome the limitations of the ICM-CFA approach. ESEM allows testing of an a priori defined structure (like CFA) while allowing non-zero cross-loadings (like EFA). This approach therefore overcomes a limitation of CFA while retaining its advantages (being model based). As shown in **Supplementary Figure 1** (Models 3 and 4), symptoms load on their own designated factors as well as non-designated factors at values close to (but not forced) zero. Indeed, outside of the ADHD field, studies have demonstrated that ESEM is superior to both EFA and CFA approaches for testing factor structures (19, 24).

Second, to overcome interchangeability problems in the bi-factor CFA models, Burns et al. (14), and Eid et al. (15) have introduced the bi-factor CFA S-1 model (also referred as "asymmetrical"). As mentioned earlier, in this model, the items in one of the group factors are selected (based generally on theory) as reference indicators for the g-factor: that is, the selected group of reference items load only on the g-factor and do not have their own specific factor. Other specific factors in the model (that are allowed to correlate with each other) are regressed on the g-factor. The resultant residual variances (i.e., true scores in the group factors modeled as specific factors that are not shared with the g-factor) are inferred as the variances for the specific factors. A feature of the g-factor and specific factors in a bi-factor S-1 model is that they have clear a priori definition and therefore allow for a clear interpretation of findings including their relationships with external correlates.

In addition, structural models also require scrutiny of reliability and external validities. It is necessary to show that the g-factor and specific factors are also clearly defined in the patterns of factor loadings and omega coefficients. Furthermore, the derived factors have to be validated against external measures. In other words, the factors need to demonstrate acceptable reliabilities and external validities (25). For ADHD, existing evidence from bi-factor CFA models shows that although the g-factor is generally clearly defined with acceptable reliability and validity (8, 26, 27), the specific factors (especially HY/IM) are often poorly defined (low or non-significant and sometimes negative loadings) and lack acceptable reliabilities (8, 26, 27).

Given the superiority of the ESEM and S-1 bi-factor approaches, we postulate that these approaches could be better candidates in identifying the optimum factor structure of the ADHD symptoms.

The ESEM approach has been applied in two studies involving ADHD symptoms in children. Arias et al. (28) obtained teacher ratings of preschool children and found stronger support for ESEM models, compared to the corresponding CFA models. The best-fitting model was the bi-factor ESEM model with three specific factors (IA, HY, and IM); notably, while the correlation between the HY and IM factors was 0.807 in the CFA model, it fell to 0.541 when examined using ESEM, thereby indicating support that there is indeed discriminant validity between HY and IM factors in three factor ADHD ESEM models. Rodenacker et al. (27) compared bi-factor CFA and bi-factor ESEM models with two specific factors (IA and HY/IM), three specific factors (IA, HY, and IM), and an incomplete model with one general ADHD and only two specific factors (IA and IM) for parent and teacher ratings of clinically referred children aged 6–18 years (60.4% with primary or secondary ADHD diagnosis). ICD-10-based models were not tested in the study. For both parent and teacher ratings, all models showed good and equivalent model fit, although the specific factors in all models for both respondent types were weakly defined. Recently, in a study involving an adult community sample, Gomez and Stavropoulos (17) found most support for the ESEM model with ICD-10 group factors for IA, motoric HY/IM, and verbal HY/IM. Thus, published studies to date provided evidence that ESEM models may offer more valid and meaningful representations of the latent structure of ADHD symptoms, in line with our postulation.

The bi-factor S−1 CFA approach has been applied to two recent studies that examined the DSM-5-based factor structure of ADHD symptoms (but together with ODD symptoms) in children. Based on trait impulsivity theory, Burns et al. (14)

used the HY/IM symptoms as the reference indicators for the g-factor. The trait impulsivity theory posits that ADHD comprises dysfunction in the mesolimbic reward pathway (29), resulting in the development of HY/IM symptoms, and IA symptoms develop later as secondary symptoms, or as expression of distinct mesocortical anomalies. Burns et al. (14) applied both the bi-factor model and the bi-factor S−1 CFA model to ADHD and ODD symptom ratings of children by mothers, fathers, and teachers. The findings from the symmetrical bi-factor CFA models were unsatisfactory, showing (i) anomalous factor loadings, (ii) a weakly defined HY/IM specific factor, and (iii) poor external validities in the associations of the g-factor and specific factors with external correlates (social impairment, academic impairment, and peer rejection). In contrast, the asymmetrical bi-factor S−1 CFA model showed clearly more interpretable results, with (i) well-defined specific factors; (ii) interpretable configuration of HY/IM items loading onto the g-factor; and (iii) expected associations for the g-factor and specific factors with the external correlates.

Junghänel et al. (30) also evaluated the merits of S-1 bi-factor CFA and examined a group of clinic-referred children with ADHD and ODD symptoms and similarly examined symmetrical CFA and bi-factor CFA models, and a series of the S-1 model with (i) HY/IM (based on DSM-5) as the reference factor; (ii) HY/IM (based on ICD-10 grouping) as the reference factor; (iii) HY (based on ICD-10) as the reference factor; and (iv) IM (based on ICD-10) as the reference factor. Their findings indicated that the S-1 models showed better fit than other models. Also, the models with either HY or IM as a reference factor had slightly better fit than the model with HY/IM as the reference factor. In these S−1 models, the g-factor and the IA-specific factors were clearly defined and demonstrated good reliabilities. Thus, these two studies provided preliminary evidence that bi-factor S-1 models offer a more valid and meaningful approach for testing the latent structure of ADHD symptoms.

To date, no study has applied the range of aforementioned models (CFA, ESEM, and S-1 bi-factor CFA) concurrently to evaluate the ADHD symptom structure in a community juvenile sample and also evaluate the differential merits of DSM-5, ICD-10, and HiTOP formulations. To address this gap, the current study sought to examine and compare the structure of ADHD symptoms in children from the general community, using CFA, ESEM, and bi-factor S-1 models—in the context of DSM-5, ICD-10, and HiTOP symptom groupings. Also, as the bi-factor CFA model violates the assumption that all group factors in the model are interchangeable, such models were not tested and reported here as they were deemed digressive and statistically inappropriate for evaluating the factor structure of the ADHD symptoms (but their findings are available upon request). In total, seven ADHD models were compared. These models are described in **Figure 1**, **Supplementary Table 2** and depicted diagrammatically in **Supplementary Figure 1**. The models tested were:

- CFA two-factor, group factors for IA & HY/IM (Model 1);
- CFA three-factor, group factors for IA, MHY/IM & VHY/IM (Model 2);
- ESEM two-factor, group factors for IA & HY/IM (Model 3);
- ESEM three-factor, group factors for IA, MHY/IM & VHY/IM (Model 4);
- s−1 BCFA, HY/IM reference factor, IA specific factor (Model 5);
- s−1 BCFA, IM reference factor, IA & HY specific factors (Model 6);
- s−1 BCFA, VHY/IM reference factor, IA & MHY/IM specific factors (Model 7).

Models 1, 3, 5, and 6 are DSM-5 based as the different symptom groups correspond to those in DSM-5, whereas Models 2, 4, and 7 are ICD-10 based as the different symptom groups correspond to those in ICD-10. In Model 7, concurrent support for the g-factor and IA-specific factors and lack of support for the MHY/IM would indicate support for the HiTop models as such a model will indicate a model with only IM (since the g-factor is index by IM symptoms) and IA symptoms (since there is a IA specific factor). All the models were tested separately for parent and teacher ratings. Additionally, we probed the reliabilities and external validities of the factors yielded in the models that were deemed potentially good.

METHODS

Participants

In total, 792 parents and 396 teachers from Victoria, Australia, completed ratings for children from of a community sample. Most parents resided in metropolitan Melbourne (58%) while the remainder (42%) was from regional and rural Victoria. Parents provided ratings ($N = 792$) for 387 (48.9%) girls and 405 (51.1%) boys from 16 randomly selected schools, and teachers rated ($N = 396$) the same 190 (48%) girls and 206 (52%) boys. Thus, 50% of children with parent ratings did not have teacher ratings. The difference in the numbers of parent and teacher ratings was because for many children, teachers did not complete the ratings, despite consent having been granted by parents. The ages of students ranged from 6 to 12 years for both parent (mean = 8.88, SD = 1.68) and teacher (mean = 8.38 years; SD = 1.74) ratings. No significant difference in age between gender was detected for students that rated their parents [$t_{(790)} = 1.166$, $p = 0.244$] and teachers [$t_{(394)} = 0.122$, $p = 0.903$).

Supplementary Table 3 shows the descriptive statistics of the 18 ADHD symptoms for parents and teacher ratings on the Disruptive Behavior Rating Scale (DBRS). **Supplementary Table 4** shows the descriptive statistics (mean and SD scores) for the five Strengths and Difficulties Questionnaire (SDQ) scales.

Measures

The Disruptive Behavior Rating Scale—Parent and Teacher Versions [DBRS; (31)]

The DBRS comprises all DSM-IV symptoms for ADHD, Oppositional Defiant Disorder, and Conduct Disorder. For both versions, only the 18 ADHD symptoms (9 IA and 9 HY/IM)

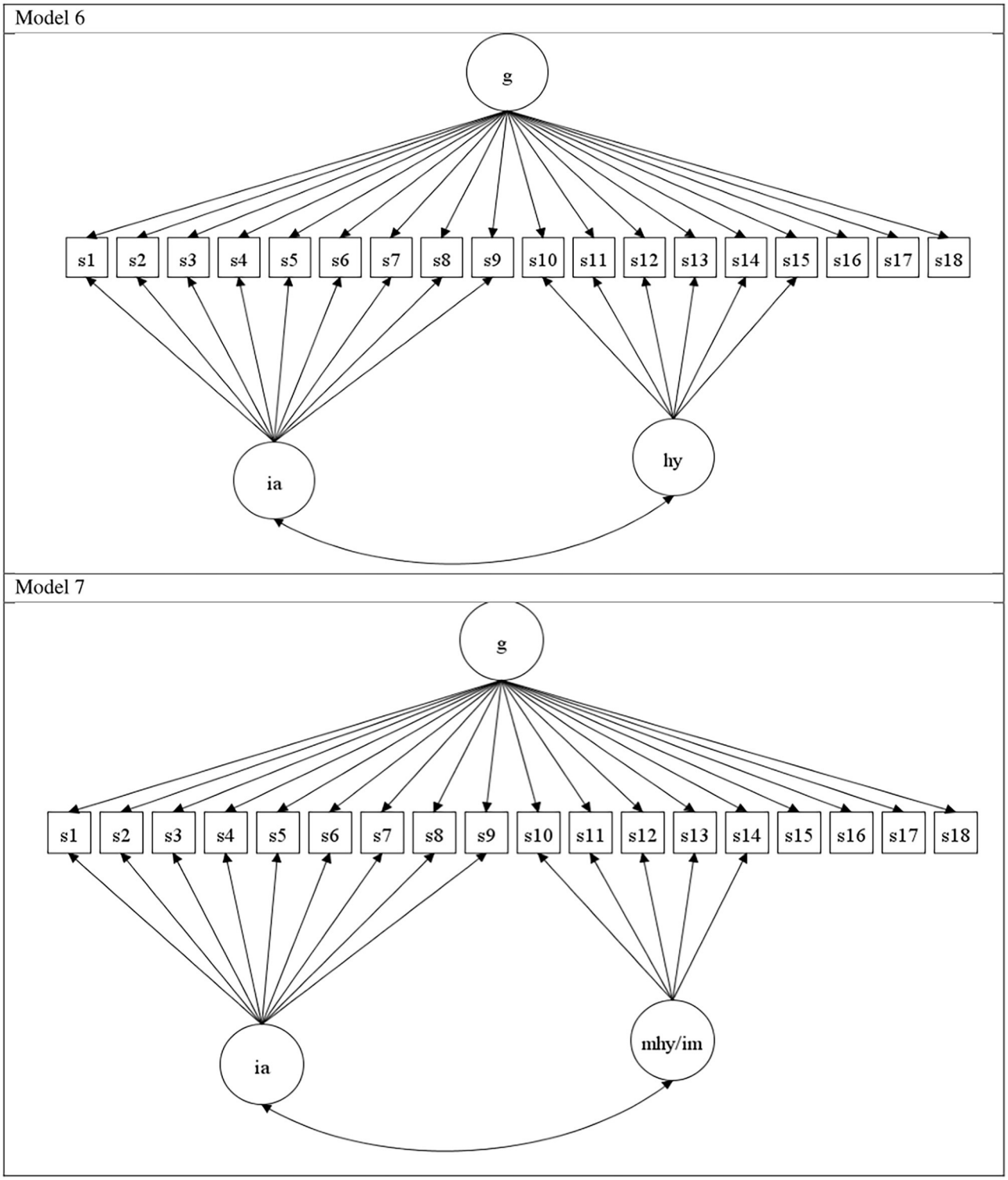

FIGURE 1 | Model 6: s – 1 bit factor, with IM as reference indicators g-factor: & IA and HY as specific factors. Model 7: s – 1 bit factor, with VHY/IM as reference indicators g-factor: & IA and MHY/IMP as specific factors. ia, inattention symptoms; hy, hyperactivity; im, impulsivity; g, general factor ADHD; mhi, motor hyperactivity/impulsivity; vhi, verbal hyperactivity/impulsivity. S1 to s18 refers to the eighteen ADHD symptoms, in the order listed in DSM-IV and **Supplementary Table 1**.

were used in the current study. Each symptom is rated on a four-point scale from 0 (never or rarely) to 3 (very often) in terms of occurrence over the previous 6 months.

Strength and Difficulties Questionnaire—Parent and Teacher Versions [SDQ; (32)]

The SDQ contains 25 items (categorized into five subscales of five items each: hyperactivity/inattention (HI), emotional symptoms (ES), conduct problems (CP), peer problems (PP), and prosocial behavior (PS). We focused on the ADHD symptoms in the DBRS and not the HI items in the SDQ in the factor analysis as the latter does not provide a complete list of the 18 DSM symptoms. The SDQ items are rated on a three-point scale from 0 (not true) to 2 (certainly true). The five SDQ subscales were used as covariates to test validity for the ADHD factors.

Procedure

A community sample of parents and teachers of children (between 6 and 12 years of age) were recruited from schools in Victoria, Australia. The study was approved by the University of Ballarat Human Research Ethics Committee, the Victorian Education Department, Catholic Education Office of Victoria, and the principals of participating schools. Following all the ethics and other approvals, classroom teachers from the randomly selected schools were given sealed envelopes containing a letter providing background to the study, the parent version of the DBRS and SDQ, a consent form, a form for parental approval for their children's class teachers to rate their children on the teacher version of the DBRS and SDQ, and a return envelope. These were forwarded to parents through their children. Approximately 1,500 envelopes were distributed. Of these, 792 were returned by parents. The DBRS was completed mostly by mothers (96%). Of the 792 students who had parental approval for their teachers to complete the DBRS and SDQ, 396 teacher questionnaires were also completed.

Statistical Analysis

Regarding statistical power, the sample size (for parent and for teacher ratings) in the current study is well above the level generally recommended for the factor analyses involving 18 indicator items (i.e., a minimum sample size of $20 \times 18 = 360$) [see (33)].

All statistical analyses were conducted using Mplus Version 7 (34). As the scores for the ADHD ratings were ordered-categorical scores, we used WLSMV extraction (35). All ESEM models in the study were conducted using geomin (oblique) rotation. For the bi-factor S−1 CFA models, the technique described by Burns et al. (14) was used. For Model 5, we used the HY/IM symptoms as indicators of the g-factor. For Models 6 and 7, we used the motoric HY/IM and verbal HY/IM symptoms, respectively, as indicators of the g-factor. In each model, the specific factors were correlated with each other and regressed on the g-factor.

Given the constraints and issues with CFA mentioned earlier, it can be anticipated that ESEM/EFA models would fit better than corresponding CFA models, and three-factor models, with one extra factor, would fit better than two-factor models. Thus, to establish the best model, we used a sequential four-step model evaluation based on four criteria that include and go beyond global fit (i) model fit criterion, (ii) clarity criterion, (iii) reliability criterion, and (iv) validity criterion. We coined this standardized approach "stepwise algorithm for model selection" (SAMS) procedure. Step 1 examined and compared the global fit values of all models tested. We selected good-fitting models, regardless of whether they differed from each other. As large samples will inflate χ^2-values, model fit was evaluated using the root mean squared error of approximation (RMSEA), comparative fit index (CFI), and Tucker–Lewis index (TLI). We deemed a model as a potentially good model if all the approximate fit indices (i.e., RMSRA, CFI, and TLI) indicated good fit. According to Hu and Bentler (36), RMSEA, values <0.06 = good fit, <0.08 = acceptable fit, and $>$ 0.08 to 0.10 = marginal fit. For CFI and TLI, values ≥ 0.95 = good fit, and ≥ 0.90 = acceptable fit. Where needed, the difference in the fit of nested models was examined using differences in RMSEA ($\geq$ 0.015) and CFI ($\geq$ 0.010) values (37).

In step 2, all models selected as potentially good models were checked for factor clarity by examining the significance of symptom factor loadings (and cross-loadings in ESEM). Factors with more significant loadings of designated symptoms and fewer loadings of non-designated symptoms were considered to be better defined. As this may leave two or more models equally supported, in steps 3 and 4 we examined the reliabilities and external validities of the factors in these equally supported models. The model with better support for reliabilities and validities of the factors was considered the optimum model.

In step 3, omega (ω) values for the factors were computed (38, 39). Relative to coefficient alpha, the ω provides a model based (and better) measure of the internal consistency of a factor (40). This term ω is used in the context of a first order CFA. In a bi-factor model, the term omega hierarchical (ωh) is used to refer to the internal consistency value for the g-factor, and the term omega-subscale (ωs) is used to refer to the internal consistency values for the specific factors (39). According to Reise et al. (41), ωh and ωs values need to be at least 0.50 with values of at least 0.75 preferred for meaningful interpretation of a scale. However, considering this value too stringent for the specific factors, Smits et al. (42) suggested the following for classifying the ωs values: substantial $\geq$0.30, moderate.20 to $<$0.30; and low $<$0.20.

In step 4, to test the external and differential validities of the ADHD g-factor and specific factors in potentially optimum models, the SDQ subscale scores for HI, CP, ES, PP, and PS were regressed on all model-derived factors. The parent SDQ subscale scores were used for models involving parent ADHD ratings, and teacher-rated SDQ scores for teacher-rated ADHD models. The external validity of the ADHD g-factors and specific factors were inferred from significant positive associations with the SDQ HI scale scores. Differences in the patterns of significant positive associations between with the ADHD g-factors and specific factors with the SDQ scale scores were interpreted as evidence of differential validity of the ADHD g- and s-factors.

RESULTS

As noted earlier, to establish the best model, we went beyond global fit. We used a sequential four-step model evaluation based (coined SAMS) on four criteria: (i) model fit criterion, (ii) clarity criterion, (iii) reliability criterion, and (iv) validity criterion.

Parent Ratings

Step 1: Examining Global Fit of Models Tested

Table 1 shows the fit values for all seven ADHD models tested, based on parent ratings. Our initial step was to identify models by "good fit criteria." Only Models 4, 6, and 7 met these criteria (good-fit values for RMSEA, CFI, and TLI). When compared using ΔCFI and ΔRMSEA values, there were no differences in fit between different pairs of these models, as the ΔRMSEA and ΔCFI values did not exceed 0.015 and 0.010, respectively.

Step 2: Examining Item-Factor Loadings in Models 4, 6, and 7

Table 2 shows the factor loadings for Models 4, 6, and 7. It also presents the number of targeted factor loadings and cross-loadings in these models. As shown in **Table 2**, only Model 7 (i.e., the ICD-10 bi-factor S−1 CFA model with verbal HY/IM as the reference factor) had all target items loading significantly on their own designated factors, and as this is a bi-factor model, there no cross-loadings. Model 6 (i.e., the DSM-5 bi-factor S−1 CFA model with IM as the reference factor) had one target item (symptom relating to "talk") with negative but not significant loading, on its designated factor, and again as this is a bi-factor model, there was also no cross-loading. Thus, there was reasonable (but not complete) clarity for this model. For Model 4 (the ICD-10 ESEM model with IA, verbal HY/IM, and motoric HY/IM as factors), all target items loaded significantly on their designated factors, and there were 32 items cross-loading significantly on on-targeted factors. Taken together, these findings indicate that Model 7 was the most clearly defined model, Model 6 also had reasonable clarity, and Model 4 was poorly defined.

For Model 4, the correlations between IA and motoric HY/IM, IA and verbal HY/IM, and motoric HY/IM and verbal HY/IM were 0.653, 0.473, and 0.663, respectively. The corresponding correlations in CFA version of this model (Model 2) were 0.806, 0.622, and 0.821, respectively. According to Brown (43), when factor correlations are <0.85, discrimination validity between the factors can be inferred. Thus, it can be taken that for Model 4 there was adequate discrimination between motoric HY/IM and verbal HY/IM. For Model 6, the correlation between IA and HY (reflective of a partial correlation between them, controlling for the g-factor) was 0.695, and for Model 7, the correlation between IA and motoric HY/IM (reflective of a partial correlation between them, controlling for the g-factor) was also 0.695. Thus, support for the discrimination between the two factors in Models 6 and 7 can be inferred. Given the findings in Steps 1 and 2, Model 7 and to a lesser degree Model 6 were retained tentatively as our preferred models. We therefore examined the ωh and ωs and external validities of the factors in both these models.

TABLE 1 | Fit of all the models tested in the study.

	Fit values			
Model (M)	**χ^2 (*df*)**	**CFI**	**TLI**	**RMSEA (90% CI)**
Parent ratings				
M 1: CFA 2-F (IA, HY/IM)	1034.79 (134)	0.937	0.929	0.092 (0.087–0.097)
M 2: CFA 3-F (IA, MHY/IM, VHY/IM)	766.17 (132)	0.956	0.949	0.078 (0.073–0.083)
M 3: ESEM 2-F (IA, HY/IM)	573.51 (118)	0.968	0.959	0.070 (0.064–0.076)
M 4: ESEM 3-F (IA, MHY/IM, VHY/IM)	355.03 (102)	0.982	0.974	0.056 (0.050–0.062)
M 5: BCFA -1-s-F (G, IA), with HY/IM as reference	880.66 (126)	0.948	0.936	0.087 (0.082–0.092)
M 6: BCFA -2-s-F (G, IA, HY), IM reference	498.52 (119)	0.974	0.966	0.063 (0.058–0.069)
M7: BCFA -2-s-F (G, IA, MHY/IM), VHY/IM reference	478.97 (120)	0.975	0.968	0.061 (0.067–0.067)
Teacher ratings				
M 1: CFA 2-F (IA, HY/IM)	609.50 (134)	0.978	0.974	0.095 (0.087–0.102)
M 2: CFA 3-F (IA, MHY/IM, VHY/IM)	465.40 (132)	0.984	0.982	0.080 (0.072–0.088)
M 3: ESEM 2-F (IA, HY/IM)	270.56 (118)	0.993	0.991	0.057 (0.046–0.066)
M 4: ESEM 3-F (IA, MHY/IM, VHY/IM)	163.93 (102)	0.997	0.996	0.039 (0.028–0.050)
M 5: BCFA -1-s-F (G, IA), HY/IM as reference	515.77 (126)	0.982	0.978	0.088 (0.081–0.096)
M 6: BCFA -2-s-F (G, IA, HY), IM reference	243.59 (119)	0.994	0.992	0.051 (0.042–0.061)
M 7: BCFA -2-s-F (G, IA, MHY/IM), VHY/IM reference	240.99 (120)	0.994	0.993	0.050 (0.041–0.060)

F, factor; IA, inattention; HY/IM, hyperactivity/impulsivity; MHY/IM, motoric hyperactivity/impulsivity; VHY/IM, verbal hyperactivity/impulsivity; CI, confidence interval; CFA, confirmatory factor analysis; ESEM, exploratory structural equation modeling; BCFA, bi-factor confirmatory factor analysis; RMSEA, root mean square error of approximation; CFI, comparative fit index; TLI, Tucker-Lewis Index; s-f, specific factor.

TABLE 2 | Factor loadings for 4, 6, and 7, based on parent ratings.

	Model 4			Model 6			Model 7		
	IA	**MHY/IM**	**VHY/IM**	**G**	**IA**	**HY**	**G**	**IA**	**MHY/IM**
Careless -IA1	**0.76****	0.08*	0.02	**0.32****	**0.70****		**0.31****	**0.70****	
Inattention -IA2	**0.69****	0.34**	0.15**	**0.56****	**0.55****		**0.56****	**0.56****	
Listen -IA3	**0.58****	0.29**	0.28**	**0.58****	**0.41****		**0.57****	**0.42****	
Instruction -IA4	**0.86****	0.02	0.18**	**0.43****	**0.73****		**0.42****	**0.73****	
Disorganize -IA5	**0.84****	0.14**	0.09**	**0.43****	**0.74****		**0.43****	**0.75****	
Unmotivated -IA6	**0.77****	0.20**	0.01	**0.39****	**0.69****		**0.39****	**0.69****	
Lose -IA7	**0.70****	0.20**	0.07	**0.41****	**0.61****		**0.41****	**0.61****	
Distracted -IA8	**0.71****	0.40**	0.18**	**0.62****	**0.56****		**0.62****	**0.56****	
Forgetful -IA9	**0.74****	0.24**	0.20**	**0.54****	**0.60****		**0.54****	**0.60****	
Fidget -HY1	0.47**	**0.56****	0.20**	**0.61****		**0.45****	**0.61****		**0.46****
Seat -HY2	0.60**	**0.52****	0.13**	**0.57****		**0.67****	**0.56****		**0.67****
Run -HY3	0.48**	**0.69****	0.24**	**0.72****		**0.45****	**0.71****		**0.45****
Quiet -HY4	0.41**	**0.47****	0.40**	**0.69****		**0.28****	**0.69****		**0.29****
Motor -HY5	0.23**	**0.71****	0.30**	**0.69****		**0.15****	**0.69****		**0.17***
Talk -HY6	0.19**	0.56**	**0.49****	**0.75****		**−0.03**	**0.74****		
Blurt -IM1	0.33**	0.38**	**0.63****	**0.81****			**0.81****		
Wait -IM2	0.39**	0.31**	**0.77****	**0.91****			**0.91****		
Interrupt -IM3	0.31**	0.34**	**0.79****	**0.87****			**0.87****		
Omega—ω_h				74			0.74		
Omega—ω_s					0.69	0.17		0.60	0.25
Number of targeted and non-targeted factor loadings									
Target items (TI)	9	5	4	18	9	6	18	9	5
Significant TI	9	5	4	18	9	5	18	9	5
Non-TI	9	13	14	0	0	0	0	0	0
Significant non-TI	9	12	11	0	0	0	0	0	0

G, general factor; IA, inattention; MHY/IM, motoric hyperactivity/impulsivity; VHY/IM, verbal hyperactivity/impulsivity. Boldface values indicate factor loadings in the primary dimension; shaded values indicate significant cross-loadings over 0.30 in absolute value, indexing salience.
$^*p < 0.05$, $^{**}p < 0.01$.

Step 3: Examining Reliabilities of Factors in Models 6 and 7

As shown in **Table 2**, the g-factor in Model 7 had sufficient reliability (ωh values >0.50) for meaningful interpretation (41). Based on guidelines (42) for classifying the ωs values, for this model, the IA-specific factor was substantial, and the value for the motoric HY/IM-specific factor was moderate. For Model 6, the g-factor also showed sufficient reliability (ωh values >0.50). Although the IA-specific factor was substantial, the value for the HY-specific factor was low. Hence, Model 7 met the reliability criterion for all its factors, whereas Model 6 did not meet this for its HY factor.

Step 4: Examining Validities of Factors in Models 6 and 7

Table 3 shows the standardized coefficients (from the regression analysis) for the predictions of all SDQ subscales by the factors in Models 6 and 7. For both models, the g-factor predicted significantly and positively all SDQ subscale scores (HI, CP, ES, PP, and PS), and the IA-specific factor predicted significantly and positively the subscale scores for HI, PP, and PS in model 6, and HI, ES, PP, and PS in model 7. For Model 6, the HY-specific factor did not predict significantly any of the SDQ scales scores, and for model 7, the motoric HY/IM-specific factor predicted significantly and positively the subscale score for HI, but not any of the other SDQ subscale scores. Only Model 7 met all criteria in the SAMS procedure.

Teacher Ratings

Step 1: Examining the Global Fit of Models Tested

Table 1 shows the fit values for all seven ADHD models tested based on teacher ratings. Only Models 4, 6, and 7 meet good global fit criteria (good fit values for RMSEA, CFI, and TLI). There were no differences in fit between these models, as the ΔRMSEA and ΔCFI values between different pairs of these models did not exceed 0.015 and 0.010, respectively. Compared to these models, the CFI values for all the other models were substantially worse.

Step 2: Examining the Item-Factor Loadings in Models 4, 6, and 7

Table 4 shows the factor loadings for Models 4, 6, and 7. It also provides a summary of the number of targeted factor loadings and cross-loadings in these models. Like the parent ratings, only

TABLE 3 | Standardized beta coefficients for the predictions of the SDQ subscale scores by the factors in models 6 and 7, based on parent and teacher ratings.

	HI	CP	ES	PP	PS
Parent ratings					
Model 6					
ADHD general factor	0.689***	0.497***	0.063	0.369***	0.369***
Inattention	0.318***	0.094	0.155	0.308*	0.308*
Hyperactivity	0.132	0.125	0.177	0.014	0.014
Model 7					
ADHD general factor	0.664***	0.557***	0.241***	0.192***	0.297***
Inattention	0.279***	0.127*	0.250***	0.078	0.224**
Motoric hyperactivity/impulsivity	0.277***	0.118	0.000	0.157	0.158
Teacher ratings					
Model 6					
ADHD general factor	0.689***	0.497***	0.063	0.120*	0.369***
Inattention	0.318***	0.094	0.155	0.207	0.308*
Hyperactivity	0.132	0.125	0.177	0.042	0.014
Model 7					
ADHD general factor	0.697***	0.501***	0.073	0.119*	0.373***
Inattention	0.312***	0.094	0.171	0.164	0.292*
Motoric hyperactivity/impulsivity	0.124	0.114	0.153	0.100	0.027

HI, hyperactivity/inattention; ES, emotional symptoms; CP, conduct problems; PP, peer problems; PS, prosocial behavior.
****p < 0.001; **p < 0.01; *p < 0.05.*

Model 7 had all target items loading on their own designated factors, and as this is a bi-factor model, there were also no significant cross-loadings. Model 6 had 1 target item (symptom relating to "talk") not loading significantly on its own designated factor, and again as this is a bi-factor model, there was no cross-loading. For Model 4, all target items loaded on their designated factors, and there were 27 significant cross-loadings on on-targeted factors. Taken together, these findings indicate that Model 7 was the most clearly defined model, Model 6 can be considered as fairly clearly defined, and Model 4 poorly defined.

For Model 4, the correlations between IA and motoric HY/IM, IA and verbal HY/IM, and motoric HY/IM and verbal HY/IM were 0.674, 0.506, and 0.692, respectively. The corresponding correlations in the CFA version of this model (Model 2) were 0.842, 0.660, and 0.853, respectively. Thus, for Model 4 there was adequate discrimination between motoric HY/IM and verbal HY/IM. For Model 6, the correlation between IA and HY (reflective of a partial correlation between them, controlling for the g-factor) was 0.796, and for Model 7, the correlation between IA and motoric HY/IM (reflective of a partial correlation between them, controlling for the g-factor) was 0.786. Thus, there was some support for the discrimination between the two factors in Models 6 and 7. Based on all the findings in Steps 1 and 2, Models 6 and 7 were retained tentatively as our preferred models. We therefore examined the ωh and ωs, and external validities of the factors in both models.

Step 3: Examining Reliabilities of Factors in Models 6 and 7

As shown in **Table 4**, for both Models 6 and 7, the g-factors had sufficient reliability (ωh values >0.50) for meaningful interpretation (41). Based on guidelines (42) for classifying the ωs values, the IA-specific factors in both models were substantial and the values for HY (Model 6) and motoric HY/IM (Model 7) specific factors were low. Hence, Models 6 and 7 met the reliability criterion for the general and IA factors, but not for the HY (Model 6) and motoric HY/IM (Model 7) factors.

Step 4: Examining Validities of Factors in Models 6 and 7

Table 3 shows the standardized coefficients (from the regression analysis) for the predictions of all SDQ subscales by the factors in Models 6 and 7. For Models 6 and 7, the g-factors predicted significantly and positively HI, CP, PP, and PS, and there was no significant prediction for ES. For both models, IA predicted SDQ HI and PS. HY (Model 6) or Motoric HY/IM (Model 7) did not predict any of the SDQ scale scores. Taken together, the significant positive associations of the ADHD g-factors and specific factors with the SDQ HI scale scores can be interpreted as supporting the external validity of all the ADHD factors in Models 6 and 7. Also, the differences in the patterns of significant positive associations between the ADHD g-factors and specific factors with the SDQ scale scores can be interpreted as evidence of differential validity of the ADHD g- and s-factors.

DISCUSSION

The current study aimed to evaluate the optimum latent structure of ADHD symptoms within the ICD, DSM, and HiTOP frameworks, by using CFA, ESEM, and bi-factor S-1 models, applied to parent and teacher ratings. Overall, our findings indicated most support for the S-1 bi-factor model (in parent and

TABLE 4 | Factor loadings for models 4, 6, and 7, based on teacher ratings.

	Model 4			Model 6			Model 7		
	IA	**MHY/IM**	**VHY/IM**	**G**	**IA**	**HY**	**G**	**IA**	**MHY/IM**
Careless -IA1	**0.94****	−0.09	0.00	**0.46****	**0.75****		**0.48****	**0.74****	
Inattention -IA2	**0.84****	−0.01	0.19**	**0.66****	**0.68****		**0.67****	**0.66****	
Listen -IA3	**0.74****	0.04	0.18**	**0.63****	**0.59****		**0.64****	**0.58****	
Instruction -IA4	**0.94****	−0.23**	0.14**	**0.53****	**0.78****		**0.54****	**0.77****	
Disorganize -IA5	**0.97****	0.04	−0.12*	**0.49****	**0.81****		**0.50****	**0.80****	
Unmotivated -IA6	**0.93****	−0.06	0.05	**0.53****	**0.75****		**0.55****	**0.74****	
Lose -IA7	**0.79****	0.35**	−0.27**	**0.52****	**0.74****		**0.54****	**0.73****	
Distracted -IA8	**0.65****	0.22**	0.18**	**0.74****	**0.56****		**0.75****	**0.55****	
Forgetful -IA9	**0.89****	0.27**	−0.27**	**0.50****	**0.80****		**0.52****	**0.79****	
Fidget -HY1	0.38**	**0.53****	0.13*	**0.78****		**0.55****	**0.79****		**0.54****
Seat -HY2	0.25**	**0.44****	0.31**	**0.80****		**0.37****	**0.81****		**0.35****
Run -HY3	0.30**	**0.55****	0.14**	**0.77****		**0.45****	**0.78****		**0.43****
Quiet -HY4	0.27**	**0.51****	0.21**	**0.79****		**0.40****	**0.79****		**0.39****
Motor -HY5	−0.23**	**0.68****	0.13*	**0.84****		**0.12***	**0.85****		**0.10****
Talk -HY6	−0.01	0.50**	**0.44****	**0.86****		**0.10**	**0.89****		
Blurt -IM1	−0.15**	0.41**	**0.69****	**0.91****			**0.90****		
Wait -IM2	0.09**	0.10	**0.85****	**0.97****			**0.97****		
Interrupt -IM3	0.09**	0.16**	**0.77****	**0.94****			**0.94****		
Omega—ω_h				0.77			0.78		
Omega—ω_s					0.61	0.14		0.69	0.16
Number of targeted and non-targeted factor loadings									
Target items (TI)	9	5	4	18	9	6	18	9	5
Significant TI	9	5	4	18	9	5	18	9	5
Non-TI	9	13	14	0	0	0	0	0	0
Significant non-TI	8	7	12	0	0	0	0	0	0

G, general factor; IA, inattention; MHY/IM, motoric hyperactivity/impulsivity; VHY/IM, verbal hyperactivity/impulsivity. Boldface values indicate factor loadings in the primary dimension; shaded values indicate significant cross-loadings over 0.30 in absolute value, indexing salience.
$^*p < 0.05$, $^{**}p < 0.01$.

teacher) comprised of (i) a g-factor based on ICD-10 Impulsivity symptoms as the reference indicators (ωh at 0.78 for teacher; at 0.74 for parent) and (ii) an inattention-specific factor (ωs at 0.69 for teacher; at 0.60 for parent)—as represented by Model 7 in **Figure 1**, **Tables 2**, **4**. In both, Model 7, the hyperactivity-specific factor however lacked clarity and reliability (ωs at 0.16 for teacher; at 0.25 for parent).

In our findings, the optimum structure of ADHD therefore embodied only the g-factor and inattention-specific factor. The latent structure from both parents' and teachers' ratings converged. Thus, our findings indicate that ADHD is best viewed as a disorder primarily reflecting impulsivity with a separable inattention (but no hyperactivity) component. In essence, ADHD may better be represented by ADID (attention-deficit impulsivity disorder). This model aligns with the HiTOP proposal for ADHD.

In this study, seven ADHD models in total were tested separately for parent and teacher ratings. Additionally, we probed the reliabilities and external validities of the factors yielded. To establish the best model, we devised a four-step sequential stepwise algorithm for model selection (SAMS) procedure, based on (i) model fit criterion, (ii) clarity criterion, (iii) reliability criterion, and (iv) validity criterion.

Supplementary Table 5 shows summaries of the criteria used for selecting the optimum model for both parent and teacher ratings, based on SAMS. For parent ratings, Model 6 (i.e., the ICD-10-based S−1 bi-factor model with motoric HY/IM as the reference factor, and IA and verbal HY/IM as specific factors) and Model 7 (i.e., the ICD-10-based S−1 bi-factor model with verbal HY/IM as the reference factor, and IA and motoric HY/IM as specific factors) were comparable in terms of meeting model fit and validity criteria. In terms of clarity criterion, Model 6 had one item that did not load on its designated factor, whereas for Model 7, all items loaded on their designated factors. In terms of reliability criterion, the g-factor and the IA specific factor in Model 6, but not the verbal HY/IM factor, showed adequate reliabilities. For Model 7, all factors showed acceptable reliabilities. For teacher ratings, Models 6 and 7 were comparable in terms of meeting model fit, reliability, and validity criteria. In terms of clarity criterion, Model 6 had one item that did not load on its designated factor, whereas for Model 7, all items loaded on their designated factors. Given these findings, we adopted Model

7 as our preferred model for both parent and teacher ratings. Our conclusion is consistent with existing literature that have also reported the strongest support for the bi-factor S−1 CFA model with verbal HY/IM as the reference factor (see 30).

Our findings have a number of implications worthy of note. First, in an S−1 model (14, 15), the g-factor has a clear a priori definition. Notably, the reference factor for the preferred S−1 model was verbal HY/IM, which is the impulsivity symptoms as listed in ICD-10, and the g-factor can therefore be best considered as predominantly reflecting impulsivity as formulated by this ICD-10 grouping. This raises the possibility that, overall, ADHD (which corresponds to the g-factor) is best viewed as a disorder reflecting impulsivity. Moreover, in the S−1 model, the variances in the specific factors are residual variances not accounted for by the general actor, and thus, the support for the IA-specific factor can be interpreted as the presence of a separate distinctive psychopathological process represented by predominantly inattention problems. Using the same line of reasoning, the lack of support for motoric HY/IM can be interpreted as the absence of a distinctive disorder reflecting predominantly hyperactive or motor-overactivity problems—above and beyond that captured by the g-factor. Our findings therefore suggest a markedly novel reconceptualization of ADHD, that ADHD is best viewed as a disorder primarily reflecting the latent trait impulsivity characterized by verbal HY/IM, but in addition, there is a separable component of predominantly inattention problems. In essence, ADHD may be re-conceptualized as "ADID" (attention-deficit impulsivity disorder).

Second, the latent structure detected as our preferred ADHD model also provides support to the HiTOP conceptualization of ADHD within the disinhibited externalizing spectrum. This spectrum is characterized by impulsivity (i.e., acting spontaneously on the spur of the moment without consideration for consequences), irresponsibility (i.e., failing to fulfill obligations or act in a dependable manner), distractibility (i.e., inattentive and not completing tasks), risk taking (i.e., sensation-seeking, engaging in potentially dangerous activities in a reckless manner), and (low) perfectionism (i.e., not completing work to acceptable standards). Notably, hyperactivity is a peripheral expression rather than a core driver of psychopathology within this conceptualization (6, 44). Our findings therefore provide preliminary evidence to support the symptom components and maladaptive traits organized by spectrum as proposed by HiTOP. These interpretations were further supported by our findings that in our preferred model (Model 7) for both parent and teacher ratings, motoric HY/IM did not predict any of the SDQ scale scores, including SDQ HI.

Third, as our preferred model (Model 7) had ICD-10-based verbal HY/IM symptoms as the reference indicators for the g-factor, and IA and motoric HY/IM as specific factors, our findings support the ICD-10 grouping of HY/IM symptoms, and the separation of IA, HY, and IM into separate groups. Related to this, in Model 6, for both parent and teacher ratings, the item referring to "talk" did not load significantly on its IM factor. However, this item loaded significantly on its designated verbal HY/IM factor in Model 7. As Model 11 aligns with how the HY/IM symptoms are grouped in ICD-10, this adds further support that ICD-10 grouping of the ADHD symptoms is more appropriate than the DSM-5 groupings of these symptoms.

Fourth, as the HY and IM factors showed high correlations in the three-factor model, there has been a tendency in past studies to favor the two-factor model over the three-factor CFA model for parsimony despite evidence of better fit for the three-factor CFA model. We have argued earlier that the high correlation between the HY and IM may have been artificially inflated due to how CFA models are parameterized. More specifically, because cross-loadings are not modeled in a CFA, the shared variances for items in different symptom groups are diverted toward the factor correlations (45). In support of this, for both parent and teacher ratings, we found higher correlations in CFA models than in corresponding the ESEM models. Indeed, the moderate correlations between the HY and IM factors, and verbal HY/IM and motoric HY/IM factors in the ESEM model, can be interpreted as sufficient support for the separation of the HY- and IM-related dimensions (43), and therefore testing three-factor ADHD models.

Fifth, for the preferred model, across parent and teacher ratings, the g-factor was associated positively with all SDQ subscale scores (HI, CP, ES, PP, and PS), and the IA-specific factor was associated positively with subscale scores for HI and PS (for parents). These findings can be interpreted to mean that other external and internalizing disorders are comorbid with ADHD via their associations with the ADHD impulsivity symptoms (as the g-factor was index by the impulsivity symptoms).

Sixth, although there is an emerging trend to examine the structure of the ADHD symptoms using ESEM with target rotation approach (17, 27, 28), our results provide stronger support for using bi-factor S−1 models, over ESEM models, in research aimed at examining the factor structure of the ADHD symptoms. In our findings, the model with verbal HY/IM symptoms as the reference indicators provided better fit than those of other reference indicators (i.e., with HY/IM, HY, IM, or motoric HY/IM); this means that verbal HY/IM symptoms are likely a more preferable reference factor and should be included in future studies for replication and exploration of bi-factor S-1 ADHD models.

LIMITATIONS

Despite the novelty of our findings, the study has several limitations. The factor structure of ADHD symptoms was examined using DBRS which is DSM-IV based. The reported high comparability in parental information obtained via rating scales and interviews (46) raises the possibility that our findings are likely to be applicable to ADHD symptom reports from clinical interviews. As our sample was a community sample, the findings may not be applicable to clinic-referred children. As noted by Junghänel et al. (30), specific factors could embody higher variance in clinic-referred samples than non-clinical samples, as distinct subtypes may be less observable in the latter. Because teachers are likely to rate more than one child, their ratings may lack independence. While this can be addressed

using the robust "sandwich-type" MLR estimator option in Mplus (34), ethics approval did not permit for the collection of identification information that would have allowed this to be applied. Additionally, 50% of children with parent ratings did not have teacher ratings because teachers did not complete or return the ratings for these children, despite consent granted by parents. This may have confounded our findings. Further studies exploring the properties of this model in different samples, involving different sources (e.g., mothers, fathers, teachers, and self), and using different methods of data collection (e.g., interviews and rating scales), controlling for the limitations highlighted here, are warranted.

Our analysis did not include the hierarchical modeling approach, and it is possible that certain aspects of ADHD could be indicators of an externalizing dimension while others of a possible separate neurodevelopmental disorders spectrum (47), and future studies could further explore this aspect. Finally, different taxonomy frameworks (e.g., DSM, ICD) were derived from factor analyses of their own field trial samples as their best-fit models. However, our study conducted a head-to-head comparison of these models in the same dataset, so that, in this comparison, the best-fitting model with the greatest clarity, reliability, and validity (based on the SAMS algorithm) could emerge as the best candidate. This approach is analogous to a head-to-head drug trial of three medications, all previously shown to be effective in treating ADHD in separate studies; a head-to-head comparison using the same research sample can empirically demonstrate which of the three medications has the largest treatment effect. Our empirical evaluation by head-to-head comparison can provide evidence to counter inference from hypothetical reasoning or extrapolation from historical findings. Our findings are, however, preliminary and need to be replicated by other studies using other samples.

SUMMARY

In summary, this is the first study to examine the factor structure of ADHD symptoms in children from the general community for both parent and teacher ratings using CFA, ESEM, and S-1 CFA procedures concurrently, in relation to conceptual differences in DSM-5, ICD, and HiTOP frameworks. The major findings and interpretations made here raise the possibility that the core symptoms for ADHD are impulsivity and inattention—and not hyperactivity. Thus, the optimum latent structure of ADHD is consistent of only two (impulsivity and inattention) and not three separate symptom groups (hyperactivity, impulsivity, inattention), as proposed in both the major clinical classification systems (DSM-5 and ICD-10). Regarding the impulsivity construct, the constituents in this dimension are in line with ICD-10 configuration—and not DSM-5. In essence, ADHD may be re-conceptualized as "ADID" (attention-deficit/impulsivity disorder). Our findings and interpretation therefore offer a different understanding of ADHD, and preliminary evidence for an entirely novel perspective in ADHD taxonomy—one that aligns with HiTOP conceptualization of ADHD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Ballarat Human Research Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

RG and VS organized the database. RG performed the statistical analysis and was assisted by VS. RG, WC, LL, RK, and DP wrote and edited sections of the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.666326/full#supplementary-material

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Altered Resting-State Brain Activity in Schizophrenia and Obsessive-Compulsive Disorder Compared With Non-psychiatric Controls: Commonalities and Distinctions Across Disorders

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Backgrounds: Schizophrenia (SCZ) and obsessive-compulsive disorder (OCD) are classified as two chronic psychiatric disorders with high comorbidity rate and shared clinical symptoms. Abnormal spontaneous brain activity within the cortical–striatal neural circuits has been observed in both disorders. However, it is unclear if the common or distinct neural abnormalities underlie the neurobiological substrates in the resting state.

Methods: Resting-state fMRI data were collected from 88 patients with SCZ, 58 patients with OCD, and 72 healthy control subjects. First, we examined differences in amplitude of low-frequency fluctuations (ALFF) among three groups. Resting-state functional connectivity (rsFC) analysis with the brain region that showed different ALFF as the seed was then conducted to identify the changes in brain networks. Finally, we examined the correlation between the altered activities and clinical symptoms.

Results: Both the patients with SCZ and OCD showed increased ALFF in the right hippocampus and decreased ALFF in the left posterior cingulate cortex (PCC). SCZ patients exhibited increased ALFF in the left caudate [voxel-level family-wise error (FWE) $P < 0.05$] and decreased rsFC between the left caudate and right cerebellum, which correlated with positive symptoms. The left caudate showed increased rsFC with the right thalamus and bilateral supplementary motor complex (SMC) in OCD patients (cluster-level FWE $P < 0.05$).

Conclusions: The hippocampus and PCC are common regions presenting abnormal local spontaneous neuronal activities in both SCZ and OCD, while the abnormality of the striatum can reflect the differences. Increased ALFF in the striatum and symptom-related weakened rsFC between the caudate and cerebellum showed SCZ specificity. Enhanced rsFC between the caudate and SMC may be a key characteristic in OCD. Our research shows the similarities and differences between the two diseases from the perspective

of resting-state fMRI, which provides clues to understand the disease and find methods for treatment.

Keywords: schizophrenia, obsessive-compulsive disorder, amplitude of low-frequency fluctuations, resting-state functional connectivity, striatum

INTRODUCTION

The categorical diagnoses according to the phenotypic definitions limit the discovery of a genetic association study in psychiatry (1, 2). The symptoms overlap among disorders, and shared biological features indicate a lack of clear boundary in traditional categorical diagnostic systems (3, 4). The recently proposed Hierarchical Taxonomy of Psychopathology model organizes psychopathology into a hierarchy with traits to address problems of diagnostic heterogeneity, comorbidity, and unreliability [The Hierarchical Taxonomy of Psychopathology (HiTOP): A Quantitative Nosology Based on Consensus of Evidence] (5), while endophenotype studies depend on neuroimaging measures to try to develop quantifiable biomarkers for deeper understanding of pathophysiology across classical diagnostic categories and to promote the presentation of a more comprehensive spectrum of psychiatric disorders (6, 7). Here, we try to find out the local spontaneous brain function activity characteristics in schizophrenia (SCZ) and obsessive-compulsive disorder (OCD), two mental disorders with common genetic factors (8, 9) and structural brain abnormalities (10, 11).

SCZ is characterized by consciousness abnormalities including hallucinations, delusions, disorganized speech, decreased motivation, and cognitive deficits (12), while OCD is identified by recurrent intrusive and unwanted thoughts, which result in distress or anxiety and repetitive behaviors (13). The obsessive thoughts in both OCD and delusional ideas in SCZ involved intrusive, unwanted, and foreign thoughts, which indicated the shared failure in monitoring their own thoughts (14). Meta-analysis showed that the total prevalence rate of OCD in SCZ was as high as 12.3% (15). The diagnosis of OCD also increases the risk of SCZ (16). Patients with both disorders showed deficient response inhibition (17) and internal source-monitoring deficits (14). As for etiology researches, the common features of the two disorders can be partially explained by shared polygenic risk (8) and shared pathways of glutamate, dopamine, and serotonin (9). However, the neurobiological substrates and the etiological relationship underlie that the tight association remains unclear.

Previous studies have reported similarities in intrinsic abnormal functions of OCD and SCZ in fronto-striatal circuits. Dysregulated dopaminergic modulation of striatal function is the basis of models that attempt to explain the mechanism of the symptoms in SCZ (18). The hypoconnectivity between the frontal lobe and dorsal striatum has been observed in individuals with SCZ (19, 20). The striatal hyperdopaminergia might disrupt signaling between the frontal cortex and striatum or drive cortical dopamine dysregulation, which results in cognition impairments (18, 21). Cortico-striato-thalamo-cortical (CSTC) circuits are hypothesized as the core neural circuits that underlie OCD, which engage functionally related regions of the cortex, striatum, and thalamus with a direct (net excitatory) or indirect (net inhibitory) pathway (13). Consistent evidence showed increased activity in the brain regions that form a CSTC loop, and overactivity of the direct pathway is hypothesized as a pathogenesis of OCD (22). Increased habit information in the balance between habitual and goal-directed behavior was associated with hyperactivation of the caudate nucleus (23). Neuroimaging studies also have found abnormal resting-state activity related to fronto-striatal circuits in OCD and SCZ. The amplitude of low-frequency fluctuations (ALFF) represents the magnitude of the regional activity amplitude and reflects the intensity of spontaneous neuronal activity. The brain regions with increased ALFF in patients with SCZ were mainly located in the bilateral striatum, medial temporal lobe, and medial prefrontal lobe (24). In patients with OCD, the values of fractional ALFF (fALFF) and the standardization index of ALFF in the putamen and superior frontal gyrus increased (25). On the other hand, a neuroimaging biomarker for functional striatal abnormalities was demonstrated to successfully distinguish SCZ from OCD (26), which suggested that the function of the striatum might reflect the specificity of SCZ to some extent. Considering the core role of the striatum in the dopamine hypotheses of SCZ and CSTC circuits, which are involved in OCD, we speculated that the abnormal function of the striatum may be the common neuropathological mechanism of SCZ and OCD and moreover a valuable marker for distinguishing them. However, there still lack the explorations of differences between SCZ and OCD in ALFF and resting-state functional connectivity (rsFC).

In this study, we aimed to explore the similarities and abnormalities in the brain intrinsic activity of SCZ patients, OCD patients, and healthy controls (HCs) using resting-state functional magnetic resonance imaging (rs-fMRI). First, we attempted to determine the brain regions showing altered local spontaneous brain activity measured by ALFF in SCZ and OCD compared with HCs, with the hypothesis that brain regions within the cortical–striatal neuronal circuits would be vulnerable. Then, we further compared the seed-based rsFC with the brain region in the above ALFF analysis as seeds in SCZ patients, OCD patients, and HCs. Finally, we tested the association between ALFF value of abnormal brain region and showed common and specific features in SCZ and OCD and clinical symptoms to explore the neurobiological mechanism underlying them.

METHODS AND MATERIALS

Participants

All participants were recruited from either the inpatient or outpatient department of Peking University Sixth Hospital

(Beijing, China). Inclusion criteria of all participants included being 18–45 years old; Han Chinese ethnicity; and right-handed. To determine SCZ and OCD diagnoses, patients were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorder, Patient Edition (SCID) by an experienced psychiatrist and should be without other comorbidities in the DSM-IV-TR Axis I Disorders (including depression). For HCs, the non-patient edition of the SCID was used to confirm the absence of mental disorders. Participants were excluded if they had the following: a history of neurological disease, a history of >5-min loss of consciousness, or MRI contraindications. This study was approved by the ethics committee of Peking University Sixth Hospital. Written informed consent was obtained from all participants or legal guardians involved in the study.

The Positive and Negative Syndrome Scale (PANSS), which consists of the positive, negative, and general psychopathology subscales, was used to assess SCZ symptoms for patients with SCZ. The Yale–Brown Obsessive Compulsive Symptom Scale (Y-BOCS), which consists of the obsessive thought and compulsive behavior subscales, was used to measure the obsessive-compulsive symptoms for patients with OCD. The Hamilton Anxiety Scale (HAMA) and 17-item Hamilton Depression Scale (HAMD-17) were also used to assess anxiety and depression for patients with OCD.

MRI Acquisition

All participants were scanned on a 3.0-T GE scanner (Discovery MR750) at the Center for Neuroimaging, Peking University Sixth Hospital. Before scanning, all participants were instructed to move as little as possible. Foam pads were used to minimize head motion. T1-weighted high-resolution structural images were acquired in a sagittal orientation using an axial 3D fast, spoiled gradient recalled (FSPGR) sequence with the following parameters: repetition time (TR) = 6.66 ms, echo time (TE) = 2.93 ms, field of view (FOV) = 256 × 256 mm^2, slice thickness/gap = 1.0/0 mm, acquisition voxel size = 1 × 1 × 1 mm^3, flip angle = 12°, and 192 contiguous sagittal slices. The resting-state functional imaging data were acquired with the following parameters: TR = 2,000 ms, TE = 30 ms, FOV = 220 × 220 mm^2, matrix = 64 × 64, flip angle = 90°, voxel size = 3.5 × 3.5 × 4.2 mm^3, 33 slices, and 240 volumes. Before scanning, all participants were instructed to move as little as possible, keep their eyes closed, think of nothing in particular, and avoid falling asleep. After scanning, they were asked whether they fell asleep to reconfirm.

Resting-State fMRI Preprocessing

Data preprocessing of resting-state fMRI was completed using DPABI (27). The following steps were performed: (1) discarding the first 10 volumes from each participant; (2) slice timing correction; (3) realigning the volumes to the middle volume; (4) coregistration using T1 images and spatial normalization by DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra); (5) linear regression to remove the effects of linear trends; (6) regressing out nuisance covariate signals including white matter and cerebrospinal fluid; and (7) temporal bandpass filtering (0.01–0.1 Hz). Then, the data were smoothed with a Gaussian filter of 6-mm full width at half maximum (FWHM) to reduce noise and residual differences. The voxel size of the image data after preprocessing is 3 × 3 × 3 mm^3.

To generate the voxel-wise ALFF maps with z-score for each individual, the images were smoothed after the first four preprocessing steps and followed (5) and (6). The ALFF values were calculated in a voxel-wise way as the averaged squared root of the frequency range of 0.01–0.1 Hz.

In addition, a volume-based framewise displacement (FD) was computed based on their realignment parameters to quantify head motion (28, 29). Any subjects with mean FD Jenkinson > 0.2 were excluded (SCZ: $n = 6$; OCD: $n = 2$; HC: $n = 0$). Finally, a total of 88 patients with SCZ, 58 patients with OCD, and 72 HC subjects were included in the further analyses.

Resting-State Functional Connectivity Analysis

Brain regions showing significantly different ALFF values between the patients with SCZ and OCD were used as seeds in the following rsFC analysis, which was performed using DPABI v4.4. First, the time series of each voxel within the seed were extracted. Second, the extracted time series of each voxel were averaged to acquire the mean time series of the seed. Third, Pearson's correlation coefficients between the mean time series of the seed and the time series of each voxel within the whole brain were calculated and used to construct each subject's rsFC map. Finally, the rsFC maps were converted into z-score maps by Fisher's z transformation to improve normality. The individual rsFC maps with z values were entered into one-way ANOVA to figure out the differences among three groups. Age, gender, education attainment, and mean FD Jenkinson were entered as covariates. A significant level was set at a cluster-level threshold of $P < 0.05$ family-wise error (FWE) corrected. The *post-hoc* pair-wise comparisons were then performed after extracting the rsFC values, and a value of $P < 0.05$ Bonferroni corrected was considered significant.

Statistical Analysis

Demographic and clinical differences between the patients with OCD, patients with SCZ, and HCs were compared by using one-way ANOVA or χ^2 test in IBM SPSS Statistics Desktop 26.

Second-level analyses for resting-state fMRI data were performed by using SPM12 (Wellcome Department of Cognitive Neurology, London, UK). One-way ANOVA was used to compare differences of ALFF among the SCZ patients, OCD patients, and HCs within the gray matter mask of the whole brain in DPABI. Age, gender, education attainment, and mean FD Jenkinson were entered as covariates. A significant level was set at a voxel-level threshold of $P < 0.05$ FWE corrected. The *post-hoc* pair-wise comparisons were then performed after extracting the ALFF values, and a value of $P < 0.05$ Bonferroni corrected was considered significant.

Relationships with symptom severity were examined by extracting ALFF and rsFC values from regions showing group differences and correlating these values with PANSS total scores, PANSS positive symptom scores, PANSS negative symptom scores, and PANSS general psychopathology scores in the SCZ

TABLE 1 | Demographics and clinical data of the patients with schizophrenia, patients with obsessive-compulsive disorder, and healthy controls.

Characteristic	SCZ	OCD	HC	F/χ^2	P
Gender (male/female)	53/35	37/21	34/38	4.270	0.118
Age (years)	25.2 ± 6.4	27.2 ± 6.6	24.4 ± 3.4	3.994	0.020
Education (years)	13.6 ± 2.9	15.1 ± 2.8	16.8 ± 2.1	29.26	<0.001
Framewise displacement	0.068 ± 0.038	0.066 ± 0.038	0.058 ± 0.034	1.428	0.242
Onset age (years)	22.1 ± 6.6	19.6 ± 5.5	-	-	-
Disease course (months)	45.8 ± 52.6	95.2 ± 66.9	-	-	-
PANSS total score	69.26 ± 14.62	-	-	-	-
PANSS positive symptoms	18.90 ± 5.86	-	-	-	-
PANSS negative symptoms	17.02 ± 5.48	-	-	-	-
PANSS general psychopathology	33.34 ± 7.98	-	-	-	-
Y-BOCS total score	-	21.46 ± 7.52^	-	-	-
Y-BOCS obsessive thinking	-	11.28 ± 3.80^	-	-	-
Y-BOCS compulsive behavior		10.18 ± 4.75^			
HAMA	-	11.15 ± 6.89†	-	-	
HAMD-17	-	7.98 ± 5.22†	-	-	-

Data are given as mean ± standard deviation. P-values refer to one-way ANOVA (parametric data) and chi-square test (categorical data).
SCZ, patients with schizophrenia; OCD, patients with obsessive-compulsive disorder; HC, healthy controls; PANSS, Positive and Negative Syndrome Scale; Y-BOCS, Yale–Brown Obsessive-Compulsive Scale; HAMA, Hamilton Anxiety Scale; HAMD-17, 17-item Hamilton Depression Scale; -, not applicable. ^N = 50; † N = 53.

group, and Y-BOCS scores, Y-BOCS obsessive thinking scores, Y-BOCS compulsive behavior scores, HAMA scores, and HAMD-17 scores in the OCD group, with age and gender as covariates. A significant level was set at a threshold of $P < 0.0125$ and $P < 0.01$ with Bonferroni correction (for SCZ: $P < 0.05/4 = 0.0125$; for OCD: $P < 0.05/5 = 0.01$).

RESULTS

There was no significant difference in gender distribution, but in age [$F_{(2,215)} = 3.994$, $P = 0.020$] and years of education [$F_{(2,215)} = 29.26$, $P < 0.001$]. The SCZ group showed the shortest years of education, and the OCD group was the oldest (see details in **Table 1**). They were all included as covariates in the following analysis. In the 88 patients with SCZ, eight patients were drug-naïve, and 80 patients received atypical antipsychotics (aripiprazole, amisulpride, olanzapine, risperidone, clozapine, quetiapine, paliperidone, and ziprasidone). The chlorpromazine equivalent dose of the antipsychotics (30) was 442.9 ± 305.7 mg/day. Of the 58 patients with OCD, 18 patients were drug-naïve, and 40 patients were taking one or more antidepressants including selective serotonin reuptake inhibitors (SSRIs) (paroxetine, sertraline, fluoxetine, escitalopram, and fluvoxamine), venlafaxine, mirtazapine, clomipramine, and amitriptyline. Thirteen patients were on combined antipsychotic medication in small doses. The fluoxetine equivalent dose of antidepressants (31, 32) was 46.3 ± 44.4 mg/day.

For ALFF, three groups showed significant differences in the right hippocampus, left posterior cingulate cortex (PCC), and left caudate (whole-brain voxel-level FWE corrected $P < 0.05$, cluster size > 30, **Table 2** and **Figure 1A**). We extracted the average value of ALFF in the above regions. Both the SCZ and OCD groups showed significantly increased ALFF values (the negative ALFF values decreased) in the right hippocampus and decreased ALFF in the left PCC than did HCs. The SCZ group showed significantly increased ALFF in the left caudate nucleus than did OCD and HC groups ($P < 0.001$, Bonferroni corrected, **Figure 1**).

Then, by using the significant cluster within the left caudate as a seed, we found that rsFC between the left caudate, right thalamus, right cerebellum posterior lobe, and bilateral supplementary motor complex (SMC) including the supplementary motor area (SMA), supplementary eye fields (SEFs), and pre-SMA were significantly different among the three groups (whole-brain cluster-level FWE corrected $P < 0.05$, cluster size > 80, **Table 3** and **Figure 2A**). The SCZ group showed significantly decreased rsFC between the left caudate and right cerebellum posterior lobe than both the OCD group and HCs. The OCD group showed increased rsFC between the left caudate and right thalamus, the left caudate, and the bilateral SMC than did both the SCZ group and HCs ($P < 0.001$, Bonferroni corrected, **Figure 2**).

We also explored the clinical correlations of these neuroimaging alterations by computing the Pearson correlation coefficient between the average ALFF and rsFC values and the scores of symptom severity in the patients, with age and gender as covariates using Bonferroni correction. For the patients with SCZ, the rsFC between the left caudate nucleus and right cerebellum was positively correlated with the PANSS positive symptom score ($r = 0.277$, $P = 0.010$).

DISCUSSION

In this study, we compared resting-state activity changes using ALFF and seed-based rsFC in patients with SCZ, patients with OCD, and HCs. We found that (1) compared with HCs, both

TABLE 2 | Results of ALFF analysis of the patients with schizophrenia, patients with obsessive-compulsive disorder, and healthy controls.

Brain region	Hemisphere	Cluster size	MNI coordinates (x, y, z)	Peak *F* value	Voxel-level P_{FWE}
Hippocampus	Right	32	21, −30, −3	35.04	<0.001
Posterior cingulate cortex	Left	47	−3, −30, 21	28.88	<0.001
Caudate	Left	36	−9, 6, 9	21.57	<0.001
			−12, 15, 9	20.67	<0.001
			−15, 18, −3	15.93	0.023

ALFF, amplitude of low-frequency fluctuations; MNI, Montreal Neurological Institute.

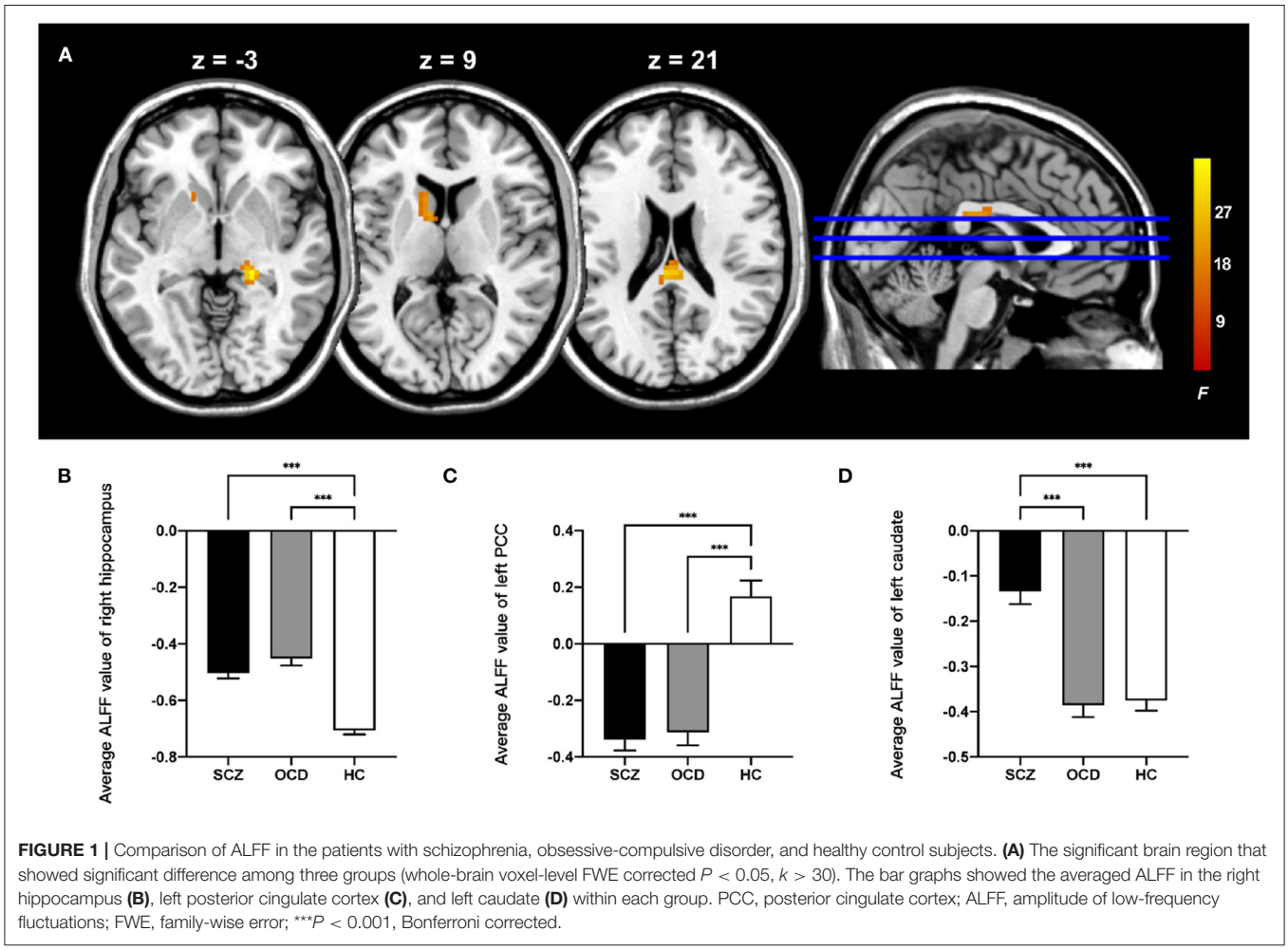

FIGURE 1 | Comparison of ALFF in the patients with schizophrenia, obsessive-compulsive disorder, and healthy control subjects. **(A)** The significant brain region that showed significant difference among three groups (whole-brain voxel-level FWE corrected $P < 0.05$, $k > 30$). The bar graphs showed the averaged ALFF in the right hippocampus **(B)**, left posterior cingulate cortex **(C)**, and left caudate **(D)** within each group. PCC, posterior cingulate cortex; ALFF, amplitude of low-frequency fluctuations; FWE, family-wise error; ***$P < 0.001$, Bonferroni corrected.

the patients with SCZ and OCD showed increased ALFF in the right hippocampus and decreased ALFF in the left PCC; (2) patients with SCZ exhibited increased ALFF in the left caudate than patients with OCD and HCs; (3) using the left caudate as a seed, patients with SCZ showed decreased rsFC between the left caudate and right cerebellum, which was correlated with the PANSS positive symptom score. Patients with OCD showed increased rsFC between the left caudate and right thalamus, the left caudate, and the bilateral SMC. Our results suggested that SCZ and OCD have common and distinct patterns of resting-state activity. Both of them exhibited abnormal ALFF in the hippocampus and PCC, while the striatum can reflect the differences. Patients with SCZ exhibited increased ALFF in the striatum and symptom-related weakened rsFC between the caudate and cerebellum. Enhanced rsFC of caudate–thalamus and caudate–SMC in OCD may be the important difference.

Commonalities

Increased Amplitude of Low-Frequency Fluctuations in the Hippocampus

The altered ALFF values in the hippocampus across SCZ and OCD were consistent with previous ALFF studies that compared

TABLE 3 | Results of ALFF-based rsFC analysis with the left caudate as the seed in the patients with schizophrenia, patients with obsessive-compulsive disorder, and healthy controls.

Brain region	Hemisphere	Cluster size	MNI coordinates (x, y, z)	Peak *F* value	Cluster-level P_{FWE}
Thalamus	Right	102	6, −27, 12	14.49	0.003
Supplementary motor complex	Right	107	27, 15, 54	12.99	0.003
Supplementary motor complex	Left	103	−21, 12, 60	12.17	0.003
Cerebellum posterior lobe	Right	92	21, −42, −51	12.74	0.006

ALFF, amplitude of low-frequency fluctuations; rsFC, resting-state functional connectivity; MNI, Montreal Neurological Institute.

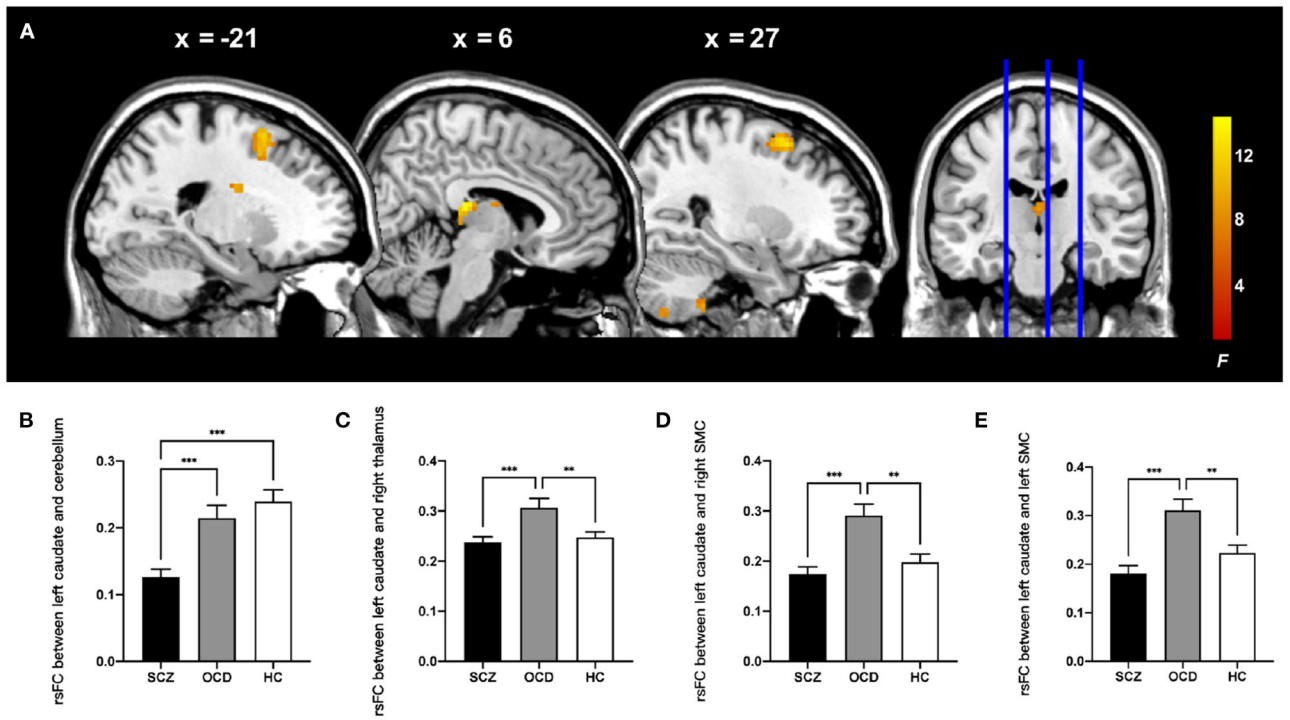

FIGURE 2 | Comparison of ALFF-based rsFC analysis with the left caudate as the seed in the patients with schizophrenia, patients with obsessive-compulsive disorder, and healthy control subjects. **(A)** The significant brain region that showed significant difference among three groups (whole-brain cluster-level FWE corrected $P < 0.05$, $k > 80$). The bar graphs showed the averaged rsFC between the left caudate and right cerebellum posterior lobe **(B)**, right thalamus **(C)**, right SMC **(D)**, and left SMC **(E)** within each group. rsFC, resting-state functional connectivity; SMC, supplementary motor complex; ALFF, amplitude of low-frequency fluctuations. $^{***}P < 0.001$, $^{**}P < 0.01$, Bonferroni corrected.

the two disorders with HCs (33, 34). The ALFF of hippocampus was increased in patients with SCZ (35) and associated with the severity of auditory and visual hallucinations (34). In patients with OCD, the ALFF of the hippocampus was also increased as compared with that of HCs, and the difference disappeared after 4-week treatment with the remission of the obsessive-compulsive symptoms (33). The hippocampus, which have been reported with both structural (reduced volume and thinner cortex) and functional abnormalities in SCZ and OCD (36, 37), might play a cardinal role in the neurobiology of both disorders through its effect on various cognitive and affective processes. Intrinsic hippocampal hyperactivity in the resting state is a characteristic feature of SCZ and related to cognitive dysfunction (38). OCD patients also exhibited cognitive impairments including attention, executive function, and memory (39). The similar higher ALFF in both SCZ and OCD represents the similar hyperactivity in the hippocampus, which may be related to the common impairment of cognitive function, especially the decline of memory ability.

Decreased Amplitude of Low-Frequency Fluctuations in the Posterior Cingulate Cortex

The PCC is highly connected to various brain regions with a high baseline metabolic rate, which is the core node of default mode network (DMN) but showed abnormal reduced glucose metabolism in SCZ (40). The ALFF and fALFF in the PCC

showed a consistent decrease in the two low-frequency bands in SCZ and schizoaffective disorder (41). The fALFF of the posterior cortex (including the occipital lobe and the precuneus/PCC) was also reduced in SCZ (42). Similarly, DMN plays a key role in the pathophysiology of OCD, although there are relatively few reports on resting state dysfunction in the PCC. One study found that the network homogeneity of the PCC/precuneus of OCD was significantly reduced, which could be used as a candidate neuroimaging index to distinguish OCD from HCs (43). Our finding of reduced ALFF of the PCC in SCZ is consistent with previous studies. OCD patients performed a disassociation between the increased behaviors and correct appraisal on the need to make the action (44). SCZ patients have deviations in self-recognition. They both show decreased insight in varying degrees, which might be correlated with the abnormal function of DMN that is involved in internal emotional processing and self-referential directed thought (45).

Distinctions

Increased Amplitude of Low-Frequency Fluctuations in the Dorsal Striatum in Schizophrenia

The ALFF of the striatum in patients with SCZ showed an increase that was specifically different from that in patients with OCD and HCs, which was similar to the findings of increased cerebral blood flow and glucose metabolism in the striatum in drug-naïve patients with SCZ (46) and consistent with the meta-analysis (24). The relationship between the striatum and SCZ is supported by the dopamine hypothesis of SCZ (18). Studies have found that dopamine-related striatal-thalamic-cortical rsFC in SCZ was abnormal in low-frequency oscillations, suggesting that the changes in dopaminergic function may lead to abnormal synchronization of neurons in subcortical circuits (47). It is proposed that the temporary retention of excessive spontaneous dopamine can temporarily combine with the striatal signaling pathway through stimulation, making irrelevant external or internal stimulation significance (18, 48). The dorsal striatum is usually involved in signaling threat-related information (49), which may explain why the delusions of SCZ patients in natural conditions are usually persecuted (18). Given another role of the dorsal striatum in the formation of habit (50) and the process of encoding stable value (51), it can be speculated that the dopaminergic dysfunction in the dorsal striatum accompanied with mental symptoms could aggravate the habit-oriented mode of cognition and rigid form of thought with unusual content (52). The increased ALFF in the dorsal striatum in SCZ may have relevance to the fact that the hallucinations and delusions of SCZ are not common in OCD.

Decreased Resting-State Functional Connectivity Between the Striatum and Cerebellum in Schizophrenia

Emerging human neuroimaging studies have discovered the existence of a large-scale cortex–striatum–thalamus–cerebellar functional loop. The cerebellum and striatum communicate with the thalamus and cortex through single and multiple synaptic connections (53) and may be sensitive to the disconnection of the whole brain in patients with SCZ, which is conceptualized as a synaptic signal communication that affects the nervous system. Ji et al. used a data-driven method to analyze the FC with the striatum and the cerebellum as independent seeds and found a high degree of similarity in the two whole-brain connection patterns in patients with SCZ with decreased rsFC between the striatum and the cerebellum (54), which is consistent with our results. The dysconnectivity in the cortico-striatal-thalamic-cerebellar pathway was strongly related to cognitive deficits (54). Dynamic stimulation of the cerebellum could affect the activities of multiple areas of the frontal cortex and effectively improve the cognitive ability of patients with SCZ (55). Given the role of the cerebellum in cognition (56), such as working memory (57), the weakened cerebellar rsFC of patients with SCZ might suggest the more severe cognitive impairment in SCZ than OCD. In addition, we observed a positive correlation between decreased caudate–cerebellar rsFC and the severity of positive symptoms, suggesting that the mild rsFC abnormalities may lead to the development of positive symptoms, whereas excessive abnormality might prevent the formation of positive symptoms (58).

Increased Resting-State Functional Connectivity Between the Striatum and Thalamus, Striatum and Supplementary Motor Complex in Obsessive-Compulsive Disorder

Previous studies suggested that OCD is related to abnormalities in the CSTC loop. The cerebral cortex projects the signal to the striatum, transmits the signal to the thalamus through the globus pallidus, and finally feeds back to the neuronal circuit of the cerebral cortex. Increased functional connectivity primarily within the CSTC circuits was observed in patients with OCD and their first-degree relatives (59). The SMC consists of the SMA, the SEFs, and the pre-SMA (60), which are important for movement preparation and behavioral sequencing. SMA send efferent neuro to the striatum directly and indirectly (60). Pre-SMA/SMA is also speculated to be related to the cause of impaired response inhibition with disability to inhibit irrelevant information and suppress responses to distractors in patients with OCD, which showed aberrant activations during working memory (61). The hyperactivity of pre-SMA during response inhibition was reported to be a candidate endophenotype of OCD (62). Furthermore, in OCD-relevant mouse model, M2 postsynaptic responses in the central striatum were significantly increased, which suggested that strengthened M2-striatal inputs might contribute in striatal hyperactivity and compulsive behaviors, where M2 is homologous to pre-SMA/SMA in human (63). SMA has also been identified as promising targets for repetitive transcranial magnetic stimulation to reduce OCD-related symptoms (64). The association of striatum and SMC may interfere with flexible transition between habitual and goal-directed behaviors, which act as impaired goal-directed behavior and more dependence on habitual behavior system, thus promoting the formation of stereotyped behavior and compulsive behavior in OCD (65). This characteristic is different from the deficit in goal-directed action in SCZ, which fails to integrate the causal knowledge of behavior outcome

relationship with the change of outcome value to modify their action (66).

Consistent with our hypothesis, the striatum is the key brain region that showed abnormality in two diseases but present different patterns of lesions, which might be associated with different clinical features. This study still has several limitations. First, the sample size of the OCD group is relatively small, and the current study does not completely match between two patient groups. The findings of this study need to be verified in a more matched and larger sample. Second, we did not assess the obsessive-compulsive symptoms in patients with SCZ, and the PANSS was not measured in the OCD group, but the patients were recruited after strict SCID screening to confirm that there was no comorbidity. The assessment of symptoms can be added in the further study to confirm the validity of our results. Third, many patients in our study were medicated before recruitment, but due to the use of different types of psychotropic medications (antipsychotics and antidepressant medications), we could not add the equivalent dosages as covariates in the statistical analysis. Future work can be carried out in un-medicated patients. Finally, it requires more experimental evidence to support the clinical application of our findings.

In summary, the hippocampus and PCC are common regions presenting abnormal local spontaneous neuronal activities in both SCZ and OCD, while the abnormality of the striatum can reflect the differences. Increased ALFF in the striatum and symptom-related weakened rsFC between the caudate and cerebellum showed SCZ specificity. Enhanced rsFC between the caudate and SMC in OCD may be a key characteristic in OCD. Our research shows the similarities and differences between the two diseases from the perspective of resting-state fMRI, which provides clues to understand the disease and find methods for treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Peking University Sixth Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YZ completed the data analysis, wrote the first draft of this manuscript, and edited the subsequent versions. YZ, JL, QL, and LL are responsible for the data collection. JL, XZ, HY, and WY gave critical revision for the manuscript. JY, DZ, HY, and WY were responsible for the designing the study. All authors have read and approved the final version of this article. We thank the National Center for Protein Sciences at Peking University in Beijing, China, for assistance with MRI data acquisition.

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Childhood Maltreatment Was Correlated With the Decreased Cortical Function in Depressed Patients Under Social Stress in a Working Memory Task: A Pilot Study

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Background: Major depressive disorder (MDD) is a common psychiatric disorder associated with working memory (WM) impairment. Neuroimaging studies showed divergent results of the WM process in MDD patients. Stress could affect the occurrence and development of depression, in which childhood maltreatment played an important role.

Methods: Thirty-seven MDD patients and 54 healthy control subjects were enrolled and completed a WM functional magnetic resonance imaging task with maintenance and manipulation conditions under stress and non-stress settings. We collected demographical and clinical data, using 17-item Hamilton Depression Scale (HAMD-17) and Childhood Trauma Questionnaire (CTQ) in MDD patients. In the WM task, we analyzed the main diagnosis effect and explored the correlation of impaired brain regions in MDD patients with CTQ and HAMD-17.

Results: No group differences were found in the accuracy rate and reaction time between the two groups. MDD patients had lower brain activation in following regions ($P_{FWE} < 0.05$). The left fusiform gyrus showed less activation in all conditions. The right supplementary motor area (SMA) exhibited decreased activation under non-stress. The anterior prefrontal cortex showed reduced activation during manipulation under stress, with the β estimations of the peak voxel showing significant group difference negatively correlated with childhood sex abuse ($P_{\text{Bonferroni}} < 0.05$).

Conclusions: In our pilot study, MDD patients had reduced brain activation, affecting emotional stimuli processing function, executive function, and cognitive control function. Childhood maltreatment might affect brain function in MDD. This work might provide some information for future studies on MDD.

Keywords: stress, major depression disorder, working memory, anterior prefrontal cortex, childhood maltreatment

INTRODUCTION

Major depressive disorder (MDD) is a common psychiatric disorder (1), which usually leads people to suffering from emotional disturbances and cognitive impairments (2, 3). Working memory (WM) involves the capability to memorize, retrieve, and utilize the information for a limited period (4) and is incredibly easily impaired in MDD patients (5, 6). Numbers of studies found widespread increased brain activations during the cognitive process in MDD patients (7), including the anterior prefrontal cortex (APFC) (8), dorsolateral prefrontal cortex (9, 10), and cingulate cortex (11). However, some studies showed hypoactive brain regions, including the frontal cortex, temporal cortex, insula, anterior cingulate cortex (ACC) and parietal cortex in depressed patients (12–14). These divergent results suggested the complexity of this issue, and potential factors might be the types of WM (15) and the levels of stress. Besides, childhood maltreatment has been considered to accelerate the development of depression (16–18). Moreover, a decreased volume of prefrontal cortex might play a mediated role in the relationship between childhood maltreatment and declined cognitive functioning (19–21). However, how can childhood maltreatment affect the WM process is complicated as stress has both direct neuroendocrine (22) and indirect methylation (23) effects on the development of depression. We hypothesized that the neural basis of the childhood maltreatment effects at different WM task conditions were different. To explore this hypothesis, we designed a WM task (24, 25) with varying subtasks (maintenance vs. manipulation) and varying stress levels (non-competition vs. competition) to compare the childhood maltreatment effects in different conditions.

MATERIALS AND METHODS

Participants

In this study, 53 MDD patients and 64 healthy controls (HCs) were recruited. The patients were outpatients recruited from Peking University Sixth Hospital. We used the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*) diagnostic criteria of depression disorder, without other comorbidities of the *DSM-IV-TR* Axis I disorders. Two psychiatrists assessed the patients by using the Mini-International Neuropsychiatric Interview (version 5.0) (26). All HCs were enrolled by advertising in the community and social media and evaluated by using the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Research Version, Non-patient Edition to exclude any mental disorder (27). The current study was approved by the ethical committee of the Peking University Sixth Hospital. All the participants were given detailed information about the purpose and procedures of the study and signed the written consents.

We used the 17-item Hamilton Depression Scale (HAMD-17) to evaluate the symptom severity (28). In addition, we used Childhood Trauma Questionnaire (CTQ) to examine how could childhood maltreatment affect brain function in adult MDD patients (29). Subjects were included using the following criteria: (1) between 18 and 55 years of age, (2) right-handed, (3) Chinese Han lineage, and (4) MDD patients needed to get a HAMD-17 score $\geq$17. Subjects were excluded with the following criteria: (1) any current or history of neurological disease, (2) a history of more than 5-min loss of consciousness, (3) contraindications for magnetic resonance imaging (MRI) scanning, (4) electroconvulsive therapy within 6 months or history of severe medical illness, (5) other genetic disease, (6) serious impulsive behavior or suicide attempts, and (7) pregnancy and lactation.

We excluded subjects with low image quality or who did not complete the task (six MDD patients and four HCs) or with an accuracy rate of the maintenance <50% under competitive/non-competitive setting (two MDD patients, no HCs) or with head motion of more than 3° rotation/3-mm translation (eight MDD patients and six HCs). Finally, 37 MDD subjects and 54 HCs were included in the analysis (**Table 1**). Among the 37 patients, 10 patients were drug-naive. In addition, 17 MDD patients were taking selective serotonin reuptake inhibitors (fluoxetine, escitalopram, sertraline), six were taking serotonin norepinephrine reuptake inhibitors (venlafaxine, duloxetine), two were taking noradrenergic and specific serotonergic antidepressants (mirtazapine), one was taking dopamine norepinephrine reuptake inhibitors, DNRIs (bupropion), and one was taking flupentixol and melitracen.

WM Paradigm and Image Acquisition

We developed an event-related "number calculation WM" task from previous works (30, 31) and newly comprised alternating competitive and non-competitive blocks (**Figure 1**). We validated that both the different subtasks and the different stress levels were successfully introduced in this task from our previous study (28), in which the detailed description of this task could be found. A 3.0-T GE Discovery MR750 scanner was used for scanning all participants at the Center for MRI Research, Peking University Institute of Mental Health. The parameters of the functional MRI are as follows: each echoplanar image included 33 (thickness/gap = 4.2/0 mm) axial slices, which covered the whole cerebrum and cerebellum (repetition time/echo time = 2,000/30 ms, flip angle = 90°, field of view = 22.4 × 22.4 cm^2, matrix = 64 × 64). The protocol parameters were selected for optimizing the quality and stability of the blood oxygenation level-dependent signal with the exclusion of the first four images as dummy scans.

Processing and Statistical Analyses of the MRI

We used MATLAB 2016b and SPM12 (http://www.fil.ion.ucl.ac.uk/spm) for analyzing the functional MRI data. The preprocessing of the data was performed as following steps: (1) slice timing correction, (2) realigning to the first volume and correcting the head motion, (3) spatially normalizing into standard stereotaxic space (Montreal Neurological Institute template) using a fourth-degree B-spline interpolation, and (4) using an 8-mm Gaussian kernel to spatial smoothing. After preprocessing, the voxel size of the image data was 3 × 3 × 3 mm^3. We modeled every task-evoked stimulus as an independent delta function, and it convolved with the typical hemodynamic

TABLE 1 | Demographic and Behavioral Characteristics of MDD patients and HCs.

Characteristic	MDD patients ($n = 37$)	HCs ($n = 54$)	t/χ^2	p
Age (years)	25.89 (4.75)	23.94 (3.05)	2.203	0.032
Gender (female/male)	23/14	29/25	0.641	0.423
Education (years)	16.54 (2.70)	16.72 (1.98)	−0.370	0.712
Duration of illness (months)	18.28 (29.92)			
HAMD-17 score	24.35 (5.60)			
CTQ total score	40.86 (10.89)			
Emotional abuse score of CTQ	8.72 (3.40)			
Physical abuse score of CTQ	6.31 (2.05)			
Sex abuse score of CTQ	5.92 (1.46)			
Emotional neglect score of CTQ	12.61 (5.11)			
Physical neglect score of CTQ	7.56 (3.02)			

MDD, major depressive disorder; HCs, healthy controls; HAMD-17, 17-item Hamilton Depression Rating Scale; CTQ, Childhood Trauma Questionnaire.

response function, controlling the systematic differences of global activity by normalizing ratio to the whole-brain global mean. And we used a 128-s high-pass filter for temporal filter. We modeled each event of task-evoked stimulus for performing trials correctly. In addition, we modeled the residual movement and incorrect response parameters as regressors of no interest. In this study, we planned to contrast the brain activation at the maintenance subtask or manipulation subtask under stress, non-stress setting and stress vs. non-stress, and between the two groups of MDD patients and HCs. Second-level analyses were subsequently taken, and the variability of intersubject was regarded as a random effect.

After controlling age, we used a flexible 2 × 2 analysis of variance in SPM12 to analyze the main effect of diagnosis, the main effect of stress, and the diagnosis × stress interaction effect. The significant level was set as $p < 0.05$ with whole-brain family-wise error (FWE) correction at both the maintenance subtask and the manipulation WM subtask. Then, we compared the main effect of diagnosis at stress maintenance, non-stress maintenance, stress manipulation, and non-stress manipulation separately in SPM12 to understand the group differences more specifically under each WM condition. The second-level analyses were carried on without any brain mask.

Statistical Analyses of the Clinical and Behavioral Data

We used a standard statistical package (IBM SPSS 26.0, Chicago, IL) to analyze demographic and clinical data, including t-test and χ^2 test. The behavioral data [accuracy rate and reaction time (RT)] of two groups at the maintenance or manipulation phase under stress or non-stress setting were analyzed by SPSS to explore the diagnosis × stress × task–difference interaction effect.

We first extracted the β estimations in the corresponding contrast images of each condition and setting in each group for the peak coordinates found in the aforementioned second-level brain image analyses. Then, we analyzed correlation between the β estimations values of the MDD group and the clinical variables (HAMD-17, CTQ). The level of statistical significance was set at $p < 0.05$ after Bonferroni correction for multiple comparisons.

RESULTS

Demographic and Behavioral Results

We studied 37 MDD patients and 54 HCs who were currently living in Beijing. Both groups had similar gender distribution and had achieved similar educational levels. While HCs were slightly younger (**Table 1**). We included age as a covariate in subsequent analyses. MDD patients had an average illness duration of 18.28 months, with a mean HAMD-17 score of 24.35. We also obtained the CTQ for MDD patients, and the results are listed in **Table 1**.

In terms of the accuracy rate, we observed a significant main effect of stress with a higher accuracy rate under the stress task ($F = 30.586$, $p < 0.001$), whereas, for task difference, we found a higher accuracy rate under maintenance task ($F = 11.598$, $p < 0.001$). The interaction effects of task difference × stress was significant ($F = 10.126$, $p = 0.002$; **Figure 2**). However, no group differences were found between MDD patients and HCs (**Table 2**). As for RT, we observed a significant main effect of task difference, with longer RT in the manipulation condition ($F = 11.473$, $p = 0.001$). Meanwhile, we observed a significant main effect of task-difference, with longer RT in the manipulation condition ($F = 362.629$, $p < 0.001$). There were no main effects of group, or interaction effect among the three factors.

WM-Related Brain Activation

During each of the WM maintenance and manipulation conditions under stress or non-stress setting in both MDD and HC groups, regions in the prefrontal, parietal, temporal, occipital cortices, and striatum were robustly activated, along with well-established deactivation in areas of default mode network during cognitive task, including the medial PFC (MPFC) and posterior cingulate cortex ($p < 0.05$, whole-brain FWE correction; **Figure 3**, **Supplementary Tables 1, 2**).

Group Differences Under WM Maintenance Condition

Under the WM maintenance condition, the main effect of stress and interaction effect of diagnosis × stress were not significant. However, the main effect of diagnosis was significant in the left fusiform, left postcentral gyrus, middle cingulum, left superior temporal gyrus, and left precuneus ($p < 0.05$ whole-brain FWE correction, cluster >50; **Table 3**).

Then, we focused on the group differences under stress setting ($p < 0.05$, whole-brain FWE correction, cluster >2; **Figure 4**). MDD patients had reduced activation in the left fusiform ($x = -50$, $y = -60$, $z = -14$, $T = 5.60$, cluster size = 49). While

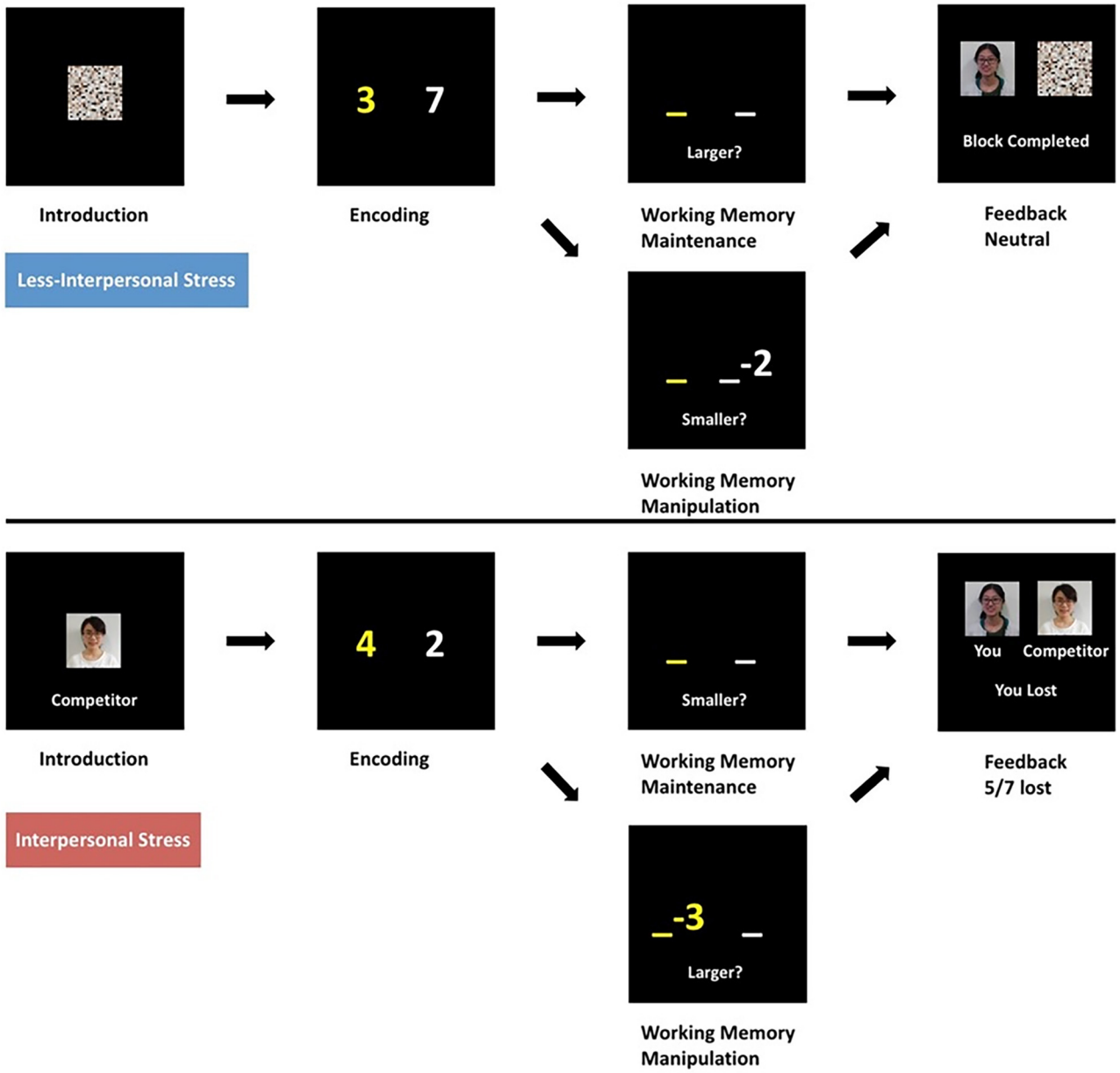

FIGURE 1 | Working memory paradigm incorporating social competition stress. In the stressed component, subjects were led to believe that they were playing against a "competitor" of similar age and gender and were judged as winning or losing based on their speed and accuracy, which subsequently resulted in ∼70% loss feedback. In the less stressed blocks, there was no competitor, and subjects received neutral feedback. In all the working memory manipulation and maintenance tasks, an array of two-number digits was encoded and held in working memory over 3 to 4 s. In working memory maintenance condition, subjects responded to which of the two maintained digits was larger or smaller as indicated. In working memory manipulation condition, subjects performed subtraction on one of the numbers held in working memory, followed by a response as to which result was larger or smaller as indicated. Subjects performed two runs counterbalanced for trial and stimuli presentation order over ∼20 min. All instructions were translated to Chinese.

under non-stress setting ($p < 0.05$ whole-brain FWE correction, cluster > 2; **Figure 4**), MDD patients had decreased activation in the right supplementary motor area (SMA) ($x = 4$, $y = 14$, z = 62, $T = 5.60$, cluster size = 13) and left fusiform gyrus ($x = -50$, $y = -60$, $z = -16$, $T = 4.92$, cluster size = 6).

Group Differences Under WM Manipulation Condition

Under the WM manipulation condition, the main effect of stress and interaction effect of diagnosis × stress were not significant. However, the main effect of diagnosis was significant in many brain regions, including the fusiform gyrus, precuneus, cingulate

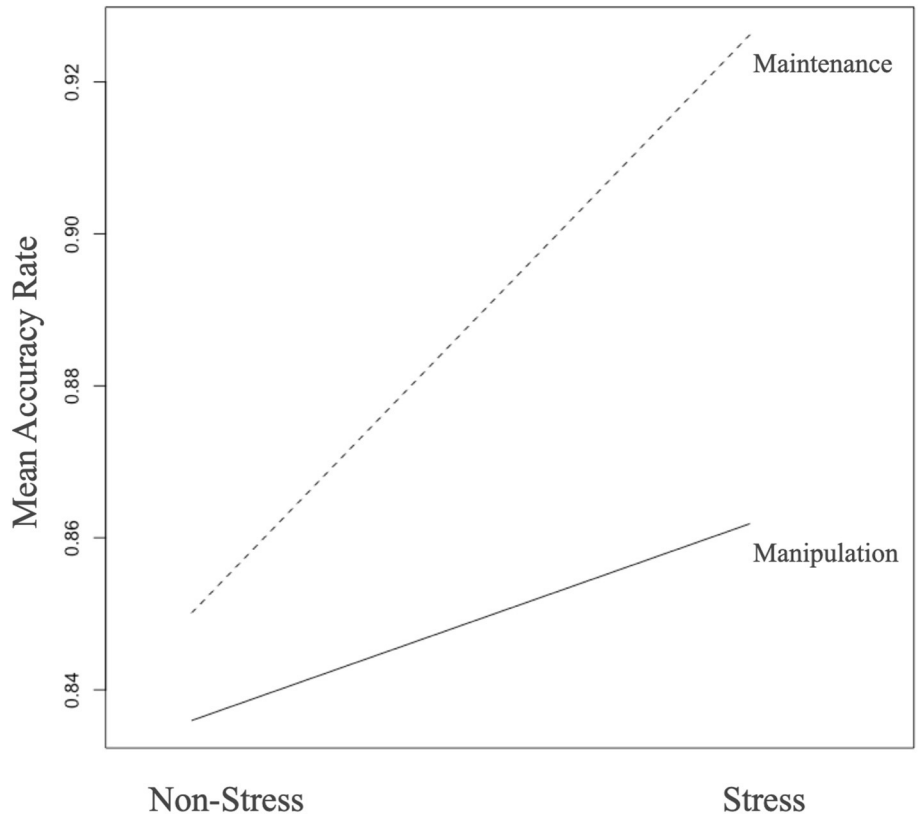

FIGURE 2 | Stress and task difference in the whole sample ($n = 91$). During the WM maintenance condition, trials with stress were associated with relatively increased accuracy ($p < 0.001$). This effect was not so evident during the WM manipulation condition, resulting in a significant task by stress interaction ($p = 0.002$).

TABLE 2 | Description of behavioral performances of MDD patients and HCs.

	MDD patients ($n = 37$)	HCs ($n = 54$)	t	p
Stress				
Accuracy in WM maintenance	0.93 (0.06)	0.92 (0.08)	0.858	0.393
RT in WM maintenance (s)	1.16 (0.26)	1.18 (0.29)	−0.229	0.820
Accuracy in WM manipulation	0.86 (0.14)	0.86 (0.11)	0.189	0.850
RT in WM manipulation (s)	1.60 (0.37)	1.54 (0.37)	0.728	0.469
Non-stress				
Accuracy in WM maintenance	0.87 (0.08)	0.84 (0.09)	1.644	0.104
RT in WM maintenance (s)	1.24 (0.30)	1.22 (0.30)	0.214	0.831
Accuracy in WM manipulation	0.83 (0.16)	0.84 (0.12)	−0.225	0.823
RT in WM manipulation (s)	1.63 (0.37)	1.61 (0.33)	0.354	0.724

MDD, major depressive disorder; HCs, healthy controls; RT, reaction time; WM, working memory.

gyrus, inferior occipital gyrus, culmen in the left hemisphere, and superior frontal gyrus, middle occipital gyrus, superior frontal gyrus, middle frontal gyrus, and pyramis in the right hemisphere ($p < 0.05$ FWE correction, cluster >50; **Table 3**).

Then, we focused on the group differences under stress setting ($p < 0.05$, whole-brain FWE correction, cluster > 2; **Figure 4**), MDD patients showed less activation in the left fusiform ($x = -52$, $y = -60$, $z = -16$, $T = 5.12$, cluster size = 14), and right APFC ($x = 32$ $y = 60$, $z = 2$, $T = 4.93$, cluster size = 3). While under non-stress setting, the main effect of diagnosis ($p < 0.05$ whole-brain FWE correction) lay in the right SMA ($x = 4$, $y = 14$, $z = 62$, $T = 5.75$, cluster size = 23) and left fusiform gyrus ($x = -50$, $y = -60$, $z = -16$, $T = 4.97$, cluster size = 7).

Correlation Analysis

In the MDD patients, we did not find any significant correlation between the HAMD-17 score and the β estimations of the peak

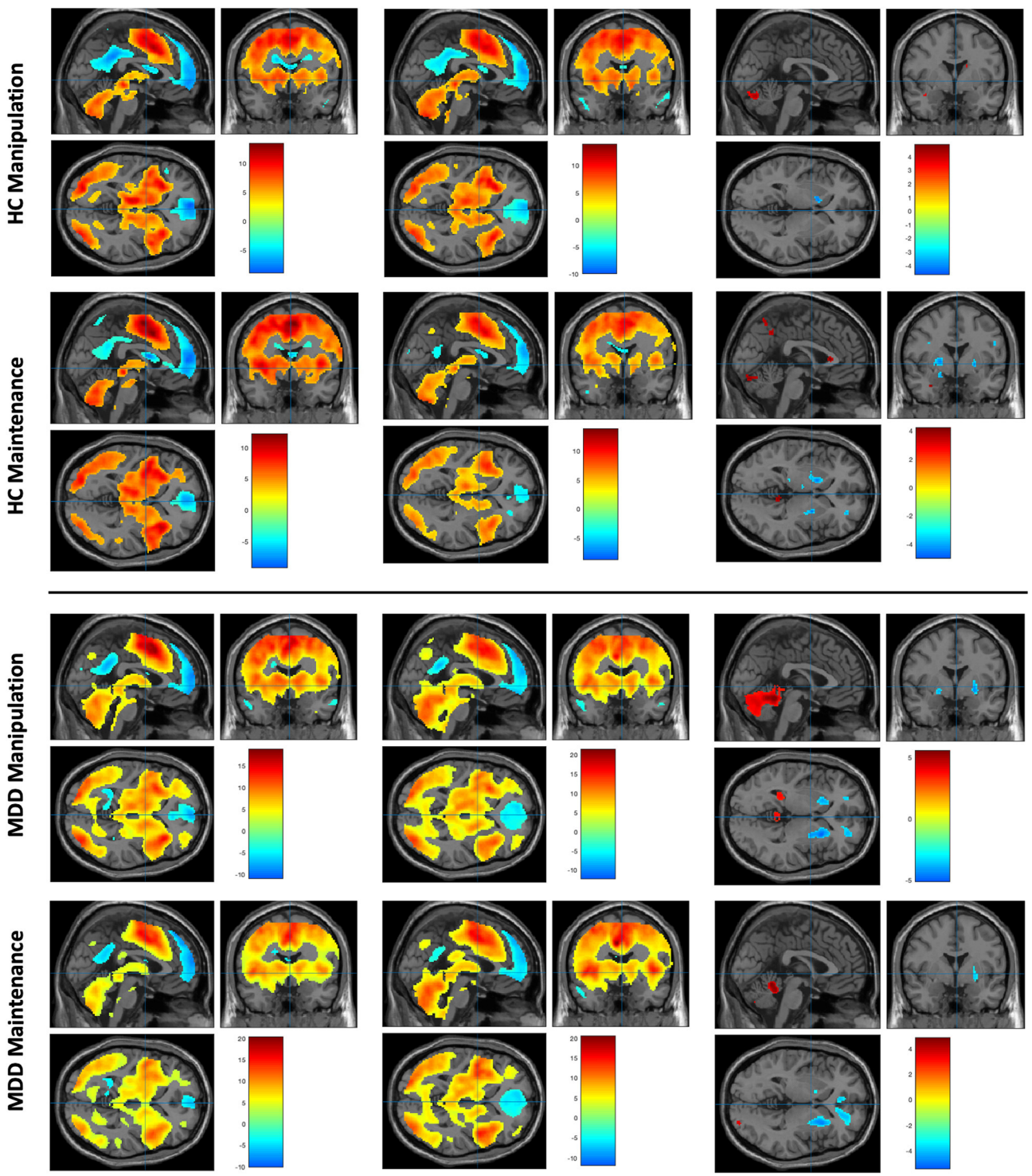

FIGURE 3 | Working memory–related brain activity and stress effect in MDD patients and healthy control subjects (data were shown for $p < 0.001$, uncorrected). Upper left: The brain activity of WM manipulation and maintenance subtasks in MDD group under non-stress setting. Upper middle: The brain activity of WM manipulation and maintenance subtasks in MDD group under stress setting. Upper right: The brain activity of comparison of stress vs. non-stress setting within the MDD group under different subtask patterns. Bottom left: The brain activity of WM manipulation and maintenance subtasks in HC group under non-stress setting. Bottom middle: The brain activity of WM manipulation and maintenance subtasks in HC group under stress setting. Bottom right: The brain activity of comparison of stress vs. non-stress setting within the HC group under different subtask patterns.

TABLE 3 | Main effect of group difference between MDD patients and HCs (controlling for age, $p < 0.05$, voxel-wise whole-brain FWE corrected, cluster size >50).

Peak Region	Cluster	*x*	*y*	*z*	*F* score
Maintenance					
L fusiform gyrus	225	−50	−60	−16	54.45
L postcentral gyrus	50	−52	−28	56	45.61
Middle cingulum	81	0	8	40	35.13
L superior temporal gyrus	60	−58	6	2	30.92
L precuneus	87	−12	−78	52	29.59
Manipulation					
R superior frontal gyrus	76	4	16	62	56.58
L fusiform gyrus	291	−50	−60	−16	50.41
L precuneus	151	−10	−76	54	43.55
R middle occipital gyrus	77	28	−94	−6	37.37
L middle frontal gyrus	135	−46	6	50	34.43
L cingulate gyrus	66	−2	8	40	34.06
L inferior occipital gyrus	87	−40	−86	−6	33.71
R superior frontal gyrus	149	30	56	−4	32.65
R middle frontal gyrus	59	44	30	42	31.97
R middle frontal gyrus	58	32	0	64	31.77
L culmen	72	−34	−42	−30	30.97
R pyramis	52	26	−70	−42	26.45

MDD, major depressive disorder; HCs, healthy controls, L, left; R, right.

voxel, which showed significant difference between HCs and MDD patients. While we found the β estimations of the peak voxel in APFC under stress manipulation task ($x = 32$, $y = 60$, $z = 2$) were negatively correlated with CTQ sex abuse ($r = -0.43$, $p = 0.008$; **Figure 4D**). These β estimations were also negatively correlated with CTQ physical neglect ($r = -0.37$, $p = 0.026$; **Figure 4D**), but could not withstand Bonferroni correction.

DISCUSSION

Main Findings

In the current pilot study, we aimed to explore the neural changes in MDD patients by investigating brain function associated with a stress-related WM task. We found that compared to HCs, MDD patients showed comprehensive less brain activation during both the WM maintenance and manipulation conditions. Particularly, we found decreased brain activation in the left fusiform under both stress and non-stress settings in both WM maintenance and manipulation conditions. Notably, the activation in the right SMA showed group differences in both WM maintenance and manipulation conditions under non-stress but not stress setting. We also found a reduced APFC activation in MDD under WM manipulation task under stress setting, which was negatively correlated with the CTQ sex abuse.

Left Fusiform Gyrus

Our study found that the activation of the left fusiform gyrus was decreased in MDD patients in both maintenance and manipulation conditions under non-stress or stress setting. The fusiform gyrus is the most crucial part of the high-level visual cortex, which is associated with the recognition of facial expressions (32, 33), integration of cognitive information, and emotional modulation (34). Previous studies had observed reduced gray matter volume, thinner cortical thickness, and less surface area of the fusiform gyrus in patients with depression (35–37). The fusiform gyrus may integrate the emotional and cognitive processes by modulating the visual stimulation processes. Moreover, compared to HCs, the connectivity between the fusiform gyrus and medial orbitofrontal cortex was decreased in MDD patients (38), which suggested that the fusiform gyrus had an indirect effect on the WM function and emotional modulation. In addition, the reduced activation of fusiform gyrus may also be related to the impaired function of the attention biases of negatively emotional stimuli (32, 39). We speculated that in the WM task, the role of the emotional stimuli process was impaired under both stress and non-stress settings or whether patients with MDD saw the face of a competitor or not.

Right Supplementary Motor Area

Meta-analyses showed consistent activation of SMA in the WM task, which indicated that the SMA included in the widespread frontoparietal network was part of the core WM network (4, 40, 41). Besides, the visual attention function of executive function is regulated by the SMA, precentral gyrus and ACC cortical network (42), which benefits the linking of sensory information to the learning and execution of movement sequences (43). Reduced SMA volumes and impairment in implicit motor sequence learning have been observed in MDD patients (44). Meanwhile, Sarkheil et al. (45) found that the SMA was associated with the psychomotor features (such as motor behavior) of depression, and they speculated that the increased functional connectivity between the SMA and other regions might suggest that recruiting more brain resources was needed for completing the more complicated task in MDD patients. Moreover, MDD patients were sensitive to stress (46). In our study, the decreased activation of SMA under non-stress but not stress setting might also support this view. As a negative stimulation, the face of a competitor might affect the visual attention of executive function, which resulted in "they potentially required additional serial mental processing steps" (47). Hence, the function of the SMA in MDD patients might be increased for making compensation in the WM task under stress, which led to increasing the activation of the SMA and reducing the difference compared to HCs.

Anterior Prefrontal Cortex

Studies showed that the APFC (Brodmann area 10, BA10) was involved in WM, episodic memory, prospective memory, and the consideration of multiple relations in the meantime (48, 49). Compared to children with non-depressed mothers, children with depressed mothers showed decreased activation in the APFC during the N-back task (50), which suggested that the activation of APFC might be an endophenotype of depression. Besides, the activation of the APFC has been observed in relatively simple tasks and would increase with the difficulty load of WM task in healthy subjects (51). Moreover, a prior work reported that higher activation in the APFC was related to WM

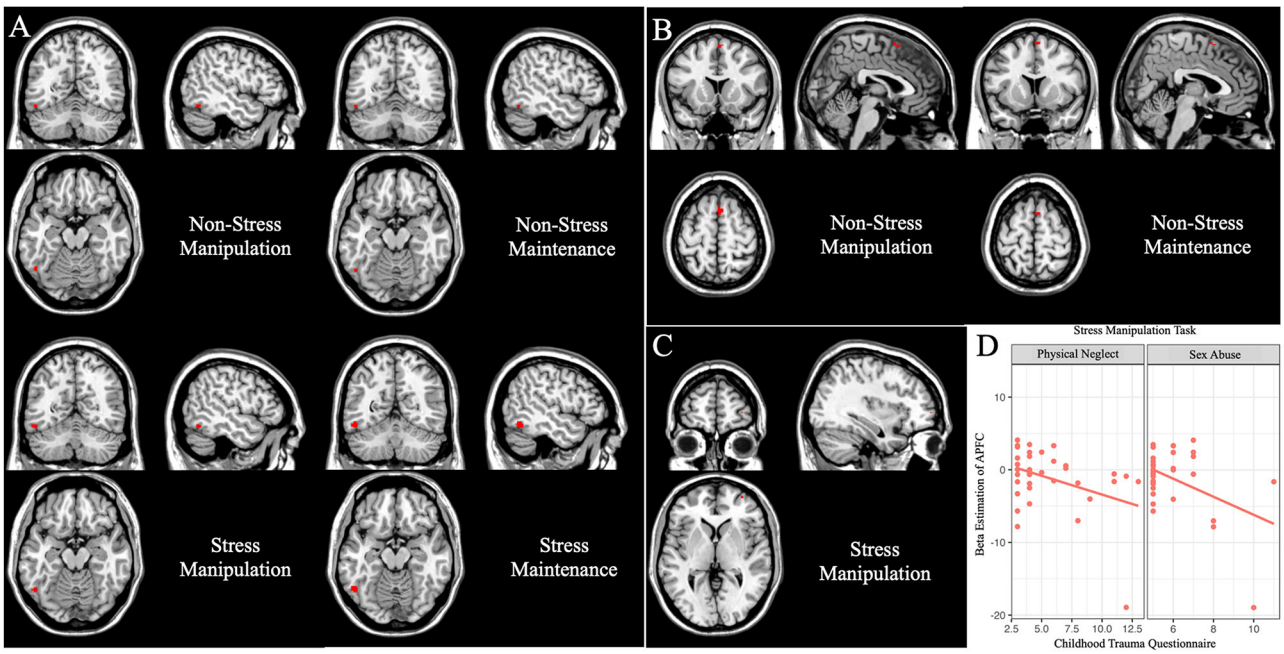

FIGURE 4 | Group differences under working memory maintenance and manipulation subtasks (data were controlling for age, $p < 0.05$, voxel-wise whole-brain FWE corrected). Main group differences under the working memory maintenance subtask. **(A)** The left fusiform gyrus showed decreased activation in MDD patients under the maintenance and manipulation conditions in stress and non-stress settings. **(B)** The right SMA exhibited reduced activation in MDD patients under the maintenance and manipulation conditions only in non-stress setting. **(C)** Under stress setting, MDD patients showed less activation in the right APFC in the manipulation condition. **(D)** In MDD group, and the β estimations of the right APFC peak voxel under stress manipulation subtask were negatively correlated with sex abuse ($r = -0.43$, $p = 0.008$) and physical neglect ($r = -0.37$, $p = 0.026$) score in the Childhood Trauma Questionnaire.

and choice-difficulty effects associated with self-control (52). Besides, APFC is a brain region that is sensitive to stress (53), and subjects with posttrauma stress disorder showed decreased gray matter volume in APFC compared with control subjects (54). Hence, MDD patients might keep the same cognitive control function with HCs under the non-stress setting, or in the maintenance condition in the stress setting. However, facing both stress and manipulation subtask, which means more choice difficulties, the cognitive control function in MDD patients was decreased compared to HCs.

Childhood Sex Abuse and APFC Activation

Childhood maltreatment, symptoms of negative emotionality, poor friend support, and externalizing problems in childhood and adolescence are risk factors for early-onset MDD patients (55, 56). Besides, childhood maltreatment can cause a series of physiological and neurohumoral reactions, including reduced volumes in the prefrontal cortex (57), and may lead individuals to being susceptible to depression (58–60). Previous studies exhibited that the volumes of ventromedial PFC and rostral prefrontal cortex were reduced in children and adults who suffered from physical and sexual abuse (61, 62). Furthermore, compared to individuals without childhood maltreatment, the activity in the MPFC was decreased in individuals who suffered from childhood maltreatment during emotional and neutral memory encoding and recognition (22). Meanwhile, substance abuse and stress can bring about long-lasting changes by modulating of gene expression or epigenetic mechanisms in the brain, and indeed an abnormal pattern of genome-wide DNA methylation in APFC of subjects with alcohol use disorder (63). In our study, childhood sex abuse might disrupt the function of APFC in direct and indirect ways, such as brain activation and DNA methylation, and then contribute to the development of depression.

LIMITATIONS

There are several potential limitations in our study. First, the sample size was not large enough. Therefore, it was only a pilot study. In the future, we need to enlarge the sample to test and verify the current findings. Second, we did not distinguish the depression subtypes, which might be the reason why there was no correlation between the β estimations of peak voxel and the HAMD-17 score. Therefore, we need to investigate the differences among different subtypes of depression and study the relationship between clinical symptoms and underline mechanism in a larger sample.

CONCLUSION

In our pilot study, the decreased brain activation of the left fusiform gyrus, SMA, and APFC helps us to understand the abnormalities of the emotional stimuli processing function,

executive function, and cognitive control function in MDD. Childhood maltreatment might play a crucial role in the development of MDD. Although, the findings of this study might not be conclusive, they could provide some information for other researchers. In the future, we need to explore the impaired brain circuits under stress, including the function and connection between the brain regions, which were found in our article in a larger sample.

DATA AVAILABILITY STATEMENT

The data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the Peking University Sixth Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WY and DZ designed and supervised the study. HT designed the task. MM, YZ, XZ, and YS recruited subjects and performed the study. MM, YZ, and XZ organized data. MM and XZ analyzed the data and wrote the paper. HY, HT, and WY gave instruction for the analysis and modified the paper. All collaborators reviewed and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.671574/full#supplementary-material

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Common and Distinct Alterations of Cognitive Function and Brain Structure in Schizophrenia and Major Depressive Disorder: A Pilot Study

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Objective: Numerous studies indicate that schizophrenia (SCZ) and major depressive disorder (MDD) share pathophysiological characteristics. Investigating the neurobiological features of psychiatric-affective disorders may facilitate the diagnosis of psychiatric disorders. Hence, we aimed to explore whether patients with SCZ and patients with MDD had the similar or distinct cognitive impairments and GMV alterations to further understand their underlying pathophysiological mechanisms.

Methods: We recruited a total of 52 MDD patients, 64 SCZ patients, and 65 healthy controls (HCs). The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery was used to assess cognitive functions. In addition, voxel-based morphometry (VBM) analysis was used to evaluate the gray matter volume (GMV) by using MRI scanning. One-way ANOVA and *post-hoc* tests were used to find the differences among the MDD, SCZ, and HCs. Finally, we explored the correlation between structural alterations and cognitive functions.

Results: Compared with that of HCs, processing speed was impaired in both patients with SCZ and patients with MDD ($F = 49.505$, $p < 0.001$). SCZ patients displayed impaired cognitive performance in all dimensions of cognitive functions compared with HCs ($p < 0.001$, except social cognition, $p = 0.043$, Bonferroni corrected). Whole-brain VBM analysis showed that both SCZ and MDD groups had reductions of GMV in the medial superior frontal cortex (cluster-level FWE $p < 0.05$). Patients with SCZ exhibited declining GMV in the anterior cingulate cortex and right middle frontal cortex (MFC) compared with HCs and MDD patients (cluster-level FWE $p < 0.05$). The mean values of GMV in the right MFC had a positive correlation with the attention/vigilance function in patients with MDD ($p = 0.014$, partial. $r = 0.349$, without Bonferroni correction).

Conclusions: In total, our study found that MDD and SCZ groups had common cognitive impairments and brain structural alterations, but the SCZ group exhibited more severe impairment than the MDD group in both fields. The above findings may provide a potential support for recognizing the convergent and divergent brain neural pathophysiological mechanisms between MDD and SCZ.

Keywords: major depressive disorder, schizophrenia, cognitive function, gray matter volume, superior frontal cortex

INTRODUCTION

Approximately 1% of the population suffers from schizophrenia (SCZ), which is one of the top 10 causes of disability worldwide (1). The clinical character of SCZ consists of varying degrees of behavioral anomalies, cognitive impairment, and emotional aberrations (2). Moreover, major depressive disorder (MDD) is a common psychiatric disorder with a high disabling effect (3) and a high relapse rate (4). It is characterized by a persistently low mood accompanied by anhedonia, psychomotor retardation (5, 6) and cognitive impairment (7). SCZ has some common symptoms overlapping with the MDD (8), such as mood symptoms, social withdrawal, and cognitive deficits (9). Moreover, they also share some common genetic loci (10). Previous data have shown that the prevalence of depressive disorder in schizophrenia was around 40% (11). The above results suggest SCZ and MDD may have some common endophenotype characteristics, while each disease has a specific pathophysiological mechanism. However, it is still unclear that the neural changes of the common and specific mechanism in SCZ and MDD.

Meanwhile, as one of the core characteristics of SCZ, cognitive impairment covers almost all main dimensions (12), including mental speed, working memory, attention, executive function, etc. (13, 14). Moreover, except mood disturbances, patients with MDD usually exhibit impairments of cognitive functions (15). Meta-analyses showed that MDD patients had moderately declined cognitive functions (16, 17). Compared with healthy controls (HCs), MDD patients exhibit decreased performance in several domains of cognitive functions, including information processing speed, working memory, verbal learning, memory, visuospatial learning and memory (15, 18–20). Hence, patients with SCZ may share considerable overlaps with MDD in several dimensions of cognitive function, especially processing speed and working memory.

The reductions in GMV of the prefrontal cortex were observed consistently in SCZ (21). Moreover, the decreased GMV in prefrontal-related regions, such as the right orbitofrontal cortex and dorsolateral prefrontal cortex was also exhibited in MDD (22). Previous study has been conducted on the GMV alterations of MDD and SCZ with the finds of the decreased GMV in middle frontal cortex (MFC) and medial prefrontal cortex (MPFC) (23). We considered that the abnormal structural alterations of the frontal cortex may be the common signatures of SCZ and MDD. However, few studies have focused on the similar or distinct GMV alterations of frontal cortex in patients with SCZ and patients with MDD. Further investigation is necessary.

In addition, structural alterations in the brain may have relationships with cognitive impairments in individuals. For instance, previous studies reported that deficit of working memory was associated with the structural changes in the prefrontal cortex, superior temporal gyrus, anterior cingulate cortex, medial frontal cortex, and hippocampal subregion in patients with SCZ (24–26). Processing speed was correlated with the structural alterations in the middle frontal gyrus, inferior frontal gyrus, bilateral orbitofrontal cortex, bilateral superior temporal gyrus, and the memory function had a correlation with the decreased GMVs in bilateral orbitofrontal cortex (27–29). Meanwhile, the GMV alterations of the inferior frontal gyrus were significantly associated with sustained attention in patients with MDD (30). Acoustic and visual attention was correlated with abnormal GMVs in the thalamus and amygdala/parahippocampal gyrus in patients with MDD (31).

Taken together, the above findings suggest that several similar or distinct cognitive impairments and frontal regional structural abnormalities might exist in patients with SCZ and patients with MDD, which the cognitive functions might have associations with the structural alterations. Besides, neuroimaging techniques have been well-known and widely applied in the study of psychiatric disorders (32). Voxel-based morphometry (VBM) is a useful approach in examining the whole-brain structural alterations (33). Hence, the aim of our study was to explore the common or distinct alterations of cognitive functions and brain structural in patients with MDD and patients with SCZ, compared with HCs by using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB), T1-weighted structural magnetic resonance imaging (MRI), and the association between cognitive function and GMV alterations.

METHODS AND MATERIALS

Subjects

A total of 64 SCZ patients, 52 MDD patients, and 65 HCs were recruited. Both the SCZ and the MDD patients were recruited from Peking University Institute of Mental Health. Patients were evaluated by two clinical psychiatrists using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria of SCZ or MDD, without any other comorbidities of the DSM-IV-TR Axis I

Disorders. HCs who were recruited from the community were assessed by psychiatrists using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-Patient Edition (SCID-I/NP) (34), and subjects with any psychiatric disorders were excluded.

The inclusion criteria were (1) being from 18 to 55 years of age, (2) having Han Chinese lineage, (3) being right-handed, and (4) patients with SCZ or MDD. The exclusion criteria were (1) diagnosis with any neurological disease, (2) being unconscious more than 5 min, (3) contraindications for MRI scanning, (4) patients who underwent electroconvulsive therapy over the previous 6 months, (5) patients with a history of any severe physical diseases, (6) patients with any monogenic inherited diseases, (6) patients with serious impulsive behavior/suicide attempts, and (7) patients during pregnancy and lactation.

There were 5 SCZ patients and 14 MDD patients who were drug-naïve. In addition, 59 SCZ patients received atypical antipsychotics (such as olanzapine, risperidone, aripiprazole, amisulpride, paliperidone, and clozapine). The Haloperidol equivalent dose of the antipsychotics was 11.03 ± 6.1 mg/day (35). In addition, 38 MDD patients received serotonin reuptake inhibitors (SSRI) (escitalopram, sertraline, fluoxetine); serotonin norepinephrine reuptake inhibitors (SNRI) (venlafaxine, duloxetine); and noradrenergic and specific serotonergic antidepressants (NaSSA) (mirtazapine). The equivalent citalopram dose of the antidepressants was 26.18 ± 11.82 mg/day (36).

The present study was approved by the Ethics Committee of the Peking University Institute of Mental Health. Informed consent forms were signed by subjects themselves or their legal guardians after getting detailed information about the study.

Cognitive Function Measurement

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) was designed to comprehensively and systematically evaluate the cognitive functions in individuals and further facilitate the development of medications for the treatment of cognitive deficits (37, 38). Also, the MCCB Chinese version has good reliability and validity for the Chinese population (39). We used the MCCB to assess the cognitive functioning of patients with SCZ, patients with MDD and HCs, including processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving and social cognition.

MRI Data Acquisition

All subjects were scanned using a 3.0-Tesla GE Discovery MR750 scanner at the Center for MRI Research, Peking University Institute of Mental Health. We collected the T1-weighted structural images of the whole brain of all subjects. The parameters of T1-weighted structural imaging were, using a T1-weighted fast spoiled gradient recalled (FSPGR) sequence, repetition time (TR) = 6.66 ms, echo time (TE) = 2.93 ms, field of view (FOV) = 256 × 256 mm^2, matrix size = 256 × 256, flip angle (FA) = 12°, voxel size = 1 × 1 × 1 mm^3, slice thickness = 1 mm, and slice gap = 0 mm. In total, it contained 192 slices of T1-weighted structural images.

Processing and Analyses of the MRI Data

Matlab 2013b and SPM (http://www.fil.ion.ucl.ac.uk/spm) were used to analyze the imaging data. We used the the VBM approach to analyzing the structural MRI data.

Structural Image Preprocessing

(1) We checked for artifacts of all images. (2) The origin of each image was corrected to match the anterior commissure. (3) The T1-weighted structural images were segmented into gray matter, white matter, and cerebrospinal fluid. (4) The segmented images were aligned and normalized from the original space to the Montreal Neurological Institute (MNI) space template using the DARTEL approach. (5) In order to reduce the effect of noise and compensate for the alignment error in the spatial normalization process, the images were smoothed with an 8 mm full width at half maximum (FWHM) Gaussian smoothing kernel.

Analysis of MRI Data

After controlling for age, gender, education, and total volume of the whole brain, we used one-way ANOVA to analyze GMV among the three groups. To avoid edge effects, voxels were included only when their absolute values were >0.2 and added a gray matter mask in the analysis. We extracted mean values of GMV of each region with significant group differences from ANOVA to perform *post-hoc* analysis. The significance level was set at $p < 0.05$ with whole-brain family-wise error (FWE) correction.

Statistical Analyses of the Demographic and Cognitive Function Data

We analyzed demographic and cognitive function data by using a standard statistical package (IBM SPSS 21.0, Chicago, IL), including one-way ANOVA, chi-square tests, and *post hoc* analysis. Given the above results of VBM analyses, we extracted the mean values of GMV from the regions of altered GMV and performed the partial correlations analysis of the cognitive functions of patients, controlling for age, gender, and education. The partial correlation analysis was performed in R. The significance level was set at $p < 0.05$ after Bonferroni correction for multiple comparisons.

RESULTS

Demographic and Cognitive Function Results

We recruited 64 SCZ patients, 52 MDD patients, and 65 HCs. All groups had similar age distribution. In addition, there were more males with SCZ—~1.5 times as many as females—which was in line with the findings that the male/female incidence rate of SCZ was about 1.4:1 (40). There were more females with MDD, approximately twice as many as males, which was consistent with the epidemiological findings that the prevalence of depression in women was about twice that of men (41).

TABLE 1 | Demographic and behavioral characteristics of schizophrenia patients, major depressive disorder patients, and healthy controls.

Characteristic	SCZ patients (SD)	MDD patients (SD)	HCs (SD)	F/X^2	*p*-value
Age (years)	26.67 (9.34)	24.98 (4.8)	25.25 (4.07)	1.55	0.317
Gender (female/male)	26/38	34/18	32/33	7.141	0.028
education (years)	13.64 (2.89)	16.04 (2.66)	16.83 (2.12)	26.685	<0.001
Speed of processing	50.36 (8.97)	59.06 (6.97)	62.68 (5.1)	49.505	<0.001
Attention/vigilance	48 (7.86)	56.4 (7.7)	58.37 (5.96)	37.208	<0.001
Working memory	47.52 (7.79)	50.17 (9.02)	53.97 (8.67)	9.442	<0.001
Verbal learning	49.95 (9.71)	60.27 (6.51)	59.05 (5.98)	33.279	<0.001
Visual learning	51.44 (9.54)	59.1 (5.46)	60.28 (5.02)	29.097	<0.001
Reasoning and problem solving	53.13 (9.64)	58.9 (7.86)	59.67 (6.62)	12.104	<0.001
Social cognition	37.17 (7.23)	40.39 (8.28)	40.62 (8.23)	3.707	0.026

SCZ, schizophrenia; MDD, major depressive disorder; HCs, healthy controls; SD, standard deviation.

Although the MDD patients and HCs had achieved similar educational levels, the SCZ patients had lower educational levels (**Table 1**). Hence, we included gender and education as covariates in subsequent analyses.

There were significant differences in cognitive functioning, including processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning, problem solving, and social cognition among the three groups (**Table 1**, **Figure 1**). *Post-hoc* analysis showed that patients with SCZ had worse performance of the cognitive functions in the whole dimension compared with HCs ($p < 0.001$, except social cognition, $p = 0.043$, Bonferroni corrected). It was noticed that compared with HCs, MDD patients also had worse performance in the field of processing speed ($t = -3.619$, $p = 0.023$, Bonferroni corrected), except SCZ patients. Meanwhile, MDD patients showed a trend of impairment in the dimension of working memory compared with HCs ($t = -3.796$, $p = 0.051$, Bonferroni corrected).

Gray Matter Volume Results

After controlling for age, gender, education and total volume of the whole brain, the GMV in the left anterior cingulate cortex (ACC) ($x = 2$, $y = 36$, $z = 26$, $T = 23.97$, cluster size = 2,181) showed significant difference among three groups, which involved the right medial of superior frontal cortex (MSFC) and right median cingulate cortex (MCC) ($p < 0.05$ whole-brain cluster level FWE corrected, **Table 2**, **Figure 2**). Among this large brain region, patients with SCZ showed less GMV in the left ACC ($x = 2$, $y = 38$, $z = 21$, $T = 4.77$, cluster size = 639), right MCC ($x = 3$, $y = 15$, $z = 39$, $T = 4.29$, cluster size = 283) and right middle fontal cortex (MFC, $x = 32$, $y = 54$, $z = 15$, $T = 4.18$, cluster size = 130) compared with patients with MDD. Besides, compared with HCs, MDD patients showed reduced GMV in the right MSFC ($x = 14$, $y = 53$, $z = 20$, $T = 4.94$, cluster size = 666) and SCZ patients had decreased GMV in the left ACC ($x = 2$, $y = 36$, $z = 26$, $T = 6.92$, cluster size = 2,181), which also extended to the right medial superior frontal cortex (MSFC) and right median cingulate cortex (MCC). Finally, we did not find any region in patients with MDD or patients with SCZ had significantly larger GMV compared with that in HCs.

Correlation Analysis

In the patients with MDD, we found the mean values of GMV in the right MFC ($x = 32$, $y = 54$, $z = 15$), which showed significant difference between patients with MDD and patients with SCZ had a significant positive correlation with the cognitive function of attention/ vigilance ($p = 0.014$, partial. $r = 0.349$, controlling for age, gender, and education, without Bonferroni correction, **Figure 3**). While we did not find the mean values of GMV in the left, ACC ($x = 2$, $y = 36$, $z = 26$) had associations with cognitive functions in SCZ patients.

DISCUSSION

In this study, we have analyzed the cognitive functioning and brain GMV changes in SCZ patients, MDD patients, and HCs. Our findings were the following: (1) compared with HCs, both the SCZ patients and MDD patients exhibited impaired cognitive functioning in processing speed, which suggested the impairment of the executive function was the common characteristic of the two diseases; (2) SCZ patients also showed deficits in cognitive functioning in the other dimensions, including attention/vigilance, working memory, verbal learning, visual learning, reasoning, problem solving, and social cognition compared with HCs, while MDD patients exhibited a trend impairment of working memory; (3) compared with HCs, both the patients with SCZ and the patients with MDD showed decreased GMV in the right MSFC; (4) patients with SCZ exhibited reduced GMV in the left ACC and right MFC compared with HCs and MDD patients; (5) the mean values of GMV in the right MFC had a positive correlation with the cognitive function in the attention/vigilance field in patients with MDD. The above results suggest that SCZ and MDD have common and distinct cognitive impairments and brain structural signatures. Both the SCZ patients and the MDD patients showed abnormal cognitive functioning with respect to processing speed and decreased GMV in the right MSFC. Moreover, patients with

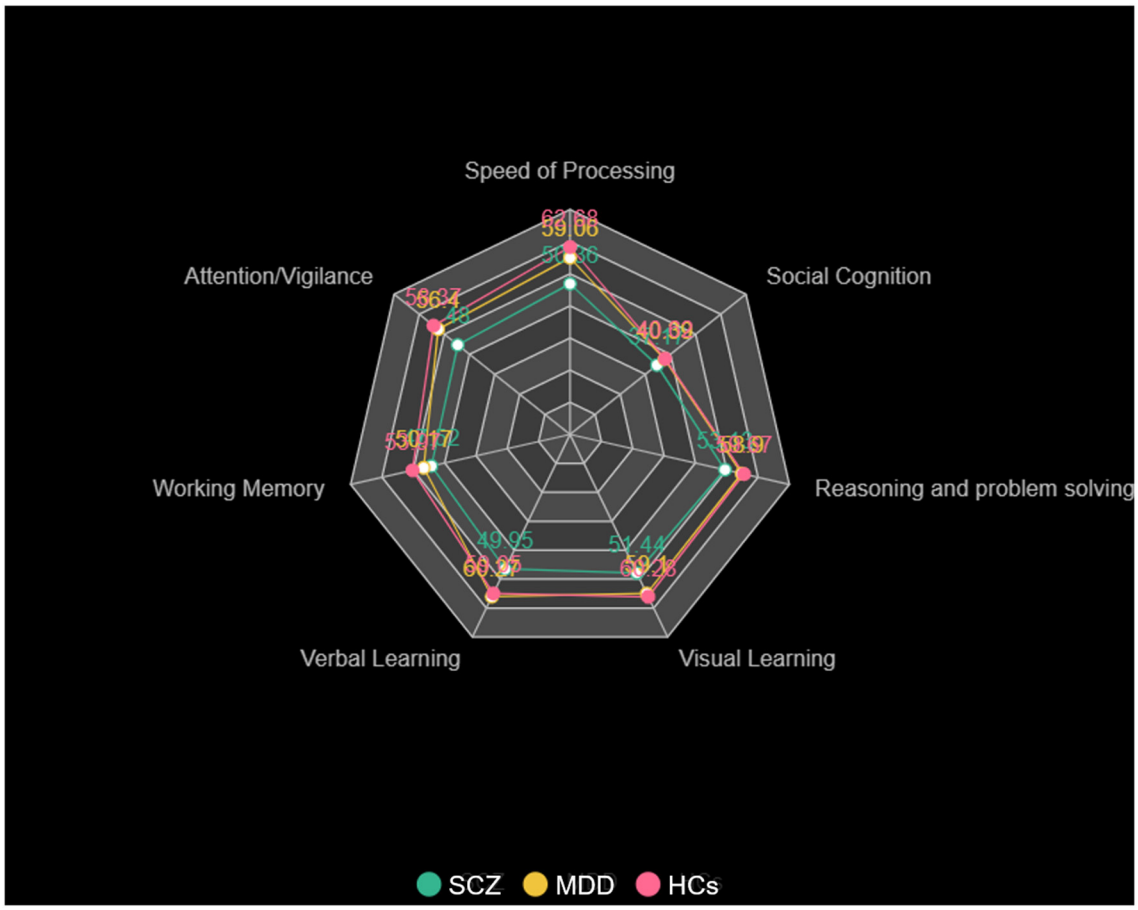

FIGURE 1 | Cognitive function of patients with SCZ, patients with MDD, and HCs. The cognitive scores for processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning, problem solving, and social cognition in patients with SCZ, patients with MDD, and HCs.

TABLE 2 | Results of GMV analysis of the patients with schizophrenia patients, major depressive disorder patients and healthy controls (controlling for age, gender, education, and total volume of the whole brain, $p < 0.05$, cluster-level whole-brain FWE corrected).

Hemisphere	Brain region	Cluster size	MNI coordinates	Peak *F*/*t* value	Cluster-level p_{FWE}
			(*x*, *y*, *z*)		
ANOVA					
Left	Anterior cingulate cortex	2,181	2, 36, 26	23.97	<0.001
Right	Medial superior frontal cortex		2, 38, 21	22.79	
Right	Median cingulate cortex		3, 21, 39	20.19	
MDD > SCZ					
Left	Anterior cingulate cortex	639	2, 38, 21	4.77	0.001
Right	Median cingulate cortex	283	3, 15, 39	4.29	0.006
Right	Middle frontal cortex	130	32, 54, 15	4.18	0.021
HC > MDD					
Right	Medial superior frontal cortex	666	14, 53, 20	4.94	0.001
Right	Medial superior frontal cortex		5, 56, 26	4.94	
Right	Superior frontal cortex		17, 57, 5	4.76	
HC > SCZ					
Left	Anterior cingulate cortex	2,181	2, 36, 26	6.92	<0.001
Right	Medial superior frontal cortex		6, 56, 21	6.45	
Right	Median cingulate cortex		3, 21, 39	6.35	

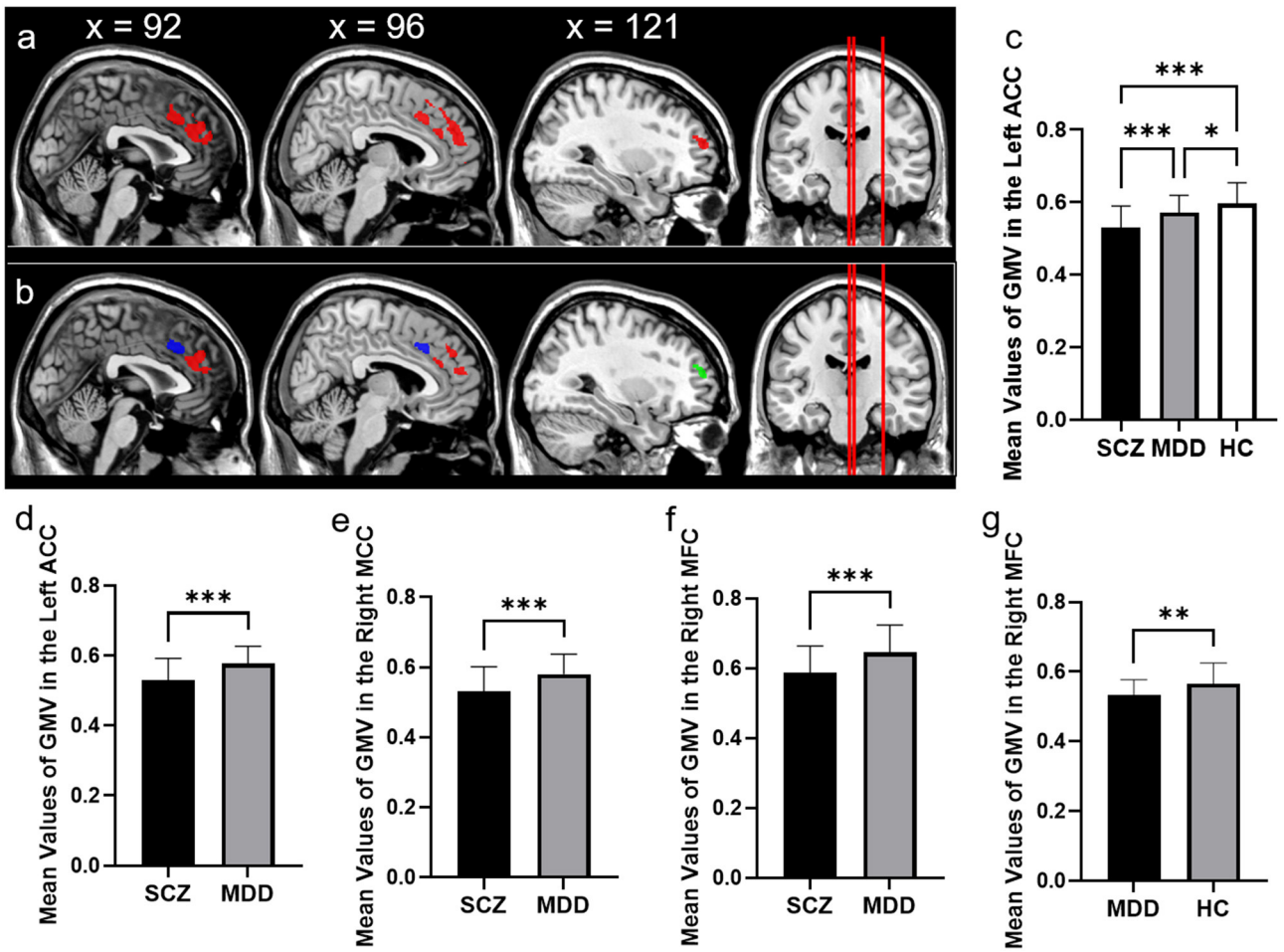

FIGURE 2 | Comparison of GMV in schizophrenia, major depressive disorder, and healthy controls. **(a)** The significant brain region that showed significant differences among patients with SCZ, patients with MDD, and HCs. **(b)** The significant brain region which showed significant differences between SCZ patients and MDD patients (controlling for age, gender, education, and total volume of the whole brain, $p < 0.05$, cluster-level whole-brain FWE corrected). The bar graphs showed the mean values of GMV in the left anterior cingulate cortex among three groups. **(c)** The left anterior cingulate cortex between SCZ and MDD. **(d)** The right median cingulate cortex between SCZ and MDD. **(e)** The right middle frontal cortex between SCZ and MDD. **(f)** The right middle frontal cortex between MDD and HC. **(g)** ACC, anterior cingulate cortex; MCC, median cingulate cortex; MFC, middle frontal cortex, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, Bonferroni corrected.

SCZ showed impaired cognitive functioning in all dimensions and less GMV in the left ACC and right MFC.

Cognitive Function

Common Cognitive Impairment in Speed of Processing

The finding that both the patients with SCZ and the patients with MDD showed information processing speed deficits was in accordance with previous research (15, 42–45). Information processing speed, as a major part of executive function, plays an important role in learning and memory cognitive function (15). The impaired function of processing speed may implicate neural circuitry underlying cognitive and mood abnormalities in individuals with depression (43, 46). Besides, previous data have also reported that the worse processing speed was related to the severity of psychosis (47, 48). Moreover, impaired processing speed can successfully predict functional outcomes in patients with SCZ and may be an important predictor of the conversion to a full-blown psychiatric disorder in individuals at high risk (47, 49–51). Therefore, the deficit in speed of information processing may be an underlying shared pathophysiological mechanism of cognitive functions, mood and psychiatric symptoms impairments between SCZ and MDD.

Distinct Cognitive Impairments in SCZ Patients

In line with our expectation, compared with HCs and MDD patients, patients with SCZ had worse cognitive function in all dimensions, including/processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning, problem solving, and social cognition. This result has been confirmed by previous studies. Although subjects showed impairments in memory, executive function, attention, and processing speed function among the three groups SCZ, MDD,

and bipolar disorder (BD), patients with SCZ exhibited more impairment than the rest of the subjects (45). SCZ has a significant association with cognitive decline (52). Cognitive impairment such as the stable phenotypes of SCZ significantly contribute to functional abnormalities in patients with SCZ (53, 54). A meta-analysis found that the reduced brain-derived neurotrophic factor (BDNF) levels and elevated C-reactive protein (CRP) in SCZ had a significant relationship with cognitive impairment, particularly in subjects with chronic SCZ (55). Moreover, the decreased GMV in the paralimbic system in SCZ had correlations with cognitive functioning, clinical variables, and symptomatology (27). These results suggest that cognitive impairment is a stable phenotype of SCZ, which has inflammatory, neurotrophic, and structural brain foundations.

Brain Structure

Common Decreased GMV in the Right MSFC

Both the SCZ group and the MDD group showed significantly reduced GMV in the right medial of superior frontal cortex, compared with that in HCs. The superior frontal cortex is generally considered a crucial brain region involving the emotional regulation and cognitive control function (56, 57). Previous studies have reported that the abnormal activity in the superior frontal cortex might be related to excessive self-referential processing and impairment in emotional cognitive control processing in patients with MDD (58). A large number of studies found that the structure of the superior frontal cortex had an important association with depressive symptoms among different populations (59–62). One study reported that the GMV alterations in superior frontal cortex was associated with the severity of depression in patients with MDD (63). Furthermore, a recent study found that the GMV of the left supplementary motor area, superior frontal cortex, and precentral gyrus had negative correlations with the hallucination severity and positively correlated with the responsive search score (64). Goghari found that compared with controls, nonpsychotic relatives of patients with SCZ exhibited less GMV in the superior and inferior frontal cortex regions, in which aspects of decreased GMV in the prefrontal cortex might reflect genetic liability for SCZ (65). Hence, the decreased GMV of the right superior frontal cortex associated with emotional regulation, cognitive control function, and psychiatric symptoms may be a potential common pathophysiological signature both of MDD and SCZ.

Distinct Decreased GMV of the Left ACC in Patients With SCZ

Our findings are consistent with previous reports that have shown that the reductions of GMV in parts of the prefrontal and cingulate were specifically related to SCZ (66, 67). The ACC has been reported to play a crucial role in pathophysiology of SCZ (68). A recent study suggested that the decreased perfusion in the ACC might be related to the development of delusions in SCZ (69). Besides, the reduction of GMV in the ACC has important associations with both of negative symptoms and positive symptoms in SCZ (66, 70). Meanwhile, the ACC is also involved in the integration of sensory stimuli, which suggests that the abnormal structure in ACC may disturb the integration of sensory stimuli and contribute to delusions and grandiosity thought disorder in patients with SCZ (70). Findings from previous proton magnetic resonance spectroscopy (MRS) research have shown that abnormal ACC glutamate and gamma aminobutyric acid (GABA) levels has been observed across the illness course, in antipsychotic-treated and drug-naive/off-medication patients with SCZ (71, 72). Thus, the decreased GMV of the right ACC may be a potential biomarker for the diagnosis and treatment of SCZ.

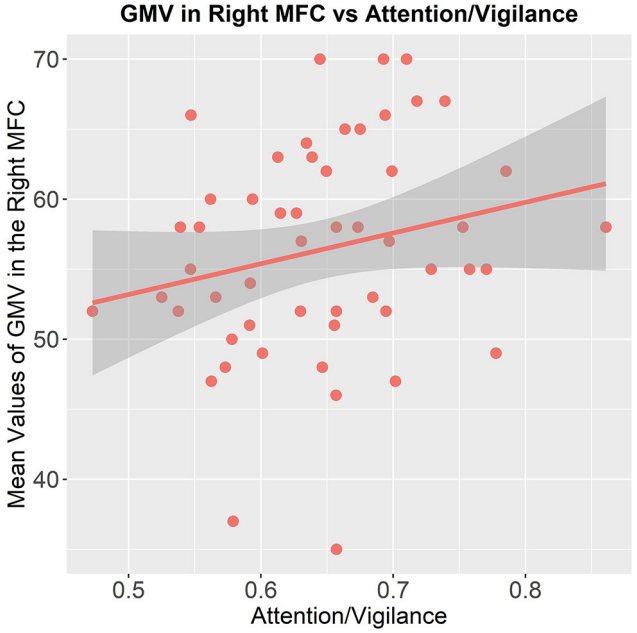

FIGURE 3 | Association between the GMV of the brain region and cognitive functioning. The mean values of GMV in the right middle frontal cortex are correlated to the attention/vigilance function in patients with MDD ($p = 0.014$, partial. $r = 0.349$, controlling for age, gender, and education, without Bonferroni correction).

The Reduction of GMV in the Right MFC Is Correlated With the Attention/Vigilance Function

A study has shown that the ventromedial frontal cortex had direct influence on attention function by the connections with higher-order sensory regions (73). In addition, the ventromedial frontal cortex can also influence selective attention processes underlying visual search through communicating with ventral visual regions (46, 74). Moreover, the integrity and coordinated function of medial PFC indeed plays an important role in the cognitive function of attention (75). A previous study reported that the dorsolateral prefrontal cortex (including the caudal MFC), supplementary motor area, and posterior cingulate cortex participated in the dorsal attention network, which would be active during attention-demanding tasks (76). Therefore, though narrowly escaping statistical significance, the decreased GMV in the right MFC may be crucial for the attention/vigilance function in MDD patients.

There are several limitations that should be acknowledged in the present study. First, the sample size is slightly small. As a pilot study, we would like to recruit more subjects to test and verify the current results. Second, the present findings may be limited by the study's cross-sectional design. Moreover, we did not distinguish between the patients treated with drugs and those without drug treatment, so the results need to be treated with caution. In the future, we would like to follow up with patients and distinguish patients treated with drugs from those without drug -treatment to further explore changes in cognitive functioning and brain structure.

Collectively, our study indicated that both abnormality of the cognitive impairment in information processing speed and reductions in GMV in the right medial superior frontal cortex were related to emotional regulation, executive control function, and psychiatric symptoms, and these may be the common pathophysiological foundations for both diseases. Besides, cognitive impairment may be the stable phenotype for patients with SCZ, and the decreased GMV of the right ACC may be a potential biomarker for the diagnosis of SCZ. The above results may provide several clues for further exploration of the diagnosis and treatment of SCZ and MDD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the Peking University Sixth Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WY and DZ designed and supervised the study. MM and YZ recruited subjects performed the study and organized the data. MM analyzed the data and wrote the paper. XZ, HY, and WY gave instruction for the analysis and modified the paper. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Impulsivity as a Risk Factor for Suicide in Bipolar Disorder

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The accurate assessment of suicide risk in psychiatric, especially affective disorder diagnosed patients, remains a crucial clinical need. In this study, we applied temperament and character inventory (TCI), Barratt impulsiveness scale 11 (BIS-11), PEBL simple reaction time (SRT) test, continuous performance task (CPT), and Iowa gambling task (IGT) to seek for variables linked with attempted suicide in bipolar affective disorder group ($n = 60$; attempters $n = 17$). The main findings were: strong correlations between self-report tool scores and objective parameters in CPT; the difference between attempters and non-attempters was found in the number of correctly responded trials in IGT; only one parameter differed between attempters and non-attempters in BPI diagnosis; and no significant differences between suicide attempters and non-attempters in TCI, BIS-11, and SRT were found. These justify the conclusion that impulsivity itself is not a strong predictor, and used as a single variable might not be sufficient to indicate the high suicide risk group among bipolar patients.

Keywords: bipolar disorder, suicide, impulsivity, neuropsychology, personality, risk factors

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INTRODUCTION

Every 40 s one person dies by suicide that is ∼800,000 people every year worldwide (1).

The most important risk factors are: barriers in access to health care; access to lethal means, trauma, or abuse; sense of isolation and lack of social support; previous suicide attempts; mental disorder; and family history of suicide (2). Those suffering from psychiatric disorders have significantly higher risks of suicide, especially in the first few months after diagnosis (3). Over 90% of individuals, who have committed suicide, fit the criteria for having a mental health problem (4). In bipolar affective disorder, 20% of patients commit suicide (5), and 25–50% of them present suicidal attempts during the illness (6). For bipolar disorder, the following suicide risk factors were identified: rapid-cycling course, mixed episodes or agitated depression, early-onset of the disease, and comorbidity with anxiety and substance use disorders (4), and also the period soon after hospital discharge (7). However, previous assessment tools used to recognize suicide risks have shown to be challenging (3) and are characterized by unsatisfactory sensitivity and specificity (8).

Apart from the current medical burden and social stressors, personality traits (9) have been investigated as distal risk factors (10, 11). The influence of decision-making includes personality traits, such as aggression, anger, hostility, emotional instability, and impulsivity (12).

Impulsivity plays an important role in predisposing to psychiatric illnesses, such as bipolar disorder, depressive disorder, behavioral and substance addictions, and personality disorders (13–15). According to diagnostic and statistical manual of mental disorders (DSM-5), impulsivity is "acting on the spur of the moment in response to immediate stimuli; acting on a momentary basis without a plan or consideration of outcomes; difficulty establishing and following plans; a sense of urgency and self-harming behavior under emotional distress. Impulsivity is a facet of the broad personality trait domain—disinhibition." Whiteside and Lynam (16) have described four subdimensions of impulsivity: urgency, lack of premeditation, lack of perseverance, and sensation seeking, whereas, Barrat impulsiveness scale subdivides impulsivity into three factors (17) subdivides impulsivity into three factors.

Brain structures involved in impulsive behavior are the orbitofrontal cortex (18), the anterior cingulate cortex, the infralimbic cortex (19), and the dorsolateral prefrontal cortex (20). Premature responses strictly corresponded with dopamine and serotonin level (21).

Patients with bipolar disorder I especially present high levels of impulsivity (15, 22). Interestingly, high impulsivity is present not only during manic or depressive episodes but also in patients with euthymia (23). Rote et al. (24) found that attentional impulsivity was higher in patients with euthymia than healthy controls and seems to be a predictive factor for severity of the illness (24). Impulsive action, especially combined with anger-related traits and novelty seeking, is a risk factor for suicidal behaviors (25). Perraud et al. (26) found that suicide attempters characterize with higher harm avoidance and novelty seeking and lower self-directedness than non-attempters. High novelty seeking presents as excessive anger, quick decision-making, and poor impulse control. These features may predispose to a particular type of suicidality (26), namely to multiple attempts and first attempt at a younger age. Relatively lower impulsivity in the attempter group was connected with higher lethality of suicide behavior (27). Other researchers found that high impulsiveness predisposes to choosing violent suicide methods (28). Although impulsivity has been associated with suicidal behavior (29) and plays a vital role in understanding many psychiatric disorders, such as mania, substance abuse, personality disorders, or attention deficit hyperactivity disorder (ADHD) (30), the results of clinical investigations are inconsistent in the field of suicidality. Impulsivity can be measured with methods based on self-reporting, such as BIS-11, Temperament and Character Inventory (TCI), or with behavioral tasks. Recently, behavioral tasks have become preferred to self-report tools because they allow to objectively measure different aspects of impulsivity. Studies demonstrate that self-report and behavioral measures of impulsivity can show independent results, not correlating with each other (31).

The aim of this study is to search for a potential auxiliary method to assess the individual predisposition of patients to act upon suicidal ideas. We hypothesize that suicide attempters differ from non-attempters in impulsivity parameters and that the trait is detectable as an intermediate phenotype. We used measurement of several aspects of impulsivity to seek its link to suicide behavior in bipolar affective disorder. Results of subjective (self-report questionnaires) and objective (computerized performance tasks) methods were compared. Subsequently, we analyzed the obtained scores in suicidal and non-suicidal patients.

MATERIALS AND METHODS

Subjects

The investigated group included only patients diagnosed with BP ($n = 60$; 21 men, 39 women). As inclusion criteria, we used the diagnosis of bipolar affective disorder, age 18–70 years and ability to perform computerized tasks, being right-handed, and lack of severe somatic and neurological problems that require immediate medical intervention. Co-occurrence of BP with other axis I disorders or personality disorders was not an exclusion criterion. The diagnosis was established with SCID-I questionnaire (The Structured Clinical Interview for DSM-IV Axis I Disorders) (32) according to DSM-IV criteria. All patients had a history of at least one in-patient clinic treatment when the diagnosis was confirmed. Data on suicidality, illness duration, and family burden were completed in an additional interview. Beck Depression Inventory, Young Mania Rating scale, and Hamilton Depression Rating scale were used to confirm the euthymic state in time point of neuropsychological computerized assessment, BIS-11, and TCI completion.

Suicide attempt was defined as self-destructive behavior of an individual with some intention to end life by himself/herself (33). About 17 patients have had a history of suicidal attempts, among them eight used violent methods [hanging, firearms, jumping from a height, deep cuts, car crash, burning, gas poisoning, drowning, electrocution, and jumping under a train according to Asberg et al. (34); Ludwig and Dwivedi (35)], and 10 individuals did not provide information about the history of suicidality, presence of thoughts, and the number or method of an attempt.

The patients received a detailed description of the study procedures and gave informed written consent for participation in the study. The protocol was approved by the Ethics Committee, Poznan University of Medical Sciences.

The Personality and Neuropsychological Assessment

One of the most commonly used self-report measures is the BIS-11 (17), which subdivides impulsivity into factors and subfactors: (1) attentional: attention; cognitive instability; attentional total; (2) motor: motor perseverance; motor total; and (3) non-planning—self-control; cognitive complexity; non-planning total. The TCI (36) is an instrument providing a deep and comprehensive model of personality. It deconstructs personality into seven dimensions (36, 37). Here, impulsivity is a subdimension of novelty seeking.

The other methods of assessing impulsivity are objective behavioral tasks, which are often computerized. They are presented in the form of games, in which the strategy, general score, and reaction time of the patient are measured. There are numerous tests that are relevant to assess reactivity, ability to inhibit action, and decision-making styles, such as simple

reaction time (SRT) test, continuous performance task (CPT), and Iowa Gambling Task (IGT).

The personality and neuropsychological assessment was performed in euthymic state (<8 points in the Beck Depression Inventory; <6 points both in Young Mania Rating scale and Hamilton Depression Rating Scale). Personality traits were depicted using TCI; total dimension scores and subdimensions were used for analyses. Impulsivity was also measured using BIS-11 and again, factors and subfactors of the scale were analyzed.

To objectively measure the impulsive behavior of patients, we used the computerized version of the SRT test, CPT, and IGT from the psychology experiment building language (PEBL) battery (38). All computer tests were performed in the same order between 9:00 a.m. and 12:00 p.m.

In the SRT, the patient was presented with a visual stimulus and was asked to respond as quickly as possible (39). In CPT, the patient was to respond to many letters, but the stimulus for which the patient should inhibit the action and not respond was the letter "X." The IGT is a test in which the patient is asked to maximize his/her profit through selection of cards from four decks. Cards from different decks are associated with different fines and rewards. Through the trial-and-error method, the patient should strive for optimal strategy (40).

Statistical Analysis

The distribution of the data was analyzed using the Lilliefors test. Nonparametric tests were applied. The Mann–Whitney *U*-test was used in the comparisons of the results of self-report questionnaires and computerized performance tasks with dichotomous variables (suicide attempts, diagnosis, and gender).

Spearman's rank correlation coefficient was performed. Power analysis was done using the G*Power program (https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower) (41). We present the raw data with power analysis and without multiple-testing correction to avoid omitting clinically important, but statistically insignificant results. The significance level was set at $p < 0.05$. Analyses were made using the STATISTICA 13.3 (StatSoft, Krakow, Poland).

RESULTS

Descriptive Results

The demographic structure and family burden of psychiatric disorders of the investigated group is presented in **Table 1**. The duration of illness was 1–49 years (mean 16.593 years; SD 11.703). The study group consisted of 39 patients with bipolar type I and 21 with type II. Suicide attempters and non-attempters groups varied in gender structure.

Suicide Attempters vs. Non-suicide Attempters

In the entire bipolar group, the Mann–Whitney *U*-test did not detect any significant differences between suicide attempters and non-attempters in TCI, BIS-11, SRT test, and IGT. Suicide attempters achieved higher scores in attentional factor of BIS-11 scale than non-attempters; however, only a statistical trend was detected ($p = 0.063$).

In CPT parameters, the difference between attempters and non-attempters was found in the number of correctly responded trials (corr trials). Non-attempters obtained a higher score than the attempters ($p = 0.040$).

Then, the analysis for the BPI subgroup was performed. The computations for the BPII subgroup were omitted due to a low number of participants. Analysis of the BPI suicide attempters vs. suicide non-attempters revealed significant differences in TCI empathy subdimension (C2 score in cooperativeness), ($p = 0.003$). Suicide attempters achieved higher scores in this variable. The results of the BIS-11 scale did not differ between BPI attempters and non-attempters.

The CPT correct response mean time was found higher for suicide non-attempters ($p = 0.019$). Another studied parameter of CPT did not occur to be significantly different. No differences were found in SRT results. Regarding the results of IGT one parameter differed between attempters and non-attempters in the BPI diagnosis. It was the number of A deck choices in the fifth block. Non-attempter have chosen this deck (less advantageous

TABLE 1 | Demographic structure of studied population.

	Bipolar (BP) affective disease			BPI	BPII	*p*
	General	Male	Female			
Number	60	21	39	39	21	0.026
Mean age (±SD)	46 (±14.24)	47 (±13.96)	45 (±14.52)	47 (±12.32)	43 (±17.36)	0.687
Mean age of disease onset (±SD)	29 (±11.73)	27 (±12.76)	30 (±11.19)	27 (±9.56)	32 (±14.60)	
Family History of psychiatric disease	45	18	27	29	16	
Family history of affective disease	18	4	14	9	9	
	Suicide attempters		**Suicide non-attempters**			
Number	17 (men:2; women:15)		43 (man:16; women:17)			0.013
Mean age (±SD)	44 (±16.27)		46 (±13.52)			0.315
Family history of suicide attempts	3		6			
Family history of committed suicide	3		7			
Diagnosis	BPI: 6 BPII: 11		BPI: 33 BPII:10			

TABLE 2 | Significant differences between suicide attempters and non-suicide attempters in the Bipolar I + II group and in Bipolar I subgroup.

	U	*Z*	*p*	Power
BPI + BPII				
BIS-11 attentional	116	1.857331	0.t063	0.61
CPT corr trials	162	−2.04798	0.040	0.39
BPI				
TCI cooperativeness C2	28.5	2.81174	0.005	0.99
CPT corr RT mean	53	−2.30717	0.021	0.4
IGT nA5	56	−2.47173	0.013	0.9

Mann–Whitney U-test.

to achieve the goal of the task) more often in the last block than attempters ($p = 0.012$; see **Table 2**).

Comparisons of The BPI and BPII Groups

Between patients diagnosed with BPI and BPII, we found no differences in the BIS-11 and TCI scales (*p*-value ranged 0.074–0.992). Regarding the neuropsychological tests, significant differences between BPI and BPII were obtained for PEBL-CPT in the following parameters: the number of correctly responded trials (corr trials) ($p = 0.003$), the rate of correctly responded trials in the whole number of trials to respond (targ acc rate) ($p = 0.004$), rate of inhibited reactions in the whole number of trials to inhibit (foil acc rate) ($p = 0.011$), early response number (commission errors) ($p = 0.008$), lack of required response number (omission errors) ($p = 0.004$), and mean response time in correct responses (Corr RT mean) ($p = 0.019$). For the SRT test, the significant difference was observed in the number of early reactions (anticipations), and the patients with BPI more often responded before the stimulus ($p = 0.008$; **Table 3**).

Male and female groups were compared. We obtained no significant difference in BIS-11 factors and subfactors, CPT, and SRT parameters. TCI scores were significantly different between men and women regarding the following personality dimensions: anticipatory worry, a subdimension of harm avoidance (Ha1) was higher in women ($p = 0.040$); sentimentality, a sub-score of reward dependence (Rd1) was higher in women ($p < 0.001$); and empathy, a subdimension of cooperativeness (C2) was higher in women as well ($p = 0.023$).

The only objectively measured variables that differ between men and women were observed in IGT. The test was split into five blocks with 20 card choices in each block. We observed the changes of parameters of decision-making between blocks. Significant differences were noticed in the sum of advantageous and disadvantageous decks chosen in blocks 3, 4, and 5. Women chose advantageous decks more often ($p = 0.003$, 0.006, and 0.002, respectively). The difference was observed in the number of deck B and D choices in block 5. Men more often chose deck B, and women more often chose deck D ($p = 0.019$ and 0.019, respectively). The trend for more advantageous choices was found in the total sum of advantageous and disadvantageous decks: women had chosen C and D decks more often ($p < 0.001$) (**Table 4**).

TABLE 3 | Comparison of CPT and SRT results between Bipolar I and Bipolar II patients.

	U	*Z*	*p*	Power
CPT				
Corr trials	185.5	−2.9624	**0.003**	0.36
Targ acc rate	189	−2.90177	**0.004**	0.35
Foil acc rate	209	−2.55529	**0.011**	0.61
Commission errors	203.5	2.65057	**0.008**	0.71
Omission errors	191.5	2.85846	**0.004**	0.34
Corr RT mean	221	2.3474	**0.019**	0.54
Error RT mean	283	1.27331	0.203	0.37
Sensitivity	308	0.84021	0.401	0.08
SRT				
Anticipations	234	2.604231	**0.009**	0.52
Delayed responses	393	−0.08707	0.930	0.05
Mean RT	302	1.52771	0.127	0.39
Median RT	310.5	1.393145	0.164	0.31

Mann–Whitney U-test. Bold values represent statistical significance.

TABLE 4 | Significant differences in the Temperament and Character Inventory (TCI) and the Iowa Gambling Test (IGT) between women and men.

	U	*Z*	*p*	Power
TCI harm avoidance HA1	198	2.05537	0.040	0.736
TCI reward dependence RD1	135.5	3.273	0.001	0.999
TCI cooperativeness C2	188.5	2.24045	0.025	0.91
blok3_sum IOWA	215	2.90502	0.004	0.59
blok4_sum IOWA	226.5	2.72296	0.006	0.51
blok5_sum IOWA	204	3.07917	0.002	0.75
nB5 IOWA	251	−2.3351	0.020	0.97
nD5 IOWA	251	2.3351	0.020	1.0
Total sum of IOWA	185	3.37996	0.001	0.79

Mann–Whitney U-test.

Correlations of Parameters Obtained in Subjective and Objective Impulsivity Measure Methods

We used Spearman's rank-order correlations method to search if parameters of TCI, BIS-11, and neuropsychological tests are correlated and if the correlation is positive or negative. The comparison showed a large number of correlations but was in majority $R < 0.6$. The most significant correlations with $R > 0.4$ are depicted in **Supplementary Table 1**. With a given sample size, power >0.9 was achieved with $R > 0.45$. The strongest correlations were revealed between Ns3 subdimension and motor BIS-11 factor ($R = 0.609$), between total Ns dimension score and motor BIS-11 factor ($R = 0.640$), and between Ha1 and BIS-11 cognitive instability score ($R = 0.606$). The correlations between self-report tool scores and objective parameters were weak. The highest observed correlations were presented between Ns4 disorderliness and median RT (from SRT) with $R = -0.553$.

DISCUSSION

In this study, we present an analysis of subjective and objective methods in impulsivity assessment, comparing its results with the individual history of suicide attempts among patients with bipolar disorder. This study design was inspired by the clinical need for a short, easy to apply and objective tool to assess suicide risk. We took into account that suicide has a strong biological root (10, 42, 43) and personality traits may serve as intermediate phenotypes (44).

The main aim of this study was to compare impulsivity parameters of suicide attempters and non-attempters in the bipolar population and seek for variables potentially indicating high-risk patients. We found that patients with BPI with suicidal history tend to present with higher empathy (C2) and in a trend toward higher attentional impulsivity in subjective assessment. In objective assessment with the use of the PEBL neuropsychological tasks, we found a higher rate of correct trials in CPT and correct response mean time for suicide non-attempters and a higher number of risky choices in the fifth block of IGT (nA5).

Available data strongly emphasizes that impulsivity impacts the course of bipolar disorder (45–47); however, regarding the use of BIS-11, results are inconsistent. Swann et al. (47) found the total score of BIS-11 to be significantly higher in bipolar suicide attempters, but more recent data did not confirm these results (48, 49). Our findings suggest that several components of impulsivity (namely attentional factor of BIS-11) may be involved in higher suicidal risk. Other researchers observed that bipolar patients present with an impulsive behavior rather due to impaired emotional regulation (emotion-triggered impulsivity) (50) than as the effect of altered executive functions. Watkins and Meyer (49) pointed that further analysis of the relationship between impulse control and suicidality should include other variables potentially influencing suicidality, such as personality traits, or substance use. There are two main approaches in the research of the role of impulsivity in suicide risk. A prospective observation of a cohort of patients [2-year follow-up study by Oquendo et al. (46)] confirmed the link between higher impulsivity and the incidence of suicidal acts. Another approach is broadening the tools in impulsivity assessment (behavioral tasks) and comparing it with personality traits as presented in this study.

Previous studies indicated that the IGT score significantly correlates with the history of suicide attempts (3). Using IGT, many studies have shown that suicide attempters present with a tendency to riskier choices, especially when the attempt was carried out using a violent mean [see a meta-analysis (51)].

In the current investigated group, we obtained results of IGT that were not fully in line with those mentioned above. Suicide non-attempters with BPI diagnosis significantly more often choose disadvantageous cards (A deck) in the late phase of the test than attempters. This could be interpreted as a stronger tendency in attempters to avoid frequent losses regardless of the total gain. Suicide attempters may also be less responsive to short-time gains offered in the deck A. Our results may be biased due to the low sample size. Cognitive load and a high number of information processing simultaneously (dividing attention) may impact the awareness of gains and losses and also the preference of deck (52).

In CPT, a higher commission error score was found in patients with bipolar disorder compared to healthy controls, with medium to large effect sizes (53). CPT commission errors were associated with the risk of suicide attempt in mood disorders. The authors "suggested that CPT performance is more closely associated with mood disorders than suicidal behavior" (54). The study by Keilp et al. (55) revealed no significant difference between suicide attempters and non-attempters in discrimination index d' [based on total commission and omission errors (56)]. In this study, we obtained significant differences in CPT (Corr RT mean) depending on the suicide history, contrasting with the results of Keilp et al. (55).

Personality traits were identified as a marker of suicidal risk (9, 57). Higher harm avoidance and mood disorder diagnosis were strong predictors of suicide attempt (58). In the term of personality traits, we obtained higher cooperativeness among suicide attempters, what needs to be thoroughly analyzed. Moreover, we observed higher scores of cooperativeness in suicide attempters than in non-attempters. Conversely, Jylhä et al. (59) indicated that low cooperativeness, low self-directedness, low reward-dependence, and high self-transcendence were associated with suicide. Other studies indicated also a higher harm avoidance and a lower persistence, with significantly lower cooperativeness in character inventory part (60). The study by Pawlak et al. (61) confirmed novelty seeking and harm avoidance to be associated with the suicide risk among bipolar patients, whereas cooperativeness appeared to play a protective role.

Currently, we obtained numerous correlations among BIS-11 and TCI scores of the self-description scales, but only a few of them were strong $R > 0.6$. A high correlation rate ($R > 0.6$) was discovered for motor BIS-11 and extravagance (Ns3) and for total novelty seeking and motor BIS-11. Similar correlations were found in literature in which research groups diagnosed substance use disorders, pathological gambling, and sexual addiction (62–64). The BIS-11 total score was significantly correlated with all TCI domains, excepting persistence, among patients with cocaine addiction (62). The authors have rarely immediately compared BIS-11 and TCI scores. The BIS-11 non-planning impulsivity score negatively correlated with the impaired IGT in alcohol-dependent subjects, but no strong correlations with TCI were reported (63). Co-occurrence of both several personality traits and impulsivity may promote risky behaviors in patients with bipolar disorder. The data indicate that several tools measure non-fully overlapping parameters.

In the study, we attempted to distinguish between patients with BPI and BPII using TCI scores.

We found no differences between patients with BPI and BPII in subjective impulsivity assessment using BIS-11 and TCI. Recent study by Izci et al. (65) showed significant differences between BPI and BPII in BIS-11, namely in attention scores (higher in BPII) and motor and non-planning impulsivity scores (higher in BPI).

An explicit distinction was noticed in the objective, behavioral measurement: CPT and SRT. Patients with BPI occurred to present more deficits in maintaining sustained attention and

higher attentional impulsivity than BPII patients. Analysis of SRT outcomes evidenced that patients with BPI differed with a higher rate of precocious reactions, whereas both CPT and SRT performance was more disturbed in the BPI group.

There is a lack of large-scale data assessing executive function differences between patients with BPI and BPII. The current approach underlines clinical (66) and genetic (67) distinction between both diagnoses, BPI and BPII that may also vary in decision-making and the impulsivity rate (68). These distinctions may impact suicidality. Our results are partially consistent with the study of Kung et al. (68) and obtained with the use of Conner's CPT-II. Here, we present the analysis performed with a similar number of patients, but a different set of variables revealed to be affected. The differences were elicited in omission errors, foil accuracy rate, and inhibition of the response on presented stimulus (correctly responded trials and target accuracy rate).

CONCLUSION

We conclude that differences between BPI and BPII in TCI, and—in terms of impulsivity—in BIS-11, are not strong enough to distinguish between diagnoses. Objective measurements showed that clinically more severe type I disorder presents with worse performance in neuropsychological tasks. According to Akiskal's theory of bipolar spectrum (69), subtypes vary in terms of clinical traits and biological background and also in suicidality with a higher prevalence for BPII disorder (70).

Differences in neuropsychological features may be biased owing to the result of sex differences. Women in our studied population tended to have a safer decision-making style and higher anticipatory worry (Ha1), sentimentality (Rd1), and empathy (C2) (data not shown). Subdivision of attempter group regarding the sex was applied, and the comparison between male and female attempters and non-attempters revealed significant differences. Suicide attempters vary from non-attempters in nA5 IGT results obtained in the entire attempters group. However, the range of results in the female attempter subgroup clearly overlaps with those obtained by female non-attempters. This example illustrates that translating statistically significant difference into clinical meaning remains challenging. We decided not to discuss all these results because of the highly limited subgroup size (female attempters $n = 15$, male attempters $n = 2$), which limits its reliability. The results should be interpreted with caution. In consequence, we did not find that suicide attempters present with higher impulsivity than non-attempters in BIS-11, possibly due to male underrepresentation in the attempters group. Available data suggest higher gambling behaviors among men (71). Undertaking risky activities, like substance abuse, may predispose to higher self-directed violence and concomitantly increase the risk of suicide in men (72).

This research confirmed that impulsivity is not the only factor increasing the risk of suicide in bipolar patients; however, it may play a significant role as the cofactor among numerous traits that constitute the risk. Moreover, subjective methods, based on self-reporting used in impulsivity assessment, like BIS-11, may not provide the clear distinction between attempters and non-attempters.

Searching for adequate tools to indicate the patients at risk for suicide remains an important field of study. The role of neuropsychological traits requires further investigation. CPT and IGT provide promise, but further investigations are needed. Moreover, a prospective study would give better insight into cause-and-effect relationships. An additional important step would be the research on biological correlates of neuropsychological variables. Our study is not free from limitations including (i) the number of study participants, (ii) lack of analysis between age and personality traits, (iii) potential influence of long-lasting experience of psychiatric disease and life-threatening situations caused by suicidal attempts on personality features, and (iv) the study shows cross-sectional, not longitudinal observation.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Poznan University of Medical Sciences, Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JP, PZ, and JT-H: conceptualization. MS and JP: methodology. PZ, KW-P, BS, and FW: manuscript preparation. MR and JP: investigation. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.706933/full#supplementary-material

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Neurocognition Function of Patients With Bipolar Depression, Unipolar Depression, and Depression With Bipolarity

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Much evidence shows that some *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5)-defined unipolar depression (UD) with bipolarity manifests bipolar diathesis. Little is known about the cognitive profiles of patients with depression with bipolarity (DWB). The study aimed to investigate the differences in cognitive profiles among patients with bipolar depression (BD), major depressive disorder (namely, UD), and DWB. Drug-naïve patients with BD, UD, and DWB and healthy controls (HC) were recruited (30 cases in each group). Cognitive function was evaluated by THINC-it (THINC-intelligent tool), Wisconsin Card Sorting Test (WCST), and continuous performance test (CPT). For THINC-it, no significant differences of the Z-scores in both objective and subjective factors were found between the DWB group and BD group, but the Z-scores in the BD group were significantly lower than those in the UD group. For WCST, significant differences were found between the BD group and DWB group in the number of responses, categories completed, trails to completed first category, perseverative responses, and perseverative errors. All the indices of WCST in the DWB group were significantly worse than those in the UD group except for trails to completed first category and total number of response correct. For CPT, only scores of leakage responses and false responses in the four-digit number in the BD group and DWB group were significantly higher than those in the UD group; no significant difference was found between the BD group and DWB group. The results indicated that patients with DWB might perform differently from those with UD but similarly to those with BD with cognition impairment.

Keywords: unipolar depression, bipolar depression, bipolarity, THINC-it, Wisconsin Card Sorting Test, continuous performance test

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INTRODUCTION

Bipolar disorder is a severe mental illness with high morbidity, high recurrence rate, and high disability, which brings the fearful burden of disease to patients, their families, and society (1). The WHO World Mental Health Survey Initiative about bipolar spectrum disorder (BSP) showed that the aggregate lifetime prevalence of BSP was 2.4% (0.6% for bipolar I disorder, 0.4% for bipolar II disorder, and 1.4% for subthreshold bipolar disorder) (2).

Compared with the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), DSM-5 expanded the connotation of bipolar disorder and divided mood disorders into bipolar disorder and depressive disorder in consideration of the differences of symptoms, genetic features, and clinical characteristics between the two disorders, which improved the diagnostic accuracy (3). Although, many differences between the two disorders have been detected like age of onset, the diagnostic rate of bipolar disorder is still lower than expected, especially for bipolar disorder type II. A previous study showed that 69% BD patients were misdiagnosed within 1 year of the onset of symptoms, with the most frequent misdiagnosis being unipolar disorder (UD) (4). Okasha et al. (5) used the Hypomania Checklist-32 to estimate the frequency of bipolar disorder among patients with a major depressive episode (MDE), and the result showed that 62% of patients diagnosed with unipolar depression were positive on the bipolar screening.

Moreover, growing evidence suggests that the DSM criteria for bipolar II disorder are so strict that some individuals who express varying manifestations of bipolar syndrome to a lesser extent are excluded (6–8). However, identifying these subthreshold individuals is of clinical importance because they are more likely to commit suicide (9), suffer more recurrent depressive episodes (10), and convert into bipolar disorders than individuals with UD (11).

Hence, the concept of bipolarity is of great importance and relevance to clinicians to promote judicious diagnosis and the use of antidepressants. Akiskal et al. (12–15) previously proposed a construct of soft bipolar spectrum (SBP) beyond bipolar I and bipolar II disorder, including bipolar II1/2 (depression with the cyclothymic temperament), bipolar III (depression with hypo/mania associated with antidepressants), and bipolar IV (depression with the hyperthymic temperament), which improved the validity of current diagnosis and was validated in the French National epidemiology of depression study. Furthermore, Ghaemi et al. (16) redefined the BSP according to some indicators of bipolarity. Therefore, although, we cannot give a bipolar disorder diagnosis to the patients with the above symptoms based on DSM-5, clinicians should also keep these "bipolarity pointers" in mind and prescribe antidepressants more charily.

It is noteworthy that cognitive impairment is a core feature of BD (17) and UD (18). Previous studies indicated that cognitive function decreased significantly in BD and UD patients during acute episodes and might persist into euthymic periods (19–21). Recently, a study conducted by Lin et al. about the differences in neurocognitive function among bipolar I disorder, bipolar II disorder, and SBP disorder showed that patients with SBP differ from patients with strict UD. Moreover, the study also showed that cognitive deficits of BSP proposed by Ghaemi were similar to the SBP (22). However, little is known about cognitive deficits in individuals with depression with bipolarity (DWB) and the extent to which they perform differently from those with UD and BD. Therefore, we hypothesized that individuals with DWB might perform differently from those with UD but similarly to those with BD. The goal of the present study was to explore neurocognitive characteristics of DWB patients.

MATERIALS AND METHODS

Subjects

Patients with MDE were recruited in Shandong Mental Health Center, from May 2019 to January 2020. Inclusion criteria and exclusion criteria were as follows.

Inclusion criteria for patients: (1) DSM-5-diagnosed MDE; (2) not treated with psychotropic or any other somatic therapies and psychotherapy within 2 months; (3) aged 18–45 years, Han Chinese; (4) education level of junior high school or above; (5) scores of Hamilton Rating Scale for Depression-17 (HAMD-17) $\geq$17, scores of Young Mania Rating Scale (YMRS) $<$6; and (6) understanding research content and providing written informed consent.

Inclusion criteria for healthy controls (HC): (1) without any mental disorders and family history of mental disorders; (2) aged 18–45 years, Han Chinese; (3) education level of junior high school or above; (4) HAMD-17 $<$7 and YMRS $<$6; and (5) understanding research content and providing written informed consent.

Exclusion criteria applied to all participants: (1) with other mental disorders; (2) history of organic brain diseases or brain trauma; (3) severe physical disease that might interfere with the study evaluations; (4) color blindness or color weakness; (5) pregnancy or lactation; and (6) alcohol or other substance usages.

After obtaining written consent, two senior psychiatrists (who had been in practice for more than 10 years) conducted clinical interviews independently applying the Structured Clinical Interview for DSM-IV-TR Axis I Disorders Patient Edition (Chinese version) to confirm the diagnoses. The inter-rater reliability between the two interviewers was high (kappa value $>$ 0.9).

Patients diagnosed with bipolar I or II disorder based on DSM-5 were in the BD group. Patients diagnosed with major depressive disorder (MDD) based on DSM-5 received another interview by a senior postgraduate to detect bipolarity. Those who met the criteria of bipolarity (as follows) were categorized into the DWB group, and others were in the UD group.

Criteria of bipolarity (16): (i) at least one MDE; (ii) no spontaneous hypomanic or manic episode; (iii) a family history of bipolar disorder in the first-degree relative, (iv) plus at least two items from criterion; (iv) if no family history of bipolar disorder is present, six of the following nine criteria are needed: (1) hyperthymic personality (at baseline, no depressed state); (2) recurrent MDEs ($>$3); (3) brief MDEs (on average, $<$3 months); (4) atypical depressive symptoms (DSM-5); (5) psychotic MDEs; (6) early age of onset of MDE ($<$age 25); (7) postpartum depression; (8) antidepressant "wear-off" (acute but not prophylactic response); and (9) lack of response to $\geq$3 antidepressant treatment trials. The present study adopted Ghaemi's criterion of bipolarity except for a mild modification in criterion (iii). Because antidepressant-induced mania or hypomania has been sufficient to establish a bipolar diagnosis according to DSM-5, it was deleted from criterion (iii) in Ghaemi's criterion.

The study protocol was approved by the Clinical Research Ethics Committee of Shandong Mental Health

Center and is compliant with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed written consent was obtained from all participants or their legal guardians after a complete and extensive description.

Evaluation Instruments and Assessment

The severity of symptoms was assessed with HAMD-17, Hamilton Rating Scale for Anxiety (HAMA), YMRS, and Clinical Global Impression Scale-Severity (CGI-S). The Mood Disorder Questionnaire (MDQ) was completed by participants.

Neurocognitive function was assessed with THINC-intelligent tool (THINC-it), Wisconsin Card Sorting Test (WCST), and continuous performance test (CPT). THINC-it is a recently validated, computerized cognitive assessment tool (http://thinc.progress.im/en) containing variants of commonly used and well-established measures of cognition. It can assess the objective [digit symbol substitution test (DSST); choice reaction time task (CRT); trail-making test B, (TMT-B); and N-back memory task (N-Back)] and subjective cognitive function (Perceived Deficits Questionnaire 5) simultaneously and can be self-administered by the patient (23). Standardized Z-scores were calculated to compare performance on both objective and subjective cognitive assessments on the THINC-it (24). WCST was used to assess executive function; the indices from WCST include total number of response (TR), number of categories completed (CC), total number of response correct (RC), total number of response errors (RE), trails to completed first category (TCFC), perseverative responses (PR), perseverative errors (PE), non-perseverative errors (nPE), and percent conceptual level responses (PCLR). CPT was applied to assess sustained attention; the indices from CPT include leakage responses (LR), false responses (FR), and mean reaction time (MRT) of three levels (two-digit, three-digit, and four-digit numbers).

Statistical Analysis

All data were analyzed with SPSS Statistics, Version 26 (Chicago, IL, USA). The Kolmogorov–Smirnov test was used to test the normal distribution of the measurement data. One-way analysis of variance (ANOVA) was used to compare the differences among groups for normal distribution data, and the Kruskal–Wallis test was performed for non-normal distribution data. Chi-square test or Fisher's exact test was conducted to analyze categorical variables. Group differences in THINC-it, WCST, and CPT indices were tested by analysis of covariance, with age, sex, and education years as covariates. The Bonferroni test as the *post-hoc* multiple comparison was used to identify the differences among four groups. In particular, the *post-hoc* comparison among three patient groups were adjusted by age, sex, education years, age of onset, number of episodes, course of disorder, duration of current depressive episode, and HAMA and HAMD scores. A two-tailed p-value of <0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

Thirty participants in each group (BD, UD, DWB, and HC) were enrolled in this study. There was no significant difference in sex, age, education years, and body mass index (BMI) among the four groups. The differences in age of onset among three patient groups were significant; however, pairwise comparison showed no significant difference after the Bonferroni adjustment. There was no significant difference in the number of episodes between the UD group and DWB group, while the number of episodes in the BD group was significantly higher than that in the UD group and DWB group. Course of disorder in the BD group was significantly higher than that in the UD group, while significant differences in the course of disease were found neither between the DWB group and UD group nor between the BD group and DWB group. No significant difference was found in the duration of the current depressive episode among three patient groups. There was no significant difference in MDQ scores between the BD and DWB groups, while the MDQ in the BD group and DWB group was significantly higher than that of the UD group. There was no significant difference in family history, course of disorder, whether with psychotic symptoms, CGI-S, scores of HAMD-17, and HAMA among the three patient groups (**Table 1**).

THINC-Intelligent Tool

Objective Cognition

The differences of Z-scores between DWB and BD, UD and DWB, and UD and HC were not significant, while Z-scores in the BD group ($p = 0.027$) were significantly lower than those in the UD group, and Z-scores in the BD group ($p < 0.001$) and DWB group ($p < 0.001$) were lower than those in the HC. As to each item of objective component, the Z-scores of all items in the three patient groups were significantly lower than those in the HC group except for the CRT. There was no significant difference in Z-score of N-Back among the three patient groups. The Z-scores of DSST and TMT-B in the BD group were significantly lower than those in the UD group and DWB group (**Table 2**).

Subjective Cognition

The difference of Z-score between the DWB group and BD group, and the DWB group and UD group was not significant, while Z-scores in the BD group ($p = 0.008$) were significantly lower than those in the UD group; and Z-scores in the three patient groups were significantly lower than those in the HC. The Z-scores in the DWB group were significantly lower than those in the UD ($p = 0.029$) after being adjusted by age, sex, education years, age of onset, number of episodes, course of disorder, duration of current depressive episode, and HAMA and HAMD-17 scores (**Table 2**).

Wisconsin Card Sorting Test

There was no significant difference in TR, PR, and PE between the BD and DWB groups. TR (BD, $p < 0.001$; DWB, $p < 0.001$), PR (BD, $p < 0.001$; DWB, $p < 0.001$), and PE (BD, $p < 0.001$; DWB, $p < 0.001$) in the BD group and DWB group were significantly higher than those in the UD group. Compared with the HC group, three patient groups had higher TR, PR, and PE.

TABLE 1 | Demographic and clinical characteristics of participants.

	BD ($n = 30$) Median (IQR 25–75)/mean ± SD	UD ($n = 30$) Median (IQR 25–75)/mean ± SD	DWB ($n = 30$) Median (IQR 25–75)/mean ± SD	HC ($n = 30$) Median (IQR 25–75)/mean ± SD	Z/χ^2	p
Sex (male/female)	16/14	13/17	14/16	15/15	0.667	0.881
Age (years)	28.5 (17, 33)	21 (19, 40)	21 (17, 31)	24.5 (19, 29.5)	2.826	0.419
Education years (years)	13.5 (11, 16)	12 (9, 15)	13 (11, 15.25)	13 (12, 15.25)	2.448	0.485
BMI	23.775 (22.4, 25.47)	21.975 (19, 26.93)	23.87 (20.1575, 25.08)	20.705 (23.145, 24.8275)	1.177	0.785
Family history (positive/negative)	4/26	4/26	5/25	NA	0.180	0.914
Age of onset (year)	17.5 (15.75, 27)	20 (18, 34)	17 (16, 22.75)	NA	7.924	0.019
Number of episodes	2.5 (2, 3)	1 (1, 2)	1 (1, 2)	NA	30.212	<0.001
Course of disorder (month)	21 (12, 36)	11 (4, 16)	14 (1, 51)	NA	11.572	0.003
Duration of current episode (month)	2.5 (1, 6)	6 (1.75, 13)	5.5 (1, 21)	NA	3.255	0.196
Whether with psychotic symptom (yes/no)	5/25	2/28	6/24	NA	2.338	0.311
CGI-S	5 (4, 6)	5 (4.75, 6)	5 (4, 6)	NA	0.396	0.820
HAMD-17	23.83 ± 2.96	24.13 ± 4.55	24.20 ± 6.01	NA	0.052	0.949
HAMA	27.50 ± 3.36	24.33 ± 5.01	25.20 ± 8.05	NA	2.380	0.099
MDQ	6.17 ± 2.52	2.73 ± 1.62	5.50 ± 2.75	NA	48.149	<0.001

BD, bipolar depression; UD, unipolar depression; DWB, depression with bipolarity; HC, healthy control; BMI, body mass index; GCI-S, Clinical Global Impression Scale-Severity; HAMD-17, Hamilton Rating Scale for Depression-17; HAMA, Hamilton Rating Scale for Anxiety; MDQ, Mood Disorder Questionnaire; SD, standard deviation; IQR, interquartile range.

TABLE 2 | Comparison of THINC-it among patients with bipolar depression, unipolar depression, depression with bipolarity, and healthy controls (mean ± SD).

	BD ($n = 30$)	UD ($n = 30$)	DWB ($n = 30$)	HC ($n = 30$)	F^1	p^1	*post-hoc*[1]	F^2	p^2	*post-hoc*[2]
Objective part	−2.85 ± 2.98	−1.40 ± 1.71	−2.51 ± 2.04	0.00 ± 1.00	11.570	<0.001	BD<UD; BD, DWB<HC	5.290	0.007	BD<UD
DSST	−3.97 ± 1.62	−2.36 ± 2.31	−2.80 ± 0.71	0.00 ± 1.00	35.371	<0.001	BD<UD, DWB<HC	6.095	0.003	BD<DWB, UD
CRT	−0.37 ± 2.00	−0.72 ± 2.18	−0.41 ± 1.57	0.00 ± 1.00	0.905	0.441		0.630	0.535	
TMT	−2.71 ± 1.90	−1.64 ± 1.98	−1.36 ± 0.86	0.00 ± 1.00	15.765	<0.001	BD<DWB; BD, UD, DWB<HC	8.594	<0.001	BD<DWB
N-Back	−2.21 ± 1.74	−1.46 ± 1.85	−1.40 ± 1.84	0.00 ± 1.00	9.252	<0.001	BD, UD, DWB<HC	1.084	0.343	
Subjective part	−4.96 ± 2.05	−3.09 ± 2.32	−4.46 ± 2.64	0.00 ± 1.00	33.208	<0.001	BD<UD; BD, UD, DWB<HC	5.611	0.005	BD, DWB<UD

THINC-it, THINC-intelligent tool; DSST, digit symbol substitution test; CRT, choice reaction time task; TMT, Trail making test B; N-Back, N-back memory task; BD, bipolar depression; UD, unipolar depression; DWB, depression with bipolarity; HC, healthy control.

[1] *Age, sex, education years as covariates among four groups.*

[2] *Age, sex, education years, age of onset, number of episodes, course of disorder, duration of current depressive episode, and HAMA and HAMD-17 scores as covariates among three patient groups.*

There was no significant difference in CC between the BD and DWB groups, neither between UD and HC groups. CC in the BD group ($p < 0.001$) and DWB group ($p = 0.006$) was lower than that in the UD group (BD, $p < 0.001$; DWB, $p = 0.006$) and HC group (BD, $p < 0.001$; DWB, $p < 0.001$). CC of the BD group was lower than that in the DWB group ($p = 0.010$) after being adjusted by age, sex, education years, age of onset, number of episodes, course of disorder, duration of current depressive episode, and HAMA and HAMD-17 scores.

RE and nPE in all three patient groups were significantly higher than those in the HC group. RE and nPE in the BD group were significantly higher than those in the DWB group (RE, $p = 0.012$; nPE, $p < 0.001$) and UD group (RE, $p < 0.001$; nPE, $p < 0.001$). RE and nPE in the DWB group were significantly higher than those in the UD group (RE, $p < 0.001$; nPE, $p = 0.001$).

RC in the BD group was significantly lower than that in the DWB group ($p = 0.030$), UD group ($p < 0.001$), and HC group ($p < 0.001$). Differences in RC between the UD group and DWB groups, as well as the UD group and HC group, were not significant. However, in comparison with the HC group, the DWB group had a lower RC ($p < 0.001$).

There was no significant difference in TCFC among the three patient groups. No significant difference in TCFC was detected between the UD group and HC group, while TCFC in the BD group and DWB group was significantly higher than that in the HC group (BD, $p = 0.007$; DWB, $p = 0.006$). In addition,

TABLE 3 | Comparison of WCST among patients with bipolar depression, unipolar depression, depression with bipolarity, and healthy controls (mean ± SD).

	BD ($n = 30$)	UD ($n = 30$)	DWB ($n = 30$)	HC ($n = 30$)	F^1	p^1	post-hoc[1]	F^2	p^2	post-hoc[2]
TR	126.83 ± 2.15	108.87 ± 17.73	122.00 ± 8.03	91.90 ± 11.93	55.793	<0.001	BD, DWB>UD>HC	22.716	<0.001	BD, DWB>UD
CC	2.43 ± 2.05	4.53 ± 1.78	3.30 ± 1.92	5.60 ± 0.93	19.487	<0.001	BD, DWB<UD, HC	16.307	<0.001	BD<DWB<UD
RC	56.37 ± 11.81	69.30 ± 9.09	64.07 ± 10.70	76.20 ± 7.41	21.502	<0.001	BD<DWB, UD, HC; DWB<HC	14.805	<0.001	BD<DWB, UD
RE	70.43 ± 13.05	39.57 ± 21.19	56.87 ± 17.65	15.37 ± 7.99	68.122	<0.001	BD>DWB>UD>HC	30.363	<0.001	BD>DWB>UD
TCFC	19.77 ± 3.75	17.30 ± 12.44	19.60 ± 6.86	13.17 ± 3.92	4.906	0.002	BD, DWB>HC	3.373	0.039	BD>UD
PR	30.03 ± 4.66	16.60 ± 11.32	23.23 ± 14.98	4.13 ± 4.10	37.378	<0.001	BD, DWB>UD>HC	43.069	<0.001	BD>DWB>UD
PE	25.53 ± 5.35	15.07 ± 13.11	24.00 ± 15.76	5.13 ± 3.47	23.065	<0.001	BD, DWB>UD>HC	16.819	<0.001	BD, DWB>UD
nPE	44.90 ± 10.33	24.17 ± 9.60	33.03 ± 10.16	10.30 ± 6.01	75.545	<0.001	BD>DWB>UD>HC	10.903	<0.001	BD>DWB>UD
PCLR	20.58 ± 8.18	56.43 ± 18.61	45.98 ± 20.59	72.92 ± 8.76	63.227	<0.001	BD<DWB<UD<HC	29.743	<0.001	BD<DWB<UD

BD, bipolar depression; UD, unipolar depression; DWB, depression with bipolarity; HC, healthy control; WCST, Wisconsin Card Sorting Test; TR, total number of response; CC, number of categories completed; RC, total number of response correct; RE, total number of response errors; TCFC, trails to completed first category; PR, perseverative responses; PE, perseverative errors; nPE, non-perseverative errors, PCLR, percent conceptual level responses.

[1] *Age, sex, and education years as covariates among four groups.*

[2] *Age, sex, education years, age of onset, number of episodes, course of disorder, duration of current depressive episode, and HAMA and HAMD-17 scores as covariates among three patient groups.*

TCFC in the BD group was significantly higher than that in the UD group ($p = 0.036$) after being adjusted by age, sex, education years, age of onset, number of episodes, course of disorder, duration of current depressive episode, and HAMA and HAMD-17 scores.

The score of PCLR in HC group was significantly higher than that in the three patient groups. PCLR in the BD group was lower than that in the DWB group and UD group ($p < 0.001$), and the DWB group scored lower than the UD group ($p < 0.005$) (**Table 3**).

Continuous Performance Test

Two- and Three-Digit Numbers

There were no significant differences in LR, FR, and MRT among three patient groups, while LR and FR in the three patient groups were higher than those in the HC group. MRT in the three patient groups was longer than that in the HC group, except for the differences of LR in two-digit numbers between BD and HC, which were not significant.

Four-Digit Numbers

There were no significant differences in LR, FR, and MRT between the BD and DWB groups; so was FR between the UD and DWB groups. LR in the BD group ($p = 0.013$) and DWB group ($p = 0.027$) was significantly more than that in the UD group. Moreover, the LR and FR of three patient groups were higher than those in the HC group. The difference of MRT among three patient groups was not significant. LR, FR, and MRT in the three patient groups were significantly higher than those in the HC group (BD, $p < 0.001$; UD, $p = 0.001$; DWB, $p < 0.001$) (**Table 4**).

DISCUSSION

Our study applied three cognitive test tools to evaluate cognition function among BD, UD, DWB, and HC groups. For THINC-it, the differences of the Z-scores in both objective and subjective parts between DWB and BD were not significant; Z-scores of the BD group were lower than those of the UD group. For WCST, differences in the TR, CC, TCFC, PR, and PE between the BD and DWB groups were not significant. All the indices of WCST in the DWB group were worse than those of the UD group except for TCFC and RC. For CPT, only leakage responses and false responses in the four-digit number of the BD and DWB groups more than the UD group, and the difference between BD and DWB were not significant.

THINC-it is the first tool that provides both objective and subjective cognition tests, and its test domain includes attention, executive function, and memory. To the best of our knowledge, this was the first study to compare cognitive deficits in BD, UD, and DWB by THINC-it. As for each item of objective component, CRT is applied to assess attention and executive function; N-Back evaluates working memory, executive function, and attention/concentration; DSST is used to identify executive functions, processing speed, and attention/concentration; TMT-B tests executive function. The Z-scores of all objective items of three patient groups were lower than those of HC, except for the CRT, and the differences of CRT among the four groups and N-Back among three patient groups were not significant. The Z-scores of DSST and TMT-B in the BD group were lower than those in UD and DWB groups. When integrating four objective items, the differences of Z-scores between DWB and BD, UD and DWB, and UD and HC were not significant, while Z-scores of the BD group were lower than those of the UD group, and Z-scores of BD and DWB were lower than those of HC. As for the

TABLE 4 | Comparison of CPT among patients with bipolar depression, unipolar depression, depression with bipolarity, and healthy controls (mean ± SD).

	BD ($n = 30$)	UD ($n = 30$)	DWB ($n = 30$)	HC ($n = 30$)	F	p	post-hoc[1]	F^2	p^2	post-hoc[2]
2-digit numbers										
LR	3.33 ± 3.93	4.10 ± 3.75	4.80 ± 4.39	1.40 ± 1.52	5.061	0.005	DWB>HC	0.429	0.653	
FR	3.00 ± 2.35	3.00 ± 3.07	2.33 ± 1.67	0.67 ± 1.03	7.740	<0.001	BD, DWB, UD>HC	0.424	0.656	
MRT (ms)	507.67 ± 53.34	534.37 ± 66.39	518.23 ± 62.98	432.52 ± 38.92	19.207	<0.001	BD, DWB, UD>HC	1.300	0.278	
3-digit numbers										
LR	5.60 ± 3.62	6.27 ± 4.11	6.33 ± 4.37	2.40 ± 1.78	7.869	<0.001	BD, DWB, UD>HC	0.977	0.381	
FR	2.83 ± 0.38	2.50 ± 2.86	2.23 ± 1.76	0.97 ± 1.16	6.256	0.001	BD, DWB, UD>HC	0.177	0.838	
MRT (ms)	533.67 ± 51.58	560.70 ± 64.80	562.99 ± 92.80	482.73 ± 58.12	8.865	<0.001	BD, DWB, UD>HC	2.187	0.119	
4-digit numbers										
LR	11.77 ± 4.24	8.57 ± 3.88	11.53 ± 4.29	3.53 ± 3.38	28.022	<0.001	BD, DWB>UD>HC	14.339	<0.001	BD, DWB>UD
FR	7.00 ± 4.55	4.23 ± 3.47	6.10 ± 2.25	1.03 ± 1.38	21.028	<0.001	BD, DWB>UD>HC	6.430	0.003	BD, DWB>UD
MRT (ms)	617.10 ± 43.12	608.78 ± 75.73	627.29 ± 104.29	528.69 ± 76.33	10.060	<0.001	BD, DWB, UD>HC	2.288	0.108	

BD, bipolar depression; UD, unipolar depression; DWB, depression with bipolarity; HC, healthy control; CPT, continuous performance test; LR, leakage responses; FR, false responses; MRT, mean reaction time.

[1] *Age, sex, and education years as covariates among four groups.*

[2] *Age, sex, education years, age of onset, number of episodes, course of disorder, duration of current depressive episode, and HAMA and HAMD-17 scores as covariates among three patient groups.*

subjective component, the difference of Z-score between DWB and BD, and DWB and UD was not significant, while Z-scores of BD were lower than those of UD, and Z-scores of three patient groups were lower than those of HC. The Z-scores of DWB were lower than those of UD. The finding showed that patients with MDE were all with cognitive impairment; BD and DWB had the more critical cognitive impairment than UD.

For WCST, all the indices of WCST in patient groups were worse than those of the HC group except for TCFC (differences of TCFC between UD and HC were not significant). There were no significant differences in TR, CC, PE, and PR between the BD group and DWB group; other indices of WCST in the BD group were worse than those of the DWB group. All the indices of WCST in the DWB group were worse than those of the UD group except for RC and TCFC. It indicated that executive function deficits in patients with MDE were worse than those of HC, deficits of executive function of patients with DWB were more similar with those of patients with BD, and deficits of executive function of patients with BD and DWB were worse than those of patients with UD. Some previous studies showed that the patients with BD in WCST were worse than those with UD and HC, even in the euthymic stage, which was in accordance with our study (25, 26). However, in the study of Lin et al. (22), the differences of indices of WCST between UD and SBP were not statistically significant, as well as between BD and SBP, which was inconsistent with this study. Another recent study also showed only minor differences in executive function between drug-naïve patients with bipolar depression and unipolar depression (27). There might be two explanations for the discrepancy: first, the criteria in the study of Lin et al. were based on the criteria proposed by Akiskal et al., although, the difference of cognition deficit between patients with SBP and patient with DWB was not significant in their study, and their criteria were based on DSM-IV; the heterogeneity of the sample between the two studies was unavoidable. Second, in the study of Lin et al., they just chose three indices of WCST to make a comparison; the differences might be detected when they use more indices.

CPT is applied to assess sustained attention and vigilance (28). In this study, all the indices of CPT in the three patient groups were worse than those in the HC group; there were no significant differences in LR, FR, and MRT of two-digit numbers and three-digit numbers among three patient groups; when it comes to four-digit numbers, the difference of MRT among three patient groups was not significant, differences of LR and FR between the BD group and DWB group were not significant, and LR and FR of the BD and DWB groups more than those of the UD group. The finding suggested that patients with MDE were attention deficit, the difference of extent of attention-deficit among three patient groups could not be detected when the task was easy, and the difference tended to be significant with the difficulty of the task increasing. Previous studies suggested impaired sustained attention present in both the euthymic stage and depressive stage, and it appeared specific to bipolar disorder (29–31).

In our study, some cognition indicators of BD were more severe than those of UD, while differences of other indicators were not significant, which were in accordance with the patterns of brain activity alterations. Recently, a voxel-based meta-analysis showed that UD and BD shared increased amplitude of low-frequency fluctuation (ALFF) in the bilateral insula (a cortical structure with extensive connections to many areas of the cortex and limbic system, which is implicated in disparate cognitive, affective, and regulatory functions) and right medial prefrontal cortex (mPFC; a critical neuronal region in regulating attention, cognitive control, motivation, and emotion), and decreased ALFF in the left cerebellum posterior lobe, suggesting that altered intrinsic activity in these regions is common to both disorders. However, they also find that increasing ALFF of the right insula was significantly greater in BD than MDD, which suggested that the impairment of cognition function in BD might be more severe than that in UD. Moreover, several

regions, including the limbic system and occipital cortex, differed between conditions, indicating that these disorders may be associated with spatially distinct patterns of brain function (32). A previous triple-network model study (involving the default mode network, central executive network, and salience network, which is associated with cognitive function, such as attention and working memory) also provided evidence about the shared and specific functional and structural alterations in BD and MDD (33).

The conception of bipolarity is not mentioned frequently because it is a series of clinical characteristics that have not been validated; however, some of them are often associated with bipolar disorder. A guideline proposed by Stahl et al. mentioned that MDE patients with the characteristics, which were coincident with bipolarity, were more likely to convert into bipolar disorder and were at risk of adverse reactions to antidepressant treatments (34). At present, little research about the neurocognitive function of patients with DWB was conducted. The study suggested that patients with DWB were similar to patients with BD in neurocognitive function impairment, which reinforced the concern that patients with UD who manifested bipolarity but did not meet the criteria of bipolar disorder based on the DSM system were actually "bipolar enough" and at risk of inappropriate antidepressant therapy.

As for clinical characteristics, times of mood episode and duration of disorder in BD were more than those in the UD group, so did to times of mood episode between the BD and DWB groups, while the differences between UD and DWB were not significant, which indicated that DWB was too hard to distinguish from bipolar disorder and MDD, especially in depression episode. MDQ, a screening tool for bipolar disorder with established sensitivity and specificity (35, 36), meets the need for distinguishing bipolar patients from patients with MDE. In the present study, there was no significant difference in MDQ score between the DWB and BD groups, and the MDQ score of the BD and DWB groups was higher than that of UD, which reinforced that patients with DWB were similar to patients with BD.

Some limitations of this study should be noted. First, this was a cross-sectional study, and the effect of disorder progression and psychotropic on cognition cannot be explored, as well as the differences of cognition among patients with BD, UD, and DWB in remission state. Second, the sample size of our study was relatively small; larger samples are needed to validate our results in the future. Third, the study of Simonsen et al. (37) found that neurocognition between bipolar I and bipolar II disorder was significantly different, but we did not conduct the subtype stratification analysis result from our small sample size.

In summary, patients with MDE were with cognition impairment; patients with DWB might perform differently from those with UD but similarly to those with BD with cognition impairment. Our finding provides evidence that bipolar disorder may have a distinct neurobiological basis compared with strict UD and may help clinicians better understand DWB patients. Given the limitations of the present study, large-sample longitudinal studies for cognition function in DWB patients are required for future validation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Clinical Research Ethics Committee of Shandong Mental Health Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZL and GX designed the study and wrote the paper. ZL and YW analyzed data. All authors participated in the step of enrollment and discussed the results, approved the final version, and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

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Polygenic Heterogeneity Across Obsessive-Compulsive Disorder Subgroups Defined by a Comorbid Diagnosis

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Among patients with obsessive-compulsive disorder (OCD), 65–85% manifest another psychiatric disorder concomitantly or at some other time point during their life. OCD is highly heritable, as are many of its comorbidities. A possible genetic heterogeneity of OCD in relation to its comorbid conditions, however, has not yet been exhaustively explored. We used a framework of different approaches to study the genetic relationship of OCD with three commonly observed comorbidities, namely major depressive disorder (MDD), attention-deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD). First, using publicly available summary statistics from large-scale genome-wide association studies, we compared genetic correlation patterns for OCD, MDD, ADHD, and ASD with 861 somatic and mental health phenotypes. Secondly, we examined how polygenic risk scores (PRS) of eight traits that showed heterogeneous correlation patterns with OCD, MDD, ADHD, and ASD partitioned across comorbid subgroups in OCD using independent unpublished data from the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH). The comorbid subgroups comprised of patients with only OCD ($N = 366$), OCD and MDD ($N = 1{,}052$), OCD and ADHD ($N = 443$), OCD and ASD ($N = 388$), and OCD with more than 1 comorbidity ($N = 429$). We found that PRS of all traits but BMI were significantly associated with OCD across all subgroups (neuroticism: $p = 1.19 \times 10^{-32}$, bipolar disorder: $p = 7.51 \times 10^{-8}$, anorexia nervosa:

$p = 3.52 \times 10^{-20}$, age at first birth: $p = 9.38 \times 10^{-5}$, educational attainment: $p = 1.56 \times 10^{-4}$, OCD: $p = 1.87 \times 10^{-6}$, insomnia: $p = 2.61 \times 10^{-5}$, BMI: $p = 0.15$). For age at first birth, educational attainment, and insomnia PRS estimates significantly differed across comorbid subgroups ($p = 2.29 \times 10^{-4}$, $p = 1.63 \times 10^{-4}$, and $p = 0.045$, respectively). Especially for anorexia nervosa, age at first birth, educational attainment, insomnia, and neuroticism the correlation patterns that emerged from genetic correlation analysis of OCD, MDD, ADHD, and ASD were mirrored in the PRS associations with the respective comorbid OCD groups. Dissecting the polygenic architecture, we found both quantitative and qualitative polygenic heterogeneity across OCD comorbid subgroups.

Keywords: obsessive-compulsive disorder, major depression, attention-deficit/hyperactivity disorder, autism, comorbidity, polygenic risk score, heterogeneity, genetic correlation

1. INTRODUCTION

Obsessive-Compulsive-Disorder (OCD) is a common, long-lasting and disabling neuropsychiatric disorder with an estimated lifetime prevalence of 1–3% (Weissman, 1998; U.S. International institutes of health (NIH), 2016). It is the fourth most common psychiatric disorder and has been ranked by the World Health Organization as being among the most disabling medical conditions world-wide as it can substantially impair the patient's social, occupational and academic functioning (Murray et al., 1996). OCD is considered a complex disorder with its risk likely being influenced by hundreds to thousands of genetic variants scattered across the genome, with small to modest additive effects (Craig, 2008; Taylor, 2013). Genome-wide association studies (GWAS) in OCD have found suggestive evidence for some single nucleotide polymorphisms (SNPs) and genes that are potentially involved in its pathogenesis (International Obsessive Compulsive Disorder Foundation Genetics, 2017). Yet, overall these findings remain rather inconclusive with no single genetic variant reliably replicating across individual studies (Sampaio et al., 2013; Bozorgmehr et al., 2017). These studies did, however, suggest that an increase in sample size will likely aid the identification of genome-wide significant loci, following the example of other psychiatric disorders like major depressive disorder (MDD) (Wray et al., 2018), attention-deficit hyperactivity-disorder (ADHD) (Demontis et al., 2019), or autism spectrum disorder (ASD) (Grove et al., 2019). Another reason for inconclusive findings may be that the majority of current studies of OCD do not account for or put enough emphasis on the heterogeneity of the disorder, though genetic findings may vary as a function of moderator variables (Mataix-Cols et al., 2005; Kulminski et al., 2016; Mattina and Steiner, 2016). One gene that is implicated in one subgroup of OCD patients may not be relevant for another, potentially making it more difficult to find true associations. As 65–85% of OCD patients manifest another psychiatric disorder concomitantly or at some other time point during their lifetime (Tükel et al., 2002; Nestadt et al., 2009; Gillan et al., 2017), often presenting very different symptoms (Ortiz et al., 2016), it raises the question whether comorbid patients form distinct (genetic) subgroups. Nestadt et al. (2009) proposed a sub-classification of OCD based on comorbidity into three subgroups, with each group being associated with distinct clinical characteristics, prevalence rates, age-of-onsets, and sex-distributions. Dissecting OCD into more homogeneous and accurate sub-phenotypes based on comorbidity, may therefore lead to the successful identification of genetic risk variants for OCD (MacRae and Vasan, 2011; Kulminski et al., 2016).

In recent years, a variety of genetic studies have shown that OCD shares some genetic background with the neuropsychiatric disorders it co-occurs with (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; O'Connell et al., 2018). The genetic correlation of OCD and tourette syndrome (TS) has been estimated at 0.41 ($SE = 0.15$) (Davis et al., 2013), with anorexia nervosa (AN) at 0.49 ($SE = 0.13$) (Yilmaz et al., 2020), with MDD at 0.21 ($SE = 0.05$) (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), with ASD at 0.12 ($SE = 0.08$) (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), and ranges between -0.17 ($SE = 0.07$) (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) and 0.67 ($SE = 0.09$) (Hirschtritt et al., 2018; Goodman et al., 2020) for OCD and ADHD. With a quantitative genetic modeling approach Du Rietz et al. (2020) showed that the phenotypic association between ADHD and an externalizing factor, also loading onto OCD, was largely influenced by genetics and it was demonstrated that both ADHD factors (inattentive and hyperactive/impulsive symptoms) were genetically related to OCD (Hirschtritt et al., 2018). PRS derived from ASD genetic data predicted 0.11% of the phenotypic variance in OCD (Guo et al., 2017). More recently, evidence for disorder-specific genetic associations has also been demonstrated. Peyrot and Price (2021) identified two SNPs distinguishing OCD and ADHD, and one SNP distinguishing OCD and ASD, using a newly developed method to quantify the genetic differences between psychiatric disorders by testing for differences in allele frequencies between cases of two disorders. It has also been shown that the majority of genes that have been implicated in OCD, ASD, schizophrenia (SCZ), and bipolar disorder (BP) are disorder-specific (O'Connell et al., 2018) and that the phenotypic differences between ADHD and OCD are reflected in altered DNA methylation at specific sites, pointing toward heterogeneous regulatory changes in both disorders (Goodman et al., 2020). As OCD shows such a high and

specific genetic overlap with its comorbid neurodevelopmental and psychiatric disorders, while at the same time also presenting very unique genetic correlates, we explored whether OCD comorbid subgroups show a heterogeneous genetic architecture depending on the combination of co-occurring disorders.

In this paper we focused on the potential heterogeneity of OCD subgroups defined by comorbidity with MDD, ADHD, and/or ASD, as these disorders form the biggest comorbidity groups in the iPSYCH OCD sample. While MDD is the most commonly co-occurring diagnosis with OCD (∼15–39.5%; Lochner et al., 2014), ADHD occurs in ∼6–34% of OCD cases (Geller et al., 2004; Anholt et al., 2010) and OCD patients have a four-fold increased risk of developing ASD (Meier et al., 2015). Because specific markers associated with OCD have not yet been identified, we applied a variety of genome-wide analyses, neither looking for specific associated SNPs nor meta-analysing the iPSYCH samples with the current PGC OCD GWAS, as the sample-size increase would have only been marginal. Instead, in a first step we used publicly available summary statistics from the PGC to compare the genetic landscape of OCD patients to patients with either MDD, ADHD, or ASD. We dissected similarities and differences in correlation patterns of the four disorders with 861 other phenotypes. In a second step we used an independent and previously unpublished OCD dataset from iPSYCH and compared the polygenic architecture of comorbid samples of patients with an OCD diagnosis and a further diagnosis of either MDD, ADHD, ASD, or any combination thereof. We explored differences in polygenic risk score (PRS) load across the different OCD comorbid groups using a multivariate (multiple outcomes) multivariable (multiple covariates) regression, as introduced by Grove et al. (2019). As training datasets we used eight phenotypes from a variety of domains (psychiatric, personality/psychological, anthropomorphic/metabolic, education, and other) that exhibited a range of differing correlation patterns with OCD, MDD, ADHD, and ASD. As OCD, MDD, ADHD, and ASD showed heterogeneous genetic patterns in the analyses in step one, we hypothesized that (a) the comorbid OCD subgroups in the iPSYCH sample would show a heterogeneous association pattern with the PRSes, depending on the training dataset and the combination of comorbid disorders in the OCD subgroup, and (b) that this heterogeneity would be in line with the correlation patterns between OCD, MDD, ADHD, and ASD and the PRS training phenotypes. We expected that the heterogeneity across OCD co-morbid subgroups in the PRS analysis would vary depending on whether the correlations of MDD, ADHD, and ASD showed the same or opposing directions as OCD with the traits used as a training dataset in the PRS analyses (see **Figure 1** for an overview of performed analyses).

2. METHODS

2.1. Subjects

2.1.1. PGC Samples

Publicly available European ancestry GWAS summary statistics of OCD, MDD, ADHD, and ASD were downloaded from the Psychiatric Genomics Consortium (PGC) website (see here). A description of sample sizes can be found in **Table 1**. Details about the cohorts and data processing have been described in the corresponding primary publications [OCD: International Obsessive Compulsive Disorder Foundation Genetics (2017), MDD: Wray et al. (2018), ADHD: Demontis et al. (2019), ASD: Grove et al. (2019)].

2.1.2. iPSYCH Comorbid OCD Sample

In the scope of the *Danish OCD and Tourette Study* (DOTS) within *The Lundbeck Foundation Initiative for Integrative Psychiatric Research* (iPSYCH), Danish nation-wide population-based case-cohort samples were collected and genotyped. The study was approved by the Regional Scientific Ethics Committee in Denmark and the Danish Data Protection Agency. All analyses of the samples were performed on the secured national GenomeDK high performance-computing cluster in Denmark (https://genome.au.dk). See Pedersen et al. (2018) for a detailed description of the overall cohort, array, genotyping, and quality control. Here we give a brief summary: The iPSYCH sample comprised 2,938 individuals with a diagnosis of OCD. All OCD patients that are included in the iPSYCH sample were either comorbid with one of the primary disorders in iPSYCH or were drawn from the population-based pool of controls. For each iPSYCH sample, DNA was obtained from the Danish Neonatal Screening Biobank (DNSB) at the Statens Serum Institut (SSI). Subsequent genotyping was performed in 23 batches on Illumina's PsychChip v 1.0 array (Illumina, San Diego, CA, USA) at the Broad Institute of MIT and Harvard (Cambridge, MA, USA). Cases were identified amongst all individuals in iPSYCH (cases and controls) as individuals that met ICD10 diagnostic criteria for OCD (F42). Controls were randomly selected (for a 4 to 1 matching with cases) from the same cohort, and excluded individuals with a diagnosis of F42. Genotypes were processed using the *Rapid Imputation and COmputational PIpeLIne for Genome-Wide Association Studies* (ricopili) (Lam et al., 2020) performing stringent quality control of the data. Samples with call rates below 98% and individuals with a mismatch between sex obtained from genotyping and registered sex in the iPSYCH database were excluded. Related individuals were removed (randomly one individual per identified pair), principle component analyses were used to exclude ancestral outliers and the data was imputed using the 1,000 Genomes Project phase 3 reference panel (The 1000 Genomes Project Consortium, 2015). The final dataset included 10,411 controls and 2,678 cases of which 366 were diagnosed with only OCD (*onlyOCD*), 1,052 with OCD and MDD (*OCD+MDD*), 443 with OCD and ADHD (*OCD+ADHD*), 388 with OCD and ASD (*OCD+ASD*), and 429 with multiple comorbid disorders (*MC*) (see **Table 1**). Of the cases in the *MC* subgroup, 127 were diagnosed with OCD, MDD, and ASD; 140 with OCD, MDD, and ADHD; 129 with OCD, ASD, and ADHD; and 33 with OCD, ASD, ADHD, and MDD.

2.2. Statistical Analyses

2.2.1. Gene-Based and Gene-Set Analysis

We performed gene-based- and gene-set association analysis of the PGC samples of OCD, MDD, ADHD, and ASD using

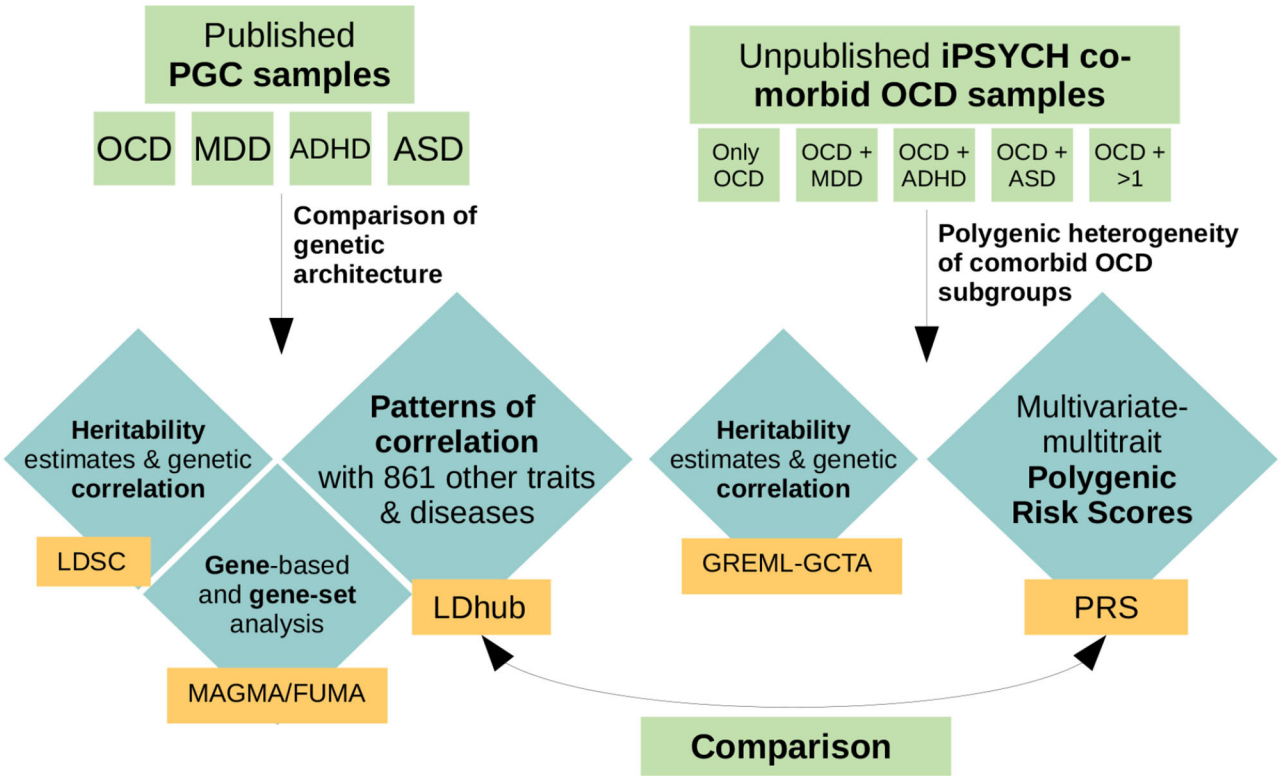

FIGURE 1 | Schematic overview of performed analyses. For the first part of the analyses, we used previously published, publicly available GWAS summary statistics of obsessive-compulsive disorder (OCD), major depressive disorder (MDD), attention-deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD) from the psychiatric genetics consortium (PGC). We used those datasets to compare the polygenic architecture of OCD, MDD, ADHD, and ASD by examining heritability estimates and genetic correlations (LDSC), their overlap in associated genes and gene-sets (MAGMA/FUMA), and compared each disorders genetic correlation pattern with 861 other traits and diseases (LDhub). For the second part of the analyses we used an independent and previously unpublished dataset from iPSYCH, comprising 2,938 individuals with a diagnosis of OCD, of which 366 presented only a diagnosis of OCD, 1,052 a diagnosis of OCD and MDD, 443 a diagnosis of OCD and ADHD, 388 a diagnosis of OCD and ASD, and 429 a diagnosis of OCD and more than one comorbidity. For these sub-groups we assessed heritability and genetic correlation estimates (GREML-GCTA) and examined the patterns of association of each comorbid OCD subgroup with eight different polygenic risk scores (PRS) based on a variety of phenotypes. In a last step we compared the patterns that evolved in the genetic correlation analysis in step one with the patterns of association that resulted from the PRS analyses of the OCD comorbid subgroups in step two.

the web-based tool *Functional Mapping and Annotation of Genome-Wide Association Studies* (FUMA) v1.3.1 (Watanabe et al., 2017) and *Multi-marker Analysis of GenoMic Annotation* (MAGMA) v1.6 (de Leeuw et al., 2015), employing a multiple regression model while accounting for linkage disequilibrium (LD) between the markers. For both analyses, the default MAGMA settings (SNP-wise model for gene analysis and competitive model for gene-set analysis) were applied. First, FUMA defines genomic risk loci on the basis of independent lead SNPs (with $r^2 < 0.1$ between the independent lead SNPs), merging LD blocks that are physically closer than 250 kb or overlapping into a single locus. Only SNPs in LD with a lead SNP and a minimum association p-value of 0.05 were included for further analysis. Each risk locus is represented by the top lead SNP with the minimum p-value in the locus. For MDD, ASD, and ADHD the minimum p-value of included lead SNPs was set to 5×10^{-8}. Because the OCD GWAS had no SNPs exceeding the genome-wide threshold of 5×10^{-8} the threshold was arbitrarily lowered to 5×10^{-6}. The minimum allele frequency (MAF) threshold was set to 0.01. One thousand genomes project phase 3 (The 1000 Genomes Project Consortium, 2015) was used as a reference panel to calculate LD across SNPs and genes and the MHC region was excluded. The gene-based p-values were computed by mapping SNPs to their corresponding gene(s) on the basis of their position in the genome. Positional mapping was based on ANNOVAR annotations and the maximum distance between SNPs and genes was set to 10 kb. To correct for multiple testing, Bonferroni correction and false-discovery rate (FDR) was applied for gene-analysis and gene-set analysis, respectively. For OCD, input SNPs were mapped to 18,709 protein-coding genes, genome-wide significance was defined at a Bonferroni corrected threshold of $p = 2.67 \times 10^{-6}$. FUMA tested curated gene-sets (c2.all) and gene ontology (GO) terms, using 10,894 gene-sets for FUMA $\leq$ version 1.3.0 (ADHD) and 10,655 gene-sets for FUMA $\geq$ version 1.3.1 (OCD, MDD, ASD). Gene-set p-values were computed using the gene-based p-values of all genes for each curated gene-set.

TABLE 1 | PGC and iPSYCH sample sizes, population prevalences and heritability estimates (h_g^2).

Phenotype	Ncases	Ncontrols	Ntotal	Popprev.	h_g^2 (SE)	*P*
PGC						
OCD	2,688	7,037	9,725	0.03	0.29 (0.05)	–
MDD	59,851	113,154	173,005	0.15	0.09 (0.01)	–
ADHD	19,099	34,194	53,293	0.05	0.21 (0.01)	–
ASD	18,382	27,969	46,351	0.01	0.11 (0.01)	–
iPSYCH						
onlyOCD	366	10,411	10,819	0.01	0.29 (0.09)	0.0003
OCD+MDD	1,052	10,411	11,543	0.005	0.08 (0.03)	0.0035
OCD+ADHD	443	10,411	10,901	0.002	0.04 (0.05)	0.2312
OCD+ASD	388	10,411	10,840	0.0003	0.03 (0.04)	0.2289
MC	429	10,411	10,890	0.0001	0.12 (0.03)	<0.0001

For PGC samples heritability (h_g^2) was estimated using LDSC, for the iPSYCH sub-samples univariate-GREML estimates of SNP-heritability are presented. All heritability estimates are reported on the liability scale (adjusted for population prevalence). Controls were the same for all iPSYCH subgroups. Abbreviations: Number of cases (Ncases), number of controls (Ncontrols), total number of individuals (Ntotal), population prevalence (Popprev.) heritability (h_g^2), standard error of the heritability estimate (SE), p-value of the heritability estimate (P), OCD subgroup with more than one comorbidity (MC). Within the MC group, 141 subjects are diagnosed with OCD, MDD, and ASD; 151 subjects are diagnosed with OCD, MDD, and ADHD, 153 subjects are diagnosed with OCD, ASD, and ADHD; and 34 subjects are diagnosed with OCD, MDD, ASD, and ADHD.

2.2.2. SNP-Heritability Estimates

SNP-heritability (h_g^2) was estimated using LDSC (Bulik-Sullivan et al., 2015a,b; Zheng et al., 2017) for the PGC samples and univariate *genetic-relationship restricted maximum likelihood* (GREML) as implemented in *Genome-wide Complex Trait Analysis* (GCTA) (Lee et al., 2011; Yang et al., 2011) for the iPSYCH OCD subgroups, as sample sizes of the subgroups were too small for LDSC and raw genotype data was available. For LDSC, freely available precomputed LD scores based on the European ancestry samples of the 1,000 G phase 3 (The 1000 Genomes Project Consortium, 2015), restricted to HapMap3 SNPs, were used. Before the analysis, standard LDSC filtering was applied. Poorly imputed SNPs with *INFO < 0.9* were removed. For the conversion of observed-scale- to liability-scale estimates, previously reported disorder-specific prevalence rates were used (see **Table 1**).

For the comorbid iPSYCH samples the univariate GREML approach of GCTA was used. After removal of ancestry outliers, counts of each sub-phenotype were the following: *controls*: 10,411, *onlyOCD*: 366, *OCD+MDD*: 1,052, *OCD+ADHD*: 443, *OCD+ASD*: 388, *MC*: 429. A genetic relatedness matrix (GRM) was fitted, thereby providing relatedness estimates for all pairwise combinations of individuals. All indels were removed and the data was filtered on *genotype probability* >0.8, *missing rate* <0.01 and *MAF* >0.05. GRM was estimated for each individual autosome and subsequently merged into a single GRM based on all autosomes. h_g^2 estimation for each OCD sub-phenotype was performed including the first four principle components (PCs) as continuous covariates together with any other PC that was nominally significantly associated to the phenotype. Waves were included as categorical indicator covariates. Lacking proper population prevalence estimates for subgroups, prevalence rates for comorbid conditions were estimated by multiplying the prevalence for each comorbid disorder with the OCD prevalence (3%). The prevalence for the OCD subgroup with more than one comorbid disorder was estimated to be lower than any of the other prevalence rates at an arbitrary value of 0.01%, as the multiplication of more than two prevalence rates would strongly underestimate the true prevalence. Because at least one other psychiatric disorder is present in approximately two thirds of OCD patients (Tükel et al., 2002; Gillan et al., 2017), the prevalence for *only OCD*, without any comorbid diagnosis, was set to 1% (one third of the general OCD prevalence). See **Table 1** for a list of all population prevalence estimates.

2.2.3. Genetic Correlation Estimates

Using LDSC (Bulik-Sullivan et al., 2015a,b) we estimated the genetic correlation (r_G) of OCD with MDD, ADHD, and ASD. We further estimated each disorder's genetic correlation with 861 other phenotypes using LDSC as implemented in LDhub (Zheng et al., 2017) (for 855 traits) and LDSC (for six additional datasets/traits not contained in the LDhub database). We corrected for multiple testing by setting the significance threshold to a Bonferroni-corrected p-value (dividing 0.05 by the number of valid tests per disorder). We then compared the correlation patterns that emerged for OCD to those of MDD, ADHD, and ASD.

Bi-variate GREML as implemented in GCTA was used to estimate the genetic correlation between the iPSYCH OCD subgroup samples. The controls were split proportionally in order to guarantee an independent control group for each comorbid subgroup in every pairwise comparison.

2.2.4. Multivariate-Multitrait PRS Analyses (PRS)

By applying multivariate (multiple outcomes) multivariable (multiple covariates) regression (Grove et al., 2019) we examined the distribution of PRSs based on OCD (International Obsessive Compulsive Disorder Foundation Genetics, 2017), neuroticism (Nagel et al., 2018), anorexia nervosa (AN)(Watson et al., 2019), bipolar disorder (BP) (Stahl et al., 2019), Educational Attainment

(EA) (Lee et al., 2018), body mass index (BMI) (Yengo et al., 2018), age at first birth (AFB) (Barban et al., 2016), and insomnia (Jansen et al., 2019), over the OCD comorbid subgroups. For the calculation of PRSs, the summary statistics of interest were clumped by applying standard ricopili parameters. Prior to clumping overlapping SNPs between the iPSYCH data and the external summary statistics were extracted and strand ambiguous A/T and C/G SNPs with a frequency between 0.4 and 0.6 were removed to avoid potential strand conflicts. PRS were generated at the default p-value thresholds of 5×10^{-8}, 1×10^{-6}, 1×10^{-4}, 0.001, 0.01, 0.05, 0.1, 0.2, 0.5, and 1 as a weighted sum of the risk allele dosages. Prior to analysis scores were normalized. After the PRS were calculated, the scores were regressed onto the OCD subgroups to evaluate the genetic overlap between the phenotypes and the OCD subgroups. Batch effects from genotyping waves and PCs in the comorbid OCD data were adjusted for in the multivariate multivariable regression. The advantage of a multivariate regression is that it can handle a possible correlation among the PRSes, making it possible to test a great number of hypotheses across PRSes and subtypes. The approach is statistically very powerful which enables us to conduct these analyses even with sample sizes too small to conduct a GWAS or LDSC analysis.

3. RESULTS

3.1. Comparing the Genetic Architecture of OCD, MDD, ADHD, and ASD

3.1.1. Gene and Gene-Set Analysis

First, we performed gene-based- and gene-set association analysis of the PGC samples of OCD, MDD, ADHD, and ASD using MAGMA/FUMA, thereby looking for potential overlaps in associated genes and gene-sets between the four disorders. When looking at 13 genes that showed suggestive association for OCD ($p < 1 \times 10^{-4}$; strongest association for *KIT Proto-Oncogene Receptor Tyrosine Kinase* on chromosome 4, $p = 2.46 \times 10^{-7}$) there was no evident overlap with significant genes of the other disorders (see **Supplementary Table 1**). Furthermore, no gene-set ($p \leq 9.7 \times 10^{-5}$) overlapped between OCD, MDD, ADHD, and ASD (see **Supplementary Table 2** for gene-set results of OCD).

3.1.2. Heritability and Genetic Correlations

Next, we computed SNP heritabilities (h_g^2) of OCD, MDD, ADHD, and ASD (see **Table 1**) and calculated cross-trait genetic correlations (r_G) between each pair of disorders using LDSC (Bulik-Sullivan et al., 2015a,b). OCD was significantly positively correlated with MDD ($r_G = 0.23$, $SE = 0.07$, $p = 0.0005$) and nominally significantly negatively correlated with ADHD ($r_G = -0.17$, $SE = 0.07$, $p = 0.02$), while the correlation between OCD and ASD did not reach significance ($r_G = 0.12$, $SE = 0.08$, $p = 0.15$).

To investigate the extent of genetic overlap between OCD and an array of other phenotypes, we estimated its genetic correlations with 861 psychiatric and other medical diseases, disorders, and traits using bivariate LD score regression (Bulik-Sullivan et al., 2015a,b; Zheng et al., 2017). The same analysis was also performed for MDD, ADHD, and ASD as we were interested in similarities and differences in patterns of correlations between the four disorders. 777 (for OCD and ADHD), 778 (for ADHD), and 779 (for MDD) genetic correlations yielded interpretable results, the remaining estimations resulted in "NA," due to small sample size and non-significant heritability. We therefore set the significance threshold to a Bonferroni-corrected p-value of $0.05/779 = 6.42 \times 10^{-5}$. Of the tested diseases and traits, 45 were significantly correlated with OCD, 249 with MDD, 285 with ADHD, and 52 with ASD (disregarding a phenotype if has been represented by a different dataset already). Forty traits overlapped between OCD and MDD, 37 between OCD and ADHD, and 12 between OCD and ASD. Nine traits were significantly associated with all four disorders, of which five demonstrated the same direction of effect (see **Supplementary Table 3**).

All phenotypes that significantly correlated with OCD were grouped into five categories: psychiatric, personality/psychological, anthropomorphic/metabolic, education, and other (see **Figure 2A**). Across the four disorders (OCD, MDD, ADHD, and ASD), differences in their patterns of correlations emerged. While all four disorders generally showed positive associations with traits in *psychiatric disorders* and *personality/psychological* traits, ASD and ADHD exhibited fewer significant and in several cases less strong associations compared to OCD and MDD. In the category of *other*, OCD was positively correlated with fertility parameters (*AFB* and *Age at last life birth*) and movement parameters, and negatively correlated with all other parameters, while ADHD and MDD generally showed the opposite pattern of correlation. While OCD and ASD positively correlated with *education* traits, ADHD and MDD negatively correlated with all *education* parameters (for *no specific qualifications* the pattern was reversed). In the category of *anthropomorphic and metabolic* traits, OCD significantly correlated negatively with all reported parameters, while MDD correlated moderately positively and ADHD strongly positively with the same phenotypes. In this category, ASD did not significantly correlate with any of the traits.

We further selected an array of traits across all five domains (see **Figure 2B**) to evaluate how PRS based on a broad spectrum of phenotypes with varying patterns of correlations with OCD, MDD, ADHD, and ASD, partition across comorbid OCD subgroups. See section 3.2.2 for details on which traits were selected for analysis.

3.2. Dissection of the Polygenic Architecture of Comorbid OCD Subgroups

3.2.1. Heritability and Genetic Correlations Among the Subgroups

Next, we explored the polygenic heterogeneity across OCD comorbid subgroups. We examined how h_g^2 partitioned across the comorbid OCD subgroups and estimated the genetic correlation among these groups using GCTA (Yang et al., 2011). Univariate GREML analysis revealed significant h_g^2 for the *onlyOCD, OCD+MDD*, and *MC* subgroups (see **Table 1** for all h_g^2 estimates). Pairwise comparisons of genetic correlations (r_G) of

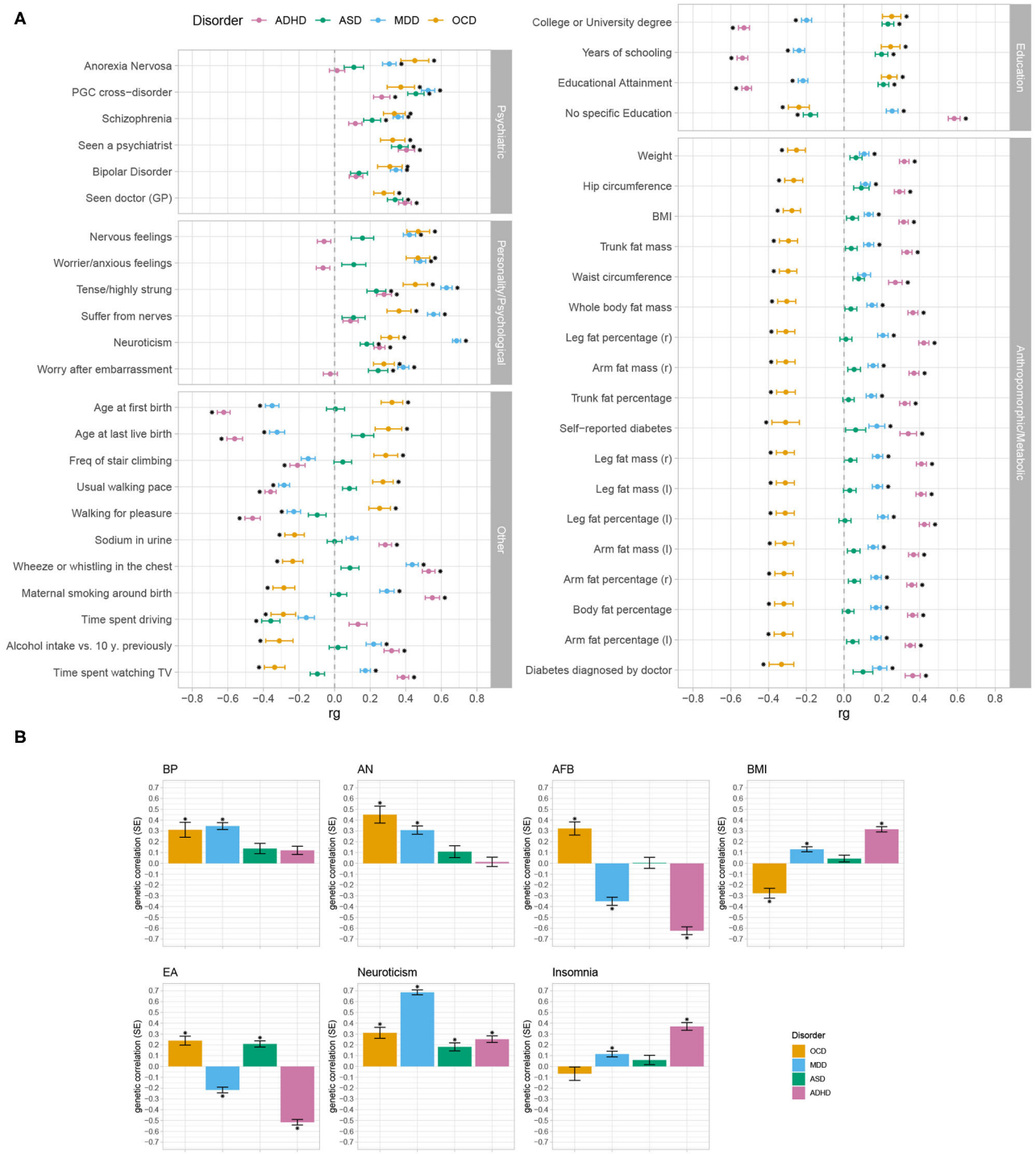

FIGURE 2 | Genetic correlation patterns of OCD, MDD, ADHD, and ASD with a wide range of other phenotypes. Bivariate LD score regression (LDSC) was used for the analysis, either as implemented in LDhub or using LDSC. Error bars represent standard errors and asterisks indicate significant associations after Bonferroni-correction (significance threshold of 6.42×10^{-5}, corrected for 779 tests) for multiple testing. **(A)** Displayed are all traits ($N = 45$) that significantly correlated with OCD (yellow), and the respective genetic correlation estimates for MDD (blue), ADHD (pink), and ASD (green), grouped into five different domains (psychiatric, personality/psychological, other, education, and anthropomorphic/metabolic). **(B)** Shows the genetic correlation estimates of OCD (yellow), MDD (blue), ADHD (pink), and ASD (green) with the seven phenotypes (bipolar disorder (BP), anorexia nervosa (AN), Age of first birth (AFB), body-mass index (BMI), educational attainment (EA), neuroticism, and insomnia) that were selected for subsequent PRS analyses. Here, bar-plots were used to enable easier comparison with the results from the PRS analyses (see **Figure 3**). See **Supplementary Table 3** for a list of all estimates and references for all used phenotypes. Asterisks indicate significant associations after Bonferroni-correction (significance threshold of 6.42×10^{-5}, corrected for 779 tests) for multiple testing).

the sub-phenotypes were estimated with bivariate GREML. Each subgroup demonstrated a high genetic correlation with all other subgroups (between 0.2 and 1; see **Supplementary Table 4** for a list of the results). Standard errors were generally very high for all pairwise correlations, making it difficult to interpret the results.

3.2.2. Cross-Trait PRS Analyses

To examine a possible polygenic heterogeneity of OCD, we further investigated how PRS trained on different phenotypes (OCD, neuroticism, EA, AN, BP, BMI, AFB, and insomnia) distribute across the iPSYCH OCD subgroups defined by a comorbid diagnosis of either MDD, ADHD, and/or ASD. Traits for the PRS analysis were selected from across all tested domains (psychiatric, personality/psychological, anthropomorphic/metabolic, education, and other) and were chosen in view of their different correlation patterns with OCD, MDD, ASHD, and ASD. Thereby, we wanted to explore whether different correlation patterns with OCD, MDD, ADHD, and ASD would translate into differing patterns in the PRS analysis across the OCD comorbid subgroups. The traits used as training datasets in the PRS analysis either showed (a) a significant correlation with OCD, MDD, ADHD, and ASD in either the same direction (BMI) or differing directions (EA); or (b) a significant correlation with OCD and either one (BP) or two (AFB, BMI, AN) other disorders; or (c) no significant correlation with OCD but a significant correlation with two other tested disorders (insomnia). Further, OCD itself was included as a training dataset for the PRS analysis. With this selection of phenotypes we aimed to explore whether a heterogeneous genetic correlation pattern between a phenotype and OCD, MDD, ADHD, and ASD translates into heterogeneous PRS loadings in the OCD comorbid subgroups.

The PRS analysis can be read as a linear regression with the beta value indicating the mean level of PRS relative to the controls, adjusted for the other variables and covariates (first four principle components and batches). First, for each phenotype, it was tested whether the betas of the PRS analyses were significantly different from zero across all OCD comorbid subgroups. Neuroticism, BP, AN, AFB, EA, OCD, and insomnia showed significant associations with the iPSYCH OCD samples ($p = 1.19 \times 10^{-32}$, $p = 7.51 \times 10^{-8}$, $p = 3.52 \times 10^{-20}$, $p = 9.38 \times 10^{-5}$, $p = 1.56 \times 10^{-4}$, $p = 1.87 \times 10^{-6}$, $p = 2.61 \times 10^{-5}$, respectively; see **Supplementary Table 5**). Of the eight phenotypes tested (neuroticism, BP, AN, AFB, EA, OCD, BMI, and insomnia) for association with the OCD comorbid subgroups, AFB ($p = 2.29 \times 10^{-4}$), EA ($p = 1.63 \times 10^{-4}$), and insomnia ($p = 0.045$) showed a significant heterogeneity across OCD subgroups. BP and AN were positively associated with all OCD subgroups, while the other traits showed significant associations with some of the OCD comorbid subgroups, but not with all (see **Figure 3** and **Supplementary Table 6**). For AFB the strongest, though non-significant, positive associations were with the *onlyOCD* group (*Beta* = 0.099, *CIl* = −0.004, *CIu* = 0.202, $p = 0.059$), followed by the *OCD+ASD* (*Beta* = 0.056, *CIl* = −0.039, *CIu* = 0.15, $p = 0.247$) group. The strongest negative association was with the *OCD+ADHD* group (*Beta* = −0.188, *CIl* = −0.288, *CIu* = −0.088, $p = 2.29 \times 10^{-4}$), followed by the, though non-significant, *MC* group (*Beta* = −0.08, *CIl* = −0.176, *CIu* = 0.015, $p = 0.098$), and *OCD+MDD* group (*Beta* = −0.067, *CIl* = −0.13, *CIu* = −0.004, $p = 0.037$) (see **Figure 3** and **Supplementary Tables 6, 7** for results of all tested phenotypes). For EA, there was a strong negative association with *OCD+ADHD* (*Beta* = −0.232, *CIl* = −0.333, *CIu* = −0.131, $p = 6.36 \times 10^{-6}$) and a trend for a positive association with *OCD+ASD* (*Beta* = 0.086, *CIl* = −0.009, *CIu* = 0.180, $p = 0.077$), while the other subgroups demonstrated scores around zero. For the PRS based on insomnia the strongest positive association was with the *OCD+ADHD* (*Beta* = 0.208, *CIl* = 0.107, *CIu* = 0.309, $p = 5.62 \times 10^{-5}$) group, followed by the *MC* (*Beta* = 0.133, *CIl* = 0.037, *CIu* = 0.229, $p = 5.62 \times 10^{-3}$) and the *OCD+MDD* group (*Beta* = 0.084, *CIl* = 0.021, *CIu* = 0.148, $p = 9.39 \times 10^{-3}$).

4. DISCUSSION

In the present study we first looked at genetic similarities and differences between OCD and the three psychiatric disorders MDD, ADHD, and ASD, with a specific emphasis on the genetic correlation patterns of each of the four disorders with 861 somatic and mental health phenotypes. In a second step we used genome-wide data of an independent set of OCD patients from iPSYCH for which we defined five OCD subgroups based on the patients' comorbidity with MDD, ADHD and/or ASD (*onlyOCD, OCD+MDD, OCD+ADHD, OCD+ASD*, and *MC*). Using eight different traits (BP, AN, AFB, BMI, EA, neuroticism, insomnia, and OCD) as training data sets, we applied PRS analysis across the comorbid OCD subgroups. Traits were selected from a variety of domains (psychiatric, personality/psychological, anthropomorphic/metabolic, education, and other), on the basis of their differential correlation patterns with OCD, MDD, ADHD, and ASD. We hypothesized that (a) the comorbid OCD subgroups show a heterogeneous association pattern with the PRSes, depending on the training dataset and the combination of comorbid disorders in the OCD subgroup, and (b) that the heterogeneous association patterns of the comorbid OCD subgroups are in accordance with the correlation patterns between OCD, MDD, ADHD, and ASD and the PRS training phenotypes that were reported in the first part of the manuscript. For example, if OCD showed a positive correlation with trait A and MDD a negative correlation with trait A, we expected that the onlyOCD group would show a higher association with the PRS based on trait A than the comorbid subgroup of OCD+MDD, while we hypothesized that a positive correlation of both, MDD and OCD, with trait A would translate into either an increased or similar association of the PRS based on trait A with the OCD+MDD comorbid subgroup compared to the onlyOCD group.

The genetic correlation patterns that emerged in the first part of the analysis are generally in accordance with symptomatic and clinical observations of OCD, MDD, ADHD, and ASD patients. As the sample size of a GWAS has an influence on the standard error and *p*-value of genetic correlation point estimates, it was expected that the OCD GWAS showed a

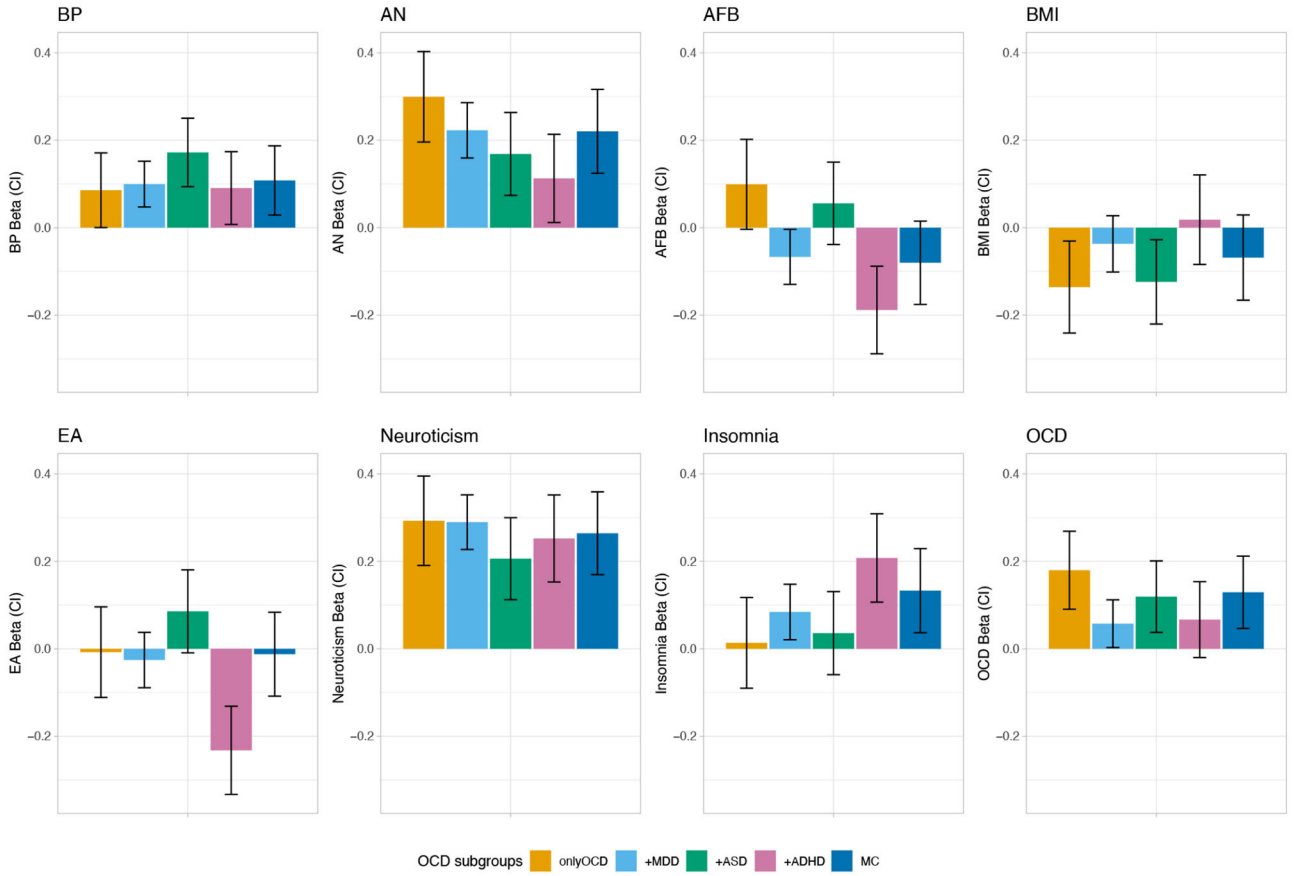

FIGURE 3 | PRS profile across distinct comorbid OCD subgroups in the iPSYCH sample. The bars show coefficients from multivariate multivariable regression of the eight normalized PRS over OCD subgroups, adjusting for the first four PCs and for 23 waves, whiskers indicate 95% confidence intervals (CI). Results are shown for eight different phenotypes: bipolar disorder (BP) (Stahl et al., 2019), anorexia nervosa (AN) (Watson et al., 2019), age at first birth (AFB) (Barban et al., 2016), body mass index (BMI) (Yengo et al., 2018), educational attainment (EA) (Lee et al., 2018), neuroticism (Nagel et al., 2018), obsessive-compulsive disorder (OCD) (International Obsessive Compulsive Disorder Foundation Genetics, 2017), and insomnia (Jansen et al., 2019).

lower number of significant genetic correlations with the 861 tested traits, as compared to the larger MDD, ADHD, and ASD GWASs. We cannot exclude the possibility that with an increase in sample sizes more genetic correlations will become significant. However, as we only consider significant genetic correlations for interpretation, this should not have an influence on the results discussed here. All four disorders displayed positive associations with most of the other psychiatric disorders and with personality/psychological parameters, such as BMI, worry, and tense feelings. The genetic correlation of OCD with anthropomorphic and metabolic traits was negative, while MDD and ADHD showed a positive correlation. This is in line with the observation that OCD is genetically positively correlated with AN (The Brainstorm Consortium et al., 2018), as AN correlates negatively with weight parameters on a symptomatic- and genetic level (Speranza et al., 2001; Duncan et al., 2017). OCD and ASD showed a positive correlation with education parameters and OCD correlated negatively with age at first birth (there was no significant correlation between ASD and age at first birth), while the pattern was reversed for ADHD and MDD. Dalsgaard et al. (2020) recently demonstrated that males with OCD achieved significantly higher school grades than individuals without a psychiatric disorder, while people with other psychiatric disorders (except AN) had significantly lower grades. It was also shown that higher education and socio-economic status are associated with higher maternal age at first birth (Van Roode et al., 2017) and that children of young mothers were disadvantaged in schooling (Fall et al., 2015).

Because the four disorders showed differential genetic correlation patterns, we presumed that the polygenic architecture of comorbid OCD subgroups would vary depending on their comorbid diagnosis. We first looked at heritability estimates and genetic correlations between the comorbid OCD subgroups. The *onlyOCD* and the *MC* group demonstrated the highest heritability estimates, while the *OCD+ASD* group displayed the lowest heritability estimates compared to all other subgroups. As sample sizes in each comorbidity group were quite low, SE were generally high and not all of the heritability estimates and none of the genetic correlation estimates between the comorbid subgroups reached significance.

In a last step we then applied PRS analysis across the iPSYCH OCD comorbid subgroups. Rather than selecting traits used as training datasets on a theoretical or clinical background, they were selected in view of their different correlation patterns with OCD, MDD, ADHD, and ASD across a wide range of psychiatric and somatic phenotypes, as we wanted to explore whether the different directions of correlations would be mirrored in the PRS analysis of the OCD comorbid subgroups. For traits for which OCD, MDD, ADHD, and ASD showed a heterogeneous genetic correlation pattern (EA, AFB, BMI) we hypothesized that PRSes based on those traits would also exhibit a heterogeneous pattern of association with the comorbid OCD subgroups. For EA and AFB the pattern of PRS loadings that emerged across the OCD comorbid subgroups closely mirrored the concordance structure of the genetic correlations between OCD and MDD, ADHD, and ASD. OCD and ASD correlated positively with Years of schooling and College or university degree, while it was the opposite for ADHD and MDD. Accordingly, in the PRS analysis the *OCD+ADHD* group had the highest negative loading for EA, while the EA PRS estimate was positive in the *OCD+ASD* group. Similarities between the correlation analysis and PRS analysis could also be shown for AFB. OCD correlated positively, MDD and ADHD negatively with AFB. ASD did not show a significant correlation. Similarly, in the PRS analysis, AFB was positively associated with disease status in the *onlyOCD* group and to a lower degree also in the *OCD+ASD* group, while it was negatively associated with the *OCD+MDD, OCD+ADHD*, and *MC* group. The PRS loadings for BMI was the most negative for the *onlyOCD* group, but also showed a negative association with *OCD+ASD* and *MC*, while, somewhat surprisingly, the other OCD subgroups were not significantly associated with the BMI PRS. One possible explanation for this pattern may be that the negative correlation between OCD and BMI and the positive correlations between ADHD and BMI, as well as between MDD and BMI translate into a null-finding in the PRS finding for BMI because the opposing correlations may evoke counteracting effects in the comorbid subgroups. As neuroticism showed a fairly homogeneous correlation with OCD, MDD, ADHD, and ASD, we expected no polygenic heterogeneity across comorbid OCD subgroups. Similarly, for AN and BP, which correlated significantly positively with OCD and MDD, and positively but non-significantly with ASD and ADHD, we expected a rather homogeneous pattern of association with PRSs across the subgroups, with stronger associations for *onlyOCD* and *OCD+MDD*. This was indeed the case, as PRSes of neuroticism, and BP were associated with OCD across all comorbid subgroups with no significant differences in estimates between the OCD comorbid subgroups. For AN, the pattern of correlations was mirrored closely in the PRS analysis—*onlyOCD* and *OCD+MDD* demonstrated the highest PRS estimates, followed by *OCD+ASD* and *OCD+ADHD*, with a significant difference between the highest estimate for *onlyOCD* and the lowest estimate for *OCD+ADHD*. Because we were also interested how PRS estimates change for traits which showed no correlation with OCD but with some of the other three disorders, we also included insomnia in the PRS analysis. While the insomnia PRS was not significantly associated with the *onlyOCD* subgroup, it showed significant associations with the *OCD+MDD*, *OCD+ADHD*, and *MC* subgroups, indicating that a comorbid diagnosis might change the association of OCD and insomnia.

To conclude, the different PRS estimates across OCD subsets provide the first evidence for a heterogeneous and qualitatively different genetic architecture of OCD subgroups defined by a comorbid diagnosis of MDD, ADHD, and/or ASD. Traits that show a heterogeneous genetic correlation pattern with OCD, MDD, ADHD, and ASD generally also exhibit a heterogeneous pattern of estimations in PRS analysis across OCD comorbid subgroups. This was especially shown for AFB, and EA. While being unique in its approach, results of the present study are in accordance with previous research by Hirschtritt et al. (2018) who examined OCD- and ADHD-symptom dimensions in TS cases and identified unique OCD symptom subgroups that were differentially associated with other comorbid psychiatric disorders. Both, OCD symptom subgroups and comorbid subgroups, may be markers of distinct underlying patterns of psychopathology and genetic architecture.

Because heterogeneous genetic architectures could potentially point toward heterogeneous disease mechanisms, the context in which OCD occurs may have implications for diagnostic criteria and treatment that might not have been considered sufficiently in past and present research and clinical practice. Pallanti et al. (2011), for example, showed that OCD in the presence of comorbid conditions is often associated with non-response to treatment, indicating differential clinical characteristics. Also, for the success of GWAS analyses, it may be beneficial to focus on (sub)phenotype definitions rather than solely relying on increasing sample size. As MacRae and Vasan (2011) and Kulminski et al. (2016) have discussed, increasing the size of many human disease cohorts is likely only to upscale the heterogeneity in parallel. Especially for cross-disorder GWAS analyses, which have gained a lot of attention recently (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Grotzinger et al., 2019; Lee et al., 2019; Abdellaoui et al., 2020), it may be crucial to account for comorbidities to avoid confounding of genetic similarities and differences between psychiatric disorders. One limitation of this study is the right censoring of comorbidities. While ADHD and ASD are neurodevelopmental disorders with mostly a childhood onset (and some persistency into adulthood), MDD usually occurs with an onset in late adolescence and adulthood. Therefore, the possibility that an individual develops a comorbidity, or another comorbidity on top of an already existing one, cannot be ruled out and may be higher for disorders with a later age of onset. Inherently, iPSYCH is a longitudinal study. As with other studies, however, it may be the case that some study participants (e.g., those originally ascertained for their ADHD and/or ASD diagnosis) were included at a time point at which the follow-up time was not sufficient to capture a later diagnosis of one of the comorbidities under study (e.g., MDD). While right censoring may dampen some of the observed effects, it is unlikely to alter the overall observations of this study and its main finding of a heterogeneous genetic architecture of comorbid subgroups.

The present study should be viewed as a pilot study and exploratory in nature. In the future, it would be of interest to conduct similar analyses with a broader range of correlated phenotypes and to include other related and comorbid disorders, such as schizophrenia, BP, AN, Tourette's syndrome and anxiety disorders. It has also been suggested that the onset of OCD (early vs. late) (Hemmings et al., 2004; Walitza et al., 2010; Taylor, 2011), sex (male vs. female) (Khramtsova et al., 2019), or different symptom dimensions of OCD (Hasler et al., 2005) present differing underlying genetic architectures.

DATA AVAILABILITY STATEMENT

The data used in this study can be made available upon request to the authors. Requests to access these datasets should be directed to Anders D. Børglum, anders@biomed.au.dk.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Scientific Ethics Committee in Denmark and the Danish Data Protection Agency. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

NS and MM contributed to the conception and design of the study. AB, OM, MN, TW, DH, and PM contributed to the conception and design of the original iPSYCH study. SM, MB-H, JB, TD, MH, JC, and JB-G contributed to the data collection and organization of the database. NS, JG, and TD performed the statistical analysis. NS wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2021.711624/full#supplementary-material

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Decision Models and Technology Can Help Psychiatry Develop Biomarkers

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Why is psychiatry unable to define clinically useful biomarkers? We explore this question from the vantage of data and decision science and consider biomarkers as a form of phenotypic data that resolves a well-defined clinical decision. We introduce a framework that systematizes different forms of phenotypic data and further introduce the concept of decision model to describe the strategies a clinician uses to seek out, combine, and act on clinical data. Though many medical specialties rely on quantitative clinical data and operationalized decision models, we observe that, in psychiatry, clinical data are gathered and used in idiosyncratic decision models that exist solely in the clinician's mind and therefore are outside empirical evaluation. This, we argue, is a fundamental reason why psychiatry is unable to define clinically useful biomarkers: because psychiatry does not currently quantify clinical data, decision models cannot be operationalized and, in the absence of an operationalized decision model, it is impossible to define how a biomarker might be of use. Here, psychiatry might benefit from digital technologies that have recently emerged specifically to quantify clinically relevant facets of human behavior. We propose that digital tools might help psychiatry in two ways: first, by quantifying data already present in the standard clinical interaction and by allowing decision models to be operationalized and evaluated; second, by testing whether new forms of data might have value within an operationalized decision model. We reference successes from other medical specialties to illustrate how quantitative data and operationalized decision models improve patient care.

Keywords: psychiatry, biomarker, digital phenotype, diagnosis, Bayesian inference, decision model

Biomarkers are crucial to medical science, so much so that even the U.S. Congress has sought to define them. The National Institutes of Health (NIH) defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (1). The U.S. Congress and Food and Drug Administration (FDA) further defined a biomarker as "a physiologic, pathologic, or anatomic characteristic or measurement" that "includes a surrogate endpoint" (2) that indirectly reflects a primary disease process. So defined, identifying and applying a biomarker in clinical practice requires that a bottom-up knowledge of pathophysiology converge and meaningfully interact with a clinician's top-down evaluation of phenomenology. A biomarker, therefore, presupposes that pathophysiology interact with phenomenology, thereby allowing clinicians to apply physiologic tools to the diagnosis and treatment of a patient's disease.

Though the American Psychiatric Association has regularly published consensus reports outlining promising biomarkers (3), the way clinicians diagnose and treat psychiatric disease remains largely unchanged. Outside of neurodegenerative conditions, no psychiatric disorder requires or has available a quantitative biomarker to establish a diagnosis, stage the progression of illness, guide the selection of treatment, or evaluate the impact of treatment (65).

Here, we suggest that the failure to define useful biomarkers rests in part on diagnostic procedures that, in their current form, cannot be fully operationalized. In turn, we argue that psychiatry's inability to operationalize clinical decision results from a reliance on imprecise, qualitative data and on data-gathering procedures that are unique to each clinician. Though this failure further suggests the need for advances in our bottom-up understanding of pathophysiologic mechanisms, here, we focus primarily on improving the clinician's top-down evaluation and diagnosis. To explicate this view, we define a series of basic concepts and build upon these concepts to show why biomarkers remain elusive in psychiatry and how we might proceed.

PHENOTYPES AND DECISION MODELS, DEFINED

Broadly speaking, a phenotype encompasses any observable characteristic, from an individual's molecular and biochemical properties to their repertoire of possible behaviors (4). In psychiatry, clinically relevant phenotypes are generally conceptualized as symptoms and signs (see **Figure 1**) (5).

Symptoms are reported by the patient (e.g., "I feel hot.") and rely on a patient's ability to sense, interpret, and convey their personal experience. Conversely, signs can be qualitatively or quantitatively observed, e.g., skin that is qualitatively "warm to the touch" can be quantified as 39°C. In the case of a qualitative sign, the sensor is the clinician's eyes, ears, or fingers; the clinician senses and summarizes the data at hand by noting that the skin is "warm to the touch." In the case of a quantitative sign, the sensor is an instrument designed to measure the phenomenon of interest; e.g., a thermometer records that the skin is 39°C.

A biomarker is a quantitative sign that, as stated above, captures some aspect of biology that is salient to health or disease. Broadly speaking, there are two classes of biomarkers: descriptive and treatment. Descriptive biomarkers screen for disease or stage disease progression (see **Table 1**). Treatment biomarkers inform therapeutic interventions that, based on their relationship to pathophysiology can be palliative, modifying, or curative. Because a biomarker's overall goal is to inform clinical reasoning, to the NIH's definition we add that a biomarker must help resolve a well-defined clinical decision within what we will call a "decision model" (33).

We introduce the term "decision model" to describe the series of strategies and policies that a clinician uses to evaluate a patient and craft a treatment plan (33). These strategies and policies can be acquired explicitly through instruction (whether clinical training or review of scientific literature) or implicitly through clinical experience. As the term suggests, a decision model informs a clinician's decision about how to seek out, combine, and act on clinical data. Within a decision model, phenotypic data inform hypotheses of how those data interrelate and guide the clinician's thoughts and actions during the exam, the purpose of which is to decide how best to intervene with treatment (6). Therefore, a decision model is fluid, evolving continuously as new data become available.

Clinical data can be assessed based on their reliability and utility; put differently, data are not equally reliable or useful. Symptoms are subjective, being a patient's expression of their personal experience. Signs are objective, being observed either by a clinician or by an instrument designed for that purpose (7). The reliability of a symptom or a sign depends on how accurately it captures a given phenomenon; in the case of a patient, how faithfully he reports his personal experience; in the case of a clinician, how skillfully she senses "warm to the touch" and a thermometer's calibration to degrees Celsius. To be of value within a decision model, data must be reliable and useful. A clinician might observe that a patient has freckles however this datapoint is unlikely to be useful in a decision model for schizophrenia; the number of freckles, therefore is unlikely to serve as a useful biomarker for schizophrenia staging or treatment. How reliably a biomarker answers a clinical question can be further assessed in terms of sensitivity, specificity, and accuracy. What makes a biomarker clinically valuable will be further discussed in a separate section, below, however, it is worth noting that once a biomarker has met acceptable criteria for reliability, it might transition to a standard clinical test that in addition relies on the accuracy, range of error, and uncertainty of the assay, instrument or clinical tool.

Decision models can be assessed based on their efficacy and efficiency. An effective decision model will improve a patient's clinical state. Because clinical work is temporal in nature (i.e., ineffectively treated disease states can progress and worsen), efficiency is an important value for a decision model. The efficiency of a decision model can be assessed by how much time and data gathering are required to reach an optimal decision. Assuming that two decision models are equally effective, a decision model that requires 5 min to gather 10 datapoints is more efficient than one that requires 20 min to gather 100. The

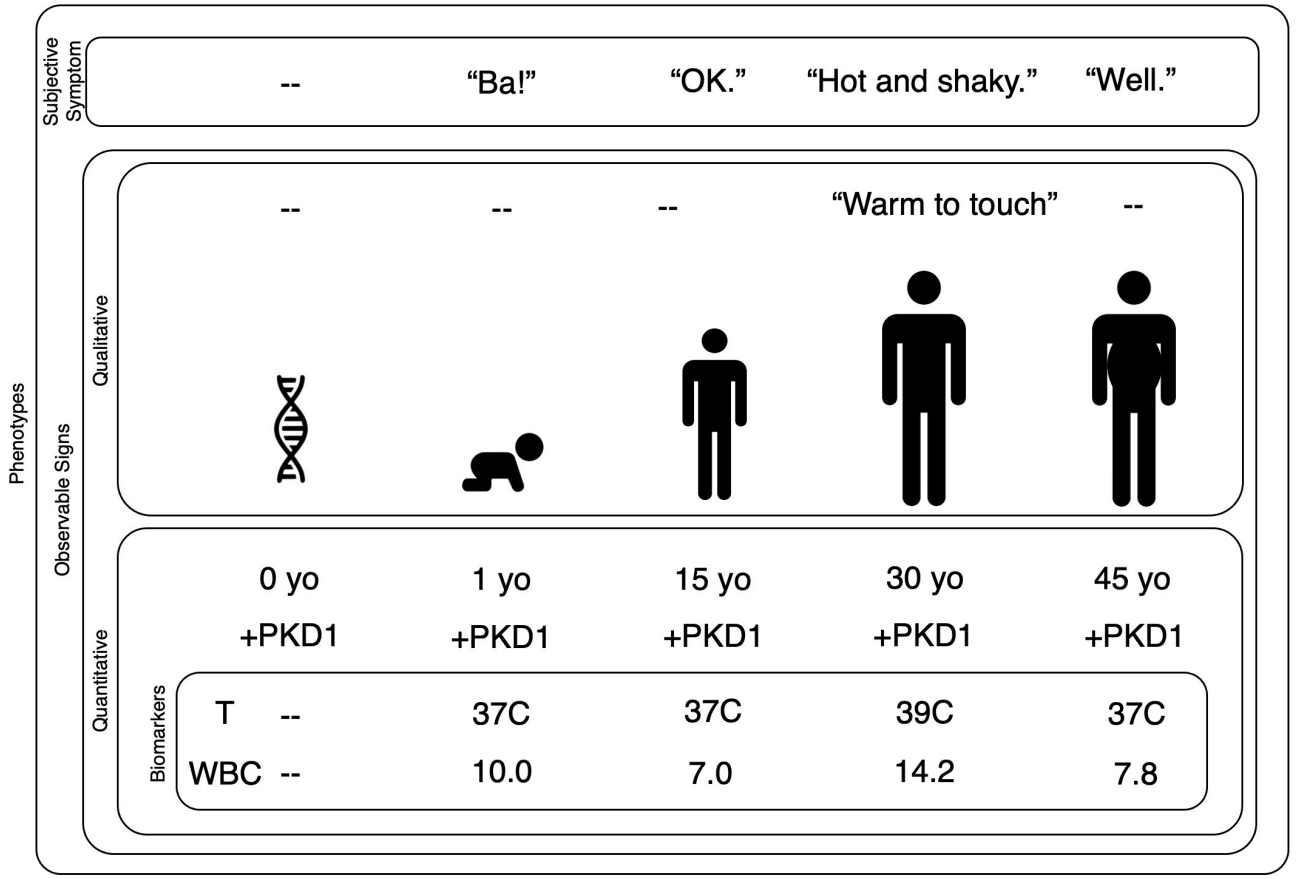

FIGURE 1 | Biomarkers are quantified phenotypes relevant to a decision model. This nested plot shows that subjective symptoms and observable signs are phenotypes. Signs can be observed with qualitative or quantitative methods. A quantitative observable sign requires the use of an instrument to measure the data of interest. A biomarker is a quantitative observable sign that has some bearing on a given decision model. In this case, we are trying to evaluate a 30-year-old man who reports he is "hot and shaky." A clinician might observe his habitus and record that the man's skin is "warm to touch." Quantitative observable signs might include his age and the presence of the PKD1 gene. Our clinical goal is to understand and treat his report of "hot and shaky," therefore, within our decision model, his age and PKD1 gene status are not necessarily relevant. His temperature and WBC are relevant because they have direct bearing on our decision model. Note that a phenotype can change over time as one's genes interact with the environment: the symptoms and signs of a bacterial infection are phenotypes that emerge only during the illness. Further note that while some phenotypes may change year-to-year or even moment-by-moment, the autosomal dominant mutation at the PKD1 gene on chromosome 16 will not change. PDK, Polycystic Kidney Disease; yo, year-old; T, temperature; C, Celsius; WBC, White Blood Count (reported as $\times 10^3/\mu$L).

TABLE 1 | Types of biomarkers.

Class	Purpose	Goal	Example
Descriptive	Screening	Indicate a possible disease process	Fever→motivates further workup
	Staging	Indicate disease stage (without explicitly informing treatment)	Creatinine→kidney disease progression
Therapeutic	Palliative	Inform treatment that does not act on pathophysiology	Painful metastatic cancer→morphine
	Modifying	Inform treatment that modifies pathophysiology	Hypertension→Anti-hypertensive
	Curative	Inform treatment that cures pathophysiology	HER-2 positivity→Herceptin MRSA→Vancomycin

importance of these criteria will become clearer, below, as we discuss formalizing and optimizing decision models.

The interaction of subjective symptoms, observable signs, and biomarkers within a decision model can be illustrated with a simple example: a patient presents to an emergency room reporting "I have the worst headache of my life."

The patient's symptom report serves as the first datapoint in the clinician's decision model for evaluating and treating the patient's headache. The clinician will populate her decision model with hypothetical causes of experiencing the "worst headache of my life" (e.g., subarachnoid hemorrhage, migraine, infection) and will use her decision model to systematically eliminate or confirm hypotheses by selectively soliciting other symptoms and signs. Data from the patient about when the headache began and whether they've had similar headaches or recent head trauma will no doubt be paired with data observed by the clinician looking for

focal neurologic deficits or measurements of temperature, blood pressure, electrolyte, and other laboratory panels. Together, these data will guide the clinician's headache decision model.

Viewed from a Bayesian perspective (8, 9), a clinician begins with a prior belief or an a-priori probability that a given disease best explains the available data based on the patient's report, clinical appearance, or disease prevalence in that clinical setting. By selectively searching for and building in additional data to her overall decision model, the clinician continuously updates the likelihood that these data can be best explained by any specific disease. As she updates these likelihoods, she decreases her uncertainty about how to treat the patient.

Technically speaking, this is a process of Bayesian belief updating that underwrites most forms of data assimilation and uncertainty quantification in the life and physical sciences—sometimes referred to as evidence accumulation (10–14). As we will see below, this process of belief updating can be cast in terms of converting a prior belief (before seeing any clinical data) into a posterior belief (after seeing the data), in a principled fashion [for a more technical example of Bayesian statistics, see (15)].

Data do not have equal utility within a decision model. In an emergency room patient who reports "worst headache of my life," the presence of fever is causally non-specific. Put differently, fever is weakly specific for multiple causes of disease. Fever might prompt a clinician to collect additional types of data, such as an analysis of cerebrospinal fluid or blood. These data are also weakly specific for a given disease cause, but as weakly specific data accumulate, the additive effect is to increase the overall likelihood of one hypothesis over competing hypotheses. For example, if a cerebrospinal fluid analysis show high levels of glucose, white blood cells and protein, these data suggest that the person's headache is caused by a bacterial meningitis. Should a cerebrospinal fluid culture identify a specific type of bacterial infection, a clinician might treat this condition with an antibiotic drug that has known efficacy against that bacteria. In this example, the clinician combined multiple forms of weakly specific data within her decision model to converge on an appropriate treatment. The process of selectively combining weakly specific though complimentary datapoints and of moving from subjective symptom to observable signs to treatment is at the heart of the medical enterprise.

Technically, this process is beautifully described in terms of the principles of optimal Bayesian design (16); namely, the clinician gathers data that she believes will most efficiently resolve her uncertainty about competing hypotheses and, overall, about how to act to treat her patient. In machine learning, this is known as the problem of active learning; namely, finding the next data point that is maximally informative in relation to beliefs about how the data were caused (12). In the neurosciences, this is known as active inference; namely, responding to epistemic affordances offered by different diagnostic avenues (17). The key problem addressed by these approaches to diagnosis is that the best data to solicit is determined by the beliefs or hypotheses currently entertained by the clinician, which is to say, by the clinician's current decision model. In other words, only if the clinician must decide whether a bacterial meningitis might have caused her patient's specific phenotype (comprising: "headache," fever, etc.), will she order a cerebrospinal fluid culture to test this hypothesis. A cerebrospinal fluid culture is not the indicated diagnostic procedure across decision models, but it is a *useful* test based on the data that the clinician has already assimilated.

In short, data are not of equal utility to all decisions within a larger decision model. The presence of a fever might be relevant to prompt further workup, but not immediately relevant to antibiotic selection. Data have utility only within the context of a specific clinical decision (18, 19). Only in rare cases do single datapoints or single forms of data independently resolve clinical decisions.

On this view, biomarkers have a special (epistemic) value because they resolve uncertainty under a particular decision model. The value of a biomarker is not in identifying a disease in isolation from other clinical data; but rather, a biomarker operates within and updates an existing decision model and, therefore, collaborates with other clinical data to decrease the overall uncertainty of a well-defined course of action.

CANDIDATE BIOMARKERS: ASSOCIATIVE AND PREDICTIVE

We broadly consider associative and predictive biomarker studies and we evaluate whether and how they could operate within decision models in psychiatry (65).

Associative biomarker studies rely on classic null-hypothesis tests to compare group means of a given parameter and, therefore, associate that parameter with a disease group. An example is whether brain structure in a group of depressed patients differs from a group of non-depressed controls (20) or whether genetic variants of the serotonin transporter gene differ in depressed and non-depressed patients who have experienced life stressors (21, 22). Other work has attempted to trace the emergence of depression by collating independently collected genetic, cellular, and whole-brain imaging datasets (23). So far, associative biomarkers have offered little clinical utility in psychiatry; the statistical methods upon which they are based are formulated at the group or population rather than the individual level. Associative biomarkers can be actionable on the individual level, but they must first be evaluated in new individuals and separate cohorts as a predictive biomarker. One example is the North American Prodromal Longitudinal Study risk calculator, which associated phenotypic variables (e.g., cognitive deficits and symptom profiles) with the risk of transitioning from clinical high risk to psychosis (24); this study is currently being evaluated in new individuals and separate cohorts as a predictive biomarker.

Predictive biomarker studies use specialized methods to identify values (whether quantitative or subjective) within a dataset, which, in combination, predict a desired variable such as a diagnosis or clinical outcome (25). For example, machine-learning models trained on a large group can be validated and applied to individuals (26). A supervised machine-learning model sieves through many candidate variables to identify which are most predictive of a disease-related target variable. An example is a recent supervised machine-learning study

that identified a pattern of life experiences, neurobiological differences, and personality traits that were predictive of binge drinking in 14-year-olds (27). An unsupervised machine-learning model looks across a similarly large number of candidate features to identify patterns that can then be assessed for common properties. Unsupervised machine-learning models are said to be unbiased and data-driven because they do not require data to be labeled *a priori* or a user to specify an outcome of interest. For example, a recent unsupervised machine-learning study identified three co-occurring symptom clusters across patient self-report and clinician-rated symptom scales that were associated with response to antidepressant and/or cognitive behavioral therapy (28, 29).

There is notable variability across the features and target variables currently explored in psychiatric biomarker development: subjective symptoms (patient self-report or behavioral trait scales) are often paired with quantitative observable signs (brain imaging, genetics, age). These features and target variables, in turn, are often evaluated within the context of a psychiatric diagnosis (see **Box 1**), which is largely based on subjective symptoms. The variability in features and target variables, therefore, could in part be explained by the field trying to define an unknown clinical landscape: because it is unclear how to best conceptualize psychiatric disorders, it is further unclear which data might afford the greatest utility in understanding them.

Notwithstanding the wide range of data across studies, the data evaluated in individual biomarker studies is narrow. Most studies associate a single form of data (e.g., genetic or neuroimaging or symptom assessment) with diagnosis. Even complex machine-learning studies that combine multiple forms of data are relatively narrow compared to the range of data a clinician routinely gathers. Although machine learning studies may provide novel insights into mental illness, they often fail to replicate and, thus far, have failed to guide clinical practice.

This is not surprising; single datapoints or even single forms of data rarely resolve a clinical course of action, even when the range of possible courses of action is known and well-described (e.g., because the common types of infection and treatment are known, there was a much smaller number of possible clinical decisions in our "hot and shaky" patient than for a given psychiatric patient, wherein the landscape is not known). Furthermore, there is a growing appreciation of the limitations of machine learning in terms of "explainability" and difficulties establishing the predictive validity of a simple set of biomarkers. With the exception of machine learning procedures based upon generative models (e.g., variational auto encoders or generative adversarial networks), most schemes suffer from the poor generalization, predictive validity, and overfitting that go hand-in-hand with an overly parameterized deep learning network.

To put it more plainly, associative biomarker studies suffer from the fallacy of classical inference, wherein an overpowered group identifies a candidate biomarker with a high statistical significance but with an effect size that is very small and essentially disappears at the single subject level. Meanwhile, predictive biomarker studies can overfit the parameters of their model to a given dataset; therefore, even though a predictive biomarker might explain a large amount of the variance, this model is useless in a novel clinical population. Although cross-validation techniques are meant to help minimize the likelihood of overfitting (25, 37), many datasets are unique, so cross-validating on an independent but similarly unique dataset does not truly demonstrate generalizability or resolve the overfitting problem (38). Grounding biomarker studies in clinical practice and making utility within a decision model a necessary component of biomarker development, therefore, might prove helpful. These technical considerations bring us back to the question of value: what gives a biomarker value and which data offer the most value to a decision model?

BOX 1 | Diagnostic Foraging.

Attempts to classify psychiatric disease have primarily focused on subjective symptoms and qualitative, observable signs. The Diagnostic Statistical Manual and International Classification of Disease use expert consensus to classify mental illnesses into binary disease categories based on combinations of subjective symptoms and observable signs (30, 31). Biomarker development has no doubt been stymied by an unavoidable corollary of combinatorial diagnostic groups: the sheer number of possible symptom combinations meeting criteria. For example, a recent commentary on the ethical implications of machine learning in psychiatry computed that there are 7,696,580,419,045 unique sets of symptoms that meet criteria for schizophrenia as defined in the Structured Clinical Interview for DSM-5 (SCID-5) (32). Similarly, because there are at least 488,425 ways to be diagnosed with a major depressive episode based on DSM-4, such top-down phenotypic imprecision was likely a reason that the first treatment-selection biomarker trial did not succeed (33). Though top-down combinations of symptoms have, in other disciplines, converged with bottom-up pathophysiology (e.g., the pill-rolling tremor, masked facies, festinating gait, and stooped posture that are pathognomonic of Parkinson's Disease and substantia nigra degeneration) sometimes they have not (e.g., dropsy). Practically, it would appear difficult to bridge bottom-up pathophysiology and seven trillion symptomatically dissimilar schizophrenias.

Other strategies suggest that behavior might be more accurately captured by considering multiple dimensions of a disease (e.g., mood state) (34) along a continuum. Yet other studies suggest that the very act of diagnosing is poorly framed and that an individual's symptom profile might be better captured with a single dimension, such as "p" (35). The Hierarchical Taxonomy of Psychopathology is an attempt to quantitatively define constellations of co-occurring signs, symptoms, and maladaptive traits and behaviors that might prove useful to clinical assessment and treatment (6, 36).

None of these taxonomies references a quantitative biomarker or attempts to define a quantitative threshold for separating a disease state from a non-disease state. As in the case of blood pressure, as the field moves toward greater understanding such a threshold will likely change, however, in the absence of quantitative measures, such a threshold cannot be evaluated and refined.

WHAT GIVES A BIOMARKER CLINICAL VALUE?

Biomarkers have value if they help clinicians better describe or better treat disease within a larger decision model (see **Table 1**). Unfortunately, many candidate biomarkers attempt to

describe disease solely in terms of diagnosis, a pursuit that has been complicated by a lack of consensus about the best way to diagnose psychiatric diseases (see **Box 1**). Indeed, it is an understandably complex (if not impossible) task to develop a biomarker for schizophrenia when there are over 7.6 trillion unique combinations of symptoms that each meets diagnostic criteria for schizophrenia (32).

For a biomarker to have value, it should guide clinical decision independent of diagnosis. In medicine, descriptive biomarkers can help screen for or stage a disease. Meanwhile, therapeutic biomarkers can guide clinical decision toward palliative, modifying, or curative treatments.

Palliative therapeutic biomarkers identify treatments that suppress the downstream manifestations of a disease: for example, an opioid might be prescribed for pain related to metastases from a HER-2 positive cancer. Palliative therapeutic biomarkers are broadly applicable across diseases because they are not related to any specific pathophysiology; opioids relieve pain related to many pathophysiologies and so a biomarker indicating that an opioid is an appropriate clinical course of action would be applicable to many diseases. Because they do not treat but rather suppress the expression of pathophysiology, many current psychiatric treatments fall in this category. For example, hydroxyzine might suppress the panic of someone with generalized anxiety disorder, but it is unlikely that panic is related to dysregulation of the histaminergic system. Or furthermore, antipsychotics and antidepressants are broadly used across psychiatric diseases because they most likely suppress the downstream effects of (rather than modify) pathophysiology. Fortunately for our patients, the majority of psychiatric therapies require little or no understanding of pathophysiology because they target downstream mechanisms that are found broadly across disorders.

Modifying and curative therapeutic biomarkers identify subsets of patients that share a pathophysiology, allowing them to be paired with treatments that target that pathophysiology. While modifying treatments temporarily (dependent on the duration of action), a curative treatment eliminates or reverses the pathophysiology. Such therapeutic biomarkers apply to a progressively narrower patient population because they would identify, in essence, a subset of a larger population that, in the absence of a biomarker, would appear clinically similar. For example, blood pressure is a valuable biomarker because without it, a clinician might not know to prescribe an otherwise well-appearing patient an anti-hypertensive.

The more deep our knowledge of bottom-up pathophysiology, the more specific the possible treatment and the less likely the associated biomarker is to be broadly applicable to the larger population. Put differently, the rarer a given pathophysiology is, the less likely a therapeutic biomarker is to provide actionable insights to the vast majority of patients. For example, research suggests that within the larger category of schizophrenia, there are the very rare Mendellian risk genes (e.g., 22q11 or GRIN2A) and the relatively more common (though still quite rare) polygenic common risk loci (39). Should treatments be identified for each specific pathophysiology, it seems unlikely that they would be applicable to the larger population of "schizophrenia," for which there are ∼7.6 trillion possible combinations of symptoms and signs (32). Likewise, testing any biomarker for a specific schizophrenia pathophysiology on a sample drawn from ∼7.6 trillion possible schizophrenias lacks face validity and is unlikely to yield positive or reproducible conclusions. Such prima facia logic suggests the need for greater phenotypic precision within operationalized decision models; in other words, for more serious consideration of the clinical data and how these data are integrated to articulate specific decisions.

Overall, the need for top-down biomarkers will grow in importance as our knowledge of bottom-up pathophysiology advances. In other words, as we deepen our understanding of the complex pathophysiology underlying phenomena of psychiatric disease, we anticipate a series of treatments that modify or cure a mechanistically precise pathophysiology. Identifying patients who could benefit from such modifying or curative treatments will require biomarkers that operate within clinical decision models. A primary task facing psychiatry, therefore, is determining which data offer the most value to a decision model.

Consider that a standard psychiatric interview gathers information about a patient's biologic, psychologic, and social history (40). A clinical evaluation might yield thousands of heterogenous datapoints that can range from: a patient's observable behavior; their reported narrative and symptomatology; results from clinical tests like blood work, urine toxicology, electrocardiogram; reports from family members, legal authorities, or other healthcare providers; the patient's socioeconomic status; and how these data change over time. Any of these data might have utility within a decision model, depending on the clinical setting and the clinician's training and experience.

Sifting through clinical data to operationalize decision models that can be tested and optimized has always been a fundamental complexity of medicine. Historically, successful strategies to develop decision models and biomarkers have been firmly rooted in physiology or in epidemiology.

BIOMARKER DEVELOPMENT STRATEGIES: PHYSIOLOGY AND EPIDEMIOLOGY

A biomarker bridges bottom-up pathophysiology and top-down phenomenology. Two strategies to biomarker development have been based in physiology and epidemiology (65). The physiology-based strategy can be considered a bottom-up approach wherein understanding the pathophysiology of a well-defined decision model leads to an understanding of how to clinically intervene. The epidemiology-based strategy can be considered a top-down approach where, in the absence of a well-defined decision model, identifying common phenomena that precede a defined clinical outcome leads to a better understanding of disease and, therefore, to identifying useful therapeutic targets. We explore both below.

The paragon of physiology-based biomarkers is the discovery of molecular disease markers in oncology. For centuries, cancer diagnosis and treatment were based on a decision model that was heavily weighted by where in the body the cancer was

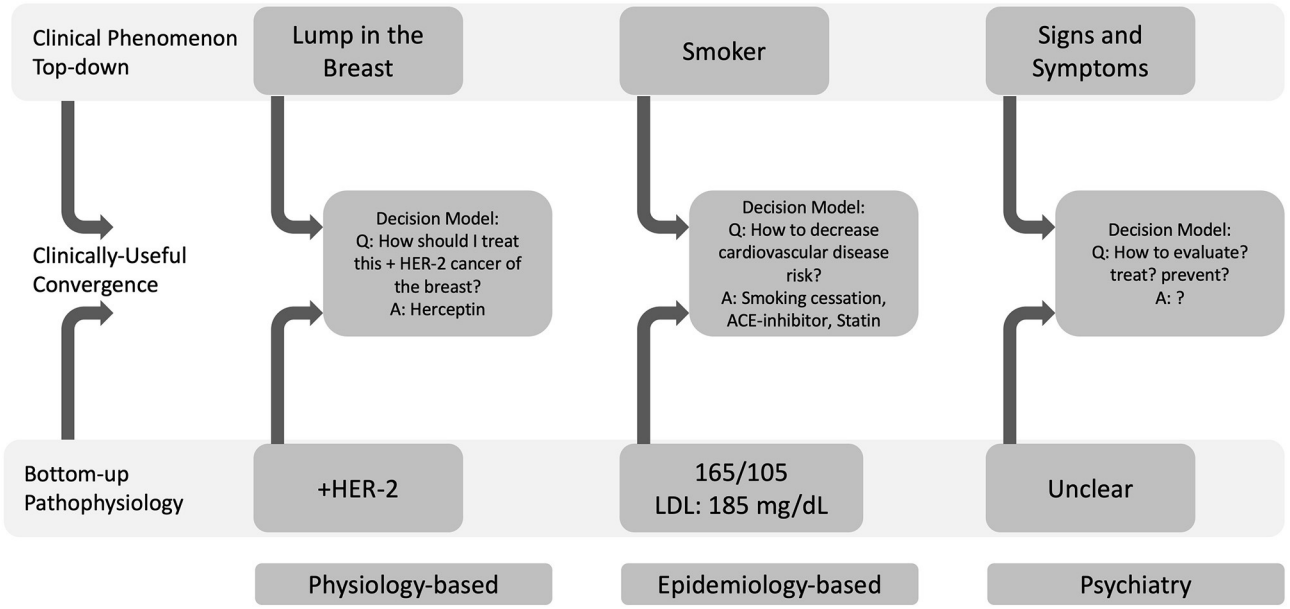

FIGURE 2 | Physiology-based (bottom-up) and epidemiology-based (top-down) approaches to biomarker development can define useful decision models. Decision models converge top-down clinical phenomena with bottom-up pathophysiology. In oncology, a physiology-based investigation indicated that HER-2 positivity in a cancer of the breast could be treated with Herceptin. In cardiology, the Framingham Heart Study's epidemiology-based approach showed that smoking behavior (a top-down phenomenon), hypertension and high cholesterol were risk factors for cardiovascular disease. In psychiatry, it remains unclear how to define and operationalize decision models to approach clinical phenomena with pathophysiology and therefore, which data will be most helpful within these larger decision models (LDL, low-density lipoprotein).

located. A patient might arrive in clinic describing symptoms of itching and tenderness over their breast. On their physical exam, a clinician might then note redness and lumps within the breast tissue, observable signs of advanced cancer. Cancer within the breast tissue was called "breast cancer" and was treated differently from cancer found elsewhere in the body. This decision model appeared straightforward, but treating cancer was capricious: two patients with breast cancer might have very different responses to the same treatment. The advent of tools to identify cell type and, subsequently, to create molecular tumor profiles that could probe the pathophysiology of cancer led to the discovery of the BRCA-2 and HER-2 gene mutations, which in turn showed that "breast cancer" was in fact a heterogenous mosaic of tumors (41). Moreover, molecular assays showed that mutations seen in some types of breast cancers were found in ovarian and prostate cancers. Such evidence demonstrated that a tumor's molecular profile could guide treatment selection. Today, cancers of the breast are routinely assayed for the HER2 molecular marker, which is directly associated with responsivity to Herceptin chemotherapy (42). Thus, HER2 is a biomarker that, in combination with other data guides a highly defined decision model toward effective treatment, as illustrated in **Figure 2**.

Exemplars of epidemiology-based biomarkers are blood pressure and blood lipid level. In combination with smoking, blood pressure and blood lipid levels are surrogate and modifiable risk factors of cardiovascular disease (CVD) (43, 44). President Franklin Delano Roosevelt's death from CVD led to the organization of the Framingham Heart Study in 1948 (44). At the time, little was known of CVD. Because little was known, it was unclear which data might be helpful in diagnosing, staging, or treating CVD; in other words, it was not clear how to define a useful decision model in CVD. Clear-cut clinical outcomes like a myocardial infarction were deemed invariably fatal and, without instruments to detect them, were diagnosed generally on autopsy (44). At that time, emerging research suggested the utility of electrocardiograms for diagnosing a myocardial infarction and for measuring blood lipids to predict MI risk. It was quite unclear which blood pressure was considered "normal" [at the time, the standard for normal systolic blood pressure was one's age plus 100 (43)]. Notwithstanding these knowledge gaps, the Framingham Heart Study's designers investigated all these seemingly disparate threads of evidence. In fact, they identified eighty phenotypic traits and measured them in 5,200 people. Over time, the Framingham Heart Study observed that cholesterol level, blood pressure, and smoking status formed a decision model that was associated with CVD at the population level (44). On the individual level, combining cholesterol level, blood pressure, and smoking status into a mathematical model of CVD led to the Framingham Risk Score (45), which described someone's risk of CVD given the magnitude of each measure (see **Figure 2**). The Framingham Risk Score subsequently generalized to novel populations (46, 47). Even though the decision model was identified at the population-level, the Framingham Risk Score is widely used by clinicians to guide treatment for individual patients and has guided decades of drug development (45) (https://www.mdcalc.

com/ascvd-atherosclerotic-cardiovascular-disease-2013-risk-calculator-aha-acc). Blood pressure and blood lipid levels are therefore biomarkers that, in combination with smoking status, form a decision model that guides clinical action by suggesting lifestyle modifications and pharmacologic treatments.

And yet, the presence of a cancer or a myocardial infarction is a binary distinction for disease: you either have it or you do not. But the line between health and disease is not always obvious, particularly for disorders of emotion, thought, and behavior (4). In psychiatry, the assumption that health and disease are discrete categories is being replaced by the observation that phenotypes present across a population are shifted toward extremes in disease (48). Similarly, observations that individual phenotypes can vary greatly across a population have led to the view that there is no universally optimal (or "healthy") profile of brain function (4). Though a distribution of continuous phenotypes might erode confidence in the possibility of categorical diagnoses in psychiatry, this has not been the case in other specialties: hypertension is parameterized as a range of blood pressures. Continuous phenotypes have the added value of expressing magnitude, which could be especially relevant given the multifactorial nature of psychiatric disease and the possibility that a decision model might draw probabilistically on multiple forms of (continuously measured) biomarkers.

Weakly specific and weakly sensitive biomarkers can guide clinical action if the decision model and, crucially, the decision in question is sufficiently well-defined. HER-2 gene positivity indicates that the drug Herceptin may be helpful in treating a very specific form of cancer. HER-2 positivity, therefore, resolves a specific treatment decision in a specific decision model: HER-2 does not resolve the treatment decisions in a "hot and shaky" patient or in a torn anterior cruciate ligament, or even in the selection of alternatives to Herceptin in a HER-2 positive breast cancer. Similarly, identifying risk factors for CVD guides clinicians to measure, trace, and then target those factors with treatment. HER-2 and CVD risk factors therefore are biomarkers that inform specific, well-defined treatment decisions within larger, well-defined decision models.

Framing clinical decision from a Bayesian perspective illustrates that, to be "fit for purpose," a biomarker must operate within a well-defined decision model to: (1) provide the clinician data they cannot currently access; (2) guide the collection of additional data; (3) uniquely resolve a well-defined treatment decision; (4) provide a convergence between top-down clinical phenomenology and bottom-up pathophysiology. Accordingly, we argue that operationalizing decision models in psychiatry is crucial if researchers hope to offer a biomarker to inform optimal decision-making (49).

OPERATIONALIZED DECISION MODELS

Psychiatry lacks operationalized decision models. This does not mean that psychiatry *has no* decision models. We reason that individual clinicians successfully treat individual patients by forming their own decision models that then guide data collection and treatment selection. In other words, psychiatrists treat patients by acting on idiosyncratic decision models. What psychiatry lacks is a way to formally describe an idiosyncratic decision model, thereby allowing it to be shared, evaluated, and optimized in terms of efficacy and efficiency. In machine learning and cognitive science, the process of optimizing a decision or generative model[1] is known as *structure learning* or—in statistics—(Bayesian) *model selection* and is one of the most important and difficult problems in the field (50–55).

Consider what happens when a clinician receives this one-line report on an intake form: "a 50-year-old man with schizophrenia is speaking to his dead girlfriend." This sentence serves as the first piece of information that, based on her clinical training, forms her preliminary decision model. If the clinician knows only that a man is speaking to his dead girlfriend, her preliminary decision model might include several hypotheses: e.g., normal or pathologic grieving, intoxication, withdrawal, trauma, or some other "organic" brain disease perhaps even a bacterial meningitis. Knowing that the patient is a 50-year-old man with schizophrenia makes a primary psychosis more likely and so what is required from a Bayesian perspective is data to eliminate the less likely but more serious hypotheses that require immediate intervention (e.g., delirium tremens from withdrawal) and to confirm a more likely hypothesis (schizophrenia). A series of standardized laboratory tests—a urine toxicology, breathalyzer, complete blood count, or blood electrolytes—would help rule out the less likely albeit more serious and easily treatable disease hypotheses. The clinician values these tests because the reliability (sensitivity, specificity, accuracy, range of error, and uncertainty) of the assays upon which they are based are regularly monitored and calibrated.

From a Bayesian perspective this is the problem of optimum Bayesian design (12, 16) or, active (Bayesian) inference (56, 57): the clinician uses standardized laboratory tests to eliminate less likely hypotheses to render the "true" disease hypothesis—and therefore the treatment decision—more certain or precise. And yet, if the clinician wanted to increase her confidence that the 50-year-old man indeed has schizophrenia, there are no standardized clinical tests she could perform. The clinician would simply ask her patient whether he experienced specific negative or positive symptoms of schizophrenia and for how long. During this conversation, the clinician would carefully observe the patient's demeanor, dress, affect, behavior, and thought process, looking for signs of schizophrenia such as blunted affect, disheveled appearance, and disorganized thought process. As the clinician accumulates more data, her relative certainty of a primary psychosis might increase—and her uncertainty about how to treat the patient would resolve. In sum, her decision model helps her organize and seek out new data, guiding her to a decision.

Framing clinical decisions with Bayesian inference allows the decision model itself to be made explicit and optimized. The clinician's decision model and implicit prior beliefs can, in

[1] Namely, a model that generates consequences from causes; in our setting, a model that generates signs, symptoms, and biomarkers from the right kind of psychiatric nosology. Inverting a generative model is the same as inferring the diagnosis, given the observable or measurable consequences of a psychiatric condition.

principle, be operationalized by mapping backwards from her final decision to the data that preceded it. In other words, it is possible to make an *objective* inference about the clinician's *subjective* inference by defining which decision model would make her ultimate decisions the most likely. This approach has already been established at the level of proof of principle in computational psychiatry, where the focus is to infer the prior beliefs of experimental subjects and, ultimately, patients using their behavioral responses to various stimuli and economic games (15, 19). However, the same procedures can, in principle, be applied to the psychiatrists using their diagnostic and treatment responses. Note the subtlety of this approach; namely, treating psychiatrists as expert Bayesian inference machines and reverse engineering the decision models that underwrite their diagnostic skills. The idea here is to operationalize decision models by making them explicit—by identifying the decision model that best explains the diagnostic behavior of one psychiatrist or another. As sentient creatures, with theory of mind, we do this all the time: for example, one can often infer what another person is thinking by watching where they are looking in a particular context. The notion here is that it could be mathematically applied to the diagnostic behavior of psychiatrists.

Operationalized decision models allow performance to be measured within and across individuals. Measuring how one clinician operates over time might identify decision efficacy and efficiency that, as expected by behavioral economists, varies with the time of day, the clinician's mood or whether they've eaten lunch or had their coffee (58). Model comparison further allows two clinicians' decision models to be formally compared by how efficiently they guide data discovery and by how effectively they arrive at a treatment decision which benefits the patient, which is further measured by clinical data.

In the case of our 50-year-old man, we could operationalize a decision model that excludes intoxication, withdrawal, or other "organic" brain diseases. This process can be operationalized because each value within a laboratory test is quantified and can therefore be mathematically modeled. We could not, however, operationalize a decision model that confirms a primary psychosis because the symptoms and signs of schizophrenia upon which a diagnosis of schizophrenia is based are not quantified (see **Table 1**). Because the symptoms and signs are not quantified, the accuracy, range of error, and uncertainty of any specific datapoint cannot be ascertained, further complicating their inclusion in an operationalized decision model.

Symptoms cannot be quantified because, by definition, they are the patient's personal experience that, in turn, relies on the patient's cognitive ability to sense, interpret, and report that experience. The reliance on self-report assumes that the relevant drivers of behavior are accessible linguistically to the reporter. But people are unaware of many of the drivers of their behavior (something called anosognosia) and, further, some forms of behavior (e.g., habits) are not represented by linguistic circuits in the way that goal-directed behaviors are and, therefore, remain difficult or impossible to articulate (59, 60). Although some symptoms are only detected by a patient's report (e.g., hallucinations), a reliance on self-report is problematic: in psychiatry, we often rely on a patient's perception of reality to diagnose disorders of reality perception.

Observable signs also rely on clinical inference. Two clinicians can observe the same patient and might disagree about whether the patient's thought process was "disorganized." And even if two clinicians agree that the patient's thoughts are "disorganized," there is no measure for *how disorganized.* Furthermore, because there is no empirical way to demonstrate how each clinician's brain *detected* the disorganization in the patient's speech (i.e., which specific words, phrases, or string of ideas in the patient's speech led each clinician to conclude the speech was disorganized), it is difficult to determine whether two clinicians agree on what "disorganized" means or whether two clinicians believe the patient's speech was disorganized for the same reason. Essentially, because we do not have direct access to the raw data a clinician solicits during her clinical exam, we cannot use model inversion to identify her data discovery procedure. An unfortunate corollary of this problem is that, right now, if a clinician attempts to treat a patient's disorganized speech with, say, an antipsychotic, there is no way to objectively ascertain whether and how much the disorganization changes with that treatment.

In sum, in the absence of quantified clinical data, we cannot operationalize how a clinician arrives at a treatment decision or how to modify treatment as the decision model updates. And in the absence of a clearly defined decision model, it is quite unclear where a biomarker might be of use. This means that the prerequisite to defining a biomarker to formalize decision models is to first develop quantitative phenotypes. We describe how this might proceed in two stages, below.

PRACTICAL STAGES OF PHENOTYPING AND DECISION MODELING

Before a biomarker can inform clinical decision, that clinical decision process must itself be explicitly formalized and evaluated. Put differently, we argue that a precondition to biomarker development is that clinically salient data be rigorously quantified and that clinical decisions be operationalized and evaluated based on those data (61). Only when both preconditions are met can statistical analyses be performed to determine *which* data are the most useful for *which* decisions. And yet it remains unclear for psychiatry which data might be the most useful to acquire and analyze.

Psychiatry is in a conundrum comparable to where the designers of the Framingham Heart study found themselves in the late 1940's: we have multiple disparate lines of thinking about the causes of mental illness that are now only beginning to coalesce into tenable hypotheses (62). Promising analyses of even the largest samples with supposedly promising statistical power and high statistical significance have repeatedly failed on the individual level (26, 63, 64). Though this failure is often attributed to the high phenotypic variability of psychiatric patients, it is worth noting again that clinicians nevertheless successfully recognize salient data and treat psychiatric illnesses

TABLE 2 | Digital phenotypes are quantitative observable signs.

Qualitative data		**Quantitative data**
Subjective symptoms	**Observable signs**	
Patient report	**Clinician observation**	**Digital phenotypes**
What's on your mind?		Search history, social media
What's your typical day like? How active are you? How much sleep do you usually get?		Actimetry, geolocation
Are you a social person? How are your relationships?		Call/text logs, social media profile
How's your mood throughout the day?		
	Affect, appearance, attitude	Facial action unit motion and fluidity analysis
	Affect, speech, thought content, thought process	Semantic analysis, natural language processing, vocal acoustics
	Psychomotor behavior	Head box analysis

This table illustrates how commonly assessed qualitative data like subjective symptoms reported by patients and observable signs observed by clinicians can be quantified as digital phenotypes. Quantitative data has the added value of being able to operate within Bayesian decision models.

on the individual level by applying their own idiosyncratic decision models.

Broadly speaking, as a field, we feel confident that facets of a patient's biological, social, and psychological history are relevant to the behavioral expressions of mental illness that we treat (40). Yet behavior itself remains a vague and poorly defined phenomenon. Behavior—whether reported by patients or observed by clinicians—is not objectively measured in a way comparable to the molecular assays, blood tests, or electrocardiograms prevalent in other medical specialties. Here, psychiatry might benefit from digital technologies that have recently emerged specifically to quantify human behavior. We reason that digital tools might help psychiatry in two stages: stage 1 would quantify data already present in the standard clinical interaction and allow decision models to be operationalized and evaluated; stage 2 would explore whether other forms of data not currently used in the clinical evaluation might have value within an operationalized decision model.

Stage 1 would quantify clinical data and operationalize the decision models currently employed in clinical practice (see **Table 2**). Before moving ahead to define new forms of data or combinations of data that *might* be relevant to clinical work (as described in stage 2), the field should instead quantify those behaviors and operationalize those decisions that we already agree are clinically relevant as rigorously as possible.

Stage 1 would involve creating video and audio recordings of clinical interactions and using digital tools to measure the data a clinician already solicits during her exam (65). A video recording can be separated into visual data and audio data. Visual data can be processed to label different parts of the body, allowing the speed, acceleration, fluidity, and coherence of movement to be measured. Facial expression can be quantified by measuring how different facial action units coordinate over time (66); not necessarily to label emotional state, but rather to measure how an individual's unique repertoire of facial expression changes over time. Body language—both the patient's and the clinician's—can be quantified as the relationship of the head to the shoulders, torso, and legs throughout the clinical interview (67). Voice data can be analyzed for its acoustic properties to measure how often a patient takes a breath, how many syllables they utter per second, how their intonation changes over time (68). Speech can be transcribed and measured using tools that can define semantic and psycholinguistic content (69–71). In essence, the mental status exam can, in theory, be measured with digital tools (66).

Practically, if a clinician was evaluating a "50-year-old man with schizophrenia is speaking to his dead girlfriend," she would proceed with her exam as usual except a video would record her interaction. Such a recording would capture the same data she is sensing with her eyes and ears except it will now be digitally. A host of mathematical tools can be applied to this digital data. In addition, the clinician's decision model can be inferred and formalized using Bayesian methods described above. Crucially, different decision models—whether from two different clinicians or from the same clinician at different timepoints—can be compared and optimized using the same Bayesian methods, thereby leading to decision models that are more efficient and effective. Once the data and decision models clinicians currently use have been formally evaluated, new forms of data can be evaluated.

Stage 2 would evaluate whether forms of data not currently used in clinical decision might add value at specified points in larger decision models. As outlined in **Table 1**, relatively new technologies such as aggregates of someone's online search (72) or social media history (73–77) might inform clinicians about how a patient's interests, self-esteem, or social relationships change over time. Paired with geolocation data, actimetry tools offer measurements for how active a patient is (78, 79), how much they are sleeping, and how these both change over time (80, 81). Daily call and text logs can provide a measure of a patient's social connectedness and engagement (82, 83). Furthermore, wearable sensors that detect heartrate variability and skin conductance during or between clinical encounters could provide a measure of a patient's stress response and how this response changes with treatment (84).

In addition, other forms of data that are not currently used in clinical practice—such as genetic information or exposome—could be more ably evaluated within an operationalized decision model. Even though each datapoint might have limited specificity and sensitivity in isolation, in combination, they might have utility at a specific decision within a larger decision model.

Rigorous measurements of behavior in the clinical setting—and especially outside of it—can help psychiatrists obtain more naturalistic and nuanced data, yet we acknowledge that it is not clear which aspects of behavior, at what time frequency, or for how long such data should be collected (85, 86). This is analogous to the measurement of body temperature of our "hot and shaky" patient treated with antibiotics; we would expect the temperature to vary over the course of the treatment. However, unless temperature is ascertained sufficiently frequently, there is no way of objectively knowing the time scale of the infection. Determining a suitable time scale (days, months, years, or decades) is largely dependent on having access to an operationalized decision model within which time scale has utility. Sampling a patient's temperature over the course of a day or week might inform a specific decision like antibiotic selection (e.g., if a patient remains febrile, it is likely an antibiotic is ineffective against a given infection), but measuring temperature over the course of a month would not.

PHENOTYPING, A PREREQUISITE TO BIOMARKER DEVELOPMENT

The relatively nascent field of Deep Phenotyping aims to collect data for large, longitudinal samples using standardized and rigorous procedures (87). Multiple on-going, large-scale, necessarily collaborative efforts are seeking to provide deep phenotypes (88) that span genetic and epigenetic data to brain imaging to digitized behavioral and online data (89, 90). Together these data seek to measure—as much as possible—an individual's biologic, social, and psychologic profile.

Although it is unclear which types of data will prove the most relevant, it is clear what we need to learn from these data: how to quantify, monitor, and modify specific decision models. The first step to modifying the course of any illness is to fully characterize that illness as it develops from health, similar to what the Framingham Heart Study has done for cardiovascular illnesses (44, 61). It is worth noting that the Framingham Heart Study did not discover physiologic concepts like cholesterol or blood pressure; these were known prior to the initiation of the study. Rather, the Framingham Heart Study motivated further investigation of this physiology by connecting it to clinical phenomenology, thus bridging bottom-up and top-down clinical evaluation. Put differently, the identification and appreciation of precise physiologic mechanisms underlying cardiovascular illnesses came only after a precise clinical decision model was defined and traced over time.

Likewise, the identification of the HER-2 biomarker required a decision model based on clinical interview (subjective symptoms), routine physical exam (observable signs), mammography, and biopsy. Only with a carefully defined phenotype was HER-2 able to add value to clinical decision by converging bottom-up and top-down assessment within a single, highly specific treatment decision: whether to prescribe Herceptin.

Therefore, as psychiatry's bottom-up understanding of pathophysiology continues to evolve, our top-down measurement and formalization of clinical phenomenology will become ever more crucial if the two fields of inquiry are to converge in meaningful ways. Though it is possible that the individual genes or pathophysiological pathways underlying clinical conditions will be associated with specific diagnoses or subtypes, this seems unlikely to be broadly applicable—given the diagnostic ambiguity across psychiatric diagnoses, the multi-determined nature, and the unclear decisions a candidate biomarker would address (91, 92). Operationalized decision models informed by quantitative phenotypes appear to be a way forward.

Endeavors of this scope and magnitude require significant investments of time and resources. Yet it is worth bearing in mind that the amount of time and resources required to gather background information necessary to provide actionable insights are an investment for future generations. Defining clinical decision models to guide treatment in the presence of disease have the added benefit of informing decision models to guide prevention before that disease emerges.

For patients, history has shown that early diagnosis and preventative treatment can alter certain disease trajectories, thereby creating an enormous benefit across a population that more than justifies the costly upfront investment (44). It is true that the development of new technologies can increase the proximal cost of healthcare delivery. At present, because the vast majority of generic psychiatric medications are inexpensive and offer palliative treatment to a broad category of patients, it may be more economic and effective to broadly offer palliative treatments than to deeply phenotype patients in an effort to identify modifying or curative treatments that help only a relative few (see **Table 1**). However, overall healthcare costs can be decreased by more effectively identifying and treating illness in the preventative stage (93). Overall, new technology (once effective) can demonstrate which preventative health measures might best promote health or reduces the economic burden of illness by decreasing inpatient admission and increasing public health and productivity. An additional added benefit of technology is that its cost decreases over time, thus expanding access to populations who previously had been unable to benefit from the healthcare for reasons of cost, geographic, or equity.

For researchers, laying a rigorous foundation for data collection, synthesis, and modeling will produce a dataset that can inform a multitude of studies, which (if the Framingham Heart Study is any indication) can yield large and compounding dividends for the scientific community. Although it is not clear what time scale and data will prove to be the most beneficial for psychiatry, what makes such an investment timely for behavioral and mental health is the fact that the necessary tools and techniques for such a study have only recently emerged.

In summary, psychiatry has yet to develop and validate biomarkers that improve clinical practice. This report represents an attempt to step back and consider why our past efforts to develop biomarkers have failed and to reframe our efforts in terms of data and decision science. As our bottom-up understanding of the pathophysiology of psychiatric illnesses continues to evolve, our top-down measurement and formalization of clinical phenomenology will become ever more crucial if the two fields of inquiry are to converge in meaningful ways. Step toward this convergence include first, rigorously quantifying clinical data and operationalizing existent psychiatric decision models and, second, evaluating where new forms of data, including candidate biomarkers, might be of value. Our hope is that making clinical decision explicit will reframe the biomarking enterprise so it might impact clinical inference and, in turn, improve the lives of our patients.

AUTHOR CONTRIBUTIONS

DSB and JK conceptualized and drafted the manuscript. JB, KB, DB, SE, KF, PF, PG, SH, AH, J-PO, AP, and DS edited and provided input. All authors contributed to the article and approved the submitted version.

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Effects of the *DRD4* −521 C/T SNP on Local Neural Activity and Functional Connectivity in Children With ADHD

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Objective: The present study aimed to investigate the effects of the dopamine receptor D4 (*DRD4*) −521 C/T single-nucleotide polymorphism on brain function among children with attention deficit hyperactivity disorder (ADHD) and to evaluate whether brain function is associated with behavioral performance among this demographic.

Methods: Using regional homogeneity, fractional amplitude low-frequency fluctuation, and functional connectivity as measurement indices, we compared differences in resting-state brain function between 34 boys with ADHD in the TT homozygous group and 37 boys with ADHD in the C-allele carrier group. The Conners' Parent Rating Scale, the SNAP-IV Rating Scale, the Stroop Color Word Test, the go/no-go task, the n-back task, and the working memory index within the Wechsler Intelligence Scale for Children-Fourth Edition were selected as comparative indicators in order to test effects on behavioral performance.

Results: We found that TT homozygotes had low behavioral performance as compared with C-allele carriers. The regional homogeneity for TT homozygotes decreased in the right middle occipital gyrus and increased in the right superior frontal gyrus as compared with C-allele carriers. In addition, the right middle occipital gyrus and the right superior frontal gyrus were used as the seeds of functional connectivity, and we found that the functional connectivity between the right middle occipital gyrus and the right cerebellum decreased, as did the functional connectivity between the right superior frontal gyrus and the angular gyrus. No statistically significant differences were observed in the respective brain regions when comparing the fractional amplitudes for low-frequency fluctuation between the two groups. Correlation analyses demonstrated that the fractional amplitude low-frequency fluctuation in the precentral gyrus for TT homozygotes were statistically significantly correlated with working memory.

Conclusions: We found differing effects of *DRD4* −521 C/T polymorphisms on brain function among boys with ADHD. These findings promote our understanding of the genetic basis for neurobiological differences observed among children with ADHD, but they must be confirmed in larger samples.

Keywords: ADHD, *DRD4* −521 C/T SNP, regional homogeneity, fractional amplitude low-frequency fluctuation, functional connectivity

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by age-inappropriate inattention, hyperactivity, and impulsivity (1). ADHD has a worldwide prevalence rate of ∼7.2% (2), with a corresponding prevalence rate of 5.6% in China (3). Male-to-female sex ratios are reported in the range of 2:1 to 4:1 (4). Symptoms persist into adulthood in ∼60% of children with ADHD (5). ADHD is usually associated with a variety of negative outcomes, including high dropout rates, social barriers, criminal behaviors, and professional failures, which may have serious impacts on individuals, families, and society (6).

Previous studies have shown that ADHD has high heritability (7). A promising candidate gene for ADHD is the gene encoding dopamine receptor D4 (*DRD4*), which is mapped to the short arm of chromosome 11 located at 11p15.5 (8). *DRD4* mediates the post-synaptic activity of dopamine and participates in cognitive functions and emotional responses, including attention, perception, planning, language, and memory (9–11). The −521 C/T single-nucleotide polymorphism (SNP), located 521 bp upstream of the transcription start site for *DRD4*, is responsible for the regulation of the transcription rate for this gene. Studies have shown that the *DRD4* −521 C/T SNP is associated with specific personality traits (12), novelty seeking, schizophrenia risk (13), cognitive impairment (i.e., speech fluency and working memory) (14), and executive dysfunction (15). *DRD4* −521 C/T polymorphisms can adjust transcription initiation frequency by changing the affinity of the *DRD4* mRNA polymerase and the respective promoter in order to increase or decrease DRD4 expression levels. A previous study reported that the transcriptional activity for the T allele in the *DRD4* −521 C/T SNP was 40% lower than that of the C allele (16). Additionally, a case-control study found that the frequency of the T allele in children with ADHD was statistically significantly higher than that of the C allele, while the frequencies of the C and T alleles in the children's neurotypical counterparts were similar (17). Therefore, based on findings within the literature to date, the T allele is considered a risk gene for ADHD. Drug therapy has proven that reductions in the dopamine neurotransmitter contribute to the etiology of ADHD. Methylphenidate acts to improve the symptoms of inattention and hyperactivity *via* the pharmacological mechanism of increasing dopamine levels from the synaptic cleft by reducing dopamine reuptake and prolonging its binding time to receptors (18–20). Moreover, the *DRD4* −521 C/T SNP has been confirmed to be a critical factor in the pathogenesis of ADHD (17, 21, 22).

Functional magnetic resonance imaging (fMRI) is becoming an increasingly common approach for understanding the pathological mechanisms mediating ADHD risk (23). Resting-state functional magnetic resonance imaging (rs-fMRI) is widely used in neuropsychological research because of its high resolution and lack of radiation; this imaging modality can more sensitively reflect differences in brain function as compared with neuropsychological tests (24). To date, there has only been one imaging study regarding the *DRD4* −521 C/T SNP. That study found that C-allele carriers and those with CC homozygous genotypes had enhanced memory functionality with respect to novel perception and salient stimulation as compared to participants with TT genotypes, which may be mediated *via* activation of the ventral striatum and hippocampus through variations in this genotype (25). At present, most research has focused on the impact of polymorphisms in the 48-bp (base pair) variable-number tandem repeat (VNTR) region in exon 3 of the *DRD4* on brain functions in children with ADHD (26–28). There have been relatively few studies on the association between the *DRD4* −521 C/T SNP in the promoter of the non-coding region for the *DRD4* and ADHD risk and outcomes. The potential effects of this polymorphism on ADHD brain function are currently unclear.

In the current study, we investigated the effects of the *DRD4* −521 C/T SNP on brain function in boys with ADHD. The relationship between brain function and behavioral performance was also explored. Brain imaging data from 71 children with ADHD were acquired using magnetic resonance scanning. The participants were divided into TT homozygous and C-allele carrier groups according to genotype. Brain indicators, such as regional homogeneity (ReHo), fractional amplitude low-frequency fluctuation (fALFF), and functional connectivity (FC), were calculated in order to detect potential differences between the two groups. Behavioral performance was assessed using the Conners' Parent Rating Scale (CPRS), the SNAP-IV Rating Scale, the Stroop Color Word Test (SCWT), the go/no-go task, the n-back task, and the working memory index (WMI) in the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) in order to test the multidimensional abilities of children with ADHD. Based on previous findings, we hypothesized that TT homozygotes would have lower levels of spontaneous neuronal activity and FC as compared with C-allele carriers. The abilities of children with the TT homozygous genotype with respect to behavioral performance were worse as compared with C-allele carriers in prior research, and there is an established correlation between behavioral performance and brain function in general.

MATERIALS AND METHODS

Participants

Seventy-one participants were recruited from the Children's Care and Mental Health Center at Shenzhen Children's Hospital. Eligible participants were diagnosed by experienced pediatricians using the Diagnostic and Statistical Manual of Mental Disorders, 4th Revision (DSM-IV). The children and their parents were interviewed *via* the Kiddie-Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version (K-SADS-PL). The inclusion criteria were as follows: (1) aged between 8 and 9 years; (2) a full-scale IQ (FSIQ) above 70 as assessed by the WISC-IV; (3) normal vision and hearing; and (4) right-handedness. The exclusion criteria were as follows: (1) such as learning disabilities, tic disorders, conduct disorders, anxiety, depression, and other mental disorders; (2) ADHD medication, behavioral training, psychotherapy, and other treatments; and (3) metal objects that are difficult to remove (i.e., tooth implants). Ethics approval was obtained from the Medical Research Ethics Committee at

Shenzhen Children's Hospital. Written informed consent was obtained from all the participants and their parents.

Genotyping

Peripheral venous blood was collected from the participants. Genomic DNA was extracted from whole blood using a Flexi Gene DNA kit (QIAGEN, Hilden, Germany). PCR amplification was performed following DNA extraction. Participants were divided into TT homozygous genotypes (TT homozygous group, $n = 34$) and C-allele carriers (C-allele carrier group, $n = 37$; TC genotype = 29, CC genotype = 8) based on genotypes detected *via* agarose gel electrophoresis.

Measurements

ADHD Symptoms

The SNAP-IV Rating Scale is mainly used for ADHD screening, auxiliary diagnosis, evaluating intelligence efficacy, and evaluating symptom improvement in children and adolescents aged 6–18 years. This scale contains 26 items, which are divided into three subscales: inattention (IA), hyperactivity/impulsivity (HI), and oppositional defiant disorder (ODD). Each item uses a 4-point Likert scale: 0 for "not at all," 1 for "a little bit," 2 for "quite a bit," and 3 for "very much." We then calculated the average score for each subscale. After receiving a questionnaire, parents rated their children's behavior and behavioral severity within the last 6 months. The completion time for the scale was ∼10 min. The SNAP-IV Rating Scale has been demonstrated to have satisfactory validity and reliability in prior research (29).

Behavioral Problems

The CPRS is used to assess common behavioral problems in children aged 3–16 years and is mainly implemented in the assessment of children with ADHD. The CPRS consists of five subscales and hyperactivity indices: conduct problems, learning problems, psychosomatic problems, impulsivity-hyperactivity, anxiety, and hyperactivity indices. There are 48 items in the CPRS. Each item is scored on a four-level scale ranging from 0 to 3: "0" indicates that there is no such problem, "1" indicates that there is an occasional or slight performance decrease, "2" indicates frequent or serious behaviors, and "3" indicates very common and/or very serious behaviors. We added the scores of the items contained in each subscale and divided the total score by the number of items in order to obtain subscale-specific scores. The number of CPRS items is moderate, its content is simple and easy to understand, and parents can complete the scale within ∼5–10 min. This scale is widely used and is a good assessment tool for children with ADHD (30).

Inhibition Control

The SCWT consists of three color-printed cards representing color tasks, word tasks, and combined color–word tasks. Each card consists of 24 words or dots. The first step of the test is to present card A (i.e., the color task), which is composed of dots of four different colors (red, green, yellow, and blue). The second step is to present card B (the word task), which is composed of words in red, green, yellow, and blue (excluding words with color meanings). The third step is to present card C (the color–word task) and represent the four words red, green, yellow, and blue with colors different from their word meanings. The participants were required to correctly read the colors of the dots and words on each card as soon as possible. Evaluators recorded the time it took participants to complete the tasks and the number of mistakes they made in each task. Interference scores indicates the ability to suppress interference. Specifically, time interference is defined as the time necessary to complete a color–word task minus the time to complete the word task; error interference is defined as the number of errors in the color–word task minus the number of errors in the word task.

The go/no-go task used "R" to indicate reactive stimuli (accounting for 80% of stimuli) and "P" to indicate non-reactive stimuli (accounting for 20% of stimuli). At the beginning of the task, the fixation point "+" was shown for 400 ms. The stimulus was then randomly presented at the center of the screen (lasting for 200 ms), with a randomly changing (800 ± 200 ms) inter-stimulus interval. The participants were instructed to press the button as quickly and accurately as possible when they saw "R" and to not press the button when they saw "P." There were 136 "R" and "44" P stimuli presented during the entirety of the task, and the total completion time was ∼5 min. The participants were required to remain quiet in the test environment. Prior to the test, participants were guided with respect to task instructions, with testers explaining the associated requirements and precautions. The recorded indices were the number of missed keys, the number of wrong keys, correct response times, and response time variations (represented by the ratio of the standard deviation of the average response time to the average response time).

Working Memory

The WISC-IV is widely used in clinical intelligence tests and presents high reliability and validity (31). The WISC-IV consists of four subscales (verbal comprehension, perceptual reasoning, working memory, and processing speed) as well as a comprehensive full-scale IQ (FSIQ). In the current study, the WMI subscale was used to evaluate working memory ability. The WMI is evaluated based on reciting numbers (also known as digit span) and letter number sequencing subtests. The reciting numbers test requires reciting numbers sequentially and inversely. Sequential reciting refers to the principal tester reading out a sequence of numbers from 2 to 11 (the first level corresponds to two numbers, and each additional level adds one number, a total of 10 levels), with the participants reciting the sequence in the same order. Within this task, when sequence is over, the reverse sequence is started. The principal tester reads a series of numbers from 2 to 9 (level 1 and level 2 correspond to two numbers, and one number is increased for each level from level 3 onward, for a total of nine levels), and the participants recites the numbers in reverse order. The sequence compositions for the sequential and reverse recited numbers are different. If a participant fails to pass the same question twice, the test is terminated. One point was awarded for each pass score for level 1, and no points were deducted for errors. The total score for the reciting numbers task is the sum of the individual scores based on reciting numbers in order and in reverse order. In the letter number sequencing test, the main tester reads a list of numbers and letters (levels 1 and 2 are composed of one letter and one number, levels 3–5 are composed of two letters and one number

TABLE 1 | Demographic and clinical characteristics of children with ADHD in the two groups.

	TT homozygous	C-allele carriers		
	***N* = 34**	***N* = 37**	**t**	***p***
Age	8.75 ± 0.55	8.88 ± 0.61	−0.913	0.365
Grade	2.82 ± 0.71	2.81 ± 0.77	0.072	0.943
FSIQ	85.76 ± 8.85	86.29 ± 7.09	−0.281	0.780
Mean FD	0.09 ± 0.06	0.08 ± 0.06	0.800	0.426
WMI	83.29 ± 10.21	87.62 ± 9.73	−1.828	0.072
CPRS				
Conduct problem	1.21 ± 0.51	1.16 ± 0.49	0.408	0.685
Learning problem	1.91 ± 0.56	1.99 ± 0.66	−0.560	0.578
Psychosomatic disorder	0.27 ± 0.35	0.30 ± 0.31	−0.335	0.739
Impulsivity-Hyperactivity	1.76 ± 0.68	1.54 ± 0.71	1.361	0.178
Anxiety	0.55 ± 0.48	0.73 ± 0.59	−1.389	0.169
Hyperactivity indices	1.64 ± 0.56	1.57 ± 0.53	0.502	0.617
SNAP-IV				
SNAP-IA	2.06 ± 0.60	1.92 ± 0.69	0.850	0.398
SNAP-HI	1.67 ± 0.64	1.53 ± 0.61	0.935	0.353
SNAP-ODD	1.29 ± 0.71	1.34 ± 0.61	−0.344	0.732
SCWT				
Time interference	19.11 ± 10.52	18.91 ± 11.69	0.074	0.942
Error interference	2.23 ± 2.11	2.18 ± 1.79	0.099	0.921
Go/no-go Task				
Number of missed keys	7.52 ± 5.57	7.75 ± 8.35	−0.134	0.894
Number of wrong keys	23.38 ± 5.53	22.75 ± 5.09	0.494	0.623
Correct response time	427.98 ± 81.61	412.06 ± 61.52	0.933	0.354
Response time variation	159.34 ± 44.47	148.97 ± 41.50	1.016	0.313
N-back Task (correct rate)				
0-Back	0.86 ± 0.16	0.88 ± 0.10	−0.655	0.514
1-Back	0.60 ± 0.25	0.62 ± 0.19	−0.417	0.678
2-Back	0.41 ± 0.15	0.40 ± 0.16	0.268	0.790

ADHD, attention deficit/hyperactivity disorder; FSIQ, Full-Scale Intelligence Quotient; FD, framewise displacement; WMI, working memory index; CPRS, Conners' Parent Rating Scale; IA, inattention; HI, hyperactivity/impulsivity; ODD, oppositional defiant disorder; SCWT, Stroop Color Word Test.

or one letter and two numbers, and one number or letter is added for each additional level from level 6 onward, a total of 10 levels); the participants recite the numbers they hear from small to large and recite the letters they hear in English alphabetical order. When the participant fails to pass the same question after three attempts, the test is terminated. One point is obtained for each pass for level 1, no points are deducted for errors, and the final score is recorded by the study evaluators. The final WMI is the composite score of the two subtests (reciting numbers and letter–number sequencing).

The n-back test was used to evaluate working memory capabilities *via* three subtasks. At the beginning of the task, the "+" fixation point appears at the center of the computer screen. After 500 ms, a 1 cm × 1 cm gray square appears randomly at the upper left corner, the upper right corner, or the lower right corner, containing the symbol "+" and lasting for 400 ms. The next gray square appears after an interval of 3,000 ms. In the 0-back task, participants were asked to press the left side of the mouse with their right index finger when the square containing the symbol "+" appeared at the upper left corner. Participants were instructed to press the right mouse button with the middle finger of their right hand if the square was to appear in the upper or lower right corner. In the 1-back task, participants were asked to press the right mouse button if the square in the next figure were to appear in the same position as the square in the previous figure and to press the left button if the presentation was different. In the 2-back task, participants were asked to press the right mouse button if the position of the square in the next figure was the same as the square in the previous graph of the previous graph and to press the left mouse button if the presentation was different. There were 30 trials in each task, and the total completion time was ∼10 min. The accuracy rate for each task was calculated as the number of gray squares with correct presses divided by the total number of gray squares for each corresponding task.

Image Acquisition

MRI data were collected using a 3.0 T Siemens Trio Tim scanner (Siemens, Munich, Germany). All participants were asked to close their eyes and to keep their bodies still during the scan. Rs-fMRI data were collected using echo planar imaging [repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, flip angle (FA)

= 90°, matrix size = 94 × 94, field of view (FOV) = 220 mm × 220 mm, volume number = 130, 36 slices, 3-mm slice thickness]. In addition, high-resolution T1-weighted images were acquired using three-dimensional magnetization-prepared rapid gradient echo imaging [TR = 2,000 ms, TE = 2.26 ms, inversion time (TI) = 900 ms, flip angle = 8°, matrix size = 256 × 200, layer number = 176, 1-mm thickness].

Data Preprocessing

DPABI 4.3 Advanced Edition software (http://rfmri.org/dpabi) based on MATLAB (2014a; MathWorks, Natick, MA, USA) was used to conduct the MRI data preprocessing and associated statistical analyses (32). The processing procedure was as follows: (1) remove first 10 time points; (2) slice timing; (3) head motion correction; (4) nuisance covariate regression (i.e., linear drift, white matter, cerebrospinal fluid); (5) spatial normalization; (6) smoothing (smooth core for 4 mm); and (7) filtering (0.01–0.10 Hz).

Head Motion Control

Image data can generate information on the mean frame-wise displacement (FD) during scanning. According to Jenkinson's relative root mean square algorithm (33), we excluded participants whose mean FD exceeded 0.2 mm. Four participants who were TT homozygous and three participants who were C-allele carriers were excluded according to this criterion. Head movement effect was controlled by including the mean FD values as covariables within subsequent statistical analyses.

Regional Homogeneity, Fractional Amplitude Low-Frequency Fluctuation, and Functional Connectivity Calculations

ReHo, fALFF, and FC analyses were performed using DPARSF5.0 Advanced Edition software (http://rfmri.org/DPARSF). ReHo is a voxel-based measure of brain activity that evaluates the similarity or synchronization between the time series of a given voxel and its nearest neighbors. The ReHo was calculated as follows: in order to reduce low-frequency drift and high-frequency noise, we performed a bandpass filter on the spatial standardized data, and Kendall's coefficient of concordance was used to calculate the similarity of the time course between a given voxel and the nearest 26 voxels (34). Next, the ReHo image for each participant was divided by the average ReHo in the brains of all participants in that group. Finally, spatial smoothing (i.e., with a smooth core for 4 mm) was performed on the ReHo brain map.

The fALFF reflects the intensity of regional spontaneous brain activity (35) and was calculated as follows. First, the functional data were preprocessed to obtain the data for linear drift removal. Next, fast Fourier transform was used to transform the time series for each voxel to the frequency domain to obtain the power spectrum. In each voxel, the square root of the power spectrum was calculated at each frequency and was averaged across the entire frequency range. The ratio of the low frequency (0.01–0.08 Hz) power spectrum to the whole frequency range was then calculated. To reduce the global effects of variability across participants, the individual fALFF map was transformed into a Z-score map *via* Fisher-Z transformation.

FC refers to the degree of correlation between the blood oxygenation level-dependent signal sequences in different brain regions within a given time dimension. The FC was calculated as follows: the brain regions with statistically significant differences in ReHo or fALFF between the two groups were defined as regions of interest (ROIs). The mean time series for all voxels in each ROI were then calculated. Pearson's correlation coefficients were used to calculate the FC between the mean time series for each ROI and that of each voxel within the whole brain. Finally, Fisher's Z-transform was used to normalize the correlation coefficients.

Statistical Analysis

For general demographic and clinical data, statistical analyses were completed using Statistical Package for the Social Sciences (SPSS) software, version 23.0 (Chicago, IL, USA). The measurement data conformed to a normal distribution, and we thus analyzed the differences in age, FSIQ, mean FD, and behavioral performance scores between the two groups using independent sample *t*-tests. The results were expressed as means ± standard deviations. When the resulting *p*-value was very close to 0.05, the effect size was further calculated. Cohen's d was used to measure effect size (36); this statistic was computed by dividing the difference between group means by the pooled standard deviation weighted by the sample size. An effect size of 0.2 corresponds to a small effect, an effect size of 0.5 corresponds to a medium effect, and an effect size of 0.8 corresponds to a large effect.

For MRI data, two sample *t*-tests were performed using DPABI 4.3 Advanced Edition Statistical Analysis to identify brain area differences between the two groups with respect to ReHo, fALFF, and FC. Age, head movement, and the WMI were taken as covariates to exclude any confounding effect on the results. The Gaussian random field (GRF) theory was used for multiple comparisons with voxel $p < 0.001$ and cluster $p < 0.05$ (two-tailed). The GRF controls the thresholds for certain error rates within test statistics in order to improve the accuracy and authenticity of the results (37).

Behavioral indicators with statistically significant differences between the two groups were selected for further correlation analyses. WMI was selected for further analysis in this study. And the fALFF/ReHo/FC clusters showing statistically significant group differences were extracted as ROI masks. The "ROI Signal Extractor" in the Utilities module of the DPABI toolkit was used to extract the time series for each group of ROIs. Finally, SPSS software was used to conduct partial correlation analyses between the ROI time series for each group and the corresponding WMI, controlling for the potentially influencing factors of age and mean FD. The correlations were considered statistically significant when *p*-values were <0.05.

Finally, controlling for age and mean FD, we calculated the partial correlation analysis between ReHo, fALFF, and working memory ability scores in each group. The GRF was used for correcting multiple comparisons (two-tailed, voxel $p < 0.001$, cluster $p < 0.05$). Time series were extracted for related brain

regions, and partial correlation analysis was performed with respect to the WMI, controlling for age and mean FD.

RESULTS

General Demographic and Clinical Data

A total of 71 children with ADHD were enrolled in this analysis (TT homozygous group = 34, C-allele carrier group = 37). Age, FSIQ, and mean FD did not differ at the level of statistical significance between the TT homozygous and C-allele carrier groups ($p > 0.05$). With respect to ADHD symptoms, the scores for the TT homozygotes were higher than those of C-allele carriers within the two subscales in the parent version of the SNAP-IV Rating Scale. In addition, we also found that TT homozygotes showed more serious behavioral problems, including inappropriate conduct, impulse hyperactivity, and behavior assessed through the hyperactivity index, as compared with C-allele carriers within univariate analyses. As negative controls, the C-allele carriers showed stronger inhibition capabilities as compared with the TT homozygous group. With respect to working memory ability, we found that the accuracies for TT homozygotes in the 0-back task and in the 1-back task were higher than that of C-allele carriers. In the 2-back task, the accuracies of the two groups were essentially the same. We found a statistically significant difference in the WMI between the two groups within univariate tests, and the *p*-value after conducting multivariate-adjusted statistical analysis was close to 0.05. We further calculated that the effect size was 0.435 (representing a moderate effect), indicating that increasing the sample size could achieve statistical significance. Although children in the TT homozygous group performed worse on clinical behavioral assessment scales as compared to C-allele carriers, the differences were not statistically significant ($p > 0.05$) (**Table 1**).

Regional Homogeneity and Fractional Amplitude Low-Frequency Fluctuation Results

Compared with C-allele carriers, TT homozygotes had decreased ReHo in the right middle occipital gyrus (MOG) (**Figure 1A**; coordinates: 36, −87, 12) and increased ReHo in the right superior frontal gyrus (SFG) (coordinates: 18, 57, 27) (GRF-corrected $p < 0.05$). The fALFF did not differ between TT homozygotes and C-allele carriers at the level of statistical significance.

Functional Connectivity Results

Considering FC based on the right MOG as a seed, TT homozygotes had reduced FC in the right MOG and the right cerebellum as compared with the C-allele carriers (**Figure 1B**; coordinates: 21, −75, −24) (GRF-corrected $p < 0.05$). Considering FC based on the right SFG as a seed, TT homozygotes had reduced FC in the right SFG and the angular as compared with the C-allele carriers (**Figure 1C**; coordinates: 39, −60, −36) (GRF-corrected $p < 0.05$).

Correlation Analysis

After comparing the behavioral indicators for the two groups, we found a large difference in the WMI between groups. Therefore, we analyzed the correlations between WMI and statistically significantly different brain regions between the groups after controlling for age and head movement (mean FD) factors. No statistically significant correlations between WMI scores and ReHo in the right MOG and in the right SFG were observed when comparing the two groups (TT homozygous, right MOG: $r = 0.047$, $p = 0.813$; right SFG: $r = -0.243$, $p = 0.213$; C-allele carriers, right MOG: $r = -0.027$, $p = 0.882$; right SFG: $r = 0.192$, $p = 0.292$). The FC between the right MOG and the cerebellum and the FC between the SFG and the angular gyrus were not statistically significantly correlated with WMI scores in either group (TT homozygous, MOG and cerebellum: $r = -0.015$, $p = 0.938$; SFG and angular gyrus: $r = -0.240$, $p = 0.219$; C-allele carriers, MOG and cerebellum: $r = -0.241$, $p = 0.184$; SFG and angular gyrus: $r = -0.123$, $p = 0.503$).

This study further calculated the association between ReHo, fALFF, and WMI scores in each group. We found a statistically significant positive correlation (**Figure 2B**; $r = 0.762$, $p < 0.001$) between fALFF in the right precentral gyrus and WMI scores in TT homozygotes (**Figure 2A**; coordinates: 27, −18, 72) (GRF-corrected $p < 0.05$). There was no statistically significant correlation between fALFF and WMI scores in the C-allele carriers. ReHo was not associated with the WMI in either group.

DISCUSSION

To our knowledge, this is the first attempt to explore the effects of the *DRD4* −521 C/T SNP on brain function in children with ADHD. The *DRD4* −521 C/T SNP controls the transcription rate for this gene, and its gene expression in turn affects the level of dopamine neurotransmitters in the brain, which is closely related to part of the pathogenesis of ADHD. We observed that compared with C-allele carriers, TT homozygotes showed decreased ReHo in the right MOG in the current study. The occipital lobe is mainly responsible for the processing of visual information and plays an important role in cognitive functions, such as working memory consolidation and attention regulation (38, 39). Sasayama et al. (40) found a decreased volume of gray matter in the bilateral occipital cortex of children with ADHD and the gray matter volume of the right occipital cortex decreased more significantly after controlling for mixed effects such as comorbidities (i.e., oppositional defiant disorder and conduct disorder). It is likely that abnormal structures may be related to lower cognitive function within ADHD. Wang et al. (41) used graph theory analysis to explore changes in the topological structure of the brain functional network in children with ADHD. They found that node efficiency in the occipital cortex was statistically significantly reduced among children with ADHD. In addition, in a 33-year longitudinal follow-up study, adult patients with persistent ADHD in childhood had statistically significantly less occipital cortex thickness as compared with adults without ADHD in childhood (42). A study based on rs-fMRI found that FC in the

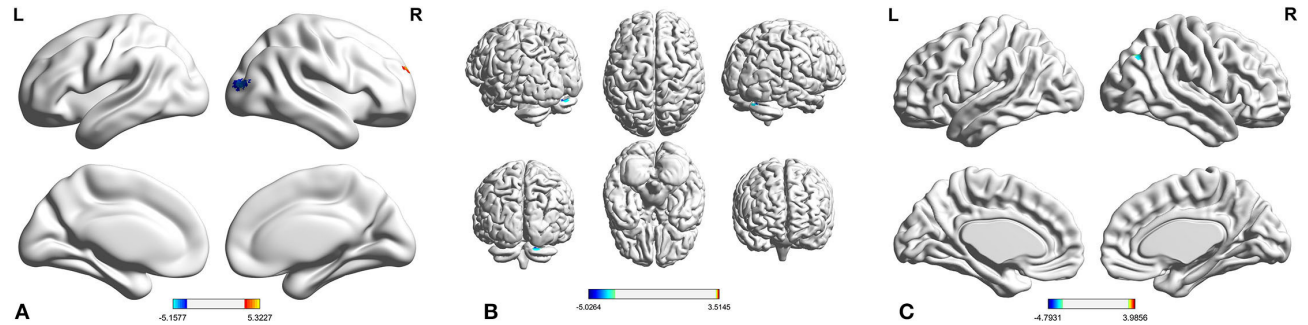

FIGURE 1 | Compared with C-allele carriers, the TT homozygous had decreased ReHo in the right MOG and increased ReHo in the right SFG **(A)**; the TT homozygous had reduced FC in the right MOG and right cerebellum **(B)**, and the TT homozygous had reduced FC in the right SFG and angular **(C)**. ADHD, attention deficit hyperactivity disorder; FC, functional connectivity; MOG, middle occipital gyrus; ReHo, regional homogeneity; SFG, superior frontal gyrus.

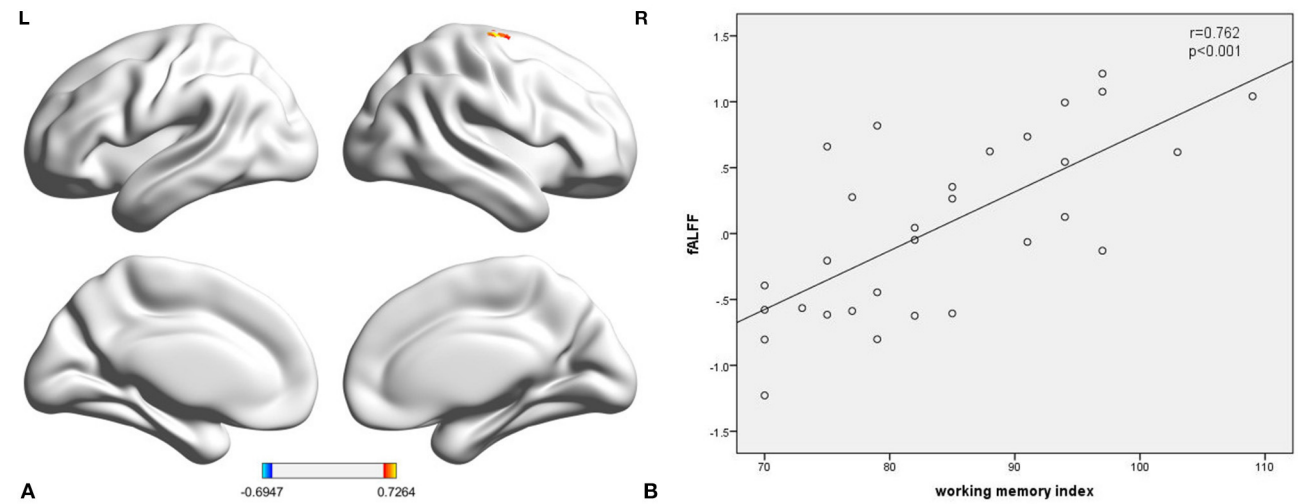

FIGURE 2 | The fALFF of the right precentral gyrus in TT homozygous was significantly correlated with working memory index ($r = 0.762$, $p < 0.001$) **(A,B)**. fALFF, fractional amplitude low-frequency fluctuation.

occipital cortex was decreased in ADHD patients, and that FC was negatively correlated with attention deficit scores (43). It was hypothesized that the decreased ReHo in the right MOG among TT homozygotes may increase the severity of their core symptoms to some extent, and that TT homozygotes may thus show more severe cognitive deficits as compared to C-allele carriers.

We also found that the TT homozygotes increased ReHo in the right SFG. Abnormal frontal lobe function is an important cause of executive dysfunction in children with ADHD (44). Dopamine neurotransmitters are mainly expressed in the prefrontal cortex and regulate changes in neuronal activity to facilitate the accurate performance of cognitive tasks (45). Peterson et al. (46) adopted the method of diffusion tensor imaging and found that, compared with normal children, the fractional anisotropy among ADHD children increased at the level of statistical significance; this effect was mainly concentrated in the right SFG. The observed increase in fractional anisotropy is closely related to the severity of ADHD symptoms. Wang et al. (47) analyzed differences in local spatiotemporal consistency between children with ADHD and neurotypical children and found that the four-dimensional (spatiotemporal) consistency of local neural activities (FOCA) in the right SFG increased among children with mixed ADHD. Ma et al. (48) used event-related fMRI to study neural responses among children with ADHD and neurotypical controls with respect to reward SCWT scores. These researchers found that reward signals among children with ADHD within the right SFG increased as compared with the control group. It is speculated that abnormal activity in the right SFG may be one of the principal mechanisms leading to deficiencies in executive function observed among children with the TT homozygous genotype.

We performed seed-based FC studies and found that, in TT homozygotes, the FC between the right MOG and the cerebellum decreased and the FC between the right

SFG and angular gyrus decreased. This indicates that TT homozygotes have a weaker brain FC network. The cerebellum plays an important role in cognition and emotion as well as in motor learning and coordination (49). Previous studies have found abnormal functional activity of the cerebellum among children with ADHD and that the cerebellum is an important brain region for ADHD with regard to executive function defects (50, 51). Some scholars have found that children with ADHD have lower long-range FC density in the cerebellum as compared with a typical developing child (52). In addition, Goetz et al. (53) found that the cerebellar symptom scores of children with ADHD decreased with age, while those of normal children remained stable. Furthermore, the cerebellar symptom scores were associated with omission errors, overall response time standard error, and prolonged stimulation intervals.

The angular gyrus plays an important role in semantic processing, word reading comprehension, number processing, memory retrieval, spatial cognition, and reasoning (54). Previous studies have found that the temporal variability of the angular gyrus is statistically significantly increased in children with ADHD (55). Compared with typically developing children, children with ADHD have statistically significantly reduced activation in the angular gyrus, which is in turn related to abilities with respect to goal-directed behavior and attention regulation (56). However, in the current study, we did not find a relationship between the WMI and brain area-specific activation. This may be because only a single WMI was selected for correlation analysis in the current study, there were no statistically significant difference between WMI for the two groups, and the sample size within this study was relatively small, limiting our statistical power to detect associations.

We compared fALFF between the two groups and found no statistically significant differences in brain regions. Our results can be explained as follows. First, both fALFF and ReHo reflect the spontaneous activity of local neurons, but the specific mechanisms mediating these effects differ. Specifically, ReHo values describe the synchronization of the activity of adjacent voxel neurons, while fALFF describes the intensity of neuron activity at the voxel level. It is likely that there were no statistically significant differences in the intensity of local neuronal activity between the two groups. Second, some scholars have proposed that ReHo can more sensitively reflect different brain functional activities as compared with fALFF (57). In addition, this study calculated correlations between ReHo, fALFF, and working memory scores in each group. We found a statistically significant positive correlation between fALFF in the right precentral gyrus and the WMI in TT homozygotes. The precentral gyrus belongs to the sensorimotor cortex and plays an important role in controlling verbal thinking, planning goal orientation, and adjusting volitional activities to ensure correct purposeful behavior. Previous studies have shown that the thickness of the precentral gyrus among children with ADHD is statistically significantly thinner than that of healthy children (58). In addition, other studies have found that the gray matter volume in the right precentral gyrus among children with ADHD is statistically significantly reduced as compared with neurotypical children (59). Our results show that the right precentral gyrus among children with ADHD who are TT homozygous shows a lower working memory ability with an accompanying decrease in fALFF. There was no statistically significant correlation between fALFF and the WMI in C-allele carriers. These previous findings support the potential link between working memory ability and fALFF within the right precentral gyrus, as observed in the current study.

In addition to the substantial strengths of this investigation. Our study has some limitations, and a larger sample is needed in the future to determine the robustness of the results. First, the inclusion criteria were strict, such that only boys with ADHD, without psychotropic drug treatment, and without any other comorbidities were enrolled in the current study; these strict inclusion and exclusion criteria restrict the generalization of our findings with respect to the entire ADHD population. Second, the differences between children with TT homozygous and C-allele carriers were not statistically significant with regard to behavioral assessment scores; this was probably due to the modest sample size of the current study, with resulting low statistical power. Third, the partial correlation analyses between ReHo/FC and working memory abilities in each group did not show statistically significant correlations. This finding may be explained by the vague boundedness of the selected behavior indicators. Future studies need to examine a wider range of behavioral indicators within correlation analyses. Fourth, the small sample size in our study limited the scope and power of ADHD subtype analyses for each group. Notably, this study attempted to be pioneering with regard to enrolling children with ADHD and examining the effects of *DRD4* −521 C/T polymorphisms *via* resting-state brain fMRI. Therefore, little existing evidence is available to support the findings of the current study.

In summary, our findings support our hypothesis that the *DRD4* −521 C/T SNP has different effects on local brain activity and FC in children with ADHD. The results of this study suggest that children with ADHD with TT homozygous genotypes may suffer from more salient brain dysfunction, which is consistent with the maladaptive behaviors observed among TT homozygotes. Due to the limitations of our study, the effects found need to be replicated first, and larger samples will be needed in the future to understand the robustness of the results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Research Ethics Committee of Shenzhen Children's Hospital. Written informed consent to participate in

this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HZ and BY conceived and designed the experiments, analyzed the data, and performed the statistical analysis. GP, LZ, and DF collected the data. HZ drafted the article with critical comments from BY. All authors contributed to the article and approved the submitted version.

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The Behavioral and Emotional Profile of Pediatric Tourette Syndrome Based on CBCL in a Chinese Sample

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Background: Tourette syndrome (TS) is a childhood-onset neuropsychiatric disorder that has a unique status of a quintessentially neuropsychiatric condition at the interface of neurology (movement disorder) and psychiatry (behavioral/emotional condition). However, the behavioral and emotional profile has seemed to be neglected in the literature thus far. This study aimed to investigate the behavioral and emotional profile of TS.

Methods: A total of 124 patients aged 6–16 years with TS were included in this study, including age- and sex-matched health control, attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and major depressive disorder (MDD) groups. The Child Behavior Checklist (CBCL) was used to screen the behavioral and emotional profile of the TS and other compared groups. The Yale Global Tic Severity Scale (YGTSS) was used to assess TS tic severity. Analysis of variance (ANOVA) was used to investigate the difference between the TS and other compared groups.

Results: The results showed that the eight factors of the CBCL had no association with motor tics, vocal tics, or tic severity ($p > 0.05$). However, positive correlations were identified between functional impairments (subscales of YGTSS) and thought problems (TP) and rule-breaking behavior (RBB). Based on the eight-factor profile of the CBCL, TS showed a similar profile to MDD but different from ADHD and OCD, which showed similar profiles.

Conclusions: Based on the assessment of the CBCL of TS, it was found that "pure" TS might show fewer behavioral and emotional problems than OCD, ADHD, and MDD. Similar behavioral and emotional profiles were identified between TS and MDD, but not OCD and ADHD. More attention needs to be paid to the thought problems and rule break problems in the CBCL in the screening stage, which might have a potential influence on the functional impairments of TS.

Keywords: Tourette syndrome, CBCL, behavioral and emotional profile, ADHD, OCD, MDD

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INTRODUCTION

Tourette syndrome (TS) is a childhood-onset neuropsychiatric disorder characterized by multiple motor tics and one or more vocal tics that persist for at least 1 year (1). TS holds a unique status of a quintessentially neuropsychiatric condition at the interface of neurology (movement disorder) and psychiatry (behavioral/emotional condition) (2). It should be noted that TS presents with symptoms that seemingly mock the divisions between neurology (motor/vocal tic symptoms) and psychiatry/psychology (that is, motor, behavioral, and emotional symptoms) (3, 4). However, when investigating TS, we should focus not only on the movement dimensions (tic symptoms) of the condition but also on the behavioral and emotional symptoms of TS.

To the best of our knowledge, the behavioral and emotional symptoms of TS include attention problems, aggressive behavior, anxiety/depressive symptoms, obsessive-compulsive symptoms, and so on (5). Most of these symptoms are associated with the comorbidities of TS. For example, high rates of comorbid attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) have been well-documented (6, 7). Moreover, major depressive disorder (MDD) has also been reported in TS (8, 9). It should be noted that comorbidities make the behavioral and emotional symptoms of TS more "complex." Some studies have highlighted that "pure" TS (only tic symptoms) might be different from TS-Plus (that is, TS+OCD, TS+ADHD) (10, 11). TS+OCD has been regarded as one of the subtypes of TS, and TS+ADHD is another subtype (12). Some studies reported that the behavioral and emotional symptoms of TS were associated with OCD-related symptoms, while some reported OCD-related symptoms in TS (12–15). However, the behavioral and emotional profile of "pure" TS might need more evidence.

Furthermore, the comorbidities of TS, such as ADHD, OCD, and MDD, suggest that there is an overlap between TS and these mental disorders (16). Most studies focus on the differences between "pure" TS and TS plus other comorbid mental disorders, but few focus on the difference between "pure" TS and other "pure" mental disorders, especially at the behavioral and emotional levels.

The Child Behavior Checklist (CBCL) is one of the most important and stable tools for identifying the behavioral and emotional profiles of mental disorders (17, 18). It can be used to screen for TS, OCD, ADHD, MDD, and more (14, 19–24). Thus, the CBCL might be a good tool to present the differences in behavioral and emotional profiles among different mental disorders.

Therefore, this study aimed to investigate the behavioral and emotional profile of "pure" TS. Furthermore, we compared the differences in behavioral and emotional profiles between TS and other mental disorders (including OCD, ADHD, and MDD); the CBCL was used to present these differences. We hypothesize that TS may show different behavioral and emotional profiles when compared with OCD, ADHD, and MDD.

MATERIALS AND METHODS

Participants

Children and adolescents (aged 6–16 years) with TS participated in this study. All participants were recruited from the Department of Psychiatry in Beijing Children's Hospital in China from 1 October 2019 to 1 September 2021. To identify patients with "pure" TS, the following criteria had to be met: (1) aged between 6 and 16 years, (2) met the Tourette syndrome diagnostic criteria according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), (3) no central nervous system diseases or intellectual disability, and (4) no comorbidities of other mental disorders. Age- and sex-matched groups with MDD, OCD, and ADHD as well as healthy controls (HCs) were also recruited. To identify the patients with "pure" MDD, OCD, and ADHD, the criterion was that all patients in these groups should not have comorbidities with other mental disorders. For example, if the included patients belong to the MDD group, they should not have OCD, ADHD, TS, or other mental disorders. The HC group did not have any mental disorders.

This study was approved by the ethics committee of Beijing Children's Hospital of Capital Medical University, and written informed consent was obtained from the legal guardians of the participants or their parents.

Scales for Assessments

YGTSS

The YGTSS is a semi-structured interview developed to assess the nature and severity of motor and vocal tics (25, 26). The assessment dimensions of the YGTSS include the number, frequency, intensity, complexity, and interference of vocal and motor tic symptoms, with a maximum score of 50 for tic severity (25 for motor and 25 for vocal tics) and 50 for the impairment caused by the tics, yielding a total maximum score of 100. The YGTSS is a widely used scale with excellent psychometric properties (27) and demonstrated excellent internal consistency ($\alpha = 0.91$) in the present sample. A child psychiatrist was invited to perform the assessment of the YGTSS.

Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)

The CY-BOCS is a semi-structured scale rated by a clinician. It was used to assess the severity of obsessive and compulsive behaviors during the previous week in patients with OCD aged 8–16 years (28). The obsessions and compulsion subtotals are derived by adding five items (time occupied, interference, distress, resistance, and degree of control, range: 0–4) related to obsessions (range: 0–20) and compulsions (range: 0–20), respectively. The total score is the sum of the obsessions and compulsion subtotals.

Depression Self Rating Scale for Children (DSRSC)

The DSRSC was used to assess depressive symptoms in young children aged 8–14 years. It measures the direction of disturbances felt in the past week (29). Three options include "Most of the time," "Sometimes," and "Never." The scores for the scale are 2, 1, or 0, and the 18 item scores are then summed to

give the total score. The maximum score is 36. The higher total scores are, the higher the depressive symptoms (30).

Swanson, Nolan, and Pelham Rating Scale–Fourth Version (SNAP-IV)

The SNAP-IV consists of 26 items rated on a 4-point scale (not at all, just a little, quite slightly, very much) (31). Three subscales were included (inattention, hyperactivity/impulsivity, and oppositional). The SNAP-IV was completed by parents and took ∼15 min. Higher scores indicate more ADHD problem symptoms. Subscale scores are calculated by creating an average (32).

The Child Behavior Checklist (CBCL)

The Chinese version of the CBCL contains 118 specific behavioral and emotional problem items and two open-ended items (33). Each symptom question in the CBCL was scored 0 (not true, as far as you know), 1 (somewhat or sometimes true), and 2 (very true or often true). The CBCL contains eight factors: Anxious/Depressed (AD), Withdrawn/Depressed (WD), Somatic Complaints (SC), Social Problems (SP), Thought Problems (TP), Attention Problems (AP), Rule-Breaking Behavior (RBB), and Aggressive Behavior (AB). Liu et al. completed a regional survey in Shandong and reported that the two-week test-retest reliability was 0.90, and the internal consistency measured by Cronbach's α was 0.93 (34). Cronbach's α was also calculated in the present study and was 0.87 for the total scale. The CBCL was completed by parents or other caregivers. All CBCL assessments were performed using the QinChao Psychological Evaluation System (version 6.0) in the psychological assessment room in the Department of Psychiatry in Beijing Children's Hospital.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA, v25.0). First, we compared age using a *t*-test and the percentage of boys using a chi-square test. Second, the mean, standard deviation (SD), kurtosis, and skewness of the CBCL and its subscales were calculated for the TS group. Third, we calculated the Pearson correlation between the YGTSS and CBCL. Fourth, multivariate analysis of variance (MANOVA) was used to compare the CBCL and its subscales in different groups (TS, OCD, ADHD, MDD, and HC). MANOVA is a procedure for comparing multivariate sample means. As a multivariate procedure, it is used when there are two or more dependent variables and is often followed by significance tests involving individual dependent variables separately (35). Bonferroni correction was used when performing multiple comparisons among the different groups. To present the behavioral and emotional profiles, T-scores were used to calculate the eight factors based on CBCL. The T-score is one form of a standardized test statistic. Formulate $T = (Z \times 10) + 50$, and formulate $Z = (X–x)/SD$. X is the value of one of the rough scores of the whole sample, and x is the mean of the whole sample. A radar chart based on T-scores was used to present the CBCL profiles of the different groups. The *p*-value (≤ 0.05) indicated significance against the null hypothesis.

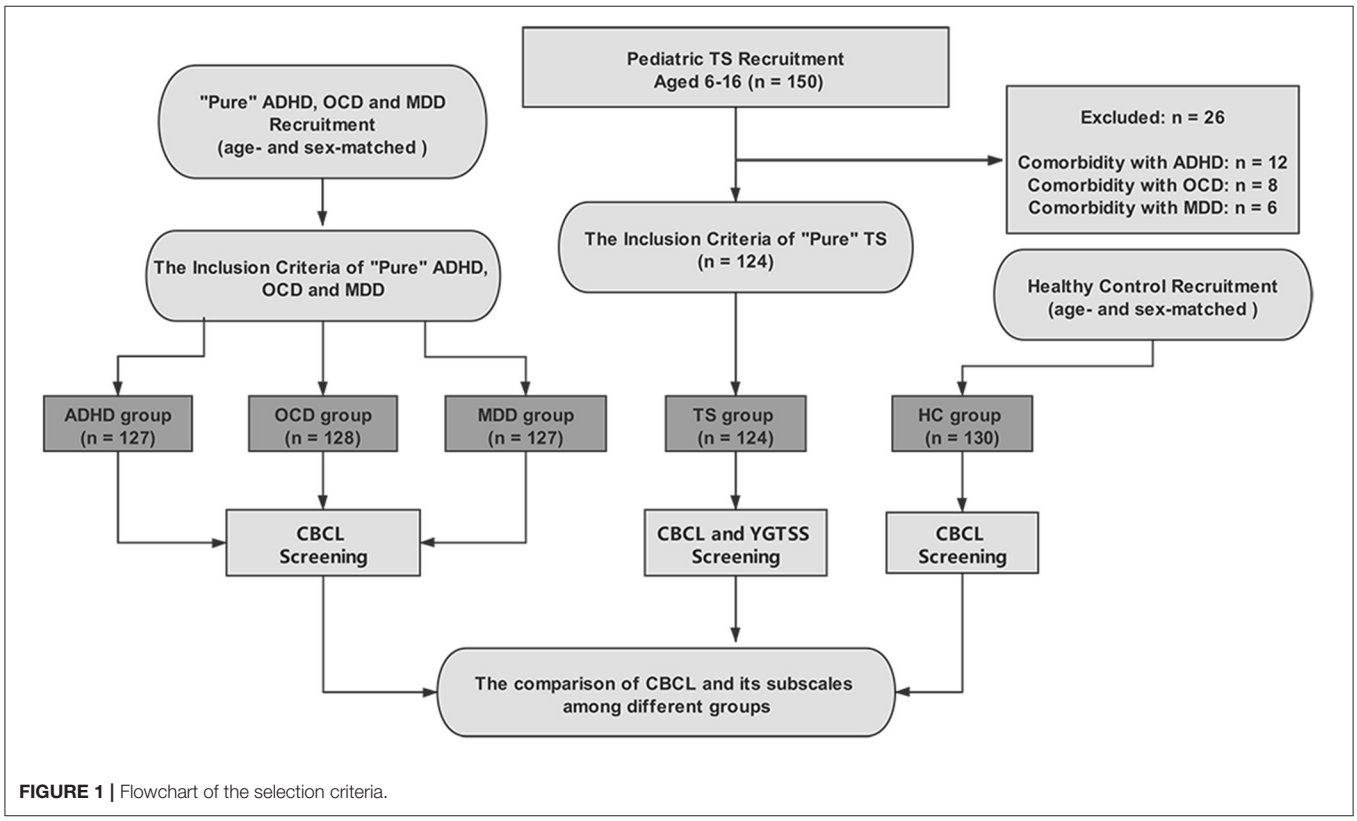

FIGURE 1 | Flowchart of the selection criteria.

RESULTS

The Identification of the TS Group and Other Groups

A total of 150 patients with TS were identified, but 26 were excluded due to comorbidities of other mental disorders. Finally, 124 patients with TS were included in the TS group. Furthermore, the age- and sex-matched groups included ADHD ($n = 127$), OCD ($n = 128$), MDD ($n = 127$), and HC ($n = 130$) groups. For more details, see **Figure 1**.

The mean age of the patients in these groups was 10.37 ± 1.91 years (TS), 10.48 ± 2.74 years (ADHD), 10.59 ± 2.45 years (OCD), 10.48 ± 3.06 years (MDD), and 10.46 ± 2.38 years (HC). No significant age differences were identified in these groups ($F = 0.128$, $p = 0.97$). For the percentage of males, the TS group was 70.97%, ADHD group was 70.08%, OCD group was 70.31%, MDD group was 69.29%, and HC group was 68.46%; there was no significant difference among these groups (chi-square = 0.13, $p = 1.00$). The mean years of education of the patients in these groups were 4.36 ± 1.87 years (TS), 4.45 ± 2.25 years (ADHD), 4.58 ± 2.21 years (OCD), 4.48 ± 2.88 years (MDD), and 4.46 ± 2.19 years (HC). For the years of education, no significant age differences were identified in these groups ($p > 0.05$). The duration of illness (years) of the patients in these groups was 2.37 ± 1.89 years (TS), 2.48 ± 1.04 years (ADHD), 2.59 ± 1.45 years (OCD), 2.48 ± 1.06 years (MDD), and 2.46 ± 1.38 years (HC). For the duration of illness, no significant age differences were identified in these groups ($p > 0.05$).

We also calculated the YGTSS scores in the TS group, and the total YGTSS score was 21.63 ± 8.94 (motor tic: 12.77 ± 4.06; vocal tic: 6.24 ± 3.53; functional impairment 2.63 ± 4.88). The CY-BOCS score of the OCD group was 15.36 ± 4.45. Three subscales of SNAP-IV scores in the ADHD group were 1.75 ± 0.43 (inattention score), 1.83 ± 0.52 (hyperactivity/impulsivity score) and 0.83 ± 0.35 (oppositional score). The DSRSC score in the MDD group was 21.31 ± 5.83.

The CBCL Profile of the TS Group

The mean, standard deviation, kurtosis, and skewness of the CBCL and its subscales were calculated in the healthy control (HC), TS, OCD, ADHD and MDD groups (for more details, see **Table 1**). Moreover, we calculated the Pearson correlation between the YGTSS and the CBCL. The results showed that the eight factors of CBCL had no association with motor tics, vocal tics, or tic severity ($p > 0.05$). However, positive correlations were identified between the function impairments (YGTSS) and the TP and RBB (subscales of CBCL) (for more details, see **Table 2**). In addition, we also calculated the mean, SD, range of scores of motor tics, vocal tics, and impairment of YGTSS in **Supplementary Table 1**.

Comparisons of CBCL Profiles Between the TS Group and Other Groups

First, we compared the total CBCL scores of all the groups and found that F was 53.55 ($p < 0.001$) (for more details, see **Supplementary Table 1**). The *post hoc* test (Bonferroni correction) showed the following relationships with respect to

TABLE 1 | The descriptive statistic for the 8 factors of the CBCL in different groups.

Syndromes	HC (n = 130)		TS (n = 123)		OCD (n = 128)		ADHD (n = 127)		MDD (n = 128)	
	Mean (SD)	Skewness/ Kurtosis	Mean (SD)	Skewness/ Kurtosis	Mean (SD)	Skewness/ Kurtosis	Mean (SD)	Skewness/ Kurtosis	Mean (SD)	Skewness/ Kurtosis
A/D	1.92 (1.85)	0.63/−0.62	4.27 (2.99)	0.14/−0.61	5.46 (3.75)	0.66/1.06	5.36 (3.67)	0.73/0.65	4.52 (3.03)	0.59/0.29
W/D	1.94 (1.75)	0.88/0.24	3.33 (2.08)	1.01/1.18	4.70 (2.97)	0.39/−0.48	4.28 (3.07)	1.16/1.46	3.84 (2.66)	4.81/−0.53
SC	2.18 (2.34)	1.72/4.75	4.76 (3.33)	0.99/0.15	4.65 (3.31)	0.56/−0.51	5.05 (3.77)	0.62/−0.16	5.28 (3.08)	0.18/−0.77
SP	2.35 (1.92)	0.56/−0.27	4.91 (2.67)	0.35/−0.66	5.38 (3.02)	0.45/0.05	5.74 (3.32)	0.49/0.80	5.16 (2.71)	0.25/−0.24
TP	1.68 (1.84)	1.29/1.43	3.94 (2.68)	0.56/−0.56	5.10 (3.40)	0.53/−0.26	5.15 (4.02)	1.80/4.78	3.74 (2.68)	0.90/0.46
AP	3.05 (2.25)	0.13/−1.05	4.96 (2.24)	0.71/−0.42	5.96 (2.87)	−0.01/−0.46	6.30 (3.11)	−0.02/0.27	5.15 (2.71)	0.19/−0.15
RBB	1.93 (1.80)	0.53/−0.88	3.37 (1.72)	0.86/2.42	4.21 (2.60)	0.85/0.48	4.33 (3.41)	1.60/4.30	3.70 (2.52)	0.64/0.25
AB	4.74 (3.62)	0.44/−0.79	6.69 (3.9)	0.61/0.26	9.67 (4.93)	0.76/0.40	10.31 (6.28)	0.64/0.48	8.93 (4.58)	0.43/−0.21
Total problems	23.76 (14.68)	−0.19/−1.50	42.79 (12.97)	0.18/0.18	52.29 (19.94)	0.58/1.00	54.90 (17.94)	1.46/4.69	47.48 (16.63)	0.01/−0.34

A/D, Anxious/Depressed; W/D, Withdrawn/Depressed; SC, Somatic Complaints; SP, Social Problems; TP, Thought Problems; AP, Attention Problems; RBB, Rule-Breaking Behavior; AB, Aggressive Behavior; HC, Health Control; TS, Tourette Syndrome; OCD, Obsessive Compulsive Disorder; ADHD, Attention Deficit and Hyperactivity Disorder; MDD, Major Depressive Disorder; SD, Standard Deviation.

CBCL profiles between the groups: TS > HC ($p < 0.001$), TS < OCD ($p = 0.001$) and ADHD ($p < 0.001$). No significant differences were identified between the TS and MDD groups ($p = 0.530$). For more details, see **Figure 2**.

Second, multivariate analysis of variance was used to compare the eight factors of the CBCL subscales in different groups (TS, OCD, ADHD, MDD, and HC). For the SC factor, TS > HC ($p < 0.001$), but no significant difference was identified among the TS, ADHD, OCD, and MDD groups. The SP factor showed the same pattern as SC, TS > HC ($p < 0.001$), but no significant differences were identified among the TS, ADHD, OCD, and MDD groups. For the A/D factor, TS > HC ($p < 0.001$), TS < OCD ($p = 0.003$) and ADHD ($p = 0.006$). The W/D factor showed the same pattern as A/D, TS > HC ($p < 0.001$), TS < OCD ($p < 0.001$) and ADHD ($p = 0.004$). The TP factor also showed the same pattern as A/D and W/D, TS > HC ($p < 0.001$), TS < OCD ($p = 0.024$) and ADHD ($p = 0.016$). The AP factor also showed the same pattern as A/D, W/D, and TP, TS > HC ($p < 0.001$), TS < OCD ($p = 0.029$) and ADHD ($p = 0.001$). For the RBB factor, TS > HC ($p < 0.001$) and TS < ADHD ($p = 0.023$). For the AB factor, TS > HC ($p = 0.012$), and TS < OCD ($p < 0.001$), ADHD ($p < 0.001$), and MDD ($p = 0.002$). For more details, see **Tables 3**, **4**.

TABLE 2 | The Pearson correlation of YGTSS and the CBCL in Tourette syndrome ($n = 124$).

	Motor Tic	Vocal Tic	Severity	Impairment	Total YGTSS
A/D	−0.04	0.16	0.06	0.06	0.07
W/D	−0.11	0.07	−0.04	0.04	0.01
SC	0.04	0.12	0.10	0.10	0.13
SP	0.02	0.07	0.06	0.09	0.10
TP	0.04	0.14	0.12	0.18*	0.20*
AP	−0.02	0.16	0.08	0.08	0.10
RBB	−0.01	0.07	0.04	0.20*	0.17
AB	0.02	−0.01	0.01	0.11	0.09
Total CBCL	−0.00	0.15	0.09	0.20*	0.19*

*A/D, Anxious/Depressed; W/D, Withdrawn/Depressed; SC, Somatic Complaints; SP, Social Problems; TP, Thought Problems; AP, Attention Problems; RBB, Rule-Breaking Behavior; AB, Aggressive Behavior; CBCL, the Child Behavior Checklist; YGTSS, Yale Global Tic Severity Scale; *p < 0.05.*

Finally, we calculated the T-scores of each group based on the 8 subscales of the CBCL. The radar chart was used to present CBCL profiles of the different groups based on the mean and SD of 8 subscales based on the T-scores (see **Figure 3**). This suggested that, based on the eight-factor profile of the CBCL, TS showed a similar pattern to MDD but different from ADHD and OCD, which showed similar profiles. AB and W/D might be more "suitable" factors to present the difference among these groups rather than SC and SP.

In addition, considering the age effect for the CBCL of different groups, we divided the whole sample into a Young

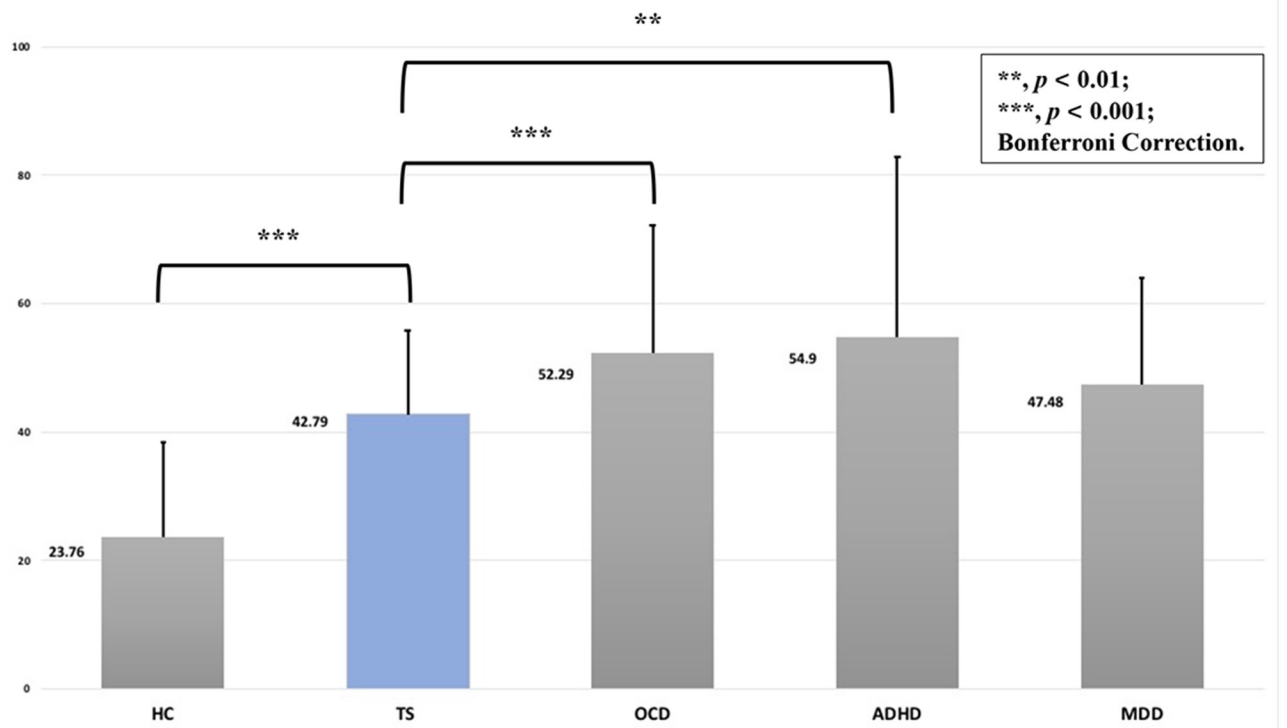

FIGURE 2 | The CBCL total scores of the TS and other compared groups.

TABLE 3 | MANOVA analysis based on CBCL.

Total of CBCL and 8 subscales		Sum of Squares	df	Mean Square	F	*P*
Total	Between Groups	78839.57	4	19709.89	53.55	$P < 0.01$**
	Within Groups	232256.05	631	368.08		
	Total	311095.63	635			
A/D	Between Groups	1056.79	4	264.20	26.99	$P < 0.01$**
	Within Groups	6176.45	631	9.79		
	Total	7233.24	635			
W/D	Between Groups	586.21	4	146.55	22.36	$P < 0.01$**
	Within Groups	4134.87	631	6.55		
	Total	4721.07	635			
SC	Between Groups	818.04	4	204.51	20.05	$P < 0.01$**
	Within Groups	6436.39	631	10.20		
	Total	7254.43	635			
SP	Between Groups	949.45	4	237.36	31.06	$P < 0.01$**
	Within Groups	4822.98	631	7.64		
	Total	5772.43	635			
TP	Between Groups	1028.88	4	257.22	28.28	$P < 0.01$**
	Within Groups	5739.36	631	9.10		
	Total	6768.24	635			
AP	Between Groups	824.19	4	206.05	29.20	$P < 0.01$**
	Within Groups	4453.03	631	7.06		
	Total	5277.23	635			
RBB	Between Groups	479.95	4	119.99	19.38	$P < 0.01$**
	Within Groups	3907.05	631	6.19		
	Total	4386.99	635			
AB	Between Groups	2735.38	4	683.86	30.24	$P < 0.01$**
	Within Groups	14268.98	631	22.61		
	Total	17004.36	635			

*AD, Anxious/Depressed; W/D, Withdrawn/Depressed; SC, Somatic Complaints; SP, Social Problems; TP, Thought Problems; AP, Attention Problems; RBB, Rule-Breaking Behavior; AB, Aggressive Behavior; CBCL, the Child Behavior Checklist; **p < 0.01. Within group variation measures how much the individuals vary from their group mean, while Between group variation measures how much the group means vary from the overall mean.*

Group (6–11 years old) and an Old Group (12–16 years old). We also used the radar chart to present the CBCL profiles of these two groups based on the T-scores. There might be a higher score on the 8 subscales of the CBCL in the Old Group than in the Young Group. For more details, see **Supplementary Figure 1**.

DISCUSSION

This study aimed to compare the behavioral and emotional profile of "pure" TS with other mental disorders. The results showed that there was no correlation between tic symptoms and behavioral and emotional problems in "pure" TS. However, TP and RBB might have a potential influence on TS function. The "pure TS" group showed higher behavioral and emotional problems than the HC group and the same level of severity of behavioral and emotional problems as the MDD group. The "pure" OCD and ADHD groups showed higher-level severities of behavioral and emotional problems than the TS group. Moreover, the difference between the TS and OCD groups was mainly in the dimensions of A/D, W/D, TP, AP, and AB. The difference between the TS and ADHD groups was mainly in the dimensions of A/D, W/D, TP, AP, RBB, and AB. The difference between the TS and MDD groups was mainly in the AB dimension. TS, OCD, ADHD, and MDD showed the same levels of SC and SP. These results indicate that the "pure" TS might have a similar behavioral and emotional profile to "pure MDD" but a different profile compared to "pure" OCD and ADHD.

In the present study, it was found that the TS group might show a similar behavioral and emotional profile to the MDD group at the behavioral level. Rizzo et al. (36) reported that depression is significantly associated with TS factors, such as tic severity, but not obsessive compulsiveness. Furthermore, we found that there was no association between tic symptoms and behavioral/emotional problems. This implies that the "pure" tic symptoms and behavioral/emotional problems are two distinct cluster symptoms. We also identified higher CBCL scores in the TS group than in the HC group. This suggests that even the "pure" TS might have some behavioral and emotional problems different from tic symptoms. Indeed, Rizzo et al. (12) also reported that emotional lability represents an intrinsic core feature of Tourette syndrome that is unrelated to comorbidity.

TABLE 4 | *Post hoc* Tests (multiple comparisons, Bonferroni correction).

Total and Subscales (CBCL)	TS vs. Groups	MD	SE	P	95% CI Lower Bound	95% CI Upper Bound
Total	HC	19.03**	2.41	$P < 0.01$	12.23	25.83
	OCD	−9.50**	2.42	$P < 0.01$	−16.32	−2.68
	ADHD	−12.11**	2.43	$P < 0.01$	−18.95	−5.27
	MDD	−4.70	2.42	0.53	−11.52	2.13
A/D	HC	2.35**	0.39	$P < 0.01$	1.24	3.45
	OCD	−1.20*	0.40	0.03	−2.31	−0.08
	ADHD	−1.09	0.40	0.06	−2.21	0.02
	MDD	−0.26	0.40	1	−1.37	0.86
W/D	HC	1.40**	0.32	$P < 0.01$	0.49	2.3
	OCD	−1.36**	0.32	$P < 0.01$	−2.27	−0.45
	ADHD	−0.94*	0.32	0.04	−1.85	−0.03
	MDD	−0.50	0.32	1	−1.41	0.41
SC	HC	2.58**	0.40	$P < 0.01$	1.45	3.71
	OCD	0.11	0.40	1	−1.03	1.24
	ADHD	−0.29	0.40	1	−1.43	0.85
	MDD	−0.53	0.40	1	−1.66	0.61
SP	HC	2.56**	0.35	$P < 0.01$	1.58	3.54
	OCD	−0.47	0.35	1	−1.46	0.51
	ADHD	−0.83	0.35	0.18	−1.81	0.16
	MDD	−0.25	0.35	1	−1.23	0.74
TP	HC	2.27**	0.38	$P < 0.01$	1.20	3.33
	OCD	−1.16*	0.38	0.02	−2.23	−0.09
	ADHD	−1.21*	0.38	0.02	−2.28	−0.13
	MDD	0.20	0.38	1	−0.87	1.27
AP	HC	1.91**	0.33	$P < 0.01$	0.96	2.85
	OCD	−1.00*	0.34	0.03	−1.95	−0.06
	ADHD	−1.34**	0.34	$P < 0.01$	−2.29	−0.39
	MDD	−0.19	0.34	1	−1.13	0.76
RBB	HC	1.43**	0.31	$P < 0.01$	0.55	2.32
	OCD	−0.85	0.31	0.07	−1.73	0.04
	ADHD	−0.97*	0.32	0.02	−1.85	−0.08
	MDD	−0.34	0.31	1	−1.22	0.55
AB	HC	1.95**	0.60	$P < 0.01$	0.27	3.64
	OCD	−2.98**	0.60	$P < 0.01$	−4.67	−1.29
	ADHD	−3.62**	0.60	$P < 0.01$	−5.31	−1.92
	MDD	−2.24**	0.60	$P < 0.01$	−3.93	−0.55

*AD, Anxious/Depressed; W/D, Withdrawn/Depressed; SC, Somatic Complaints; SP, Social Problems; TP, Thought Problems; AP, Attention Problems; RBB, Rule-Breaking Behavior; AB, Aggressive Behavior; CBCL, the Child Behavior Checklist; HC, Health Control; TS, Tourette Syndrome; ADHD, Attention-Deficit/Hyperactivity Disorder; OCD, Obsessive-Compulsive Disorder; MDD, Major Depressive Disorder; *$p < 0.05$; **$p < 0.01$.*

This implies that some emotional problems might also be associated with "pure" TS. This might be the most likely reason for the similar behavioral and emotional profile for "pure" TS and MDD. Further evidence is needed to investigate the association between tic symptoms and depressive symptoms in the future.

Furthermore, in the present study, we also found a difference in AB between "pure" TS and MDD. Compared with MDD, OCD, and ADHD, "pure" TS showed less aggressive problems. Aggressive behavior can be found in young patients with MDD (37), ADHD (38, 39), and OCD (40). Recently, a study reported that there was no association between aggressive behavior and tic symptoms, but comorbid ADHD and OCD increased the risk of aggressive behavior in patients with tic disorders (41). This suggests that aggressive behavior might be associated with comorbidities of TS but not with tic symptoms. This might be regarded as one of the most important behavioral indicators to distinguish the "pure" TS from OCD, ADHD, and MDD.

In the present study, we found confirmed differences between TS and ADHD at the behavioral level. "Pure" ADHD might present more ADHD-related behavioral problems (such as AP, AB, and RBB), which is different from tic symptoms. Furthermore, ADHD-related behavioral problems might also

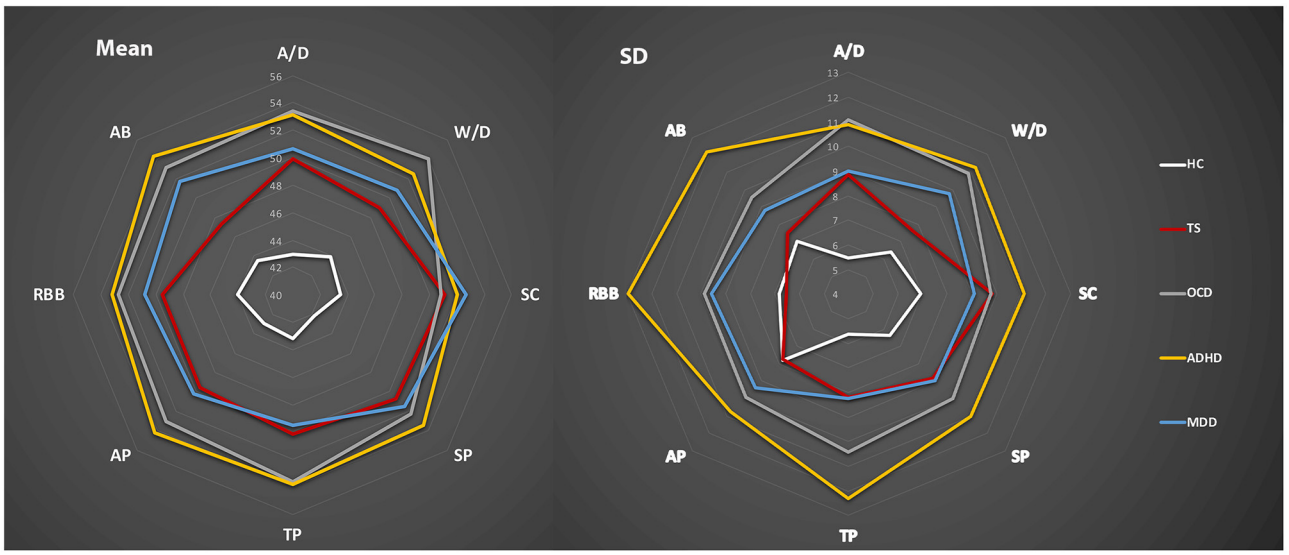

FIGURE 3 | The CBCL profile of the TS and other compared groups.

lead to emotional problems, which might be the reason why ADHD showed higher scores for A/D and W/D than TS. Furthermore, similar results were obtained when TS was compared with OCD. The OCD group showed higher levels of behavioral problems in AP, AB, RBB, and TP, as well as emotional problems in A/D and W/D. However, for the RBB, the TS and OCD groups showed similar scores. It should be noted that ADHD and OCD were the two most common comorbidities for TS, and both tend to persist (15). Both the genetic and phenotypic overlap of ADHD/OCD and TS have been reported (42). Moreover, it has been suggested that OCD and ADHD in TS predict worse outcomes of TS (43). The results of this study indicate that the comorbidities of ADHD and OCD in TS might increase behavioral and emotional problems and make the profile of TS more complex. Taken together, "pure" TS showed fewer behavioral and emotional problems, but with the comorbidities of ADHD or OCD, more behavioral and emotional problems might be identified. The dimension of OCD-related symptoms indicated that compulsivity is a clearly distinguished dimension for TS. How tics with both compulsivity and impulsivity, such as self-injurious behaviors and coprolalia, relate to the profile of CBCL in terms of the relationship between tics and OCD might be an important research direction for TS. Other behavioral and emotional problems, such as ADHD-related symptoms, might be another dimension of TS.

Notably, we identified the relationship between TP and the function of TS, which indicates that this dimension of behavioral and emotional problems might influence the functional impairment of TS. Although TP is clinically useful for identifying psychotic symptoms in children, it also includes items for the assessment of obsessive thoughts and compulsions, self-harm, picking at parts of the body, and more (44). These items have shown a robust association with the functional impairment of TS (45–47).

RBB has been shown to be associated with antisocial behavior problems, which are key factors in the development of youth violence and aggression (48, 49). This suggests that more attention should be given to RBB problems at the screening stage of TS. It should be noted that AB and RBB always showed a closed relationship. Therefore, there might be somewhat contradictory evidence that RRB had a significant correlation with functional impairments, while AB had a fairly low correlation. RBB had a much higher kurtosis than AB, and the correlation might be caused by the presence of a small number of TS participants with high RBB.

Compared to RBB, TP had less significant kurtosis. Therefore, TP may be more closely related to TS than RBB, and compulsivity indicated by TP may be a feature of TS, even if OCD is not comorbid.

Overall, in the present study, we found that "pure" TS might show fewer behavioral and emotional problems than OCD and ADHD. Similar behavioral and emotional profiles were identified between TS and MDD, but not OCD and ADHD. These results indicate that comorbidities (such as OCD and ADHD) might make the behavioral and emotional profiles more complex. Aggressive problems might be an important factor in distinguishing "pure" TS from OCD, ADHD, and MDD. Furthermore, we need to pay more attention to TP and RBB problems in the screening stage of TS, which might have a potential influence on the functional impairments of TS.

This study has two limitations. First, a limited number of participants were included in this study. A larger sample size and follow-up studies of behavioral and emotional profiles for TS are needed to confirm these results. Second, anxiety disorders are also a common comorbidity of TS but were not included in this study. Third, information about the medication used is absent. Previous studies have found that the medicine used for the treatment of tic symptoms might also influence behavioral and

emotional symptoms (50–52). Therefore, when we investigate the behavioral and emotional profiles in TS in future studies, we need to consider the influence of medicine, especially second-generation antipsychotics.

CONCLUSION

This study explored the behavioral and emotional profiles of TS. Similar behavioral and emotional profiles were identified between TS and MDD, rather than OCD/ADHD. Aggressive behavior might be an important factor in distinguishing "pure" TS from OCD, ADHD, and MDD. More attention needs to be paid to the TP and RBB problems of the CBCL, which might have a potential influence on the functional impairments of TS.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committees of Beijing Children's Hospital of Capital Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YC and YiL took the initiative. JC and YaL finished the data collection. YiL performed the data analysis and finished the draft. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.784753/full#supplementary-material

Supplementary Figure 1 | The CBCL profile of the Young Group and Old Group.

Supplementary Table 1 | The subscales of YGTSS.

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Gray Matter Alterations in Pediatric Schizophrenia and Obsessive-Compulsive Disorder: A Systematic Review and Meta-Analysis of Voxel-Based Morphometry Studies

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Objective: The aim of this study is comparing gray matter alterations in SCZ pediatric patients with those suffering from obsessive-compulsive disorder (OCD) based on a systematic review and an activation likelihood estimation (ALE) meta-analysis.

Methods: A systematic literature search was performed in PubMed, Elsevier, and China National Knowledge Infrastructure (CNKI). A systematic review and an ALE meta-analysis were performed to quantitatively examine brain gray matter alterations.

Results: Children and adolescents with schizophrenia had decreased gray matter volume (GMV) mainly in the prefrontal cortex (PFC), temporal cortex (such as the middle temporal gyrus and transverse temporal gyrus), and insula, while children and adolescents with OCD mainly had increased GMV in the PFC and the striatum (including the lentiform nucleus and caudate nucleus), and decreased GMV in the parietal cortex.

Conclusions: Our results suggest that gray matter abnormalities in the PFC may indicate homogeneity between the two diseases. In children and adolescents, structural alterations in schizophrenia mainly involve the fronto-temporal and cortico-insula circuits, whereas those in OCD mainly involve the prefrontal-parietal and the prefrontal-striatal circuits.

Keywords: schizophrenia, obsessive-compulsive disorders, activation likelihood estimation, gray matter, children and adolescents

INTRODUCTION

Schizophrenia (SCZ), a severe psychiatric disorder characterized by symptoms such as hallucinations, delusions, disorganized thinking, amotivation, and cognitive dysfunction, has an onset in childhood and adolescence (1). Another serious psychiatric disorder that also often onsets in childhood and adolescence is obsessive-compulsive disorder (OCD), which is characterized by intrusive thoughts and repetitive and ritualistic behaviors (2). High comorbidity of OCD has been reported among patients with schizophrenia (3). A prior diagnosis of OCD and age of <20 years at

OCD onset are associated with higher rates of subsequently diagnosed schizophrenia (4, 5). Some studies have found that SCZ and OCD share some demographic and clinical characteristics (6). These findings suggest that SCZ and OCD share common neuropathology. Therefore, many studies have compared SCZ and OCD to investigate their multidimensional heterogeneity.

Both SCZ and OCD have been recognized as neurodevelopmental disorders (7). Brain structural and functional abnormalities have been observed in SCZ and OCD at the early stages of life (8, 9). Indeed, some neuroimaging studies have compared brain structural abnormalities in adults with SCZ and OCD; however, the results of these studies are largely inconsistent. For example, Zhang et al. found that patients with SCZ and those with OCD lost similar gray matter (GM) volume in the right anterior cingulate (10). However, another study suggests that compared with patients with OCD, those with SCZ had reduced GM volume mainly in the prefrontal gyrus (including the left precuneus, left superior frontal gyrus, right middle frontal gyrus, etc.) (11). The above studies indicate that further investigations are warranted to compare gray matter volume differences between SCZ and OCD.

Notably, a meta-analysis of imaging studies (i.e., activation likelihood estimation [ALE] analysis) might serve as an important tool to confirm the structural and functional abnormalities in SCZ and OCD. Previously, to investigate the differences between SCZ and OCD, Goodkind et al. (12) performed a voxel-based morphometry (VBM)-based meta-analysis of 193 studies. They reported GM loss in the dorsal anterior cingulate cortex (dACC) and bilateral insula, brain areas that relate to executive functions. A secondary analysis of mega- and meta-analytical findings revealed that regions such as the hippocampus and fusiform gyrus exhibited high conformity to the shared morphometric signature of SCZ and OCD (13). Nevertheless, since existing research is limited to comparisons of adult populations, the similarities and differences in GM alterations among children and adolescents with either SCZ or OCD remain largely unknown. Indeed, previous studies found widespread structural brain changes in both pediatric OCD and adult OCD, but different age stages might indicate different structural alterations (14, 15). For example, by assessing cortical thickness and surface area, Boedhoe et al. (16) found that the parietal cortex was consistently implicated in both adults and children with OCD, but the temporal and frontal cortex changes were different during different stages of development and illness.

It should be noted that few studies have compared brain structural abnormalities in children and adolescents with SCZ and those with OCD. To the best of our knowledge, only one comparative study reported that children and adolescents with SCZ have more widespread white matter abnormalities than those with OCD (17). Children and adolescents with SCZ generally have decreased cortical GM, particularly in the frontotemporal cortical areas (18, 19). On the other hand, GM alterations present not only in the classical fronto–striatal–thalamic circuit but also in the parietal and occipital cortices have been found in pediatric OCD (14, 16, 20). However, further meta-analytical research into GM alterations in children and adolescents with SCZ and those with OCD is required.

Currently, there is no comparison between the two patient groups (SCZ and OCD) is performed in children and adolescents. The aim of this study is comparing gray matter alterations in SCZ patients with those suffering from OCD. First, a systematic review was performed to summarize the gray matter alterations in both SCZ and OCD. Second, an ALE meta-analysis was performed to quantitatively examine brain gray matter alterations. We hypothesized that shared GM alterations between SCZ and OCD should be within GM loss in the fronto–striatal–thalamic circuit. Thus, we intend to provide some neural indicators for children and adolescents with SCZ and those with OCD.

MATERIALS AND METHODS

Literature Search

Literature searches were performed in online databases, including PubMed, Web of Science and China National Knowledge Infrastructure (CNKI). We used the keywords and combinations of the following search terms with the following search expressions: ("schizophrenia" OR "obsessive-compulsive disorder") AND "structural" AND "MRI" AND "gray matter." Additionally, the reference lists of relevant articles were obtained and screened for any additional studies missed by the database search. Next, the titles and abstracts of the articles identified were screened according to the inclusion criteria. After this screening stage, the full journal articles were checked to determine whether they met the criteria of the included studies. Studies were independently cross-checked by two researchers to identify relevant articles. Articles published up to 31 August 2021 were included.

Inclusion and Exclusion Criteria

The following inclusion criteria were used to identify relevant studies for our meta-analysis: (1) English or Chinese language studies from peer-reviewed journals, (2) age of patients at diagnosis of SCZ or OCD (age: <18 years), and (3) VBM studies (both the whole brain analyses and ROI analyses were included). The exclusion criteria were as follows: (1) patient sample size < 10 and (2) duplicate studies.

Systematic Review and ALE Meta-Analysis

First, a systematic review was performed. The key step of the systematic review is data extraction. The extracted data included the "Sample Size," "Age," "Males Percentage," "Duration of Illness (DOI)," as well as the "Brain regions of Gray matter alterations" (if the gray matter decreased, Patients< Controls, it will be marked A; if Patients> Controls, B was marked).

Second, based on the inclusion and exclusion criteria for the included studies, an ALE analysis was performed. The last BrainMap application, the Java-based version of Ginger ALE, is used for performing activation likelihood estimation (ALE) meta-analyses on sets of coordinates extracted from the database in Talairach or MNI space. In the present study, Ginger ALE version 3.0.2 was adopted in the present meta-analysis of the included VBM studies that reported the foci of

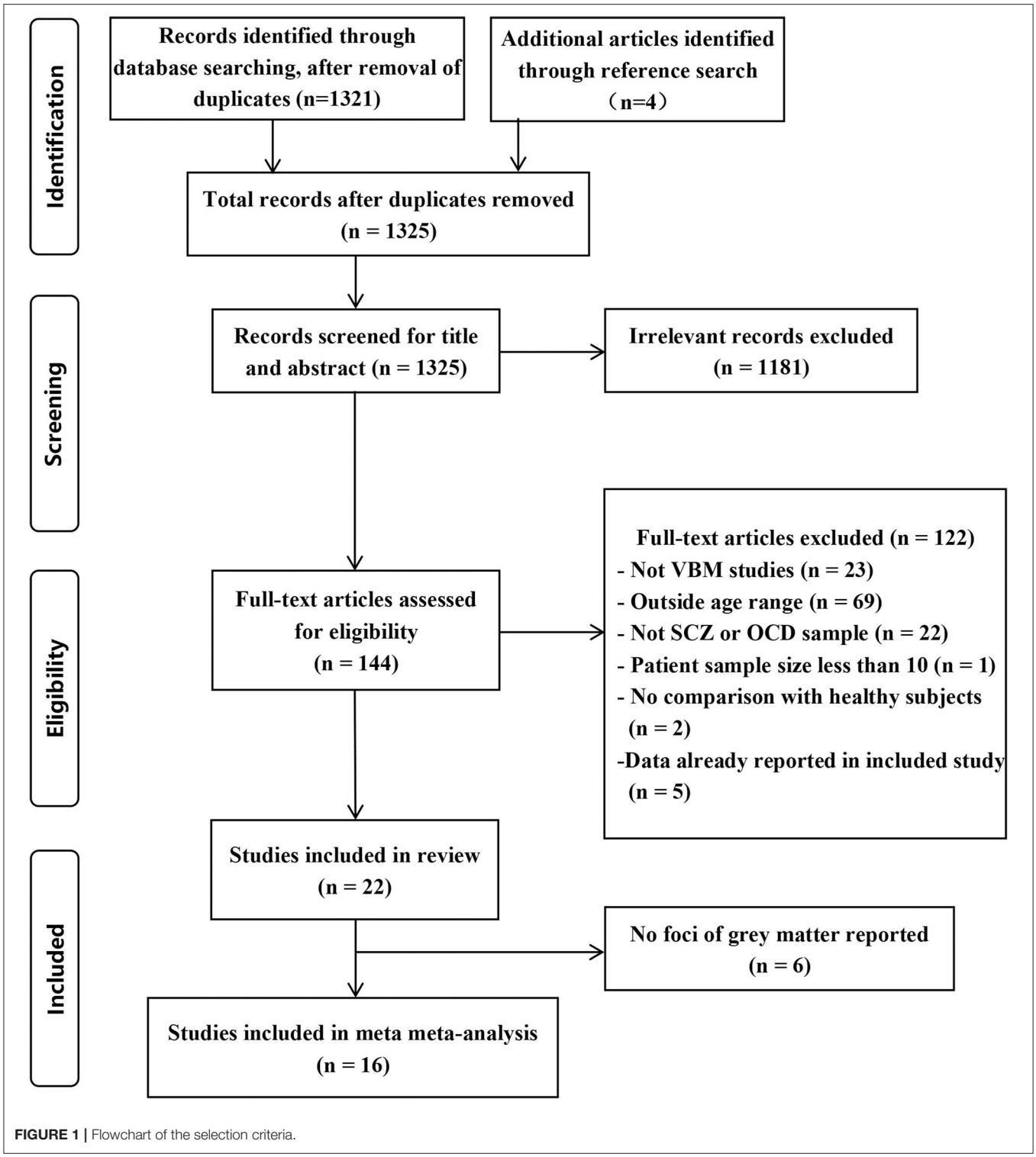

FIGURE 1 | Flowchart of the selection criteria.

GM changes (21). ALE analyses were conducted in Montreal Neurological Institute (MNI) space; however, if coordinates were originally reported in Talairach space, they were converted into MNI space with the Lancaster transform using the icbm2tal transformation function implemented within GingerALE (22). The resulting statistical maps were corrected for a threshold at $p < 0.001$ (False Discovery Rate correction, FDR) with a cluster extent threshold of 50 voxels. For visualization, whole-brain maps of threshold ALE maps were imported into multi-image analysis Mango (http://ric.uthscsa.edu/mango) and

TABLE 1 | Demographic and clinical characteristics of the 22 voxel-based morphometry studies.

References	Patients					Controls			Brain regions of gray matter alterations	
	Sample size	Age	Males%	DOI	Treatment	Sample size	Age	Males%	Patients< Controls (A)	Patients> Controls (B)
SCZ studies										
Wen et al. (23)	29	14.93 ± 1.60	34	NR	NR	28	16.00 ± 0.47	43	Hippocampus (A)	
Gao et al. (24)	39	13.5 ± 2.3	44	5 ± 3	0	39	13.3 ± 2.0	36	R insula, L IFG, L limbic edge (A)	
Zhang et al. (25)	26	16.87 ± 1.05	50	3.61 ± 3.50	0	26	16.81 ± 0.75	50	L parietal postcentral gyrus, L parahippocampa (A)	
Castro-Fornieles et al. (26)	34	15.2 ± 1.7	71	NR	NR	70	15.3 ± 1.5	60	No positive results	
Zhang et al. (27)	37	15.5 ± 1.8	46	16.0 ± 14.4	0	37	15.3 ± 1.6	46	R STG, R MTG (A)	
Tang et al. (28)	29	16.5 ± 0.9	45	9.3 ± 4.6	79	29	16.6 ± 0.8	55	L STG, L MTG (A)	
James et al. (29)	32	16.3 ± 1.2	69	21.6 ± NR	100	28	16.4 ± 1.4	64	PFC, STG, ITG (A)	
Yoshihara et al. (30)	18	15.8 ± 1.3	50	14.4 ± 10.8	94	18	15.8 ± 1.8	50	L parahippocampal, IFG, STG (A)	
Janssen et al. (31)	25	15.4 ± 1.8	76	3.5 ± 2.2	NR	25	15.4 ± 1.6	69	L medial frontal gyrus, L MFG (A)	
Douaud et al. (32)	25	16.3 ± 1.3	72	16.8 ± 8.4	100	25	16.0 ± 1.7	68	SMA, R ACC, R dorso-lateral PFC (A)	
Pagsberg et al. (33)	15	15.6 ± 1.8	47	NR	NR	29	16 ± 1.9	38	No Positive Results	
OCD studies										
Cheng et al. (34)	30	10.8 ± 2.1	60	NR	0	30	10.5 ± 2.2	60	L IPL(A), Putamen, L OFC (B)	
Jayarajan et al. (35)	15	14.13 ± 1.79	53	16.8 ± 12.9	86	15	14.31 ± 2.12	53	L ACC (A)	
Lázaro et al. (36)	62	15.4 ± 2.1	58	28.29 ± 24.16	84	46	15.3 ± 2.1	48	No Positive Results	
Huyser et al. (37)	29	13.78 ± 2.58	28	31.2 ± 27.6	0	29	13.60 ± 2.73	28	L superior frontal pole, L insula (B)	
Lázaro et al. (38)	27	15.6 ± 1.5	56	NR	100	27	16.1 ± 1.3	48	No Positive Results	
Zarei et al. (39)	26	16.6 ± 1.5	54	63.6 ± 40.8	62	26	16.5 ± 1.4	54	Caudate, R putamen (B)	
Britton et al. (40)	15	13.5 ± 2.4	60	49.2 ± 24.0	100	20	13.6 ± 2.4	65	Medial frontal gyrus, OFC; R ACC (B)	
Lázaro et al. (41)	15	13.7 ± 2.5	53	21.2 ± 16.6	0	15	14.3 ± 2.5	53	Parietal lobes(A)	
Szeszko et al. (42)	37	13.0 ± 2.7	38	43.2 ± NR	0	26	13.0 ± 2.6	35	Occipital cortex (A); OFC, STG, parietal lobe (B)	
Gilbert et al. (43)	10	12.9 ± 2.7	60	NR	0	10	13.4 ± 2.6	60	L ACC, medial SFG (A)	
Carmona et al. (44)	18	12.86 ± 2.76	72	NR	56	18	13.03 ± 3.04	72	Frontal lobe, cingulate cortex (A)	

SCZ, schizophrenia; OCD, obsessive-compulsive disorder; y, years; m, months; DOI, duration of illness; SD, standard deviation; NR, not recorded; R, right; L, left; IFG, inferior frontal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; PFC, prefrontal cortex; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; SMA, supplementary motor area; IPL, inferior parietal lobule; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex.

overlaid onto a standardized anatomical template (the ICBM-152 brain template) (22).

RESULTS

Identification of Included Studies

The identification procedure of the studies can be found in **Figure 1**. Initially, we identified 21 English language studies and 1 Chinese language study according to the criteria. We list the exclusion information in **Supplementary Table 1**.

Systematic Review of Included Studies

The VBM datasets were obtained from 11 SCZ studies and 11 OCD studies. The baseline characteristics of all participants and the brain regions of gray matter alterations are summarized in **Table 1**. Two SCZ studies found GM volume changes without reporting the foci (23, 29). Four studies did not find any significant differences in GM volume between patients and healthy controls (26, 33, 36, 38). It seems that children and adolescents with schizophrenia had decreased gray matter volume (GMV), mainly in the prefrontal cortex (PFC), temporal cortex and insula, while children and adolescents with OCD mainly had increased GMV in the PFC and the striatum, but decreased GMV in the parietal cortex.

ALE Analysis in Children and Adolescents With SCZ and OCD

For the ALE analysis, there were 7 SCZ studies (including 199 patients with SCZ and 225 control subjects) and nine OCD studies (including 195 patients with OCD and 189 control subjects). ALE analysis in children and adolescents with SCZ revealed that GM volume was significantly reduced in the bilateral medial frontal gyrus, right middle frontal gyrus (MFG), bilateral inferior frontal gyrus (IFG), bilateral superior frontal gyrus (SFG), bilateral temporal sub-gyrus, and so on (for more details, see **Table 2**; **Figure 2**).

For children and adolescents with OCD, GM volume was significantly reduced in the left supramarginal gyrus, left cuneus, left middle occipital gyrus, right IFG, right SFG, bilateral

TABLE 2 | Results of ALE analyses on gray matter reduction in SCZ.

Cluster #	Volume (mm^3)	Peak ALE value	MNI coordinates (x,y,z)			Brain regions
1	96	0.009153046	48	−10	−16	(R) Temporal Sub-Gyral (BA21)
2	96	0.008924574	36	21	3	(R) Insula (BA13)
3	96	0.008930734	0	44	28	(L) Medial Frontal Gyrus (BA9)
4	80	0.009246408	54	18	9	(R) Inferior Frontal Gyrus (BA44)
5	64	0.008868549	−54	−22	−12	(L) Middle Temporal Gyrus (BA21)
6	56	0.008880154	−50	−16	−22	(L) Temporal Sub-Gyral (BA20)
7	56	0.008856174	−12	−90	6	(L) Lingual Gyrus (BA17)
8	56	0.008856174	50	−22	8	(R) Transverse Temporal Gyrus (BA41)
9	56	0.008856174	−48	−18	10	(L) Transverse Temporal Gyrus (BA41)
10	56	0.008856174	−46	18	12	(L) Inferior Frontal Gyrus (BA44)
11	56	0.008856174	20	−60	14	(R) Posterior Cingulate (BA30)
12	56	0.008856174	50	−24	20	(R) Insula (BA13)
13	56	0.008856174	−50	8	20	(L) Inferior Frontal Gyrus (BA9)
14	56	0.008856175	20	44	20	(R) Medial Frontal Gyrus (BA9)
15	56	0.008856174	−38	−16	24	(L) Insula (BA13)
16	56	0.008858921	14	40	30	(R) Medial Frontal Gyrus (BA9)
17	56	0.008856174	24	−70	32	(R) Precuneus (BA31)
18	56	0.008856176	20	44	32	(R) Superior Frontal Gyrus (BA9)
19	56	0.008856174	14	8	34	(R) Cingulate (BA24)
20	56	0.008856174	38	10	38	(R) Medial Frontal Gyrus (BA6)
21	56	0.008856174	60	−16	44	(R) Postcentral Gyrus (BA3)
22	56	0.008856174	−40	−36	46	(L) Inferior Parietal Lobule (BA40)
23	56	0.008856235	−22	18	48	(L) Superior Frontal Gyrus (BA6)
24	56	0.008929286	−10	−38	70	(L) Postcentral Gyrus (BA5)

SCZ, schizophrenia; ALE, activation likelihood estimation; MNI, Montreal Neurological Institute; R, right; L, left; BA, Brodmann area.

MFG, right precentral gyrus, right paracentral lobule, right precuneus, bilateral cingulate, and right culmen. Simultaneously, GM volume was significantly increased in the left medial frontal gyrus, right MFG, right IFG, left SFG, striatum and so on (for more details, see **Tables 3**, **4**; **Figure 3**).

DISCUSSION

The current systematic review and ALE meta-analysis revealed that children and adolescents with either SCZ or OCD have significant GMV abnormalities in multiple brain regions. However, despite being relatively consistent with the existing literature, our findings showed heterogeneous results. First, both children and adolescents with SCZ and those with OCD showed GMV alterations in the prefrontal cortex (PFC), which included the medial frontal gyrus and MFG (BA9, BA10). Notably, in this area, GMV was decreased in children and adolescents with SCZ and increased in those with OCD. Second, children and adolescents with SCZ showed decreased GMV in the temporal cortex (especially in the MTG and the transverse temporal gyrus) and insula. However, for children and adolescents with OCD, loss of GM was found in the parietal cortex, mainly in the supramarginal gyrus. Third, children and adolescents with OCD had a greater striatal GM volume, including the lentiform nucleus and caudate nucleus, than control subjects. Overall, we found that children and adolescents with SCZ and those with OCD have significant GMV abnormalities in multiple brain regions. For the cortical cortex, a decrease in GMV was observed mainly in the areas of the PFC (medial frontal gyrus and MFG), temporal cortex (especially in the MTG and transverse temporal gyrus), and insula in children and adolescents with SCZ. In children and adolescents with OCD, an increase in GMV was observed in the PFC, while a decrease in GMV was observed in the parietal cortex (supramarginal gyrus). For subcortical regions, we found that children and adolescents with OCD had a greater striatal volume, including the lentiform nucleus and caudate nucleus.

Gray matter loss in the PFC has been previously reported in children and adolescents with SCZ. In addition to the VBM studies in our meta-analysis, studies using the "region of interest" (ROI) approach suggested that children and adolescents with SCZ had a deficit in GM volume in the PFC (45–47). In addition, longitudinal magnetic resonance imaging studies have reported that children and adolescents with SCZ showed greater progressive frontal GM loss over years after illness onset than healthy individuals (48, 49). Recently, a large-scale study concluded that individuals with schizophrenia have a widespread thinner cortex and smaller surface area in frontal lobe regions (50). Supplementing previous research, the results of this study indicate that GM loss in the PFC might occur at an earlier course of SCZ.

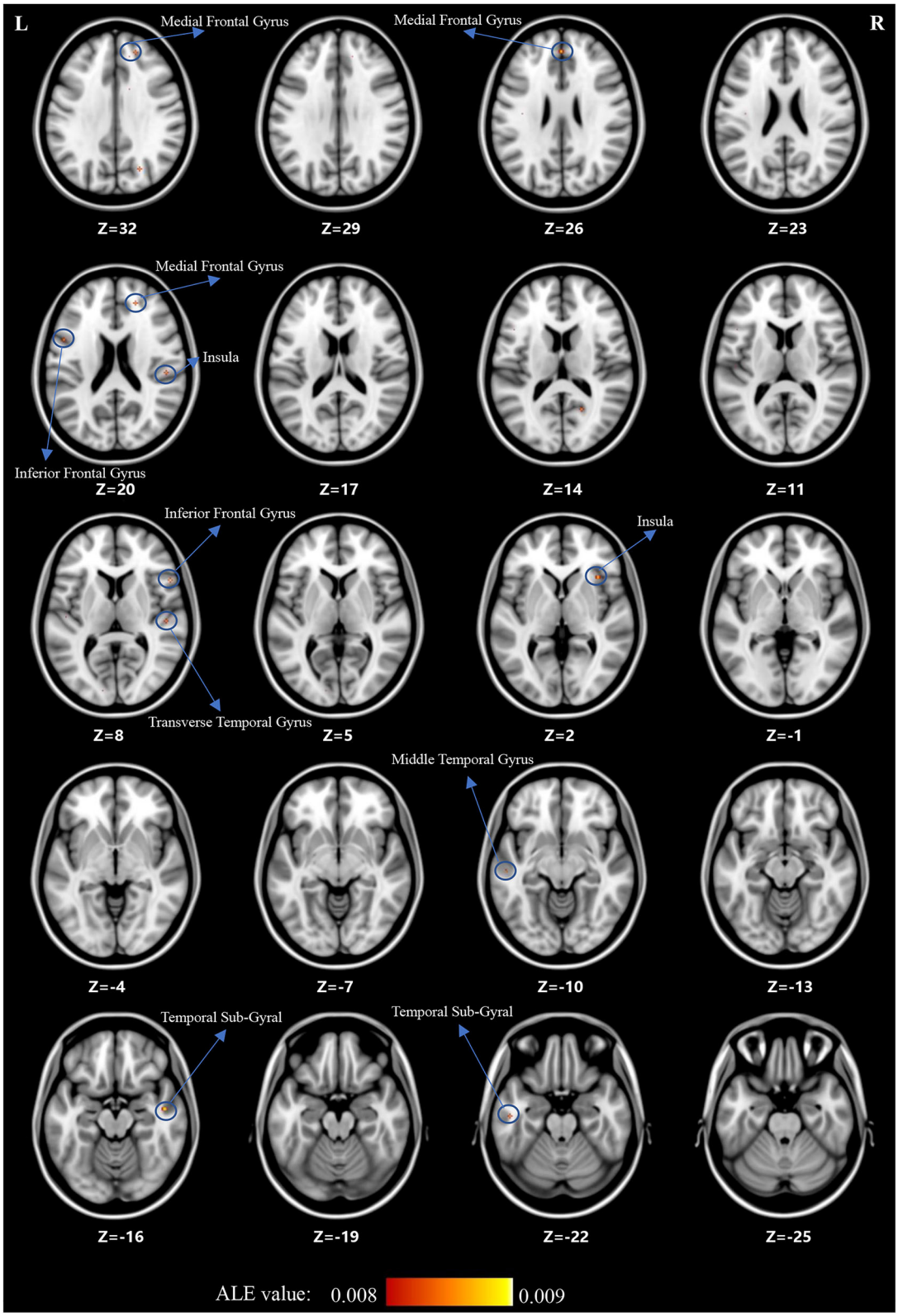

FIGURE 2 | The gray matter reduction (red) in SCZ based on ALE analysis.

TABLE 3 | Results of ALE analyses on gray matter reduction in OCD.

Cluster #	Volume (mm^3)	Peak ALE value	MNI coordinates (x,y,z)			Brain regions
1	312	0.013117323	−62	−52	38	(L) Supramarginal Gyrus (BA40)
2	96	0.008858794	−11	−88	13	(L) Cuneus (BA17)
3	96	0.008858794	−27	−84	13	(L) Middle Occipital Gyrus (BA18)
4	96	0.00766531	44	13	35	(R) Precentral Gyrus (BA9)
4		0.007424954	43	13	30	(R) Inferior Frontal Gyrus (BA9)
5	96	0.00766531	25	29	42	(R) Superior Frontal Gyrus (BA8)
5		0.007424954	27	24	43	(R) Superior Frontal Gyrus (BA8)
6	96	0.00766531	3	−13	48	(R) Paracentral Lobule (BA31)
6		0.007424954	8	−11	49	(R) Paracentral Lobule (BA31)
7	80	0.009176578	16	−63	−4	(R) Culmen
8	64	0.007424954	53	27	21	(R) Middle Frontal Gyrus (BA46)
9	64	0.007424954	−45	25	23	(L) Middle Frontal Gyrus (BA46)
10	64	0.007424954	15	−53	41	(R) Precuneus (BA31)
11	64	0.007424954	15	−37	43	(R) Cingulate Gyrus (BA31)
12	64	0.007424954	1	−31	47	(L) Cingulate Gyrus (BA31)

OCD, obsessive-compulsive disorder; ALE, activation likelihood estimation; MNI, Montreal Neurological Institute; R, right; L, left; BA, Brodmann area.

We found an increase, rather than a decrease, in GMV of the PFC in children and adolescents with OCD, in contrast to that reported in a previous meta-analysis (20). These discrepancies can be explained by the differences in the OCD studies included. We excluded a study reporting a lower PFC volume because of the small sample size (51) and two studies reporting a greater PFC volume (34, 40). Recently, a large-scale graph analysis of brain structural covariance networks found that the PFC exhibited OCD-related alterations in the trajectories of brain development and maturation (52). Similar to SCZ, the results of the present study also indicated that GM alterations might occur at an earlier course of OCD.

The PFC plays an essential role in the organization and control of goal-directed thoughts and behaviors (53). Furthermore, the PFC orchestrates a wide range of cognitive and affective neuronal functions thanks to its extensive reciprocal connections to nearly all cortical and subcortical structures (53). The PFC dysconnectivity pattern in patients with SCZ is associated with the severity of cognitive impairments (such as impaired working memory) (54). Disruption of executive functions that are PFC-regulated may lead to the generation of obsessions and compulsions in patients with OCD (55). Several functional imaging studies have consistently highlighted abnormal activity patterns in PFC regions and connected circuits in SCZ and OCD during both symptom provocation and performance of neurocognitive tasks (54, 55). Our results hint at GM alterations in the PFC shared by children and adolescents with SCZ and those with OCD, which might account for comorbid cognitive deficits in both disorders.

In terms of other cortical abnormalities, GMV in the temporal cortex was decreased in children and adolescents with SCZ, whereas GMV in the parietal cortex was decreased in children and adolescents with OCD. Previous studies have reported a decreased GMV in the temporal cortex as well as in the PFC (47, 48). Regions in the temporal lobe are associated with auditory hallucinations, thought disorder, and memory dysfunction and are key characteristics of schizophrenia (28). In a previous study, loss of GM in the temporal cortex was negatively correlated with positive symptoms in SCZ (28). Several studies have verified the relationship between frontotemporal functional dysconnectivity and auditory hallucinations during different tasks, suggesting a source-monitoring impairment (56). The parietal cortex has been continuously implicated in the pathophysiology of both adult and pediatric OCD (16, 57). It has been hypothesized that the repetitive behaviors in OCD reflect the problems in set-shifting (58), in which the supramarginal gyrus plays a key role (59). Moreover, the supramarginal gyrus is part of the inferior parietal lobule (IPL). As an important node in both the fronto-parietal network and the default mode network, the IPL is considered to underlie OCD symptoms, such as the inability to eliminate persistent intrusive thoughts (60). In general, GM deficits in the temporal cortex in SCZ patients are associated with positive symptoms, whereas GM deficits in the parietal cortex in OCD patients may be the basis of compulsive behavior. These results tap into the heterogeneity of the two diseases.

Another key observation in this meta-analysis is that GM volume is reduced in the insula among children and adolescents with SCZ. A decrease in GM volume in the insula was found in adults with early-onset schizophrenia (61). A meta-analysis of ROI studies reported medium-sized bilateral GM volume reduction in the insular cortex in schizophrenia, which showed no progression with illness stage (62). Volume reduction in the insular cortex may constitute an important neuropathology in schizophrenia. Significant and widespread dysconnectivity of insula subregions is observed in schizophrenia, which correlates with cognitive function (63). Individuals with schizophrenia have impaired anterior

TABLE 4 | Results of ALE analyses on gray matter increase in OCD.

Cluster #	Volume (mm^3)	Peak ALE value	MNI coordinates (x,y,z)			Brain regions
1	608	0.016521817	−26	12	2	(L) Lentiform Nucleus (Putamen)
2	304	0.009560066	20	20	−2	(R) Caudate (Caudate Head)
		0.008989162	14	16	−2	(R) Caudate (Caudate Head)
3	224	0.009225059	−12	66	−10	(L) Medial Frontal Gyrus (BA10)
		0.008012949	−18	58	−10	(L) Superior Frontal Gyrus (BA10)
4	200	0.00917098	−18	56	10	(L) Superior Frontal Gyrus (BA10)
		0.008015263	−8	56	10	(L) Medial Frontal Gyrus (BA10)
5	112	0.009076225	−14	38	−22	(L) Medial Frontal Gyrus (BA11)
6	96	0.008518396	−30	−19	19	(L) Claustrum
7	96	0.008858794	13	−52	63	(R) Precuneus Gray (BA7)
8	80	0.009176578	20	34	−23	(R) Inferior Frontal Gyrus (BA47)
9	80	0.008632486	26	−5	2	(R) Lentiform Nucleus (Putamen)
10	80	0.00881557	−50	−26	29	(L) Inferior Parietal Lobule (BA40)
11	80	0.009176578	8	−69	58	(R) Superior Parietal Lobule (BA7)
12	80	0.009176578	−12	−65	62	(L) Superior Parietal Lobule (BA7)
13	64	0.008552016	45	3	−25	(R) Superior Temporal Gyrus (BA38)
14	64	0.008079925	−12	14	2	(L) Caudate (Caudate Head)
15	64	0.008495986	32	3	45	(R) Middle Frontal Gyrus (BA6)

OCD, obsessive-compulsive disorder; ALE, activation likelihood estimation; MNI, Montreal Neurological Institute; R, right; L, left; BA, Brodmann area.

insula-related large-scale brain networks, especially the central executive and default mode networks (64). The disrupted processing in the insula or a network involving the region could contribute to many sensory deficits found in schizophrenia. Failure of this process may lead to internally generated sensory information being attributed to an external source, which in turn contributes to hallucinations (65).

For subcortical regions, we found that the striatal volume was greater in pediatric OCD, consistent with findings of a previous meta-analysis (20). The aforementioned GM alterations in the PFC combined with our findings support theories of prefrontal–striatal circuit abnormalities in pediatric OCD (66). The prefrontal–striatal circuit, the main part of inhibitory control networks, includes several brain regions, such as the ventrolateral prefrontal cortex, anterior insula, supplementary motor area, dACC, and the striatal, thalamic, and dorsolateral prefrontal cortex (67). In OCD, deficits in inhibitory control were thought to underlie the poor control over obsessions and compulsions (68, 69). The prefrontal–striatal circuit is also part of the cortico-striatal-thalamo-cortical (CSTC) pathway. Hyperactivity in the CSTC pathway is thought to underlie the manifestation of OCD (70). Moreover, a meta-analysis of executive function in OCD showed that OCD is associated with broad impairments in executive function (71). Indeed, the impaired executive function in OCD also showed an association with the prefrontal–striatal circuit (55). Meanwhile, GMV in the striatum was greater in OCD than in attention-deficit hyperactivity disorder and autism spectrum disorder (72, 73). In addition, no alterations in striatal volume were found in children and adolescents with SCZ. The results suggest that greater striatal volume may be a disorder-specific neural structural biomarker of pediatric OCD relative to other psychiatric disorders.

Several limitations were noted in the current study. First, the number of studies in our ALE meta-analysis was small. Based on a recent simulation study (74), a recommendation was made to include at least 17–20 experiments in ALE meta-analyses to have sufficient power. However, the present schizophrenia meta-analysis is based on only seven studies, and the meta-analysis on OCD patients contains only nine studies. Therefore, the power can be assumed to be very weak, and the results can only be regarded as indicators for future studies. Second, Müller et al. (75) reported 10 simple rules for neuroimaging meta-analysis. One of the rules is that a cluster-level Family Wise Error (FWE) correction is recommended for ALE meta-analyses, but in the present study, a loose correction (FRD correction, $p < 0.001$) was used to obtain more results, which made our results preliminary and highly heterogeneous. Third, in line with most voxelwise meta-analyses, our study was based on brain coordinates extracted from published studies rather than raw statistical brain maps. This may also lead to less accurate results (76). Fourth, due to the limited sample size, we did not consider the influencing factors (e.g., treatment, age, and duration of illness). For example, it was consistently reported that both anatomical and functional brain components, including the frontal and temporal lobes, basal ganglia, limbic system and several key components within the default mode network, changed in patients with SCZ after antipsychotic treatment (77). The influence of antidepressants was also reported in OCD (78). However, the influence of medicines on the brains of patients with mental disorders might be an important direction for future studies.

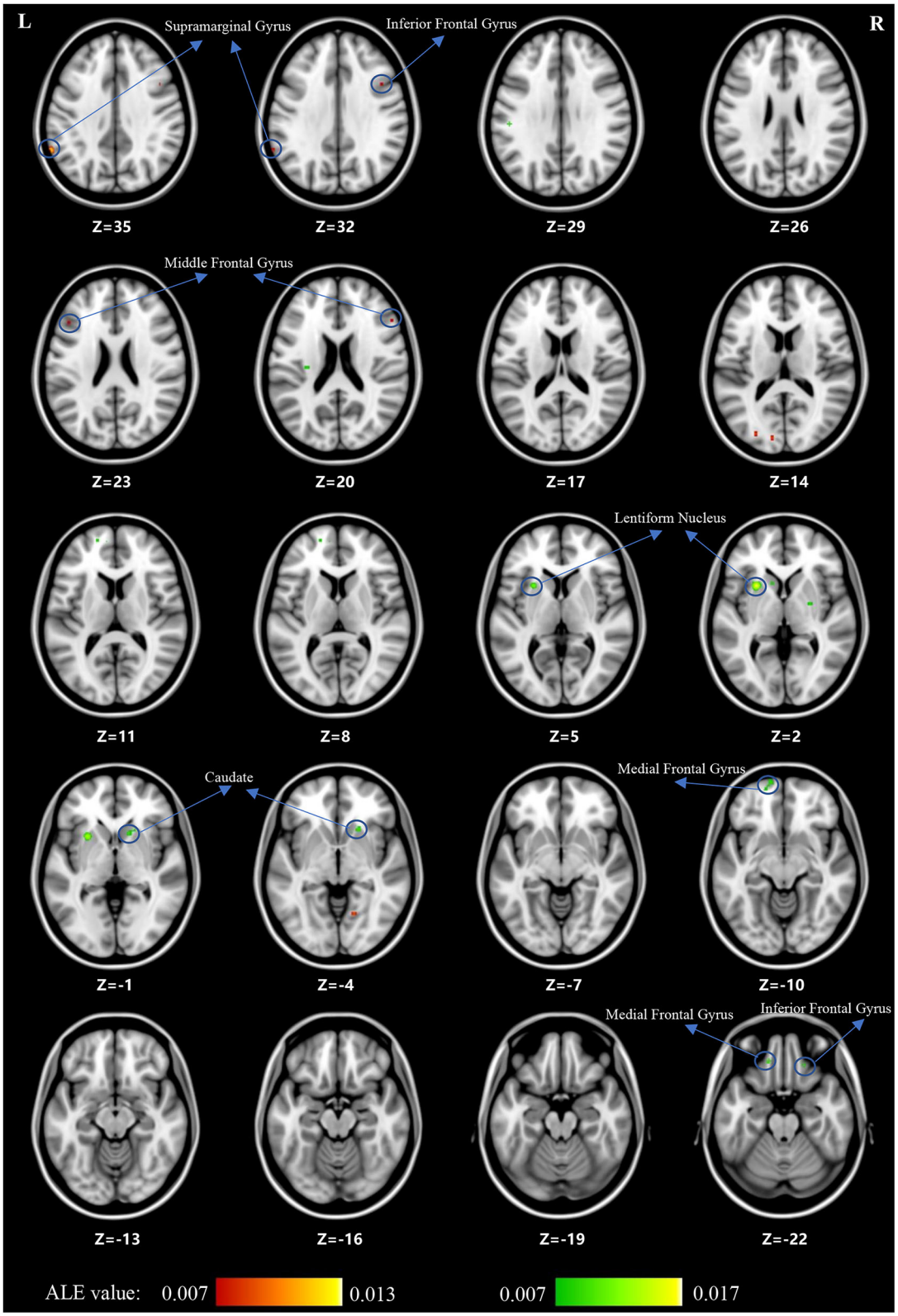

FIGURE 3 | The gray matter reduction (red) and increase (green) in OCD based on ALE analysis.

CONCLUSIONS

In children and adolescents with SCZ, GM alterations are observed in the PFC, the temporal cortex, and the insula. In children and adolescents with OCD, GM alterations are exhibited in the PFC and striatum. These results suggest that GM abnormalities in the PFC may be a good indicator of the homogeneity between these two disorders. It is suggested that the majority of children and adolescents with SCZ have core defects in the prefrontal-temporal and cortico-insula circuits, whereas those with OCD have core defects in the prefrontal-parietal and the prefrontal-striatal circuits.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

YC and YiL took the initiative. FWe, JY, LY, FWa, DW, JZ, CY, JC, and YaL finished the study search and data extraction. YiL performed the data analysis. JL finished the draft. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.785547/full#supplementary-material

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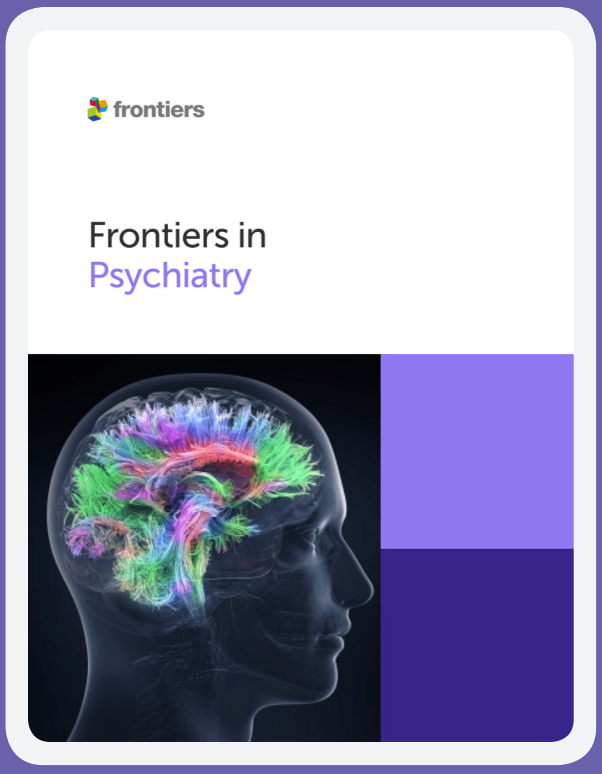

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