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REVIEW

Genetic and Neuroimaging Features of Personality Disorders: State of the Art

Guorong Ma[1,2] · Hongying Fan[1] · Chanchan Shen[2] · Wei Wang[1,2]

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Abstract Personality disorders often act as a common denominator for many psychiatric problems, and studies on personality disorders contribute to the etiopathology, diagnosis, and treatment of many mental disorders. In recent years, increasing evidence from various studies has shown distinctive features of personality disorders, and that from genetic and neuroimaging studies has been especially valuable. Genetic studies primarily target the genes encoding neurotransmitters and enzymes in the serotoninergic and dopaminergic systems, and neuroimaging studies mainly focus on the frontal and temporal lobes as well as the limbic-paralimbic system in patients with personality disorders. Although some studies have suffered due to unclear diagnoses of personality disorders and some have included few patients for a given personality disorder, great opportunities remain for investigators to launch new ideas and technologies in the field.

Keywords Heritability · Genetic · Neuroimaging · Personality disorder · Psychiatric disorder

✉ Wei Wang
wangmufan@msn.com; drwangwei@zju.edu.cn

[1] Department of Clinical Psychology and Psychiatry, Zhejiang University School of Medicine, Hangzhou 310058, China

[2] Department of Psychology and Behavioral Sciences, Zhejiang University College of Science, Hangzhou 310007, China

Introduction

Personality disorders are characterized by an enduring pattern of inner experience and behavior that deviates markedly from the expectations of others or the related culture. Patients with personality disorders have pervasive and long-standing traits which affect their perception, cognition, emotions and behavior, as well as their ability to function in interpersonal or other social roles [1]. In one diagnostic system, the Diagnostic and Statistical Manual of Mental Disorders - 5th edition (DSM-5) [1], personality disorders are divided into three clusters: cluster A, which includes paranoid, schizoid, and schizotypal types; cluster B, antisocial, borderline, histrionic, and narcissistic; and cluster C, avoidant, dependent, and obsessive-compulsive.

An investigation conducted by the World Health Organization has shown that the prevalence estimates are 6.1% for any personality disorder, and 3.6%, 1.5%, and 2.7% for Clusters A, B, and C respectively [2]. This investigation also disclosed that personality disorders are significantly elevated among males, the previously married (Cluster C), the unemployed (Cluster C), the young (Cluster A and B), and the poorly-educated, and implies an environmental influence on the etiology of these disorders. Besides the studies of environmental factors such as those focusing on childhood maltreatment or other traumatic experiences, biological investigations of personality disorders have been highly productive [3]. The biologically-oriented studies begin with genes, followed by the genetic influence on neurons through neurotransmitters and enzymes, and further with the structure and function of the central nervous system.

Biomarkers for personality disorders, as well as other mental or somatic disorders, can help align the clinical classification with biology-based evidence [4], thus

improving diagnostic accuracy, offering clues for research and treatment, and identifying high-risk populations. Potential biomarkers lie in abnormalities of gene sequences, neurotransmitter systems, and the structure and function of the brain [5]. Recent years have witnessed increasing attention to the neurobiological bases of personality disorders, especially the genetic and neuroimaging aspects. We therefore summarize the up-to-date neurobiological findings on personality disorders, organized around their genetic and neuroimaging features. Evidence of neurotransmitter, neurophysiological, or other biological contributions to the pathology of personality disorders is increasing and has been mentioned elsewhere [3–5].

Genetic Findings

Personality disorders originate in early childhood, and both the environmental and genetic backgrounds are involved in their etiopathologies. Disturbance of early attachment formation and childhood traumatic events are key etiological factors. However, with the collective use of family, twin, and adoption studies, increasing evidence has shown that genetic factors have a fundamental influence on the development of a personality disorder [6]. Personality disorders are not simple or direct consequences of bad parenting or child abuse, but are also rooted in interactions between an abnormal temperament (usually considered to be genetically fixed) and an adverse environment [5].

The genetic variants that mediate the risk for personality disorders remain largely unknown. Candidate genes include those that regulate neurotransmitters such as serotonin, dopamine, norepinephrine, and amines, which play important roles in mood regulation, suicidality, aggression, impulsivity, lack of empathy, and other important subdomains of the symptomatology of personality disorders. However, not all types of personality disorder have received equal genetic investigation. The relatively-frequently studied types are the paranoid, schizotypal, borderline, and antisocial disorders. Some of the well-designed studies describing the molecular and genetic aspects of the disorders are listed in Table 1.

Paranoid Personality Disorder

Paranoid personality disorder is often described as a lifelong but non-psychotic tendency of responding to other people with habitual and characteristic suspiciousness. Clinically, the disorder is closely associated with schizotypal personality disorder and schizophrenia [21], and is seldom targeted as an isolated type in terms of pathophysiology and management. For instance, almost no neurobiological studies, and no research on somatic or psychotherapeutic treatment has been devoted exclusively or even primarily to the disorder [21]. Two possible reasons for this situation are the difficulties in recruiting patients of this kind, and the lack of assurance among researchers about the independent occurrence of this disorder. Available data seem to favor the latter explanation, since in most cases trait-paranoia is better explained by other psychiatric disorders including the underlying personality disorders [21]. Some social studies however, have shown that paranoid personality disorder is strongly associated with a reduction in the quality of life [22]. Regarding its epidemiological features, this disorder has a prevalence of 2.4% in the general population [23], and 0.4–27.6% in the clinical setting [24].

The heritability of paranoid personality disorder has been estimated at 50% in a study of 122 twins aged 4–15 years [25], and at 21% [26] and 28% [27] in others, although these studies suffered equally from imperfect test-retest reliability of the measurement for personality disorder [28]. In a study that used both self-report questionnaires and interviews as measures of personality disorder, the heritability estimate reached 66% [29]. Unfortunately, few neurobiological studies have been performed exclusively on this disorder so far. Most findings specific to paranoid personality disorder or paranoia have been from participants predominantly with schizophrenia spectrum disorders, which include schizotypal or schizoid personality disorder and schizophrenia.

A study of patients with affective disorder and schizophrenia spectrum disorders and healthy controls has identified an association between the short (S) allele and short/short (S/S) allele genotypes of the serotonin-transporter gene-linked polymorphic region (5-HTTLPR) with lower scores on the Paranoia Scale of the Minnesota Multiphasic Personality Inventory [7], suggesting that the S/S allele genotype might minimize the expression of the paranoid trait. The alpha-1C subunit of the L-type voltage-gated Ca^{2+} channel (CACNA1C) couples transient activation of the inward Ca^{2+} current to transcriptional regulation and plays important roles in dendritic development, neuronal survival, synaptic plasticity, memory formation, learning, and behavior. A gene study has demonstrated that CACNA1C (rs1006737) is positively associated with paranoid ideation scores as assessed by the Schizotypal Traits Questionnaire [9, 10]. Catechol-o-methyltransferase (COMT), on the other hand, is an enzyme that metabolizes the neurotransmitters dopamine, adrenaline, and noradrenaline. A group of investigators have revealed that individuals with the Val/Val genotype score significantly higher on the paranoid factor of the Schizotypal Personality Questionnaire than those with the Met/Val genotype, suggesting a positive association between the COMT Val allele and the paranoid factor [8].

Table 1 Genetic studies on paranoid, schizotypal, antisocial personality disorders and related traits

Polymorphism investigated	Target group	Analysis	Findings	Authors
Paranoid personality disorder				
Serotonin transporter 5-HTTLPR	114 (35 males) affective disorder, 110 (63 males) schizophrenia spectrum disorders, 124 (46 males) controls	ANOVA	Short allele genotype of 5-HTTLPR associated with lower paranoid score on MMPI	Golimbet *et al.*, 2003 [7]
Catechol-O-methyltransferase $Val^{158}Met$	1657 young males aged 18–24 years	ANOVA	Positive association between Val allele and paranoid factor	Smyrnis *et al.*, 2007 [8]
CACNA1C rs1006737	530 randomly-selected males	ANOVA	A-allele associated with higher paranoid ideation scores on STQ	Roussos *et al.*, 2011 [9]
	50 (31 males) schizotypal personality disorder, 48 (28 males) controls	Student's *t*-test	Associated with paranoid ideation scores of STQ	Roussos *et al.*, 2013 [10]
Schizotypal personality disorder				
Catechol-O-methyltransferase $Val^{158}Met$	67 schizotypal personality disorder patients	χ^2, MANCOVA, ANCOVA	Related to prefrontal cortex-dependent performance	Minzenberg *et al.*, 2006 [11]
	154 patients with other personality disorders, 60 controls		Might contribute to the deficit in prefrontal-dependent memory processes	
	908 young males aged 18–24 years	ANOVA	Positively associated with magical thinking, constricted affect, odd speech, negative factor, disorganization symptoms, paranoid factor scores as well as total score on SPQ	Smyrnis *et al.*, 2007 [8]
	522 (267 males) psychiatrically normal individuals	ANOVA	Met/Met and Val/Met carriers score highest in an executive function test	Sheldrick *et al.*, 2008 [12]
			Met/Met genotype carriers are more disorganized than those with the Val/Val genotype	
	27 (10 males) unaffected first-degree relatives of schizophrenic patients	ANOVA	Val/ Val carriers had highest mean score on full SPQ.	Schürhoff *et al.*, 2007 [13]
	22 (8 males) unaffected first-degree relatives of bipolar probands		Val allele associated with higher positive and negative dimension scores on SPQ	
	57 (32 males) controls			
	465 (231 males) healthy community dwelling adults	Regression, ANOVA	Weak association with the odd speech subscale on SPQ	Ma *et al.*, 2007 [14]
			Weak association with disorganization factor on SPQ (when only males analyzed)	
			Individuals with Val/Val genotype showed the lowest SPQ scores (when only males analyzed)	
p250GAP rs2298599	431 (210 males) schizophrenia, 572 (267 males) controls	ANOVA	A/A genotype frequency higher in patients	Ohi *et al.*, 2012 [15]
			A/A carriers showed higher scores on schizotypal traits	
CACNA1C rs1006737	50 schizotypal personality disorder, 48 controls	Student's *t*-test	Associated with paranoid ideation subscale of STQ	Roussos *et al.*, 2013 [10]

Table 1 continued

Polymorphism investigated	Target group	Analysis	Findings	Authors
Antisocial personality disorder				
Serotonin transporter 5-HTTLPR 5-HTTVNTR **Dopamine transporter** DATVNTR	311 male heroin-dependents with ASPD 277 male heroin-dependents without ASPD 194 male controls	Multifactor dimensionality reduction	Higher 12R/10R genotype frequency in 5-HTTVNTR of heroin-dependents with ASPD than both controls and heroin-dependents without ASPD The interaction of 5-HTTVNTR and DATVNTR is associated with ASPD in male heroin-dependents at the trend level 10R allele of 5-HTTVNTR and 9R allele of DATVNTR positively associated with higher risk of co-occurring ASPD in male heroin-dependents	Yang *et al.*, 2012 [16]
Dopamine D2 receptor TaqI	115 male alcohol-dependents, 114 controls	Student's *t*-test, regression	Interaction between A1 allele and harm-avoidance have a significant effect on predicting the number of ASPD symptoms	Bau *et al.*, 2000 [17]
	103 male alcohol-dependents	χ^2	A1 allele carriers have a higher prevalence of ASPD	Ponce *et al.*, 2003 [18]
synaptosomal-associated protein 25 DdeI MnlI	91 male offenders, 38 healthy controls	ANOVA	MnlI T/T and DdeI T/T genotypes more frequent in males with ASPD than in normal controls	Basoglu *et al.*, 2011 [19]
Adenosine triphosphate-binding cassette, sub-family B, member 1 rs4728702	1379 (739 males) participants	Genome-wide complex trait analysis	Associated with adult antisocial behavior	Salvatore *et al.*, 2015 [20]

Note: ASPD, antisocial personality disorder; CACNA1C, voltage-dependent L-type Ca^{2+} channel, alpha 1C subunit; DATVNTR, dopamine transporter variable number of tandem repeats; MMPI, Minnesota Multiphasic Personality Inventory; SPQ, Schizotypal Personality Questionnaire; STQ, Schizotypal Traits Questionnaire; 5-HTTLPR, serotonin-transporter gene-linked polymorphic region; 5-HTTVNTR, serotonin transporter introns 2 variable number of tandem repeats

Schizotypal Personality Disorder

Schizotypal personality disorder is characterized by a high level of odd, eccentric appearance and behavior, restricted affect, aloofness, and lack of friends [1]. A similarity between this disorder and schizophrenia in their genetic predispositions has been identified [30], and this contributes to the fact that schizotypal personality disorder is among the few personality disorders that has received more interest from investigators. Both family and twin studies have found evidence that this disorder is heritable, and is determined by both familial-genetic and unique environmental factors [29, 31, 32]. A psychometric-genetic study has indicated that different phenotypic classes of schizotypal personality disorder are associated with different genetic contributions [33].

Molecular and genetic studies of schizotypal personality disorder have been conducted on three genes: COMT, CACNA1C, and Disrupted In Schizophrenia, the latest findings of which are summarized in Table 1. Sheldrick *et al.* [12] investigated the COMT $Val^{158}Met$ polymorphism, along with cognitive function and the personality traits of 522 healthy individuals, and noted that this genotype was associated, in an allele-dosage-dependent fashion, with performance in an executive function test, Met/Met carriers scoring highest. Interestingly, participants carrying the Met/Met genotype also scored higher in the disorganization domain of the Schizotypal Personality Trait Questionnaire. Similar results were obtained in healthy male participants [14], in whom the Met load of the COMT gene was positively associated with the scores on some schizotypal traits, including the disorganization factor, the constricted affect subscale, and the total score on the questionnaire. Nevertheless, in a study of 67 patients with schizotypal personality disorder, 154 with non-schizotypal personality disorder, and 60 healthy volunteers,

allelic variation in COMT activity was unrelated to the diagnosis of schizotypal personality disorder, whereas the COMT genotype was associated with performance on prefrontal cortex-dependent tasks, and seemed to contribute to the deficit in prefrontal-dependent memory processes in this disorder as it does in schizophrenia [11]. However, other results were quite the opposite of these findings, the Val allele showing a positive relationship with disorganization symptoms, magical thinking, odd speech, and other symptoms of schizotypy [8]. The inconsistencies might be due to the sample size or ethnicity, but encourage further studies on the role of the dopaminergic system and the COMT gene, or even of gender in the etiology of schizotypal personality disorder.

Meanwhile, an association between the Disrupted In Schizophrenia gene and the social anhedonia trait, a cardinal symptom of schizophrenia spectrum disorder, has been reported [34]. Variants of the p250 guanosine triphosphatase-activating protein gene have been found to play a role in the negative schizotypy dimension and interpersonal schizotypy factors [15]. Montag *et al*. [35] examined dopamine receptor D3 (DRD3) Ser9Gly polymorphism and its role in schizotypal personality, but found no significant association between the two parameters.

Borderline Personality Disorder

Borderline personality disorder is characterized by dysfunctions in the emotional, interpersonal, and behavioral realms. Patients with this disorder often display marked impulsivity and a pattern of instability in interpersonal relationships, self-image recognition, and affective control [1, 36]. These patients can show a wide range of dissociative experiences, including absorption, amnesia, or depersonalization [37]. The disorder affects ~0.5–5.9% of the general population [38–40] and estimates of heritability range from 35% to 69% [27, 32, 41–43]. A well-written review [44] has summarized the familial and twin designs, gene association investigations, and gene-environment interactions in this disorder.

Association studies of borderline personality disorder have mainly focused on genes involved in the serotonin-ergic and dopaminergic systems. Tryptophan hydroxylase (TPH) functions in 5-HT synthesis from the amino-acid tryptophan. Most studies have shown that the two isoforms of TPH (TPH-1 and TPH-2) are associated with borderline personality disorder, such as the suicidal behavior component [44].

Serotonin transporter (5-HTT) genes, especially 5-HTTLPR, are associated with borderline, depressive, anxious, and obsessive-compulsive characteristics, but not with suicidal and self-injury behavior. Whether the S or L genotype of 5-HTTLPR predisposes to emotional problems remains an open question. A study on school bullying revealed that children with the S/S genotype of 5-HTTLPR are at greater risk for developing emotional problems after bullying than those with the S/L or L/L genotype [45]. In another study on adolescents by Amstadter *et al*. [46], participants with the S/S or S/L allele of 5-HTTLPR performed worse on distress intolerance. An earlier study indicated that all serious life events except for rape are associated with decreased impulsivity in 5-HTTLPR S/S or S/L carriers, and with increased impulsivity in L/L carriers [47]. Serotonin receptor (5-HTR) genes, other than the 5-HTR2C gene, are unlikely to play a major role in the genetic susceptibility to borderline personality disorder [48, 49].

On the other hand, monoamine oxidase A (MAOA) is an enzyme that degrades monoamines, serotonin in particular, after their reuptake from the synaptic cleft. It has been shown that patients with borderline personality disorder have a variable number of tandem repeats of the MAOA gene different from healthy volunteers [50]. The dopamine transporter gene has also been associated with this disorder; for instance, the TaqI B1 and A1 alleles of the dopamine D2 receptor (DRD2) gene are associated with borderline personality disorder traits. The interaction between the 7-repeat allele of the DRD4 gene and socioeconomic status influences impulsivity in the disorder [51]. As noted above, COMT is an enzyme that breaks down dopamine, while brain-derived neurotrophic factor (BDNF) is involved in neurogenesis, synaptogenesis, and serotonin regulation. Both the COMT $Val^{158}Val$ and BDNF $Val^{66}Val$ polymorphisms might play a role in mediating the influence of childhood maltreatment on the pathology of borderline personality disorder [44]. These genes, as well as 5-HTT, are pronounced along with their polymorphisms in borderline personality disorder, bipolar disorder, unipolar depression, and post-traumatic stress disorder [52], indicating that these pathologies share similar genetic backgrounds.

Lubke *et al*. [53] performed a genome-wide association study of borderline personality features and revealed a signal on chromosome 5 corresponding to serine incorporator 5 - a protein involved in myelination. This suggests that a lack of serine incorporator 5 contributes to the development of psychiatric disorders that are characterized by a lack of social interaction. Lately, researchers have demonstrated a role of the genetics of the hypothalamo-pituitary-adrenal axis in the pathogenesis of borderline personality disorder [54]. The data, including the allele-frequencies of 47 polymorphisms in 10 hypothalamo-pituitary-adrenal axis genes, were from 481 patients with borderline personality disorder and 442 healthy volunteers. The results showed that polymorphic variants in the FK 506-binding protein and corticotrophin-releasing hormone

receptor genes are associated with features of borderline personality disorder.

Besides, accumulating evidence supports gene-environment correlation models for the neuropathology of borderline personality disorder; this indicates that people at risk of this disorder are more likely to have been exposed to environments that might trigger this disorder [55]. Nonetheless, it is still too early to draw conclusions from the existing data on any gene-environmental models of the etiology of borderline personality disorder.

Finally, it should be noted that the genetic findings on borderline personality disorder hold many inconsistencies, which might be due to the clinical heterogeneity of this disorder. As some researchers have suggested, more case-control association studies should focus on identifying genetically-homogeneous subgroups of patients with specific trait dimensions, such as affective dysregulation, impulsivity, or self-harm, rather than cohorts of patients with borderline personality disorder as a whole [56].

Antisocial Personality Disorder

Antisocial personality disorder is characterized by a pervasive pattern of disregard for social norms and violation of the rights of others [1]. This disorder has other synonyms such as psychopathy or dissocial personality disorder. Psychopathy, not used in the DSM-5 system, is a personality disorder with affective deficits characterized by impulsivity, superficial charm, shallow affect, manipulativeness, and callousness [57]. Antisocial personality disorder and psychopathy are overlapping constructs, since nearly all cases of psychopathy (as measured by the Hare Psychopathy Checklist-Revised [58]) meet the criteria of antisocial personality disorder [59]. Some authors have even suggested that antisocial personality disorder and psychopathy are extremes on a continuum [57].

It has been estimated that genetic factors account for approximately half of the variance in antisocial behavior [60]. In a meta-analysis of twin and adoption studies on antisocial behavior, Rhee and Waldman [61] reported that 32% of the variance could be explained by additive genetic factors, 9% by non-additive genetic factors, 16% by shared environmental factors, and 43% by non-shared environmental factors. These results are consistent with a heritability estimate of 38% for antisocial personality disorder traits reported later [27]. Regarding the antisocial personality trait and behavior, Ferguson [62] reported that genetic influence explained 56% of the variance in these parameters. Compared to the difference of genetic influences on aggressive and non-aggressive rule-breaking antisocial behaviors, the influence of genes on aggressive antisocial behavior was estimated at 65%, and on non-aggressive antisocial behavior at 48% [63]. However, the heritability estimate of psychopathy is ~50–80% [64]. With regard to antisocial behavior, the varied heritability estimates might be due to different sample features such as age, gender, nature (community or clinical), and methodology [57].

Genetic studies on antisocial personality disorder have focused on two genes, 5-HTT and MAOA [67]. A meta-analysis by Ficks and Waldman [65] included 18 studies on 5-HTTLPR and 31 on MAOA. The results yielded a moderate and significant association between the S allele of 5-HTTLPR and antisocial behavior (a broader concept believed to characterize antisocial personality disorder), and a significant positive association between the low-activity allele (S) of variable number of tandem repeats of the MAOA promoter and antisocial behavior [65]. The male preponderance of antisocial behavior is believed to be a result of the MAOA gene being located on the X chromosome. According to the principles of X-linked gene expression, in males (who have only one copy of X-linked genes) any deleterious mutation would result in a failure of the function encoded by the gene [68]. Besides the genetic mechanism of MAOA dysfunction, epigenetic mechanisms that contribute to MAOA dysregulation in antisocial offenders have emerged recently, and these might help to explain an association between hypermethylation of the MAOA promoter and antisocial personality disorder [69]. In addition, the low-activity variant of MAOA or 5-HTTLPR might interact with childhood maltreatment, and thus might contribute to the development of both antisocial personality disorder and anxiety, which is hypothesized to explain the comorbidity of these conditions [70].

Compared to the serotoninergic system, fewer studies have examined the role of the dopaminergic system in antisocial personality disorder (Table 1). Some findings have suggested a positive role of DRD2 polymorphism in the disorder. In alcoholic males [17], there is a positive relationship between the TaqI A1 allele of DRD2 and the number of antisocial personality symptoms. Another study showed that alcohol-dependent patients who are carriers of the DRD2 TaqI A1 allele have a high prevalence of antisocial personality disorder [16]. However, another study showed that none of the polymorphisms of DRD2 and DRD4 are associated with antisocial behavior or conduct disorder, a problem prevalent in youngsters <18 years old [71].

The gene coding for synaptosomal-associated protein 25 (SNAP25), a presynaptic plasma membrane protein that plays an important role in the docking and fusion of the synaptic vesicle membrane, is also associated with antisocial behaviors. The MnII (rs1051312) T/T and DdeI (rs3746544) T/T genotypes of the SNAP25 gene are more frequent in male patients with antisocial personality disorder [19]. However, no significant association of this gene

with psychopathy has been identified, suggesting a difference between psychopathy and antisocial personality disorder [19]. In individuals from alcoholic families, Dick *et al.* [66] found that the rs279871 genotype of gamma-aminobutyric acid receptor subunit alpha-2 is positively associated with the antisocial personality disorder trait.

Meanwhile, a gene × environment interaction effect of low-activity MAOA and maltreatment on antisocial behavior has also been widely reported [72–76]. However, investigators such as Ficks and Waldman [65] have criticized findings of this kind, stating that many findings are still fraught with methodological and interpretive flaws.

Other Personality Disorders

Compared to the four personality disorders discussed above, the genetic underpinnings of other types of personality disorder have received less attention. Schizoid personality disorder is characterized by a pervasive pattern of detachment from social relationships, lack of desire for intimacy, and indifference to the approval or criticism of others [1], affecting 0.8%–3.1% of the general population [23, 38]. Its heritability estimates are about 26%–29% [26, 32, 77]. Some genetic investigations have suggested an association between polymorphism of the 5-HTTLPR gene and the schizoid trait [7, 78] by showing that the S/S genotype minimizes the expression of the trait. Others have failed to detect a significant difference between individuals with the S and L genotypes [79]. Besides, some results have suggested an involvement of the adrenergic alpha 2A gene in the disorder [80].

Narcissistic personality disorder is characterized by grandiosity in fantasy or behavior, need for admiration, and lack of empathy [1]. It has a prevalence of 6.2% in the general population, higher in men (7.7%) than in women (4.8%) [81]. Its heritability estimate is 77% based on a clinical sample [32] and 24% in the general population, and there is no shared environmental influence or sex effect [27]. Limited results have revealed an association between 5-HTTLPR and the narcissism trait; for example, Sadeh *et al.* [82] reported an interaction between 5-HTT and the availability of socioeconomic resources based on the narcissism score of the 20-item self-report Antisocial Process Screening Device [83].

Histrionic personality disorder has a pattern of excessive emotional expression and attention-seeking as its essential features [1]. It affects about 1.84% of the general population [77], and its heritability estimate is about 63% based on a clinical sample [32], and about 31% in the general population [27]. In the latter study by Torgersen *et al.* [27], no shared environmental influence or sex effect was found. To the best of our knowledge, there are no reports of a molecular/genetic association with the disorder yet.

Avoidant personality disorder is characterized by social inhibition, feelings of inadequacy, and hypersensitivity to negative evaluation [1]. Its prevalence ranges from 2.4% to 5.0% [23, 77], and its heritability estimate is 28% based on a clinical sample [32] and 35% in a community sample [27]. Considering that these heritability studies had low test-retest reliability [84], Gjerde *et al.* [85] performed a longitudinal, population-based twin study, and reported a heritability estimate of 67%. Despite the high prevalence and the serious handicaps it brings to patients' lives, genetic research on this disorder is very limited, either alone or jointly with other personality disorders [86]. Nevertheless, associations between avoidant personality disorder and 5-HTTLPR and DRD3 polymorphisms have been reported [87, 88], but these associations were significantly heterogeneous and were no longer significant when the random-effects model was applied.

Dependent personality disorder is described as a pervasive and excessive need to be taken care of, wherein the individual exhibits longstanding, inflexible, excessive dependency, which leads to submissive and clinging behavior, fear of separation, and difficulties in social and occupational functioning [1]. The prevalence of this disorder is about 0.49% according to an American survey conducted in 2001–2002 [77]. Its heritability estimate is about 28%–66% [28, 32, 89]. There is little empirical research regarding its etiology or genetic background. However, family environment, social learning, severe childhood illness, and biological predisposition have demonstrated contributions to the development of the disorder [90].

Obsessive-compulsive personality disorder is characterized by a pattern of preoccupation with orderliness, perfectionism, and mental and interpersonal control at the expense of flexibility, openness, and efficiency [1]. It has the highest prevalence of all personality disorders (7.78%) in the general American population [77], and its heritability estimates are about 27%–77% [28, 32]. The 2-repeat allele of the DRD4 exon III polymorphism, the T/T genotype of the DRD4 -521 C/T polymorphism, and the Gly9/Gly9 genotype of the DRD3 Ser9/Gly polymorphism are associated with an increased rate of obsessive-compulsive personality disorder symptomatology [87]. These associations have been confirmed by a meta-analysis showing that an individual with the Gly/Gly genotype is 2.4-times more likely to develop this disorder [91].

Summary

Apparently, the genetic studies on personality disorders are still sparse, while identifying genes that pose risks of a personality disorder can offer etiopathological understanding and aid in the development of treatment not only for personality disorders, but also other psychiatric

disorders. The limited numbers of these investigations might partly be due to the limitations of genetic methodologies, since identifying a candidate gene today consumes a great deal of time and effort. Therefore, investigators are looking forward to more advanced methodologies in genetics that can be applied to personality disorder patients. In the meantime, new perspectives regarding the precise definitions of these personality disorders are also needed. The current diagnostic system is ambiguous and poses problems when trying to compare the genotypes of different but seemingly overlapping personality disorders. With the present findings in mind, one might anticipate a focus on looking for answers to the questions of how to detect high-risk personality disorders at earlier stages, and how nature and nurture interact. Results from these approaches would help to develop early interventions for personality disorders and related psychiatric problems.

Neuroimaging Findings

The neuroimaging techniques used in personality disorder research, as in other research domains, fall into two broad categories. Structural imaging techniques provide images of brain structure; they include computerized tomography (CT) and magnetic resonance imaging (MRI). Functional imaging techniques provide images that display brain activity; they include functional MRI (fMRI), single-photon emission CT (SPECT), and positron emission tomography (PET). Cranial CT has revealed volumetric abnormalities in regions and their ratio to the whole brain in personality disorders [92]. However, due to the poor resolution of this technique, it is difficult to apply quantitative analyses [92]. The advent of MRI has truly revolutionized the field of neuroimaging. In the following, we summarize the latest neuroimaging findings on personality disorders, especially those obtained with MRI. Again, we begin with four personality disorders, the schizotypal, borderline, antisocial, and narcissistic types, which have received relatively more attention worldwide. Some important findings of the neuroimaging aspects characterizing these disorders are listed in Table 2.

Schizotypal Personality Disorder

Clinically, schizophrenia spectrum disorders are defined as a continuum ranging in severity from schizophrenia and schizotypal personality disorder to prototypical schizophrenia-related personality disorder, and schizophrenia-like symptoms [93, 112–115]. This might be one of the reasons why schizotypal personality disorder is rarely studied alone. However, findings from studies of this disorder, including neuroimaging results, would help to understand the pathologies of schizophrenia and other major psychotic disorders, and to develop treatment strategies [93, 116] (Table 2).

Cortical regions Findings on volumetric changes in the frontal lobe in schizotypal personality disorder have demonstrated a positive correlation between volume and the severity of symptoms [117–119]. These results are distinct from those obtained in schizophrenia, which implies that the sparing of frontal lobe involvement in schizotypal personality disorder is a "protective factor" against the development of frank psychoses [116]. Apparently, this hypothesis of a larger-than-normal volume is considered to be an over-simplification [92]. The functional neuroimaging findings are also inconsistent: a recent PET study reported no association between schizotypal personality disorder and dopamine D1 receptor availability in the prefrontal cortex [120], while early studies revealed greater activation in the middle frontal gyrus [116].

A volumetric reduction in the temporal lobe has frequently been reported in schizotypal personality disorder, especially in the superior temporal gyrus and mostly specific to the left hemisphere, the fusiform, and the middle temporal gyri [98]. Compared with schizophrenia patients, in whom the volumetric reduction in the temporal lobe appears to progress over time, the reduction in patients with schizotypal personality disorder is relatively stable [96, 121]. The involvement of the left temporal lobe in the reduction suggests that auditory and language-related functions are affected in these patients [116].

Lener *et al.* [114] used the diffusion tensor imaging (DTI) technique to compare the white matter tract coherence across the schizophrenia spectrum. They found that schizophrenia patients showed lower fractional anisotropy in the temporal lobe and cingulum compared with both healthy volunteers and schizotypal personality disorder patients. The patients, however, showed lower fractional anisotropy in the corpus callosum genu compared with healthy volunteers. Generally speaking, greater white matter disruptions are associated with more severe symptoms over the schizophrenia spectrum [114].

Limbic and paralimbic systems Compared with healthy controls, patients with schizotypal personality disorder have an increased putamen volume, and the enlargement is more pronounced at the ventral and dorsal levels, but not in the caudate [99]. It has been shown that a larger putamen is correlated with a better antipsychotic treatment effect in schizophrenia [122]. These findings indicate a protective role of a larger putamen in schizotypal personality disorder [99]. However, other investigators have consistently found a volume reduction or deformation in the caudate rather than the putamen in schizotypal personality disorder [123, 124]. In addition, a reduced caudate volume is involved in deficits in both the spatial and verbal working memory domains of the disorder [125].

Table 2 Neuroimaging studies on schizotypal, antisocial, and narcissistic personality disorders

Group investigated	Medication	Diagnostic criteria	Recruitment strategy	Findings	Author
Schizotypal personality disorder					
47 (29 male) SPD, 72 (38) schizophrenia, 81 (46) healthy controls	Antipsychotics, 7 naïve	ICD-10, CASH	Hospital clinic	Increased pituitary volume	Takahashi *et al*., 2009 [94]
27 (16) SPD; 52 (24) BPD; 45 (19) healthy controls	22 naïve, 5 free	DSM-IV, SCID-I, SIDP	Not known	Reduced volume in superior temporal gyrus in SPD compared with BPD and healthy controls	Goldstein *et al*., 2009 [95]
12 SPD; 19 healthy controls; 17 schizophrenia	Antipsychotics	ICD-10, CASH, DSM-IV	Hospital clinic	Reduced volume in planum temporale in SPD and schizophrenia compared with healthy controls Reduced volume in caudal superior temporal gyrus in patients with SPD or schizophrenia compared with healthy controls Reduced volume in right caudal superior temporal gyrus in schizophrenia compared with healthy controls	Takahashi *et al*., 2010 [96]
33 (18) SPD, 38 (16) healthy controls	Free	DSM-IV, SIDP-IV	Advertisement (90%); Hospital clinic (10%)	Reduced volume in anterior limb of internal capsule at more ventral level	Hazlett *et al*., 2012 [97]
54 male SPD, 54 male healthy controls	Naïve	DSM-III, DSM-IV, SCID-II	Advertisement	Reduced volume of cortical grey matter Reduced grey matter in temporal regions of bilateral superior and middle temporal gyri, fusiform gyrus, and left inferior temporal gyrus; frontal regions of the bilateral superior and middle frontal gyri, orbitofrontal cortex, insula, cingulate gyrus (both anterior and posterior), and right precentral gyrus; parieto-occipital regions of bilateral postcentral gyrus, right supramarginal gyrus, precuneus, and inferior occipital gyrus	Asami *et al*., 2013 [98]
76 (60) SPD; 148 (99) healthy controls	Naïve	DSM-IV	Advertisement (90%); Hospital clinic (10%)	Larger putamen bilaterally Larger ventral striatum bilaterally	Chemerinski *et al*., 2013 [99]
59 (30) healthy controls	Naïve	DSM-III	Advertisement	Positive correlation between positive SPQ schizotypy score and grey matter in the left anterior cingulate cortex and right supplementary motor area Positive correlation between negative SPQ schizotypy score and grey matter in the precuneus (right > left), left inferior parietal cortex, right superior frontal gyrus, right inferior frontal gyrus, right inferior temporal gyrus, and left inferior frontal cortex Positive correlation of CAPE positive symptom dimension and grey matter in left frontal cortex, and a smaller cluster in the left inferior parietal cortex Positive correlation of CAPE negative symptom dimension and grey matter in the left inferior parietal cortex, right supplementary motor area, left precuneus, and right inferior temporal gyrus	Nenadic *et al*., 2015 [100]

Table 2 continued

Group investigated	Medication	Diagnostic criteria	Recruitment strategy	Findings	Author
18 male SPD, 18 male healthy controls	Naïve	DSM-IV	Advertisement	Reduced functional connectivity in right transverse temporal gyrus and left middle temporal gyrus Reduced activation in cerebellum Increased functional connectivity in bilateral superior temporal gyrus and sub-lobar regions, including bilateral putamen and caudate, bilateral posterior cingulate gyrus	Zhang *et al.*, 2014 [101]
Antisocial personality disorder					
12 male violent offenders with substance use disorder; 12 male violent offenders without substance use disorder; 13 substance use disorders; 14 healthy controls	Free of alcohol or drugs	DSM-IV, PCL-SV	Advertisement, Penitentiaries and forensic facilities	Higher total grey matter volume in violent offenders with substance use disorder than in violent offenders without substance use disorder Higher grey matter volumes in mesolimbic areas (including left nucleus, bilateral amygdala, and right caudate head) in violent offenders than non-offenders Lower grey matter volume in the left anterior insula in violent offenders than non-offenders Lower grey matter volume in medial orbitofrontal cortex (Brodmann area 11), ventromedial prefrontal cortex (Brodmann areas 9, 10), and premotor area (Brodmann area 6) with substance use disorder than without substance use disorder	Schiffer *et al.*, 2011 [102]
18 male ASPD; 24 male substance dependence; 30 healthy males, 12 females	Not known	DSM-IV, SCC	Employment agencies	Reduced orbitofrontal, middle frontal, and rectal gyral grey matter volume in ASPDs Lower orbitofrontal and middle frontal volumes in ASPD than in patients with substance dependence and healthy controls Lower rectal gyral volume in ASPD than in healthy controls Lower right middle frontal volume in ASPD than in substance dependence and healthy controls Lower left middle frontal volume in ASPD than in substance dependence and healthy controls Reduced orbitofrontal volume in females associated with increased antisocial behavior and personality Lower whole-brain corrected orbitofrontal grey volume in males than in females	Raine *et al.*, 2011 [103]
27 ASPD without psychopathy; 17 ASPDs with psychopathy; 22 healthy controls	Not known	DSM-IV, PCR	National Probation Service, Advertisement	Less grey matter in bilateral anterior rostral medial prefrontal cortex, bilateral anterior temporal areas, and bilateral anterior insula in ASPD with psychopathy than in healthy controls Lower grey matter volume bilaterally in anterior rostral medial prefrontal and temporal pole regions in ASPD with psychopathy than in ASPD without psychopathy	Gregory *et al.*, 2012 [104]

Table 2 continued

Group investigated	Medication	Diagnostic criteria	Recruitment strategy	Findings	Author
13 male ASPDs; 13 male schizophrenia with violent offenders; 15 male schizophrenia without violent offenders; 15 healthy males	Free of substance abuse	DSM-IV, PSD	Advertisement Hospital clinic	Lower whole brain and temporal lobe volumes in ASPD than in healthy controls Lower whole brain and hippocampal volumes in violent offenders compared than in controls Greater putamen volume in ASPD than in healthy controls Greater putamen volume in violent offenders than in healthy controls Lower thalamic volume in patients with psychosocial deprivation (including childhood physical and sexual abuse) than in patients without psychosocial deprivation and healthy controls Negative association between thalamic volume and abuse ratings (physical and sexual) in violent individuals **Whole sample:** Increased total score on psychosocial deprivation associated with reduced volumes of the temporal lobe and thalamus, and increased putamen size Increased ratings of physical abuse associated with reduced volumes of whole brain, cerebellum, temporal lobe, and thalamus and increased putamen Increased ratings of sexual abuse associated with reduced thalamic volume Total score on psychosocial deprivation negatively associated with grey matter volume in left prefrontal cortex **Violent offender sample:** Increased total score on psychosocial deprivation correlated with reduced thalamus and increased of occipito-parietal volume Increased ratings of physical abuse associated with reduced volume of thalamus **Non-violent offender sample:** Increased total score on psychosocial deprivation correlated with reduced occipito-parietal volume Increased ratings of sexual abuse associated with reduced occipito-parietal volume Increased total score on psychosocial deprivation associated with reduced grey matter volume in left precentral gyrus and (at the trend level) reduced grey matter volume in left middle frontal gyrus	Kumari *et al*., 2013 [105]

Table 2 continued

Group investigated	Medication	Diagnostic criteria	Recruitment strategy	Findings	Author
15 male ASPD, 15 healthy males	Free	ICD-10, PCL-R	Advertisement Forensic inpatient units	Reduced white matter fractional anisotropy bilaterally in genu of corpus callosum Reduced white matter fractional anisotropy in uncinate fasciculus, inferior fronto-occipital fasciculus, anterior corona radiata, and anterior limb and genu of internal capsule of right hemisphere Reduced white matter fractional anisotropy in temporo-occipital course of inferior longitudinal and inferior fronto-occipital fasciculus of left hemisphere	Sundram *et al.*, 2012 [106]
11 non-liars; 10 mild liars; 11 severe liars	Alcohol or illicit drug-free	PDQ-4, PDI-IV	School for Youth Offenders	Decreased activation in bilateral dorsolateral prefrontal cortex extending into the middle frontal gyrus, left inferior parietal lobule including supramarginal gyrus, and bilateral anterior cingulate gyrus/medial superior frontal gyrus positively associated with capacity for deception among people with ASPD	Jiang *et al.*, 2013 [107]
17 (10 males) conduct disorder aged 12–18 years, 24 (15 males) age- and sex-matched controls	Negative for recent marijuana, cocaine, and heroin use	DSM-IV, K-SADS-PL	Advertisement	Reduced white matter fractional anisotropy in fibers in anterior and superior corona radiata bilaterally, bilateral fronto-occipital fasciculus in both frontal and temporal areas, bilateral superior longitudinal fasciculus in parietal lobe and left inferior longitudinal fasciculus (primarily in temporal and occipital regions) Reduced fractional anisotropy the bilateral anterior limbs of internal capsule, bilateral midbrain, bilateral posterior thalamic radiation/sagittal strata, and bilateral superior and middle cerebellar peduncles Reduced fractional anisotropy in small regions of anterior, superior, and posterior corona radiata, left hemisphere tracts between frontal and posterior regions, and several subgyral white matter regions in the frontal and parietal lobes linked to greater conduct disorder symptom count	Haney-Caron *et al.*, 2014 [108]
32 ASPD, 35 healthy controls	Alcohol or illicit drug-free	DSM-IV	School for Youth Offenders	Decreased amplitude of low-frequency fluctuation in frontal cortex (including right orbitofrontal cortex, extending to right ventrolateral prefrontal cortex, insula, and anterior superior temporal cortex) Decreased amplitude of low-frequency fluctuation in temporal cortex (middle and superior left temporal pole and anterior right inferior temporal gyrus)	Liu *et al.*, 2014 [109]
Narcissistic personality disorder					
17 (12 male) NPD, 17 (12) healthy controls	Antipsychotics, 3 naïve	SCID-II	Advertisement, Hospital clinics	Reduced grey matter volume in left anterior insula Reduced grey matter volume in right anterior insula (marginally significant) Reduced grey matter volumes in left anterior insular region, bilateral superior frontal gyrus (including dorsolateral and medial areas) and bilateral middle frontal gyrus Reduced grey matter volumes in right rostral and left median cingulate cortex, parts of pre- and post-central gyri	Schulze *et al.*, 2013 [110]

Table 2 continued

Group investigated	Medication	Diagnostic criteria	Recruitment strategy	Findings	Author
6 male NPD, 48 healthy males	Antidepressants, 4-free	SCID-II, DSM-IV	Hospital clinics	Reduced grey matter in right middle frontal gyrus Reduced grey matter in left medial prefrontal cortex/anterior cingulate cortex, left middle occipital cortex, left fusiform/inferior temporal cortex, right superior temporal cortex, left lingual gyrus Reduced fractional anisotropy in right frontal lobe, right anterior thalamic radiation, right anterior temporal lobe, left anterior/lateral temporal lobe, and right brain stem	Nenadic *et al*., 2015 [111]

ASPD, antisocial personality disorder; BPD, borderline personality disorder; CAPE, community assessment of psychic experiences; CASH, Comprehensive Assessment of Symptoms and History; DSM: Diagnostic and Statistical Manual of Mental Disorder; ICD: International Classification of Diseases; K-SADS-PL, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children; NPD, narcissistic personality disorder; PCL-SV, Hare Psychopathy Checklist: Screening version; PCR, Psychopathy Checklist-Revised; PDI, personality disorder interview; PDQ, Personality Diagnostic Questionnaire; SIDP, Structured Interview for DSM-IV Personality Disorders; SPD, schizotypal personality disorder; SPQ, Schizotypal Personality Questionnaire; SCC, Self-Report Crime Checklist; SCID, Structured Clinical Interviews for Diagnosis

Other subcortical regions, such as the anterior limb of the internal capsule that connects thalamic structures to prefrontal cortex and cingulate gyrus [119], as well as interconnecting structures of the thalamus [126], are also reduced in length in schizotypal personality disorder. Recently, Nenadic *et al.* [100] reported a positive correlation between the precuneus and negative symptoms of schizotypal personality disorder as measured by the Schizotypal Personality Questionnaire and Community Assessment of Psychic Experiences. To examine the role of the default-mode network, Zhang *et al*. [101] conducted a study on 18 patients with schizotypal personality disorder and 18 healthy participants, and found increased connectivity in its anterior and posterior components. In the anterior component, healthy participants showed an increased functional connectivity in both the medial frontal lobes and the anterior lobe of the cerebellum, while schizotypal personality disorder patients showed increased functional connectivity in the bilateral superior temporal gyrus and sub-gyral regions. In the posterior component, healthy volunteers showed decreased functional connectivity in bilateral posterior cingulate gyri, and increased functional connectivity in the posterior lobe of the cerebellum, right transverse temporal gyrus, and left middle temporal gyrus compared to patients with schizotypal personality disorder.

Borderline Personality Disorder

Borderline personality disorder is characterized by emotion dysregulation, which is linked to prominent impulsive behavior [127, 128]. In addition to genetic research (see above), progress in neuroimaging studies of this disorder has also been fruitful. Cerebral CT scan reports in patients with borderline personality disorder began in the early 1980s, but no significant structural changes were identified [129]. Again, MRI technology has opened new windows on our understanding of the disorder. Recently, two reviews [128, 130] have been published on this topic.

Cortical regions A good account of neuroimaging findings on regional cortical changes in borderline personality disorder is given by Krause-Utz *et al*. [130]. Most findings involve a reduction in the total volume or grey matter in regions such as the orbitofrontal cortex, dorsolateral prefrontal cortex, and anterior cingulate cortex. Among these, the orbitofrontal and dorsolateral prefrontal cortices play critical roles in regulatory processes, such as the downregulation of activation in the limbic and subcortical brain areas and in impulse control; the anterior cingulate cortex plays a role in emotion processing, salience detection, inhibitory control, and pain processing. DTI studies have also detected reduced white matter connectivity in the frontal cortex [131]. Sato *et al*. [132] have shown that, among others, the orbitofrontal, rostral anterior cingulate, posterior cingulate, and middle temporal cortices are the most informative regions that can be used to discriminate borderline personality disorder patients from healthy volunteers. There are some changed brain regions even in young patients with borderline personality disorder. For example, the volumes of the orbitofrontal cortex, anterior cingulate cortex, dorsolateral prefrontal cortex, and left caudal superior temporal gyrus are reduced, the white matter fractional anisotropy in occipitofrontal and uncinate fascicule is decreased, and the tract-specific

fractional anisotropy of the fornix is also decreased in this disorder [130].

Lately, de Araujo Filho *et al.* [133] used a surface-based processing approach and measured five morphometric features of the orbitofrontal cortex: cortical thickness, surface area, mean curvature, depth of sulcus, and metric distortion. Their results revealed that patients with borderline personality disorder have reduced values for all five features in the right medial orbitofrontal cortex, while in the left medial orbitofrontal cortex they have reduced cortical thickness and mean curvature but increased metric distortion. However, these findings were obtained in a group of female borderline patients with a past psychiatric history, mainly mood disorders. Rossi *et al.* [134] used Cortical Pattern Matching, a technique that allows the accurate mapping of cortical grey matter density, to investigate grey matter changes over the whole cortex in patients with borderline personality disorder and in age- and sex-matched healthy participants. The results showed widespread regions of cortical alteration in borderline patients. For instance, the greatest degree of low tissue density was found in the bilateral superior temporal gyri and the inferior and middle frontal gyri. In addition, the anterior and posterior cingulate cortices showed lower density mainly in the left hemisphere, while the grey matter density loss in the parietal cortex (supramarginal and angular gyrus) involved the right hemisphere. The temporal lobe showed decreased density on the lateral and medial left cortices, including the parahippocampal gyrus. Moreover, the visual cortex and the fusiform gyrus also mapped a large region of low density in patients.

Limbic and paralimbic systems Numerous studies have reported volumetric reductions in the limbic and paralimbic systems, particularly in the amygdala and hippocampus [135]. Niedtfeld *et al.* [136] further confirmed that the volume loss in the amygdala in patients with borderline personality disorder is independent of a comorbid posttraumatic stress disorder. Other findings revealed that the volume reduction in borderline personality disorder is mainly in the bilateral hippocampal tail as well as the left hippocampal head and body [130]. Nevertheless, in a recent MRI study of 39 psychiatric inpatients and outpatients with borderline personality disorder and 39 healthy participants, researchers segmented the hippocampus and its substructures manually on MRI scans, but found no differences between the two groups in the volumes of these substructures [137]. Lischke *et al.* [138] investigated the fractional anisotropy, axonal anisotropy, and radial diffusivity in the uncinate fasciculus, a major white matter tract connecting the amygdala to the cingulate and prefrontal cortices, and found that patients with borderline personality disorder had lower fractional anisotropy and higher radial diffusivity in the uncinate fasciculus than healthy participants. These similarities between borderline personality disorder and affective disorders might also be supported by neuroimaging. For example, a smaller hippocampus and amygdala has been found in all these disorders [52].

Antisocial Personality Disorder

A meta-analytical study has shown that reduced volume and function in the prefrontal cortex are the most replicated neuroimaging findings in patients with antisocial personality disorder [139]. For instance, violence is associated with cortical thinning in the medial inferior frontal and lateral sensory motor cortices, particularly in the right hemisphere [140]. Moreover, antisocial personality disorder and schizophrenia, both of which are associated with violent behavior, have different neuroimaging features: antisocial personality disorder itself exhibits cortical thinning in the inferior mesial frontal area, while this disorder and schizophrenia both exhibit reduced activation in the left sensorimotor area [140]. Some findings have also suggested that male preponderance in antisocial personality disorder might be partly explained by the smaller orbitofrontal and middle frontal volumes in males than in females [103]. However, some investigators have questioned whether the reduced volume in prefrontal regions is associated with antisocial personality disorder, or whether they result from comorbid disorders, such as substance-use disorder or childhood maltreatment. Moreover, it remains an open question whether the relationship is causal, i.e., whether the anatomical abnormality causes the psychological and behavioral abnormality, or *vice versa*; if the latter holds true, then how the interactions between antisocial personality disorder and comorbid conditions have a joint influence on anatomical abnormalities needs to be investigated [141].

Later, Liu *et al.* [109] reported that patients with antisocial personality disorder have significantly reduced low-frequency fluctuations in the right orbitofrontal cortex, left temporal pole, right inferior temporal gyrus, and left posterior lobe of the cerebellum compared with healthy volunteers. Significant reduction of the white matter fractional anisotropy and increased mean diffusivity have been reported in antisocial patients compared with healthy participants. The fractional anisotropy is bilaterally reduced in the genu of the corpus callosum, while in the right frontal lobe, fractional anisotropy reduction has been found in the uncinate fasciculus, inferior fronto-occipital fasciculus, anterior corona radiata, and anterior limb and genu of the internal capsule in patients [106] (Table 2).

Narcissistic Personality Disorder

Despite its high prevalence rate [81, 142], severe functional impairment [81, 143], and high suicide rate [144], virtually

no empirical studies had been conducted on the neurobiological underpinnings of narcissistic personality disorder until Schulze *et al*. [110] published their research on grey matter abnormalities in such patients. They compared the patients with matched healthy volunteers regarding the global brain tissue volumes and local abnormalities of grey matter volume. Their results showed a smaller grey matter volume in the left anterior insula in patients, which positively correlated with self-reported emotional empathy. It is interesting to note that, prior to this study, Marissen *et al*. [145] had failed to detect differences between narcissistic personality disorder and healthy controls on the self-report of empathy, while narcissistic patients generally performed worse on a facial emotion recognition task than healthy and psychiatric control participants. It might be interesting if tasks such as those adopted by Marissen *et al*. [145] are used in neuroimaging explorations. In addition, compared with healthy controls, patients with narcissistic personality disorder have a smaller grey matter volume in the fronto-paralimbic regions, specifically in the left anterior insula, rostral and medial cingulate cortex, and dorsolateral and medial prefrontal cortex [110]. These regions are commonly implicated in the representation of empathy [146, 147], particularly the left anterior insula. Hence, it is conceivable that the impairment of empathy might be attributable to variations in these regions [110]. This possible link between empathy and neurobiological abnormality in the left anterior insula, in line with findings in healthy individuals [148], was supported at the trend level in the study by Schulze *et al*. [110]. On the other hand, Nenadic *et al*. [111] used both voxel-based morphometry and DTI in narcissistic personality disorder patients and healthy volunteers. They found that the grey matter variations in narcissistic patients were concentrated in the right prefrontal and bilateral medial prefrontal areas, in line with the findings of Schulze *et al*. [110]. Nevertheless no significant difference in the insular cortex was identified, probably due to the small sample size in the study of Nenadic *et al*. [111]. The DTI findings complemented the grey matter findings, revealing lower activity in the right frontal lobe, right anterior thalamic radiation, right anterior temporal lobe, left anterior/lateral temporal lobe, and right brain stem of patients with narcissistic personality disorder [111]. Critical neuroimaging findings on this disorder are summarized in Table 2.

Other Personality Disorders

Compared with the four personality disorders discussed above, other types have received even less attention concerning their biological underpinnings. In patients with obsessive-compulsive personality disorder, a reduction of grey matter volume mostly in the dorsolateral and prefrontal cortex, right insula, and cingulate, especially the posterior cingulate and parahippocampus, has been described [149]. In addition, at the neuroimaging cluster-level, Payer *et al*. [150] found that cluster C personality disorder symptomology (mostly the obsessive-compulsive type), as assessed with the Structured Clinical Interview for DSM-IV Axis II Personality Disorder, is associated with a greater striatal surface area localized to the caudate tail, smaller ventral volumes, and greater cortical thickness in the right prefrontal cortex. They also reported smaller ventral striatum volumes and greater cortical thickness in orbitofrontal cortex in their sample of cluster C personality disorders. Recently, a research group used fMRI to seek differences between avoidant personality disorder patients and healthy volunteers in reacting to and reappraising aversive social images [151]. They found that the patients with avoidant personality disorder presented heightened activity in the amygdala, particularly during the anticipation of reappraising negative images [151]. Unfortunately, no neuroimaging studies have been conducted exclusively on paranoid personality disorder, although several organic brain injuries might contribute to paranoid symptoms [152] or traits such as jealousy [153]. The situation for other personality disorders such as the schizoid, histrionic, and dependent types is even worse; almost no neuroimaging data has been collected.

Summary

Neuroimaging techniques have greatly enriched the field of brain research, and have also added extensive new knowledge regarding personality disorders. Just like their clinical manifestations, personality disorders often show overlaps in some regions and share abnormal brain structures and functions. In paranoid personality disorder, available evidence points to an altered amygdala; in schizotypal, to the temporal lobe and cingulum; in borderline, to the prefrontal cortex and striatum; in antisocial, to the prefrontal region; and in narcissistic and obsessive-compulsive, to the fronto-paralimbic regions. Nonetheless, disentangling the overlapped regions for each individual personality disorder might offer clues for future investigations.

Another interesting topic worth further exploration is the "protective factor" hypothesis, which is revealed by inconsistencies between findings from the personality disorders and their derivatives, the more severe forms of mental disorder. Hopefully, a "protective factor" might prevent personality disorders from developing into a more severe condition. An investigation into this hypothesis might sharpen the view that the brain as a self-modulated system modulates its own development. If this is the case, knowing the structure and function of the modulatory

circuit in personality disorders depends on techniques that include neuroimaging.

General Discussion and Future Perspectives

We have attempted to establish an up-to-date picture of the genetic and neuroimaging findings in personality disorders. We highlight the facts that these genetic and neuroimaging biomarkers bring a better understanding of the related pathologies, and enhance the accuracy of diagnosing these disorders. Actually, some investigators have explored both cerebral volume and genetic alterations in male twins with disordered personality traits [154]. They found phenotypic and genetic correlations between the left amygdala and positive emotionality, and genetic and non-shared-environment correlations between the thickness of left medial orbitofrontal cortex and negative emotionality. This endeavor is in line with the advocacy of an improved classification system of mental disorders based on neurobiological evidence [155].

In fact, the neurobiological findings in personality disorders are already extensive, but not equally distributed in each type. In some personality disorders, research is still at an early stage or just beginning. In general, cluster A and B disorders tend to be associated with the 5-HT gene system, while cluster C disorders tend more to the dopaminergic system. However, it is difficult to conduct a systematic comparison among all ten personality disorders defined by DSM-5 [1]. Regarding the data available for one disorder or one research topic, there are still inconsistencies that are probably due to either the study protocol or to the characteristics of participants. Although an accurate localization of all critical genes is still not easy, studies on personality disorder pathogeneses have revealed that the clinical traits are heritable and are co-modified by genetic and environmental interactions [156]. Nevertheless, the neuroimaging features of some personality disorders are abundant. One particular case is the frontal lobe, where there is either a volumetric or a functional decrease in all but schizotypal personality disorder, indicating that this type differs from the other types in executive or thinking strategies. Moreover, neuroimaging findings might in help the development of pharmacological and psychotherapeutic interventions for some disorders [157].

On the other hand, more research is needed on the under-investigated types, such as the paranoid, schizoid, histrionic, avoidant, dependent, and obsessive-compulsive disorders. These types equally affect the quality of life of patients and their relatives, being economically burdensome and debilitating. Besides, a comprehensive understanding of a personality disorder contributes to a fuller knowledge of related mental disorders, since each functions as a fundamental example of a variety of psychiatric disorders.

The current review suffers from some limitations. First, we only focused on the genetic and neuroimaging findings. Although these aspects are of great importance and have made critical contributions to our understanding of personality disorders, findings from other methodologies such as neurochemistry and neurophysiology have also provided insights into their pathology. Second, an in-depth comprehensive discussion of the diagnostic system for personality disorders would also be highly valuable, since some of the studies we reviewed only covered the personality disorder-related behaviors and the main clinical characteristics or traits, instead of the disorder itself. Nevertheless, an optimistic view of the underdeveloped research areas and the problematic diagnostic classification of personality disorders would encourage international investigators in their basic and clinical research on mental disorders. Future studies should also place more emphasis on young people, since investigation into the etiopathology throughout the life-span would be an important step toward effective prevention and early intervention strategies [158].

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