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REVIEW

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

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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

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

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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 $\sim$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 serotoninergic 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 $\sim$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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References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders 5th ed. Washington, DC: Am Psychiatr publishing, 2013.
2. Huang Y, Kotov R, De Girolamo G, Preti A, Angermeyer M, Benjet C, *et al.* DSM-IV personality disorders in the WHO World Mental Health Surveys. Br J Psychiatry 2009, 195(1): 46–53.
3. New AS, Goodman M, Triebwasser J, Siever LJ. Recent advances in the biological study of personality disorders. Psychiatr Clin North Am 2008, 31(3): 441–461.
4. Singh I, Rose N. Biomarkers in psychiatry. Nature 2009, 460(7252), 202–207.
5. Paris, J. Clinical implications of biological factors in personality disorders. Can Psychol 2015, 56(2): 263–266.
6. Fontaine N, Viding E. Genetics of personality disorders. Psychiatry 2008, 7(3): 137–141.
7. Golimbet VE, Alfimova MV, Shcherbatikh T, Kaleda VG, Abramova LI, Rogaev EI.. Serotonin transporter gene polymorphism and schizoid personality traits in patients with psychosis and psychiatrically well subjects. World J Biol Psychiatry 2003, 4(1): 25–29.
8. Smyrnis N, Avramopoulos D, Evdokimidis I, Stefanis CN, Tsekou H, Stefanis NC. Effect of schizotypy on cognitive performance and its tuning by COMT val 158 Met genotype variations in a large population of young men. Biol Psychiatry 2007, 61(7): 845–853.
9. Roussos P, Giakoumaki SG, Georgakopoulos A, Robakis NK, Bitsios P. The CACNA1C and ANK3 risk alleles impact on affective personality traits and startle reactivity but not on

cognition or gating in healthy males. Bipolar Disord 2011, 13(3): 250–259.
10. Roussos P, Bitsios P, Giakoumaki SG, McClure MM, Hazlett EA, New AS, *et al.* CACNA1C as a risk factor for schizotypal personality disorder and schizotypy in healthy individuals. Psychiatry Res 2013, 206(1): 122–123.
11. Minzenberg MJ, Xu K, Mitropoulou V, Harvey PD, Finch T, Flory JD, *et al.* Catechol-O-methyltransferase Val158Met genotype variation is associated with prefrontal-dependent task performance in schizotypal personality disorder patients and comparison groups. Psychiatr Genet 2006, 16(3): 117–124.
12. Sheldrick AJ, Krug A, Markov V, Leube D, Michel TM, Zerres K, *et al.* Effect of COMT val 158 met genotype on cognition and personality. Eur Psychiatry 2008, 23(6): 385–389.
13. Schürhoff F, Szöke A, Chevalier F, Roy I, Méary A, Bellivier F, *et al.* Schizotypal dimensions: an intermediate phenotype associated with the COMT high activity allele. Am J Med Genet 2007, 144(1): 64–68.
14. Ma X, Sun J, Yao J, Wang Q, Hu X, Deng W, *et al.* A quantitative association study between schizotypal traits and COMT, PRODH and BDNF genes in a healthy Chinese population. Psychiatry Res 2007, 153(1): 7–15.
15. Ohi K, Hashimoto R, Nakazawa T, Okada T, Yasuda Y, Yamamori H, *et al.* The p250GAP gene is associated with risk for schizophrenia and schizotypal personality traits. PLoS One 2012, 7(4): e35696.
16. Yang M, Kavi V, Wang W, Wu Z, Hao W. The association of 5-HTR2A-1438A/G, COMTVal158Met, MAOA-LPR, DATVNTR and 5-HTTVNTR gene polymorphisms and antisocial personality disorder in male heroin-dependent Chinese subjects. Progress in Neuro-Psychopharmacology and Biol Psychiatry 2012, 36(2): 282–289.
17. Bau CH, Almeida S, Hutz MH. The TaqI A1 allele of the dopamine D2 receptor gene and alcoholism in Brazil: association and interaction with stress and harm avoidance on severity prediction. Am J Med Genet 2000, 96(3): 302–306.
18. Ponce G, Jimenez-Arriero MA, Rubio G, Hoenicka J, Ampuero I, Ramos JA, *et al.* The A1 allele of the DRD2 gene (TaqI A polymorphisms) is associated with antisocial personality in a sample of alcohol-dependent patients. Eur Psychiatry 2003, 18(7): 356–360.
19. Basoglu C, Oner O, Ates A, Algul A, Bez Y, Cetin M, *et al.* Synaptosomal-associated protein 25 gene polymorphisms and antisocial personality disorder: Association with temperament and psychopathy. Can J Psychiatry 2011, 56(6): 341–347.
20. Salvatore JE, Edwards AC, McClintick JN, Bigdeli TB, Adkins A, Aliev F, *et al.* Genome-wide association data suggest ABCB1 and immune-related gene sets may be involved in adult antisocial behavior. Translational Psychiatry 2015, 5: e558.
21. Triebwasser J, Chemerinski E, Roussos P, Siever LJ. Paranoid personality disorder. J Personal Disord 2013, 27(6): 795–805.
22. Cramer V, Torgersen S, Kringlen E. Personality disorders and quality of life. A population study. Compr Psychiatry 2006, 47(3): 178–184.
23. Torgersen S, Kringlen E, Cramer V. The prevalence of personality disorders in a community sample. Arch Gen Psychiatry 2001, 58(6): 590–596.
24. Zimmerman M, Rothschild L, Chelminski I. The prevalence of DSM-IV personality disorders in psychiatric outpatients. Am J Psychiatry 2005, 162: 1911–1918.
25. Coolidge FL, Thede LL, Jang KL. Heritability of personality disorders in childhood: a preliminary investigation. J Personal Disord 2001, 15(1): 33–40.
26. Kendler KS, Czajkowski N, Tambs K, Torgersen S, Aggen SH, Neale MC, *et al.* Dimensional representations of DSM-IV cluster A personality disorders in a population-based sample of Norwegian twins: a multivariate study. Psychol Med 2006, 36(11): 1583–1591.
27. Torgersen S, Czajkowski N, Jacobson K, Reichborn-Kjennerud T, Røysamb E, Neale MC, *et al.* Dimensional representations of DSM-IV cluster B personality disorders in a population-based sample of Norwegian twins: a multivariate study. Psychol Med 2008, 38(11): 1617–1625.
28. Reichborn-Kjennerud T, Czajkowski N, Neale MC, Ørstavik RE, Torgersen S, Tambs K, *et al.* Genetic and environmental influences on dimensional representations of DSM-IV cluster C personality disorders: a population-based multivariate twin study. Psychol Med 2007, 37(05): 645–653.
29. Kendler KS, Myers J, Torgersen S, Neale MC, Reichborn-Kjennerud T. The heritability of cluster A personality disorders assessed by both personal interview and questionnaire. Psychol Med 2007, 37(05): 655–665.
30. Tsuang MT, Stone WS, Faraone SV. Schizophrenia: a review of genetic studies. Harv Rev Psychiatry 1999, 7(4): 185–207.
31. Battaglia M, Bernardeschi L, Franchini L, Bellodi L, Smeraldi E. A family study of schizotypal disorder. Schizophr Bull 1995), 21(1): 33.
32. Torgersen S, Lygren S, Øien PA, Skre I, Onstad S, Edvardsen J, *et al.* A twin study of personality disorders. Compr Psychiatry 2000, 41(6): 416–425.
33. Battaglia M, Fossati A, Torgersen S, Bertella S, Bajo S, Maffei C, *et al.* A psychometric genetic study of schizotypal disorder. Schizophr Res 1999, 37(1): 53–64.
34. Tomppo L, Hennah W, Miettunen J, Järvelin MR, Veijola J, Ripatti S, *et al.* Association of variants in DISC1 with psychosis-related traits in a large population cohort. Arch Gen Psychiatry 2009, 66(2): 134–141.
35. Montag C, Hall J, Plieger T, Felten A, Markett S, Melchers M, *et al.* The DRD3 Ser9Gly polymorphism, machiavellianism, and its link to schizotypal personality. J Neurosci, Psychol, Econ 2015, 8(1): 48–57.
36. Barker V, Romaniuk L, Cardinal RN, Pope M, Nicol K, Hall J. Impulsivity in borderline personality disorder. Psychol Med 2015, 45(09): 1955–1964.
37. Zanarini MC, Ruser T, Frankenburg FR, Hennen J. The dissociative experiences of borderline patients. Compr Psychiatry 2000, 41(3): 223–227.
38. Coid J, Yang M, Tyrer P, Roberts A, Ullrich S. Prevalence and correlates of personality disorder in Great Britain. Br J Psychiatry 2006, 188(5): 423–431.
39. Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, *et al.* Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 2008, 69(4): 533–545.
40. Lenzenweger MF, Lane MC, Loranger AW, Kessler RC. DSM-IV personality disorders in the National Comorbidity Survey Replication. Biol Psychiatry 2007, 62(6): 553–564.
41. Distel MA, Trull TJ, Derom CA, Thiery EW, Grimmer MA, Martin NG, *et al*.. Heritability of borderline personality disorder features is similar across three countries. Psychol Med 2008, 38(09): 1219–1229.
42. Kendler KS, Aggen SH, Czajkowski N, Røysamb E, Tambs K, Torgersen S, *et al.* The structure of genetic and environmental risk factors for DSM-IV personality disorders: a multivariate twin study. Arch Gen Psychiatry 2008, 65(12): 1438–1446.
43. Torgersen S, Myers J, Reichborn-Kjennerud T, Røysamb E, Kubarych TS, Kendler KS. The heritability of cluster B personality disorders assessed both by personal interview and questionnaire. J Personal Disord 2012, 26(6): 848–866.
44. Amad A, Ramoz N, Thomas P, Jardri R, Gorwood P. Genetics of borderline personality disorder: systematic review and proposal of an integrative model. Neurosci Biobehav Rev 2014, 40: 6–19.

45. Sugden K, Arseneault L, Harrington H, Moffitt TE, Williams B, Caspi A.. Serotonin transporter gene moderates the development of emotional problems among children following bullying victimization. J Am Acad Child Adolesc Psychiatry 2010, 49(8): 830–840.
46. Amstadter AB, Daughters SB, MacPherson L, Reynolds EK, Danielson CK, Wang F, *et al.* Genetic associations with performance on a behavioral measure of distress intolerance. J Psychiatr Res 2012, 46(1): 87–94.
47. Wagner S, Baskaya Ö, Lieb K, Dahmen N, Tadić A. The 5-HTTLPR polymorphism modulates the association of serious life events (SLE) and impulsivity in patients with borderline personality disorder. J Psychiatr Res 2009, 43(13): 1067–1072.
48. Ni X, Chan D, Chan K, McMain S, Kennedy JL. Serotonin genes and gene–gene interactions in borderline personality disorder in a matched case-control study. Prog Neuropsychopharmacol Biol Psychiatry 2009, 33(1): 128–133.
49. Tadić A, Elsäßer A, Victor A, von Cube R, Başkaya Ö, Wagner S, *et al.* Association analysis of serotonin receptor 1B (HTR1B) and brain-derived neurotrophic factor gene polymorphisms in Borderline personality disorder. J Neural Transm 2009, 116(9): 1185–1188.
50. Ni X, Sicard T, Bulgin N, Bismil R, Chan K, McMain S, *et al.* Monoamine oxidase a gene is associated with borderline personality disorder. Psychiatr Genet 2007, 17(3): 153–157.
51. Sweitzer MM, Halder I, Flory JD, Craig AE, Gianaros PJ, Ferrell RE, *et al.* Polymorphic variation in the dopamine D4 receptor predicts delay discounting as a function of childhood socioeconomic status: evidence for differential susceptibility. Soc Cogn Affect Neurosci 2013, 8(5): 499–508.
52. Agius M, Lee J, Gardner J, Wotherspoon D. Bipolar II disorder and borderline personality disorder–co-morbidity or spectrum. Psychiatr Danub 2012, 24, S197–201.
53. Lubke GH, Laurin C, Amin N, Hottenga JJ, Willemsen G, van Grootheest G, *et al.* Genome-wide analyses of borderline personality features. Mol Psychiatry 2014, 19(8): 923–929.
54. Martín-Blanco A, Ferrer M, Soler J, Arranz MJ, Vega D, Calvo N, *et al.* The role of hypothalamus–pituitary–adrenal genes and childhood trauma in borderline personality disorder. Eur Arch Psychiatry Clin Neurosci 2015: 1–10.
55. Carpenter RW, Tomko RL, Trull TJ, Boomsma DI. Gene-environment studies and borderline personality disorder: a review. Curr Psychiatry Rep 2013, 15(1): 1–7.
56. Pascual JC, Soler J, Barrachina J, Campins MJ, Alvarez E, Perez V. Failure to detect an association between the serotonin transporter gene and borderline personality disorder. J Psychiatr Res 2008, 42(1): 87–88.
57. Werner KB, Few LR, Bucholz KK. Epidemiology, comorbidity, and behavioral genetics of antisocial personality disorder and psychopathy. Psychiatr Annu 2015, 45(4): 195–199.
58. Hare RD. The Hare Psychopathy Checklist-Revised: PLC-R. Multi-Health Systems, 1999.
59. Hare RD. Psychopathy a clinical construct whose time has come. Criminal Justice and Behavior 1996, 23(1): 25–54.
60. Moffitt TE. The new look of behavioral genetics in developmental psychopathology: gene-environment interplay in antisocial behaviors. Psychol Bull 2005, 131(4): 533–554.
61. Rhee SH, Waldman ID. Genetic and environmental influences on antisocial behavior: a meta-analysis of twin and adoption studies. Psychol Bull 2002, 128(3): 490–529.
62. Ferguson CJ. Genetic contributions to antisocial personality and behavior: A meta-analytic review from an evolutionary perspective. J Soc Psychol 2010, 150(2): 160–180.
63. Burt SA. Are there meaningful etiological differences within antisocial behavior? Results of a meta-analysis. Clin Psychol Rev 2009, 29(2): 163–178.
64. Gunter TD, Vaughn MG, Philibert RA. Behavioral genetics in antisocial spectrum disorders and psychopathy: A review of the recent literature. Behav Sci Law 2010, 28(2): 148–173.
65. Ficks CA, Waldman ID. Candidate genes for aggression and antisocial behavior: a meta-analysis of association studies of the 5HTTLPR and MAOA-uVNTR. Behav Genet 2014, 44(5): 427–444.
66. Dick DM, Agrawal A, Schuckit MA, Bierut L, Hinrichs A, Fox L, *et al.* Marital status, alcohol dependence, and GABRA2: evidence for gene-environment correlation and interaction. J Stud Alcohol 2006, 67(2):185–194.
67. Retz W, Rösler M. The relation of ADHD and violent aggression: What can we learn from epidemiological and genetic studies? Int J Law Psychiatry 2009, 32(4): 235–243.
68. Eme R. MAOA and male antisocial behavior: a review. Aggression and Violent Behavior 2013, 18(3): 395–398.
69. Checknita D, Maussion G, Labonté B, Comai S, Tremblay RE, Vitaro F, *et al.* Monoamine oxidase A gene promoter methylation and transcriptional downregulation in an offender population with antisocial personality disorder. Br J Psychiatry 2015, 206(3): 216–222.
70. Coid J, Ullrich S. Antisocial personality disorder and anxiety disorder: A diagnostic variant? J Anxiety Disord 2010, 24(5), 452–460.
71. Beaver KM, Wright JP, DeLisi M, Walsh A, Vaughn MG, Boisvert D, *et al.* A gene × gene interaction between DRD2 and DRD4 is associated with conduct disorder and antisocial behavior in males. Behav Brain Funct 2007, 3(1): 30–30.
72. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, *et al.* Role of genotype in the cycle of violence in maltreated children. Science 2002, 297(5582): 851–854.
73. Beach SR, Brody GH, Gunter TD, Packer H, Wernett P, Philibert RA. Child maltreatment moderates the association of MAOA with symptoms of depression and antisocial personality disorder. J Fam Psychol 2010, 24(1): 12–20.
74. Byrd AL, Manuck SB. MAOA, childhood maltreatment, and antisocial behavior: Meta-analysis of a gene-environment interaction. Biol Psychiatry 2014, 75(1): 9–17.
75. Philibert RA, Wernett P, Plume J, Packer H, Brody GH, Beach SR. Gene environment interactions with a novel variable Monoamine Oxidase A transcriptional enhancer are associated with antisocial personality disorder. Biol Psychol 2011, 87(3): 366–371.
76. Taylor A, Kim-Cohen J. Meta-analysis of gene–environment interactions in developmental psychopathology. Dev Psychopathol 2007, 19(04): 1029–1037.
77. Grant BF, Hasin DS, Stinson FS, Dawson DA, Chou SP, Ruan WJ, *et al.* Prevalence, correlates, and disability of personality disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. J Clin Psychiatry 2004, 65(7): 948–958.
78. Golimbet VE, Alfimova MV, Sherbatikh TV, Rogaev EI. Serotonin transporter gene polymorphism and personality traits measured by MMPI. Russian Journal of Genetics 2003, 39(4): 435–439.
79. Blom RM, Samuels JF, Riddle MA, Bienvenu OJ, Grados MA, Reti IM, *et al.* Association between a serotonin transporter promoter polymorphism (5HTTLPR) and personality disorder traits in a community sample. J Psychiatr Res 2011, 45(9): 1153–1159.
80. Comings DE, Gonzalez NS, Li SC, MacMurray J. A "line item" approach to the identification of genes involved in polygenic behavioral disorders: the adrenergic α2A (ADRA2A) gene. Am J Med Genet 2003, 118(1): 110–114.
81. Stinson FS, Dawson DA, Goldstein RB, Chou SP, Huang B, Smith SM, *et al.* Prevalence, correlates, disability, and

comorbidity of DSM-IV narcissistic personality disorder: results from the wave 2 national epidemiologic survey on alcohol and related conditions. J Clin Psychiatry 2008, 69(7): 1033–1045.
82. Sadeh N, Javdani S, Jackson JJ, Reynolds EK, Potenza MN, Gelernter J, *et al.* Serotonin transporter gene associations with psychopathic traits in youth vary as a function of socioeconomic resources. J Abnorm Psychol 2010, 119(3), 604–609.
83. Frick PJ, Hare RD. Antisocial Process Screening Device: APSD. Toronto: Multi-Health Systems, 2001.
84. McGlashan TH, Grilo CM, Sanislow CA, Ralevski E, Morey LC, Gunderson JG, *et al.* Two-year prevalence and stability of individual DSM-IV criteria for schizotypal, borderline, avoidant, and obsessive-compulsive personality disorders: toward a hybrid model of axis II disorders. Am J Psychiatry 2005, 162(5): 883–889.
85. Gjerde LC, Czajkowski N, Røysamb E, Ystrom E, Tambs K, Aggen SH, *et al.* A longitudinal, population-based twin study of avoidant and obsessive-compulsive personality disorder traits from early to middle adulthood. Psychol Med 2015, 45(16): 3539–3548.
86. Alden LE, Laposa JM, Taylor CT, Ryder AG. Avoidant personality disorder: Current status and future directions. J Personal Disord 2002, 16(1): 1–29.
87. Joyce PR, Rogers GR, Miller AL, Mulder RT, Luty SE, Kennedy MA. Polymorphisms of DRD4 and DRD3 and risk of avoidant and obsessive personality traits and disorders. Psychiatry Res 2003, 119(1): 1–10.
88. Munafo MR, Clark TG, Moore LR, Payne E, Walton R, Flint J. Genetic polymorphisms and personality in healthy adults: a systematic review and meta-analysis. Mol Psychiatry 2003, 8(5): 471–484.
89. Gjerde LC, Czajkowski N, Røysamb E, Ørstavik RE, Knudsen GP, Østby K, *et al.* The heritability of avoidant and dependent personality disorder assessed by personal interview and questionnaire. Acta Psychiatrica Scandinavica 2012, 126(6): 448–457.
90. Disney KL. Dependent personality disorder: A critical review. Clin Psychol Rev 2013, 33(8): 1184–1196.
91. Light KJ, Joyce PR, Luty SE, Mulder RT, Frampton C, Joyce LR, *et al.* Preliminary evidence for an association between a dopamine D3 receptor gene variant and obsessive-compulsive personality disorder in patients with major depression. Am J Med Genet 2006, 141(4): 409–413.
92. Fervaha G, Remington G. Neuroimaging findings in schizotypal personality disorder: a systematic review. Progress in Neuro-Psychopharmacology and Biol Psychiatry 2013, 43: 96–107.
93. Dickey CC, McCarley RW, Shenton ME. The brain in schizotypal personality disorder: a review of structural MRI and CT findings. Harv Rev Psychiatry 2002, 10(1): 1–15.
94. Takahashi T, Suzuki M, Velakoulis D, Lorenzetti V, Soulsby B, Zhou SY, *et al.* Increased pituitary volume in schizophrenia spectrum disorders. Schizophr Res 2009, 108(1): 114–121.
95. Goldstein KE, Hazlett EA, New AS, Haznedar MM, Newmark RE, Zelmanova Y, *et al.* Smaller superior temporal gyrus volume specificity in schizotypal personality disorder. Schizophr Res 2009, 112(1): 14–23.
96. Takahashi T, Suzuki M, Zhou SY, Tanino R, Nakamura K, Kawasaki Y, *et al.* A follow-up MRI study of the superior temporal subregions in schizotypal disorder and first-episode schizophrenia. Schizophr Res 2010, 119(1): 65–74.
97. Hazlett EA, Collazo T, Zelmanova Y, Entis JJ, Chu KW, Goldstein KE, *et al.* Anterior limb of the internal capsule in schizotypal personality disorder: fiber-tract counting, volume, and anisotropy. Schizophr Res 2012, 141(2): 119–127.
98. Asami T, Whitford TJ, Bouix S, Dickey CC, Niznikiewicz M, Shenton ME, *et al.* Globally and locally reduced MRI grey matter volumes in neuroleptic-naive men with schizotypal personality disorder: association with negative symptoms. JAMA Psychiatry 2013, 70(4): 361–372.
99. Chemerinski E, Byne W, Kolaitis JC, Glanton CF, Canfield EL, Newmark RE, *et al.* Larger putamen size in antipsychotic-naïve individuals with schizotypal personality disorder. Schizophr Res 2013, 143(1): 158–164.
100. Nenadic I, Lorenz C, Langbein K, Dietzek M, Smesny S, Schönfeld N, *et al.* Brain structural correlates of schizotypy and psychosis proneness in a non-clinical healthy volunteer sample. Schizophr Res 2015, 168(1): 37–43.
101. Zhang Q, Shen J, Wu J, Yu X, Lou W, Fan H, *et al.* Altered default mode network functional connectivity in schizotypal personality disorder. Schizophr Res 2014, 160(1): 51–56.
102. Schiffer B, Müller BW, Scherbaum N, Hodgins S, Forsting M, Wiltfang J, *et al.* Disentangling structural brain alterations associated with violent behavior from those associated with substance use disorders. Arch Gen Psychiatry 2011, 68(10): 1039–1049.
103. Raine A, Yang Y, Narr KL, Toga AW. Sex differences in orbitofrontal gray as a partial explanation for sex differences in antisocial personality. Mol Psychiatry 2011, 16: 227–236.
104. Gregory S, Simmons A, Kumari V, Howard M, Hodgins S, Blackwood N. The antisocial brain: psychopathy matters: a structural MRI investigation of antisocial male violent offenders. Arch Gen Psychiatry 2012, 69(9): 962–972.
105. Kumari V, Gudjonsson GH, Raghuvanshi S, Barkataki I, Taylor P, Sumich A, *et al.* Reduced thalamic volume in men with antisocial personality disorder or schizophrenia and a history of serious violence and childhood abuse. Eur Psychiatry 2013, 28(4): 225–234.
106. Sundram F, Deeley Q, Sarkar S, Daly E, Latham R, Craig M, *et al.* White matter microstructural abnormalities in the frontal lobe of adults with antisocial personality disorder. Cortex 2012, 48(2): 216–229.
107. Jiang W, Liu H, Liao J, Ma X, Rong P, Tang Y, *et al.* A functional MRI study of deception among offenders with antisocial personality disorders. Neuroscience 2013, 244: 90–98.
108. Haney-Caron E, Caprihan A, Stevens MC. DTI-measured white matter abnormalities in adolescents with Conduct Disorder. J Psychiatr Res 2014, 48(1): 111–120.
109. Liu H, Liao J, Jiang W, Wang W. Changes in low-frequency fluctuations in patients with antisocial personality disorder revealed by resting-state functional MRI. PLoS One 2014, 9(3): e89790.
110. Schulze L, Dziobek I, Vater A, Heekeren HR, Bajbouj M, Renneberg B, *et al.* Gray matter abnormalities in patients with narcissistic personality disorder. J Psychiatr Res 2013, 47(10): 1363–1369.
111. Nenadic I, Güllmar D, Dietzek M, Langbein K, Steinke J, Gaser C. Brain structure in narcissistic personality disorder: A VBM and DTI pilot study. Psychiatry Res: Neuroimaging 2015, 231(2): 184–186.
112. Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D. The Roscommon family study: I. Methods, diagnosis of probands, and risk of schizophrenia in relatives. Arch Gen Psychiatry 1993, 50(7): 527–540.
113. Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D. The Roscommon Family Study: III. Schizophrenia-related personality disorders in relatives. Arch Gen Psychiatry 1993, 50(10): 781–788.
114. Lener MS, Wong E, Tang CY, Byne W, Goldstein KE, Blair NJ, *et al.* White matter abnormalities in schizophrenia and schizotypal personality disorder. Schizophr Bull 2014, 41(1): 300–310.
115. Siever LJ, Koenigsberg HW, Harvey P, Mitropoulou V, Laruelle M, Abi-Dargham A, *et al.* Cognitive and brain function in

schizotypal personality disorder. Schizophr Res 2002, 54(1): 157–167.
116. Rosell DR, Futterman SE, McMaster A, Siever LJ. Schizotypal personality disorder: a current review. Curr Psychiatry Rep 2014, 16(7): 1–12.
117. Hazlett EA, Buchsbaum MS, Haznedar MM, Newmark R, Goldstein KE, Zelmanova Y, *et al.* Cortical gray and white matter volume in unmedicated schizotypal and schizophrenia patients. Schizophr Res 2008, 101(1): 111–123.
118. Kühn S, Schubert F, Gallinat J. Higher prefrontal cortical thickness in high schizotypal personality trait. J Psychiatr Res 2012, 46(7): 960–965.
119. Suzuki M, Zhou SY, Hagino H, Takahashi T, Kawasaki Y, Nohara S, *et al.* Volume reduction of the right anterior limb of the internal capsule in patients with schizotypal disorder. Psychiatry Res: Neuroimaging 2004, 130(3): 213–225.
120. Thompson JL, Rosell DR, Slifstein M, Girgis RR, Xu X, Ehrlich Y, *et al.* Prefrontal dopamine D1 receptors and working memory in schizotypal personality disorder: a PET study with [11C] NNC112. Psychopharmacology 2014, 231(21): 4231–4240.
121. Takahashi T, Zhou SY, Nakamura K, Tanino R, Furuichi A, Kido M, *et al.* A follow-up MRI study of the fusiform gyrus and middle and inferior temporal gyri in schizophrenia spectrum. Progress in Neuro-Psychopharmacology and Biol Psychiatry 2011, 35(8): 1957–1964.
122. Mitelman SA, Canfield EL, Chu KW, Brickman AM, Shihabuddin L, Hazlett EA, *et al.* Poor outcome in chronic schizophrenia is associated with progressive loss of volume of the putamen. Schizophr Res 2009, 113(2): 241–245.
123. Koo MS, Levitt JJ, McCarley RW, Seidman LJ, Dickey CC, Niznikiewicz MA, *et al.* Reduction of caudate nucleus volumes in neuroleptic-naive female subjects with schizotypal personality disorder. Biol Psychiatry 2006, 60(1): 40–48.
124. Levitt JJ, Styner M, Niethammer M, Bouix S, Koo MS, Voglmaier MM, *et al.* Shape abnormalities of caudate nucleus in schizotypal personality disorder. Schizophr Res 2009, 110(1): 127–139.
125. Levitt JJ, McCarley RW, Dickey CC, Voglmaier MM, Niznikiewicz MA, Seidman LJ, *et al.* MRI study of caudate nucleus volume and its cognitive correlates in neuroleptic-naive patients with schizotypal personality disorder. Am J Psychiatry 2002, 159(7): 1190–1197.
126. Takahashi T, Suzuki M, Zhou SY, Nakamura K, Tanino R, Kawasaki Y, *et al.* Prevalence and length of the adhesio interthalamica in schizophrenia spectrum disorders. Psychiatry Res: Neuroimaging 2008, 164(1): 90–94.
127. Crowell SE, Beauchaine TP, Linehan MM. A biosocial developmental model of borderline personality: elaborating and extending Linehan's theory. Psychol Bull 2009. 135: 495–510.
128. van Zutphen L, Siep N, Jacob GA, Goebel R, Arntz A. Emotional sensitivity, emotion regulation and impulsivity in borderline personality disorder: A critical review of fMRI studies. Neurosci Biobehav Rev 2015, 51: 64–76.
129. Schmahl C, Bremner JD. Neuroimaging in borderline personality disorder. J Psychiatr Res 2006, 40(5): 419–427.
130. Krause-Utz A, Winter D, Niedtfeld I, Schmahl C. The latest neuroimaging findings in borderline personality disorder. Curr Psychiatry Rep 2014, 16(3): 1–13.
131. Rüsch N, Bracht T, Kreher BW, Schnell S, Glauche V, Il'yasov KA, *et al.* Reduced interhemispheric structural connectivity between anterior cingulate cortices in borderline personality disorder. Psychiatry Res: Neuroimaging 2010, 181(2): 151–154.
132. Sato JR, Filho GM, Araujo TB, Bressan RA, Oliveira PP, Jackowski AP. Can neuroimaging be used as a support to diagnosis of borderline personality disorder? An approach based on computational neuroanatomy and machine learning. J Psychiatr Res 2012, 46(9): 1126–1132.
133. de Araujo Filho GM, Abdallah C, Sato JR, de Araujo TB, Lisondo CM, de Faria ÁA, *et al.* Morphometric hemispheric asymmetry of orbitofrontal cortex in women with borderline personality disorder: A multi-parameter approach. Psychiatry Res: Neuroimaging 2014, 223(2): 61–66.
134. Rossi R, Lanfredi M, Pievani M, Boccardi M, Rasser PE, Thompson PM, *et al.* Abnormalities in cortical gray matter density in borderline personality disorder. Eur Psychiatry 2015, 30(2), 221–227.
135. Nunes PM, Wenzel A, Borges KT, Porto CR, Caminha RM, de Oliveira IR. Volumes of the hippocampus and amygdala in patients with borderline personality disorder: a meta-analysis. J Personal Disord 2009, 23(4): 333–345.
136. Niedtfeld I, Schulze L, Krause-Utz A, Demirakca T, Bohus M, Schmahl C. Voxel-based morphometry in women with borderline personality disorder with and without comorbid posttraumatic stress disorder. PLoS One 2013, 8(6): e65824.
137. Kreisel SH, Labudda K, Kurlandchikov O, Beblo T, Mertens M, Thomas C, *et al.* Volume of hippocampal substructures in borderline personality disorder. Psychiatry Res: Neuroimaging 2015, 231(3): 218–226.
138. Lischke A, Domin M, Freyberger HJ, Grabe HJ, Mentel R, Bernheim D, *et al.* Structural alterations in white-matter tracts connecting (para-) limbic and prefrontal brain regions in borderline personality disorder. Psychol Med 2015, 45(15): 3171–3180.
139. Yang Y, Raine A. Prefrontal structural and functional brain imaging findings in antisocial, violent, and psychopathic individuals: a meta-analysis. Psychiatry Res: Neuroimaging 2009, 174(2): 81–88.
140. Narayan VM, Narr KL, Kumari V, Woods RP, Thompson PM, Toga AW, *et al.* Regional cortical thinning in subjects with violent antisocial personality disorder or schizophrenia. Am J Psychiatry 2007, 164(9): 1418–1427.
141. Glenn AL, Johnson AK, Raine A. Antisocial personality disorder: a current review. Curr Psychiatry Rep 2013, 15:427.
142. Ritter K, Roepke S, Merkl A, Heuser I, Fydrich T, Lammers CH. Comorbidity in patients with narcissistic personality disorder in comparison to patients with borderline personality disorder. Psychother Psychosom Med Psychol 2010, 60(1): 14–24.
143. Miller JD, Campbell WK, Pilkonis PA. Narcissistic personality disorder: Relations with distress and functional impairment. Compr Psychiatry 2007, 48(2): 170–177.
144. Pompili M, Ruberto A, Girardi P, Tatarelli R. Suicidality in DSM-IV cluster B personality disorders. An overview. Annali dell'Istituto Superiore di Sanità 2003, 40(4): 475–483.
145. Marissen MA, Deen ML, Franken IH. Disturbed emotion recognition in patients with narcissistic personality disorder. Psychiatry Res 2012, 198: 269–273.
146. Fan Y, Duncan NW, de Greck M, Northoff G. Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. Neurosci Biobehav Rev 2011, 35(3): 903–911.
147. Lamm C, Decety J, Singer T. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. Neuroimage 2011, 54(3): 2492–2502.
148. Fan Y, Wonneberger C, Enzi B, De Greck M, Ulrich C, Tempelmann C, *et al.* The narcissistic self and its psychological and neural correlates: an exploratory fMRI study. Psychol Med 2011, 41(08): 1641–1650.
149. Reetz K, Lencer R, Steinlechner S, Gaser C, Hagenah J, Büchel C, *et al.* Limbic and frontal cortical degeneration is associated with psychiatric symptoms in PINK1 mutation carriers. Biol Psychiatry 2008, 64(3): 241–247.

150. Payer DE, Park MTM, Kish SJ, Kolla NJ, Lerch JP, Boileau I, *et al.* Personality disorder symptomatology is associated with anomalies in striatal and prefrontal morphology. Front Hum Neurosci 2015, 9:472.
151. Denny BT., Fan J, Liu X, Ochsner KN, Guerreri S, Mayson SJ, *et al.* Elevated amygdala activity during reappraisal anticipation predicts anxiety in avoidant personality disorder. J Affect Disord 2015, 172: 1–7.
152. Birkeland SF. Paranoid personality disorder and organic brain injury: a case report. J Neuropsychiatry Clin Neurosci 2012, 25(1): E52.
153. Luaute JP, Saladini O, Luaute J. Neuroimaging correlates of chronic delusional jealousy after right cerebral infarction. J Neuropsychiatry Clin Neurosci 2008, 20(2): 245–247.
154. Lewis GJ, Panizzon MS, Eyler L, Fennema-Notestine C, Chen CH, Neale MC, *et al.* Heritable influences on amygdala and orbitofrontal cortex contribute to genetic variation in core dimensions of personality. Neuroimage 2014, 103, 309–315.
155. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC 2013. BMC Med, 11(1), 126.
156. Kapfhammer HP. Neurobiological underpinnings of personality disorders. Acta Neuropsychiatrica 2009, 21(S2): 7–9.
157. Tang Y, Jiang W, Liao J, Wang W, Luo A. Identifying individuals with antisocial personality disorder using resting-state FMRI. PLoS One 2013, 8(4): e60652.
158. Chanen AM, Jovev M, McCutcheon LK, Jackson HJ, McGorry PD. Borderline personality disorder in young people and the prospects for prevention and early intervention. Curr Psychiatry Rev 2008, 4(1): 48–57.