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Genetics of resilience: Implications from genome-wide association studies and candidate genes of the stress response system in posttraumatic stress disorder and depression

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Abstract

Resilience is the ability to cope with critical situations through the use of personal and socially mediated resources. Since a lack of resilience increases the risk of developing stress-related psychiatric disorders such as posttraumatic stress disorder (PTSD) and major depressive disorder (MDD), a better understanding of the biological background is of great value to provide better prevention and treatment options. Resilience is undeniably influenced by genetic factors, but very little is known about the exact underlying mechanisms. A recently published genome-wide association study (GWAS) on resilience has identified three new susceptibility loci, *DCLK2*, *KLHL36*, and *SLC15A5*. Further interesting results can be found in association analyses of gene variants of the stress response system, which is closely related to resilience, and PTSD and MDD. Several promising genes, such as the *COMT* (catechol-O-methyltransferase) gene, the serotonin transporter gene (*SLC6A4*), and neuropeptide Y (*NPY*) suggest gene × environment interaction between genetic variants, childhood adversity, and the occurrence of PTSD and MDD, indicating an impact of these genes on resilience. GWAS on PTSD and MDD provide another approach to identifying new disease-associated loci and, although the functional significance for disease development for most of these risk genes is still unknown, they are potential candidates due to the overlap of stress-related psychiatric disorders and resilience. In the future, it will be important for genetic studies to focus more on resilience than on pathological phenotypes, to develop reasonable concepts for measuring resilience, and to establish international cooperations to generate sufficiently large samples.

KEYWORDS

depression, genetic risk factors, posttraumatic stress disorder, resilience, vulnerability

1 | INTRODUCTION

Besides diagnostics and treatment of neuropsychiatric disorders, prevention and the identification of risk factors are fundamental to promote mental health. Therefore, research on resilience increased rapidly over the last decades. Resilience is defined as the ability to adapt to stress while maintaining healthy mental and physical performance. The American Psychological Association defines resilience as "[…] the process of adapting well in the face of adversity, trauma, tragedy, threats or significant sources of stress—such as family and

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relationship problems, serious health problems or workplace and financial stressors. It means 'bouncing back' from difficult experiences" (APA, 2018). Since all individuals are at some point exposed to stressful life events or traumas, understanding of how some of us can cope with such experiences and others not, is crucial to maintaining or regaining mental health in society. In this context, a better understanding of the genetic mechanisms underlying resilience is important to improve treatment and prevention strategies and to implement personalized medicine.

In the past 20 years there have been enormous developments in the discovery of genetic factors associated with complex psychiatric diseases such as schizophrenia (Giegling et al., 2017) and Alzheimer's disease (Kunkle et al., 2019), but also with personality traits (Sanchez-Roige, Gray, MacKillop, Chen, & Palmer, 2018) and intelligence (Savage et al., 2018). However, there are very few studies that have investigated the genetic impact on resilience. An important reason for this is the large number of resilience-related indicators, so that the measurement of resilience is neither clearly operationalized (Rodriguez-Llanes, Vos, & Guha-Sapir, 2013) nor a gold standard has been defined (Windle, Bennett, & Noyes, 2011). Moreover, the focus has so far been less on health-promoting factors than on disease-associated and deficit-oriented aspects. One way to counter this problem, at least in part, and still being able to draw conclusions about the underlying genetic mechanisms of resilience, is to consider studies in which vulnerable phenotypes have been investigated. Why this is a reasonable approach becomes apparent when one considers resilience and vulnerability as the poles of a continuum (Haddadi & Besharat, 2010; Kim-Cohen & Turkewitz, 2012). In addition, there is an overlap of indicators between vulnerable phenotypes, especially post-traumatic stress disorder (PTSD) and major depressive disorder (MDD), and psychological resilience, which is reflected by the fact that after a trauma or an adverse life event, a lack of resilience can contribute to the development of PTSD or MDD (Ahmadpanah et al., 2017; Mattson, James, & Engdahl, 2018). Thus, genetic case–control studies comparing individuals who have developed a mental disorder after stress exposure with those who have not developed mental problems provide a way to identify genetic factors associated with resilience, since these studies compare resilient and nonresilient phenotypes. Moreover, there is evidence for mechanisms that predict vulnerability to stress and susceptibility to PTSD and MDD in the face of stress and trauma (Southwick & Charney, 2012; Wu et al., 2013).

Based on these preliminary considerations, this review is structured as follows: The first section focuses on the heritability of resilience. As there are few studies on this issue, it is necessary to use other resources to gain a deeper insight into the genetic background of resilience. Therefore, the second section gives an overview of studies that have investigated associations of vulnerable phenotypes with genetic variants of the neuroendocrine stress response system. It is assumed that the stress response system plays a key role for resilience (Feder, Nestler, & Charney, 2009), so that the focus in this section is on the serotonergic, noradrenergic, and dopaminergic systems as well as the hypothalamic–pituitary–adrenal axis (HPA axis), neuropeptide Y (NPY), and brain-derived neurotrophic factor (BDNF). In particular, results will be presented that have revealed a gene × environment interaction in the development of mental disorders and thus suggest a connection with resilience. In the third section, results of genome-wide association studies (GWASs) on resilience, PTSD and MDD will be presented, as they offer a relatively new approach to the identification of hypothesis-free phenotype-associated genetic variants and thus an opportunity to gain direct insights into the genetics of resilience. Finally, the discussion section contains a summary of the most important results, a conclusion on the current state of knowledge and an outlook for the future.

2 | METHODS

A MEDLINE (PubMed) research was conducted for this review. First of all, studies were considered in which genetics and heritability of resilience were addressed. Since the literature in this field is limited, we have included studies that have investigated the association of genetic variants of the stress response system with psychiatric disorders and have therefore considered PTSD and MDD as outcome variables in terms of a lack of resilience. It should be noted that the focus was on studies from the last 10 years and that not all studies were included, in particular those with very small sample sizes and those from which no relationship to resilience could be derived. Finally, a systematic search for GWAS on resilience, PTSD and MDD was conducted to use this new and promising approach, which has led to a significant development in genetic research in recent years.

3 | HERITABILITY OF RESILIENCE

Most of the knowledge about the heritability of resilience derives mainly from twin studies. In a study of more than 1,000 pairs of twins in childhood, genetic and environmental factors affecting resilience were investigated, with 46% of the variance of cognitive and 70% of the variance of behavioral resilience being explained by genetic effects (Kim-Cohen, Moffitt, Caspi, & Taylor, 2004). A study carried out by Wolf et al. (2018) on 3,318 male twin pairs from the Vietnam Era Twin Registry, which included analyses of genetic and environmental influences on the severity of PTSD symptoms as measured by the PTSD Checklist (Weathers et al., 2017) and an assessment of resilience, measured with the Connor–Davidson Resilience Scale-10 (Connor & Davidson, 2003), revealed a heritability of resilience of 25% and PTSD of 49%. Resilience and PTSD were negatively correlated at $r = -.59$, and 59% of this correlation was attributable to a single genetic factor, whereas the remainder was due to a single nonshared environmental factor (Wolf et al., 2018). Another study investigating the genetic contribution to resilience in a genome-wide approach with 8,734 participants from the GS:SHFS study (Generation Scotland:Scottish Family Health Study) confirmed the heritability of resilience, but the estimated phenotypic variance of 8% attributable to genetic factors was significantly lower than in the aforementioned studies (Navrady et al., 2018). This study also investigated the influence of genetic factors on different coping styles (task-

oriented, emotion-oriented, avoidance-oriented coping), which are closely related to resilience (Iacoviello & Charney, 2014). Interestingly, a large genetic correlation between emotion-oriented coping and resilience was found, which indicates a common genetic background of these traits (Navrady et al., 2018). Amstadter, Maes, Sheerin, Myers, and Kendler (2016) found in patients with MDD and generalized anxiety disorder (GAD) that 42% of MDD heritability and 60% of GAD heritability are due to genetic factors influencing resilience, suggesting shared heritability of these diseases and resilience. These findings support an impact of genetics on resilience, whereby the studies differ in the extent of heritability. There is also evidence that the investigation of PTSD and MDD may allow conclusions to be drawn about the genetic background of resilience, as there is at least a partial overlap between resilience and these psychiatric disorders.

4 | CANDIDATE GENES OF THE NEUROENDOCRINE STRESS RESPONSE SYSTEM

Several neurotransmitter systems contribute to resilient responses to stress and are implicated in the development of PTSD and MDD. Genetic variants of the noradrenergic, dopaminergic, and serotonergic systems, as well as genes encoding for neurotrophic factors or genes related to the HPA axis have been most extensively studied (Sheerin, Lind, Bountress, Nugent, & Amstadter, 2017; Wu et al., 2013). The following sections provide an overview of the main results of association studies on genetic variants of the stress response system with PTSD and MDD in the context of resilience.

4.1 | Serotonergic system

The serotonergic system is connected to the function of two key stress response systems: the HPA axis (Leonard, 2005) and the locus coeruleus (LC)–norepinephrine (NE) system (Goddard et al., 2010).

A promising gene from this neurotransmitter system is the *SLC6A4* gene (solute carrier family 6 member 4), encoding the serotonin transporter (SERT). Within the promotor region of *SLC6A4*, there is a polymorphism (serotonin transporter-linked polymorphic region; 5-HTTLPR) with short (S) and long (L) repeats, with the S allele leading to decreased SERT expression compared to the L allele (Lesch et al., 1996). A meta-analysis showed that the S allele is associated with increased stress sensitivity (M. Zhao et al., 2017) and furthermore, S allele carriers are more likely to develop MDD, which has already been proven in several studies (López-León et al., 2008). Overall, there seems to be an association between the promoter polymorphism of the *SLC6A4* gene, depression and environmental interactions, as carriers of the low-active S allele had a markedly elevated risk of developing depression under stress exposure, which was demonstrated in a meta-analysis of 54 studies (Karg, Burmeister, Shedden, & Sen, 2011). This study also found evidence for the association of the S allele with stress sensitivity and depression in maltreated children. A connection of the S allele was also shown in an increased risk for PTSD in patients with childhood adversity and adult traumatic events (Xie et al., 2009). A dose-dependent relationship between *SLC6A4* variants and emotional resilience was additionally demonstrated in a study on 423 psychology students, with lower resilience scores found in S allele carriers (Stein, Campbell-Sills, & Gelernter, 2009). However, a number of meta-analyses investigating the *SLC6A4* × environment interaction revealed mixed results, and the effect, if present, is modest and unlikely to be generalized (Culverhouse et al., 2018; Karg et al., 2011; Munafò, Durrant, Lewis, & Flint, 2009; Risch et al., 2009; van der Auwera et al., 2018). Taken together, S allele carriers are more likely to develop stress-related psychiatric disorders, such as PTSD and MDD, which may be due to lower resilience in S allele carriers.

In addition to the *SLC6A4* gene, serotonin receptors and enzymes of the serotonin metabolism have been investigated. The mitochondrial enzyme monoamine oxidase A (MAOA) is responsible for the degradation of serotonin as well as epinephrine and NE and a meta-analysis found an association between a variable number of tandem repeats polymorphism (uVNTR) in the *MAOA* promoter region and MDD, but limited to Asians (Fan et al., 2010). In addition, epigenetic modifications by DNA methylation of the *MAOA* gene have been associated with PTSD (increased methylation status) and panic disorder (decreased methylation status) as well as the occurrence of positive and negative life events (Domschke et al., 2012; Ziegler et al., 2017). Another enzyme in the serotonin metabolism is tryptophan hydroxylase 2 (*TPH2*), the rate-limiting enzyme in the synthesizing pathway for brain serotonin (Invernizzi, 2007). A higher risk for MDD has been reported for two independent SNPs of *TPH2* (Gao et al., 2012), with the T allele of rs4570625 being associated with smaller volumes of bilateral amygdala and hippocampus, a typical finding in emotion-related psychiatric disorders (Inoue et al., 2010). Genetic variants of the genes *HTR1A* (5-hydroxytryptamine receptor 1A; Kishi et al., 2013) and *HTR2A* (X. Zhao et al., 2014) appear to be associated with depression and of *HTR2C* with depressive symptoms in women and elevated cortisol levels induced by acute mental stress, implying a direct link between *HTR2C* and HPA axis activation (Brummett et al., 2012; Brummett, Babyak, Kuhn, Siegler, & Williams, 2014).

4.2 | Dopaminergic and noradrenergic systems

Dopamine emerges in several, relatively confined groups of neurons projecting to various brain areas including the prefrontal cortex, nucleus accumbens (NAcc), hippocampus, and amygdala. Differences in striatal dopamine transporter (DAT) density in PTSD patients compared to healthy, traumatized individuals, suggest an influence of the dopaminergic system on vulnerable phenotypes and resilience (Hoexter et al., 2012). In a meta-analysis by Li et al. (2016), two genetic variants in genes of the dopaminergic system with increased susceptibility to PTSD were detected, namely the VNTR polymorphism in the promoter region of the human DAT gene (*SCL6A3*) and a polymorphism (rs1800497) in the dopamine receptor D2 gene (*DRD2*). *DRD2* has also been shown to regulate synaptic modification in response to stress (Perreault, Hasbi, O'Dowd, & George, 2014; Sim et al., 2013). In addition, both genes, *SCL6A3* and *DRD2*, are

associated with MDD, whereby the association of *DRD2* has been demonstrated in a large GWAS with 130,664 cases and 330,470 controls (López-León et al., 2008; Wray & Sullivan, 2017). Also an influence on resilience could have variants of the *DRD4* gene (dopamine receptor D4), where carriers of seven or more copies of a VNTR polymorphism in the third exon had a seemingly protective effect and thus an increase of resilience if they suffered adversity during childhood. Conversely, this effect was not observed when no childhood trauma occurred.

The catecholamine NE is released from its main production site—the LC in the pons—upon stress-induced activation of the noradrenergic system and transported to its various projection sites, including amygdala, hippocampus, hypothalamus, and prefrontal cortex (Bandelow et al., 2017). β-adrenergic receptors as well as α-adrenergic receptors and the NE transporter are considered to be involved or affected in various psychiatric disorders and resilience (Borodovitsyna, Flamini, & Chandler, 2017; Krystal & Neumeister, 2009). So far, however, there are no conclusive results on genetic variants of the NE system related to resilience.

One potential candidate affecting both the dopaminergic and noradrenergic systems is the enzyme catechol-O-methyltransferase (COMT). The SNP rs4680 (Val^{158}Met), which affects the activity of encoded COMT, is probably the most replicated disease-relevant polymorphism of this system. The Met allele is associated with a decreased COMT enzyme activity and thus higher NE and dopamine levels (Chen et al., 2004). Homozygous carriers of the Met allele show lower emotional resilience against negative mood states in humans (Smolka et al., 2005) and exaggerated stress reactivity in mice (Papaleo et al., 2008). The Met allele was found to be associated with decreased inhibition-related activation in the hippocampus, which in turn was associated with PTSD and depression symptoms in patients with childhood trauma (van Rooij et al., 2016). An accumulation of the Met allele was also found in individuals who developed PTSD after being exposed to urban violence (Valente et al., 2011). A study on genocide survivors showed, that Val allele carriers exhibited an elevated risk for PTSD, depending on the number of lifetime traumatic events, while Met/Met homozygotes were at high risk for PTSD regardless of the traumatic load (Kolassa, Kolassa, Ertl, Papassotiropoulos, & de Quervain, 2010). The presence of the *COMT* Met allele also leads to a stronger cortisol stress response in children (Armbruster et al., 2012). These results imply an interaction of the *COMT* variants with stress and thus suggest an influence on resilience. However, it should not go unmentioned that the study data on *COMT* and PTSD are inconsistent and that a meta-analysis of five studies did not show any significant effect (Li et al., 2016).

4.3 | Hypothalamic–pituitary–adrenal axis

The HPA axis is a major neuroendocrine system that affects various organ systems and plays a fundamental role in mediating stress response which is supported by the fact that disturbances in normal HPA function are associated with depressive and anxiety symptoms (Russell et al., 2018; Russo, Murrough, Han, Charney, & Nestler, 2012). With regard to the HPA axis, several genes and their potential impact on vulnerable phenotypes have been studied, but there are few studies that have investigated the link between genes of this hormone system and resilience. However, a connection between the HPA system and resilience processes is supported, for example, by the observation of an altered HPA reactivity in later life depending on the presence of adverse life events in early life (Romeo, 2015). For the corticotropin-releasing hormone receptor *CRHR1*, several polymorphisms are associated with a reduced risk of depressive symptoms after being exposed to early life stress (for review see Laryea, Arnett, & Muglia, 2012). And another study on gene × environment interactions in children revealed an association between *CRHR1* haplotypes with resilience depending on their maltreatment status (Cicchetti & Rogosch, 2012). A similar gene × environment effect has been found in two studies that investigated maltreatment during childhood, with *CRHR1* variants appearing to moderate the risk of depressive symptoms in adulthood (Bradley et al., 2008; Polanczyk et al., 2009). Such gene × environment interactions are a strong indication of a genetic impact on resilience, as variations in resilient behavior after adversity or stress may be caused by a different genetic composition. In addition, significant associations of genetic variants in the *CRHR1* gene have been detected in PTSD patients (Boscarino, Erlich, Hoffman, & Zhang, 2012; White et al., 2013; Wolf et al., 2013).

Studies focusing on the relationship between variants of the glucocorticoid receptor gene (*NR3C1*) and resilience have not yet been conducted. However, epigenetic modifications by DNA methylation related to trauma exposure have been shown, although the results of these studies were inconsistent (Watkeys, Kremerskothen, Quidé, Fullerton, & Green, 2018). There is also evidence that *NR3C1* polymorphisms are associated with PTSD symptoms and depression (Hauer et al., 2011; Lian et al., 2014; Peng, Yan, Wen, Lai, & Shi, 2018).

Another gene of the HPA axis is the FK506-binding protein 5 gene (*FKBP5*), which interacts with the glucocorticoid receptor binding heat-shock protein 90 (HSP90). Elevated FKBP5 levels lead to a decreased negative feedback regulation of the HPA axis and glucocorticoid receptor resistance, which is probably responsible for a dysregulated stress response (Binder et al., 2008). In several association studies, genetic variations in the *FKBP5* gene were associated with PTSD occurrence and severity, depending on the presence of childhood trauma (Binder et al., 2008; Buchmann et al., 2014; Comasco et al., 2015; Watkins et al., 2016). These results were substantiated in a recently published study showing a gene × environment interaction between *FKBP5* polymorphisms and childhood abuse to predict the risk for PTSD (Tamman et al., 2019). Such findings can help to identify patients with an increased risk of mental disorders and to implement personalized medicine in the future. Moreover, common allelic variants in the FKBP5 gene are associated with an increased risk of developing affective disorders like anxiety, depression, and PTSD (Criado-Marrero et al., 2018).

A higher risk for depression susceptibility after maltreatment in childhood was also found for haplotypes of the mineralocorticoid receptor (*NR3C2*), whereby a relationship between *NR3C2* variants and current depressive symptoms and lifelong MDD diagnosis has

been demonstrated in two samples (Vinkers et al., 2015). Since the HPA axis is the most important physiological stress response system (Silverman & Deuster, 2014), genetic variations in this system are likely to influence resilience and contribute to psychiatric disorders in vulnerable phenotypes.

4.4 | Neuropeptide Y

Neuropeptide Y is a biologically active peptide and acts as a neuromodulator in the brain. In several brain regions (hippocampus, hypothalamus, LC, and amygdala) corticotropin-releasing hormone mediated anxiogenic effects are counteracted by NPY, which is necessary for the compensation of stress reaction and homeostasis (Thorsell et al., 2000).

Polymorphisms within the *NPY* locus affect *NPY* expression and it has been reported that *NPY* haplotypes that mediate lower *NPY* expression are associated with diminished resilience to stress (Zhang et al., 2012; Z. Zhou et al., 2008). In addition, several polymorphisms in the *NPY* gene have been described in connection with anxiety-related disorders, early childhood adversity, and early life stress. Various studies on gene × environment interactions of the *NPY* promotor variant rs16147 in traumatized subjects revealed promising results. One study showed that the C allele of this polymorphism is associated with anxiety and depressive symptoms depending on childhood adversity (Sommer et al., 2010), while T allele homozygotes were at higher risk of developing a GAD after high hurricane exposure (Amstadter et al., 2010). A gene × environment interaction study of the same SNP for a divergent stress-induced response of cortisol and adrenocorticotropic hormone levels depending on adversity exposure of the participants during childhood was also demonstrated (Witt et al., 2011). And in two cohorts of traumatized participants, T allele carriers of rs16147 adopted better traumatic stress than C homozygotes and developed a higher positive future focus, which is a relevant aspect of resilience (Gan, Chen, Han, Yu, & Wang, 2019). Based on these studies, an influence of this promoter polymorphism in interaction with environmental factors on resilience is likely, which could possibly be mediated by differential expression of the protein.

Other polymorphisms of the NPY region have been associated with increased susceptibility to anxiety disorders in case of early life stress (Donner et al., 2012). Studies on associations of NPY variants with depression are inconsistent, whereby a recently published GWAS–environment interaction study in depression conducted by the childhood trauma working group of the Psychiatric Genomics Consortium-major depressive disorders (PGC-MDDs) detected a polymorphism (rs3214187) located near the *NPY* gene ($p = 7.4 \times 10^{-7}$; van der Auwera et al., 2018).

4.5 | Neuronal and synaptic plasticity

According to the neurotrophic hypothesis of MDD, the disease may be associated with impaired structural plasticity and cellular resilience, with a key role of BDNF, a neurotrophin highly expressed in the hippocampus and involved in the regulation of synaptic plasticity, neurogenesis, neuronal survival, and differentiation (Ferrari & Villa, 2017). It has been repeatedly demonstrated that BDNF is a contributing factor to a variety of psychiatric disorders, and it is known that BDNF levels are affected by stress in PTSD and MDD patients (Casey et al., 2009; Duman, 2009; Duman & Monteggia, 2006).

Association studies on the functional *BDNF* Val^{66}Met polymorphism (rs6265) revealed inconsistent results regarding the influence on stress response and resilience. Although there were studies that found no significant association between the polymorphism Val^{66}Met and PTSD diagnosis (Rakofsky, Ressler, & Dunlop, 2012), further studies, including a meta-analysis, discovered an increased risk for PTSD and the severity of PTSD symptoms in Met allele carriers (Bruenig et al., 2016; Dai et al., 2017). An interesting approach, which explored possible causes of this connection was followed in a study by Felmingham et al. (2018), which showed that Met allele carriers presented more severe PTSD symptoms in addition to poorer fear extinction learning, which is crucial for PTSD treatment. An overlap with resilience is possible, because disturbed fear extinction can lead to the development or maintenance of mental illnesses and a lack of resilience (Shansky, 2015).

Stressful early life events in combination with the Val^{66}Met variant are able to predict syndromic depression and anxiety with an association of increased depression for Met allele carriers and increased anxiety in Val/Val homozygotes (Gatt et al., 2009), indicating a gene × environment interaction. These findings suggest a role of the Val^{66}Met polymorphism in modulating the relationship between stress and MDD (Hosang, Shiles, Tansey, McGuffin, & Uher, 2014) as well as the risk of late life depression (Tsang, Mather, Sachdev, & Reppermund, 2017).

Other genes that are relevant for neuronal and synaptic plasticity and that are also linked to nonresilient phenotypes are *CREB1* and *CACNA1C*. *CREB1* (cyclic adenosine monophosphate response element-binding protein 1) encodes a downstream effector of BNDF that increases the expression of BDNF target genes (Juhasz et al., 2011). Polymorphisms in *CREB1* have been reported to modulate the risk of different major psychiatric disorders including MDD (Xiao et al., 2017), while no association has been found with PTSD (Serretti et al., 2013). The *CACNA1C* gene (calcium voltage-gated channel alpha 1C subunit) is involved in the regulation of calcium-mediated membrane depolarization and modulates intracellular signaling, gene transcription, and synaptic plasticity (Bhat et al., 2012). *CACNA1C* has been proposed as a susceptibility gene for various psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). The effect of *CACNA1C* polymorphisms on MDD susceptibility was confirmed by a meta-analysis that extracted genotypic data from available GWAS and performed a candidate gene study in an independent sample (Rao et al., 2016).

5 | GENOME-WIDE ASSOCIATION STUDIES

Genome-wide association studies represent the methodological answer to the observation of the highly polygenic component of psychiatric traits, including MDD and PTSD, and of course resilience

(Peterson et al., 2017). In addition, GWAS enable the detection of genetic variants associated with specific phenotypes that could not be discovered with conventional hypothesis-based strategies. This provides a completely new starting point for a better understanding of pathophysiological mechanisms and factors that influence disease development, as well as for the investigation of complex traits or constructs such as resilience.

To date there is only one GWAS on resilience, which was published recently by Stein et al. (2019). Since PTSD in particular, but also MDD, can occur frequently due to trauma, stress a result of a lack of resilience, these phenotypes are useful to identify new potential loci that can then be further investigated to assess possible effects on resilience. For this reason, the next section summarizes the first GWAS on resilience on the one hand and the most important GWAS results on PTSD and MDD on the other. Tables 1 and 2 additionally provide an overview of all GWA studies on PTSD and MDD carried out so far.

In the only GWAS on resilience to date, US soldiers of European descent were studied, and resilience was measured using a five-item self-report questionnaire and by measuring the outcome using the Composite International Diagnostic Interview screening scales to record the common stress-related psychiatric disorders MDD, PTSD, GAD, and panic disorder. The meta-analysis of the three cohorts of this study with a total of 11,492 participants revealed a genome-wide significant locus on chromosome 4 in an intergenic region upstream to *DCLK2* (doublecortin-like kinase 2). A further analysis using a genome-wide gene-association study (GWGAS) revealed an aggregation of several polymorphisms on chromosome 16 in the *KLHL36* region (Kelch-like family member 36). The analyses of prospective outcome-based resilience were performed in a smaller sample (N = 1,939), with no SNP reaching genome-wide significance. However, if only those participants who had experienced high stress exposure (N = 581) were considered, a genome-wide significant polymorphism was detected less than 0.1 Mbp downstream from *SLC15A5* (Solute Carrier Family 15 Member 5; Stein et al., 2019).

There are significantly more GWAS on posttraumatic stress disorder, although most of them do not have well-powered samples (Table 1). The first GWAS by Logue et al. (2013), involving military veterans, identified the retinoid-related orphan receptor alpha (*RORA*) as best association with PTSD. Another study detected the Tolloid-like 1 gene (Xie et al., 2013) and *LINC01090* as a risk factor for PTSD (Guffanti et al., 2013). A study on 3,394 US Marines reported genome-wide association for *PRTFDC1* (phosphoribosyl transferase domain containing 1 gene) as a potential predictor of combat stress vulnerability and resilience (rs6482463; OR = 1.47, $p = 2.04 \times 10^{-9}$; Nievergelt et al., 2015). In a study (New Soldier Study) combining 3,167 PTSD patients and 4,607 trauma-exposed controls, a genome-wide significant locus was found in *ANKRD55* on chromosome 5 (rs159572; OR = 1.62; $p = 2.34 \times 10^{-8}$), which persisted after adjustment for cumulative trauma exposure (OR = 1.64; $p = 1.18 \times 10^{-8}$) in the African-American samples (Stein et al., 2016). *ANKRD55* has previously been associated with diabetes mellitus type 2 (Harder et al., 2013) and various autoimmune diseases, such as rheumatoid arthritis (Viatte et al., 2012) and multiple sclerosis (Alloza et al., 2012), suggesting a genetic overlap of these diseases, as PTSD is also associated with autoimmune diseases and diabetes. Restricted to the European ancestry subgroup, a genome-wide significant association near zinc finger protein 626 gene (*ZNF626*) on chromosome 19 (rs11085374; OR = 0.77; $p = 4.59 \times 10^{-8}$) was detected. The Psychiatric Genomics Consortium-PTSD continues to encourage the further discovery of genes involved in the pathology and susceptibility to PTSD (Banerjee, Morrison, & Ressler, 2017). The largest GWAS on PTSD so far (including 20,730 samples: 15,548 controls, 5,182 cases) revealed no genome-wide significant association with the disease in a multiethnic PGC-PTSD cohort, but suggested a robust genetic overlap with bipolar disorder and schizophrenia (Duncan et al., 2018). A previously found overlap of PTSD with MDD could not be confirmed, but this as well as the failure to detect genome-wide significant associations was attributed to the relatively low power of the PTSD and MDD studies. Nevertheless, the top pathway was the neurotrophic factor-mediated Trk receptor signaling pathway, which includes BDNF and which also showed overlaps to resilience (see section "Neuronal and synaptic plasticity").

Although sample sizes were much higher than in PTSD, the identification of MDD-associated loci that reached genome-wide significance in GWAS was challenging, in particular because of the high genetic heterogeneity and high prevalence of MDD (Table 2). These considerations at least partially explain the negative results reported by the first GWAS, which included <10,000 cases (Lee et al., 2012; Lewis et al., 2010; Muglia et al., 2010, 2010, 2010; Ripke et al., 2013; Shyn et al., 2011; Sullivan et al., 2009; Wray et al., 2012). Some genes identified in these earlier studies did not reach genome-wide significance, but were replicated in subsequent GWAS or associated with other relevant traits, notably *BICC1* (Lewis et al., 2010; Ryan et al., 2016) and *PCLO* (Sullivan et al., 2009; Wray & Sullivan, 2017), while *CACNA1C* (Wray et al., 2012) was identified as a pleiotropic gene across major psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Upregulation of *BICC1* (Bicaudal C homolog 1) and downregulation of BDNF/TrkB signaling were observed in both hippocampus and cortex after application of chronic unpredictable stress in a mouse model of depression (Zhou et al., 2017). In addition, treatment with antidepressants reduced the expression of *BICC1*, and the knockdown of this gene in the hippocampus also prevented anhedonia, a key feature of depression in the same model in rats (Ota, Andres, Lewis, Stockmeier, & Duman, 2015). Moreover, there is evidence that *BICC1* associated polymorphisms affect the capability of the *BICC1* promoter to respond to PKA (protein kinase A) signaling in amygdala neurons (Davidson et al., 2016). Since the amygdala PKA pathways are implicated in fear learning and mood, there is a potential link of alterations of *BICC1* activity in MDD as well as resilience mechanisms.

In recent years, larger samples have been collected (up to 130,664 cases and 330,470 controls) to obtain statistical power for the identification of an increasing number of genome-wide significant loci and replicated findings. The most recent PGC GWAS identified 44 independent loci that were associated with MDD at genome-wide level, with 14 of these loci being significant in a prior MDD GWAS (Wray & Sullivan, 2017). Replicated variants were found in particular in the

TABLE 1 Summary of genome-wide association studies (GWASs) that investigated the genetics of posttraumatic stress disorder (PTSD)

Study (PMID)	Sample size	Replication sample	Ancestry	Main findings
Logue et al. (2013) (22869035)	295 Cases and 196 controls	43 Cases and 41 controls	White, non-Hispanic (discovery); African American (AA) (replication)	One SNP with genome-wide significance was discovered within the *RORA* gene (p = 2.5e−08) without replication in the replication sample. Nominal significance of other SNPs in the *RORA* region in the replication sample
Xie et al. (2013) (23726511)	European: 300 cases and 1,278 controls African American: 444 cases and 2,322 controls	European: 207 cases and 1,692 controls African American: 89 cases and 655 controls	European AA	In the combined European sample, top hit with genome-wide significance (p = 3.97e−08) and further SNPs with suggestive significance in the *TLL* gene. No replication in the African American samples
Guffanti et al. (2013) (24080187)	413 Cases and 319 controls	578 Cases and 1963 controls	AA (discovery); European (replication)	Genome-wide significance (p = 5.09e−08) in the discovery sample for rs10170218 in a long intergenic noncoding RNA (AC068718.1) and suggestive evidence for *HLA-G3*, *LARGE*, *TMCC3*, *C7orf53*, and an intergenic region. Suggestive evidence for lincRNA AC068718.1 in the replication sample
Nievergelt et al. (2015) (25456346)	940 Cases and 2,554 controls	313 Cases and 178 controls	European, AA, Hispanic, other (discovery) White, non-Hispanic (replication)	Meta-analysis of all ancestral groups of the replication sample found genome-wide hit in *PRTFDC1* (p = 2.04e−09); no significance of this region in the replication sample. Eleven SNPs with suggestive significance in the discovery sample meta-analysis
Almli et al. (2015) (25988933)	63 Cases and 84 controls	2006 Females and 862 males	Mixed sample	One genome-wide significant hit (rs717947) in the *COL4A2* region (p = 1.28e−08). Replication of the top hit in females, but not in males. The SNP was associated with methylation status of the gene
Ashley-Koch et al. (2015) (26114229)	759 non-Hispanic White and 949 non-Hispanic black individuals		Non-Hispanic White-non-Hispanic black individuals	No genome-wide significant hit; suggestive SNPs in the meta-analysis of both samples in *AK092087*, *PRKG1*, and *DDX60L*
Stein et al. (2016) (27167565)	Cohort 1:1,245 cases and 2,291 controls Cohort 2:895 cases and 618 controls	672 Cases and 3,335 controls	European, AA, Latino	In the meta-analysis of detection samples, one genome-wide significant hit on chromosome 19 (*ZNF626*) in European samples (p = 4.59e−08) and one on chromosome 5 (*ANKRD55*) in AA samples (p = 2.34e−08). No replication in the replication sample
Kilaru et al. (2016) (27219346)	1,158 Cases and 2,520 controls	134 Cases and 246 controls	AA (discovery) Mixed (replication)	Genome-wide significant associations in *NLGN1* (p = 1.0e−7) and *ZNRD*-AS1 (p = 1.0e−07). Replication of the *NLGN1* locus, with a LD-independent SNP found in the replication sample
Melroy-Greif, Wilhelmsen, Yehuda, and Ehlers (2017) (28262088)	254 Cases	258 Cases	Mexican (discovery) American Indian (AI) (replication)	Association analysis in trauma-exposed subjects with sum PTSD symptoms. No genome-wide significant hut, but *OR11L1* with suggestive significance. No suggestive or genome-wide hit in the AI sample. No replication of *OR11L1*

(Continues)

TABLE 1 (Continued)

Study (PMID)	Sample size	Replication sample	Ancestry	Main findings
Duncan et al. (2018) (28439101)	5,182 Cases and 15,548 controls		AA, European, Latino, South African	No genome-wide significant hit in the meta-analysis of the combined sample. One genome-wide hit in the AA sample located in the *KLHL1* gene on chromosome 13 (rs139558732, p = 3.33e−08). Genetic overlap with schizophrenia and bipolar disorder
Wilker et al. (2018) (30467376)	924 Cases	371 Cases	African	Association tests with lifetime PTSD risk revealed suggestive significance for one SNP on chromosome 2, two SNPs on chromosome 3, two SNPs on chromosome 5, one SNP on chromosome 6, and one SNP on chromosome 13. Replication of one SNP (rs3852144) on chromosome 5

Abbreviations: AA, African American; AI, American Indian.

regions of *RERE*, *VRK2*, *RSRC1*, *PUM3*, *SORCS3*, *OLFM4*, *BAG5*, *DCC*, *L3MBTL2*, long intergenic nonprotein coding RNA genes (*LINC01360* and *LINC00461*) and intergenic regions (rs11135349 and a deletion spanning 5p11 region). Most of these significant loci were shared with the 23AndMe GWAS (Hyde et al., 2016), some with the SSGAC (Okbay et al., 2016) and CHARGE (Hek et al., 2013) depressive symptoms studies, but very limited overlaps were reported with CONVERGE results (CONVERGE consortium, 2015), a consortium that collected a quite homogeneous Han Chinese sample (females with recurrent MDD). One reason for this could be the relatively low trans-ancestry genetic correlation of MDD across European and Chinese. Among the replicated genome-wide associations, *NEGR1* (neuronal growth regulator 1) shows a role in synaptic plasticity in MDD-relevant brain regions such as the cortex, hypothalamus, and hippocampus (Hashimoto, Maekawa, & Miyata, 2009; Sanz, Ferraro, & Fournier, 2015; Schäfer, Bräuer, Savaskan, Rathjen, & Brümmendorf, 2005). *DCC* (Netrin 1 receptor) also looks promising as it is one of the most relevant genes contributing to the association between the NETRIN signaling pathway and MDD in different samples (Zeng et al., 2017).

For the vast majority of the detected genes associated with PTSD and MDD, pathophysiological mechanisms and their participation in disease development are not known yet. Whether or not there is a link to resilience must be evaluated after the function and the effects of the associated genes have been clarified.

6 | DISCUSSION

Most people are confronted with stress, trauma, and tragedy at some point in their lives and do not develop mental disturbances as a result. This ability to deal with and overcome adversity encompasses the complex construct of resilience. A number of resilience-promoting factors have been identified in the past, including early life influences such as supportive, attentive, and responsible parenting, a loving and supportive environment, positive relationships with adults and peers (Masten et al., 1999), experience of overcoming manageable life challenges (Southwick & Charney, 2012), or avoidance of repeated exposure to uncontrollable stress and trauma (Green et al., 2010). Other factors that indicate resilient behavior in adulthood include adaptive stress responses, rapid stress recovery, high coping self-efficacy, strong cognitive reappraisal and emotion regulation, and self-confidence, to name only a few (Southwick & Charney, 2012). These insights already help today to assist people in difficult life situations and to avert greater harm. However, in order to better understand resilience, it is crucial to study and understand the underlying genetic and neurobiological processes. Such knowledge could make a significant contribution to improving health care. On the one hand, people who have an increased risk of developing mental disorders could be better identified and assigned to a more intensive treatment. After a catastrophic event, such as a natural disaster or a war, it would be of great benefit to identify precisely those of the many victims who would benefit from intensive therapy, or those who do not have a higher risk of developing a psychiatric disorder subsequently. If this concept is further developed, a fundamental understanding of the molecular mechanisms of resilience can also help to tailor targeted, individualized therapies to the needs of patients, which certainly include both psychotherapy and drug treatment that directly target resilience-promoting pathways. On the other hand, this knowledge can also be useful for the reduction of mental distress and the prevention of psychiatric disorders in order to reduce the frequency of occurrence of such disorders and the severity of symptoms. But these thoughts are currently still dreams of the future.

Although there have been enormous developments in the field of resilience research in recent years, there are still very few studies in the field of genetics. Reasons for this are, for example, the lack of opportunities for genotyping on a large scale until a few years ago, but also the previously small samples and the imprecise operationalization of resilience. Nevertheless, there is no doubt that resilience is partly influenced by genetic factors. The heritability of

TABLE 2 Summary of genome-wide association studies (GWASs) that investigated the genetics of major depressive disorder (MDD)

Study (PMID)	Sample size	Replication sample	Ancestry	Main findings
Sullivan et al. (2009) (19065144)	1,738 Cases and 1,802 controls	6,079 Cases and 5,893 controls	European	Suggestive nonsignificant signals in the region of *PCLO* (top SNPs: rs2715148 and rs2522833, $p \geq 7.7e{-}07$).
Muglia et al. (2010) (19107115)	1,022 Cases and 1,000 controls	492 Cases and 1,052 controls	European	Meta-analysis of the two samples provided no significant results. Top signal in rs4238010, intergenic ($p = 5.8e{-}06$).
Lewis et al. (2010) (20516156)	1,636 Cases and 1,594 controls	1,418 Cases and 1,052 controls	European	Suggestive nonsignificant signals in *BICC1* ($p \geq 1.3e{-}07$). In women (1,152 cases), genome-wide association was observed for rs9416742 in *BICC1* ($p = 1.8e{-}08$). In the meta-analysis of the two samples no significant signal and no replication of *BICC1* signals, top suggestive signals were intergenic (one 29.7 kb from *NLGN1*, $p = 8.54e{-}06$)
Shyn et al. (2011) (20038947)	1,221 Cases and 1,636 controls	2,736 Cases, 1,792 controls	European	No significant findings in the discovery sample. In the meta-analysis nonsignificant suggestive signals in *ATP6V1B2* ($p = 6.78e{-}07$), SP4 ($p = 7.68e{-}07$), and *GRM7* ($p = 1.11e{-}06$)
Lee et al. (2012) (23149448)	4,346 MDD cases and 4,430 controls (meta-analysis of three GWAS)	/	European	No significant SNP in the meta-analysis. Gene-set analysis showed enrichment of the glutamatergic synaptic transmission set (GO:0035249, corrected $p = .029$). Genes intersecting with MDD-associated genomic regions included *GRM8*, *CACNA1A*, *UNC13A*, *PARK2*, *SLC1A4*, *SHC3*, *MET*, *NR4A2*, *MDGA2*, *PDE4B*, *PDE4D*, *PDE3A*, *GRIN2A*, *GRIN3A*, *GRIA4*, *GRIK4*, *NRXN1*, *NCF2*, *MUSK*, *DMXL2*, *SYNPR*, *SYT9*, *C16orf70*
Wray et al. (2012) (21042317)	2,431 Cases and 3,673 controls	3,332 Cases and 3,228 controls	European	No significant finding in the discovery sample or in the meta-analysis. No replication of *PCLO* signals. Gene-based tests showed association with *GAL* in the meta-analysis. Other candidate genes found by previous GWAS did not survive multiple testing correction and top ones were *IL10*, *OPRM1*, *HTT*, *HTR1B*, *GRIN1*, and *CACNA1C*
Ripke et al. (2013) (22472876)	9,240 MDD cases and 9,519 controls	6,783 MDD cases and 50,695 controls; 6,998 bipolar disorder cases and 7,775 controls	European	No significant association in discovery or validation samples or secondary analyses (by sex, recurrent MDD, early onset, etc.). Fifteen genome-wide significant SNPs in the mega-analysis with bipolar disorder, all were in a 248 kbp interval of high LD on 3p21.1
Hek et al. (2013) CHARGE study (23290196)	34,549 Subjects with measure of depressive symptoms	16,709 Subjects with measure of depressive symptoms	European	No locus reached the genome-wide significant threshold in the discovery sample or replication sample. In the meta-analysis rs161645 (5q21) was associated with depressive symptoms ($p = 4.78e{-}10$)
CONVERGE consortium (2015) (26176920)	5,303 Cases and 5,337 controls (all women)	3,231 Cases and 3,186 controls	Han Chinese	Two significant loci were replicated in the independent sample: One near the *SIRT1* gene ($p = 2.53e{-}10$), the other in an intron of the *LHPP* gene ($p = 6.45e{-}12$). They were not replicated in PGC data
Okbay et al. (2016) SSGAC study (27089181)	105,739 Patients with a continuous measure of depression; two case–control samples including a total of 16,471 cases and 58,835 controls	75,607 Cases and 231,747 controls	European	Two significant loci were associated with depressive symptoms and replicated (rs7973260, $p = 1.8e{-}09$; rs62100776, $p = 8.5e{-}09$). These SNPs are intron variants of *KSR2* and *DCC* genes, respectively

(Continues)

TABLE 2 (Continued)

Study (PMID)	Sample size	Replication sample	Ancestry	Main findings
Hyde et al. (2016) 23AndMe study (27479909)	75,607 Cases and 231,747 controls	45,773 Cases and 106,354 controls + PGC data (9,240 cases and 9,519 controls)	European	Seven independent significant SNPs identified in the discovery sample (p < 5e−08) within *OLFM4*, *TMEM161B-MEF2C*, *MEIS2-TMCO5A*, *SPPL3-HNF1A*, *N6AMT1*, *NEGR1*, *EP300*. In meta-analysis with PGC data, only the *N6AMT1* locus was not represented at p < 5e−06 and SNPs in the *OLFM4*, *TMEM161B-MEF2C*, *MEIS2-TMCO5A*, and *NEGR1* reached genome-wide significance. In the independent replication cohort SNPs in the *TMEM161B-MEF2C* and the *NEGR1* locus were replicated. In the joint analysis of all data sets, 15 independent loci reached genome-wide significance, including T*MEM161B-MEF2C*, *NEGR1*, *OLFM4*, *MEIS2-TMCO5A*
Direk et al. (2017) (28049566)	9,240 MDD cases and 9,519 controls; 51,258 subjects with measure of depressive symptoms	6,718 MDD cases and 13,453 controls; 8,157 subjects with measure of depressive symptoms	European	One SNP was associated with the broad depression phenotype (rs9825823, p = 8.2e−09) located in an intron of the *FHIT* gene and the association was replicated in an independent sample
Power et al. (2017) (27519822)	8,920 Cases and 9,519 controls	13,238 Cases and 124,230 controls	European Chinese	One genome-wide significant (p = 5.2e−11) locus was associated with adult-onset MDD (>27 years) (rs7647854, intergenic, with flanking genes including *C3orf70*, *VPS8*, *EHHADH*, *MAP3K13*) and it was replicated in independent cohorts. *PRS* showed that earlier-onset MDD was genetically more similar to schizophrenia and bipolar disorder than adult-onset MDD
Howard et al. (2017) (29187746)	2,659 Cases and 17,237 controls	8,508 Cases and 16,527 controls	European	Genome-wide haplotype-based analysis identified one haplotype (located at 6q21) that was significant in the discovery sample and nominally significant in the validation cohort
Wray and Sullivan (2017) Major Depressive Disorder Working Group of the PGC, 2017	130,664 Cases and 330,470 controls (seven cohorts)	CHARGE, SSGAC, 23AndMe, and CONVERGE were used for comparison	European	Meta-analysis of seven cohorts identified 44 independent loci that were statistically significant (p < 5e−08). Of these 44 loci, 30 were novel and 14 were significant in a prior study of MDD or depressive symptoms, including *OLFM4*, *NEGR1*, *LRFN5*. Gene-wide analyses identified 153 significant genes that included *CACNA1E*, *CACNA2D1*, *DRD2*, *GRIK5*, *GRM5*, and *PCLO*
Xiao et al. (2018) (28990594)	89,610 Cases and 246,603 controls (meta-analysis of three studies)	46,505 Cases and 108,672 controls (two studies)	European Chinese	In the discovery meta-analysis, rs9540720 in the *PCDH9* gene was associated with MDD (p = 1.69e−08) and the result was confirmed in the meta-analysis including two additional data sets (p = 1.20e−08)
Hall et al. (2018) (29317602)	10,851 Cases and 32,211 controls	/	European	Genome-wide meta-analysis of MDD in males yielded one genome-wide significant locus (p = 2.29e−08) on 3p22.3, with three genes in this region (*CRTAP*, *GLB1*, and *TMPPE*) were associated with the phenotype in gene-based tests, but independent replication was lacking

Abbreviation: PGC, Psychiatric Genomics Consortium.

resilience was repeatedly demonstrated in twin studies, although the proportion of the genetic impact between these studies varied markedly (Connor & Davidson, 2003; Kim-Cohen et al., 2004), as well as in the so far only GWAS on resilience in which SNP-based heritability was estimated at 16% (Stein et al., 2019).

In this first GWAS on resilience, some interesting genome-wide significant hits were obtained, although the sample, especially the outcome-based analysis, was small. An interesting candidate among the significant hits was *DCLK2*, a member of the doublecortin family of kinases that promote survival and regeneration of neurons (Nawabi

TABLE 3 Overview of the most promising genes implicated in resilience

Gene	Chr.	Polymorphism	Allele type	Assumed effect of the gene on resilience	References
BDNF	11	rs6265	C/T (Val^{66}Met)	Association of the Met allele with PTSD risk and severity Additionally poorer fear extinction learning Interaction of genotype and stressful early life events to predict depression (Met) and anxiety (Val)	Bruenig et al. (2016), Dai et al. (2017) Felmingham et al. (2018), Gatt et al. (2009), Hosang et al. (2014), Tsang et al. (2017)
COMT	22	rs4680	G/A (Val^{158}Met)	Interaction of lifetime trauma load and Val allele, while Met homozygotes have generally higher risk for PTSD Met allele carriers with decreased emotional resilience against negative mood states Interaction of genotype and childhood trauma leads to altered hippocampal activation (Met allele and childhood trauma is associated with reduced hippocampal activation, opposite effect in Val homozygotes); positive correlation of hippocampus activation and resilience	Kolassa et al. (2010), Smolka et al. (2005), van Rooij et al. (2016)
CRHR1	17	rs7209436 rs110402 rs242924	C/T G/A G/T	Interaction of the genotype with childhood abuse influences depressive symptoms in adults	Laryea et al. (2012)
DCLK2	4	rs4260523 (intergenic variant ~70 kbp upstream)	A/G	Genome-wide association (p = 5.65e−09) with self-assessed resilience measured with the STARRS (Army study to assess risk and resilience in service members) five-item self-report questionnaire	Stein et al. (2019)
FKBP5	6	rs9296158 rs3800373 rs1360780 rs9470080	A/G C/A T/C T/C	Interaction of genotype and childhood trauma modulates PTSD risk	Binder et al. (2008), Buchmann et al. (2014), Comasco et al. (2015), Watkins et al. (2016)
KLHL36	16	–	–	Significant association of *KLHL36* in an analysis of a self-assessed resilience questionnaire (STARRS) in a genome-wide gene-association study (GWGAS) revealed (p = 1.89e−06)	Stein et al. (2019)
NPY	7	rs16147	C/T (2 kbp upstream variant)	C allele is associated with anxiety and depressive symptoms depending on childhood adversity T homozygotes with higher risk for generalized anxiety disorder after high hurricane exposure Better adaption to traumatic stress with positive future focus in T allele carriers	Sommer et al. (2010), Amstadter et al. (2010), Gan et al. (2019)
SLC6A4	17	5-HTTLPR	S/L allele	Increased risk for developing PTSD under stress in S allele carriers; independent interaction of stressful life events and childhood adversity with S allele in PTSD Increased risk in S allele carriers for developing depression under stress; association of the S allele with elevated stress sensitivity S allele carriers with lower resilience scores	Xie et al. (2009), M. Zhao et al. (2017), Karg et al. (2011), Stein et al. (2009)

Abbreviations: Chr., chromosome; 5-HTTLPR, serotonin transporter-linked polymorphic region; PTSD, posttraumatic stress disorder.

et al., 2015). Stein et al. (2019) additionally discussed the possibility of *DCLK2* being an expression quantitative trait locus in the frontal cortex that could alter brain structure or cognitive function and thus resilience. Interestingly, the top hit is located approximately 0.4 Mbp downstream from the neighboring gene, the *NR3C2* gene, which is also discussed in the context of resilience in this review (Vinkers et al., 2015). Since there are no further genome-wide studies and so far only a few genetic studies on resilience, it makes sense to refer to psychiatric diseases, as these can often occur after stress and trauma as a result of a lack of resilience (Southwick & Charney, 2012). The

occurrence of PTSD and MDD can be used as outcome variables, which can at least indirectly give a hint to possible genetic resilience factors. This is underlined by the fact that when a polymorphism is associated with a stress-related mental illness, one allele of this polymorphism is associated with a higher and the other with a lower disease risk. In other words, one allele is associated with the resilient phenotype and the other allele with the nonresilient phenotype.

In connection with resilience, the neuroendocrine stress response system in particular is attributed a major role (Feder et al., 2009). A promising candidate is the *SLC6A4* gene, which encodes the serotonin transporter (SERT). Several studies have shown an association between the S allele variant of this gene and PTSD and MDD in relation to experienced stress and adversity (Karg et al., 2011; Xie et al., 2009) as well as a lower level of resilience in S allele carriers (Stein et al., 2009). Another promising candidate of the catecholaminergic system is *COMT*, whose variants also show a gene × environment interaction effect, with Met allele carriers who experienced trauma or adversity in childhood exhibiting a greater risk for the development of PTSD and depression and thus appearing to be less resilient (Valente et al., 2011; van Rooij et al., 2016). The HPA axis also appears to have an influence on resilience, particularly for the *CRHR1* and *FKBP5* genes, with interesting results suggesting a link between genetic variants and maltreatment during childhood and the development of PTSD and depression (Bradley et al., 2008; Polanczyk et al., 2009; Tamman et al., 2019). Although the HPA axis is such an important part of the stress response system, there are relatively few studies that address resilience. Table 3 gives an overview of the most promising genes implicated in resilience.

Many other susceptibility genes have been discovered for PTSD and MDD (Tables 1 and 2), but the exact function of the respective genes and the corresponding proteins is often unclear. Whether these genes also have an impact on resilience must be clarified in future research projects. However, GWAS offer a promising approach to discover new common genetic variants, as a hypothesis-driven methodology is not necessary. This development is also facilitated by the fact that GWAS have been increasingly implemented since 2008, as the costs for genome sequencing began to decrease dramatically and became more feasible in large samples. This made it possible to identify previously unknown interacting genetic factors by investigating large cohorts of PTSD and MDD patients. Furthermore, a growing number of genome sequencing projects on large samples from the general population are expected to provide new and notable findings about the genetics of psychiatric disorders in the near future (e.g., "Genomic Aggregation Project" in Sweden (Bergen & Sullivan, 2017) and "All of Us" in the United States (https://allofus.nih.gov/).

Although there are several studies that suggest a genetic influence on resilience processes, investigations on large samples, possibly also in a longitudinal approach, are necessary in order to shed light on the underlying genetic processes of resilience. Collaboration in consortia, such as the Psychiatric Genomics Consortium (PGC), has helped to expand the sample sizes for psychiatric disorders research. This might also be an approach for gathering sufficiently large samples to study resilience in the future. Within this context, it will also be necessary to operationalize resilience uniformly and not only to investigate disease-associated phenotypes, which is almost exclusively the case so far. This could also involve focusing on resilience-related features such as coping styles, cognitive assessment, emotionality, and cognitive self-regulation, which can be helpful to address the problem from the nondisease-related side.

Further research into resilience is of great importance, also to better understand the healthy functioning of the human mind and to identify factors that could prevent the occurrence of mental disorders. This is also necessary in order to develop precise psychotherapeutic interventions and pharmacological treatments that selectively target resilience associated signaling pathways, in order to specifically promote resilience, avert consequential damage, and strengthen prevention.

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CONFLICT OF INTEREST

Alessandro Serretti is or has been consultant/speaker for: Abbott, Abbvie, Angelini, Astra Zeneca, Clinical Data, Boehringer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, Servier. The other authors declare that they have no conflict of interest.

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