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Genetic approaches to understanding post-traumatic stress disorder

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Abstract

Post-traumatic stress disorder (PTSD) is increasingly recognized as both a disorder of enormous mental health and societal burden, but also as an anxiety disorder that may be particularly understandable from a scientific perspective. Specifically, PTSD can be conceptualized as a disorder of fear and stress dysregulation, and the neural circuitry underlying these pathways in both animals and humans are becoming increasingly well understood. Furthermore, PTSD is the only disorder in psychiatry in which the initiating factor, the trauma exposure, can be identified. Thus, the pathophysiology of the fear and stress response underlying PTSD can be examined and potentially interrupted. Twin studies have shown that the development of PTSD following a trauma is heritable, and that genetic risk factors may account for up to 30–40% of this heritability. A current goal is to understand the gene pathways that are associated with PTSD, and how those genes act on the fear/stress circuitry to mediate risk *vs.* resilience for PTSD. This review will examine gene pathways that have recently been analysed, primarily through candidate gene studies (including neuroimaging studies of candidate genes), in addition to genome-wide associations and the epigenetic regulation of PTSD. Future and on-going studies are utilizing larger and collaborative cohorts to identify novel gene candidates through genome-wide association and other powerful genomic approaches. Identification of PTSD biological pathways strengthens the hope of progress in the mechanistic understanding of a model psychiatric disorder and allows for the development of targeted treatments and interventions.

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Introduction

Epidemiological studies worldwide have documented a high rate of traumatic events including life-threatening accidents, rape, combat, physical violence, witnessing the death or injury of others and natural disasters. Several clinical and demographic risk factors that increase the risk of developing post-traumatic stress disorder (PTSD) in trauma survivors have been identified; these include female gender, severity and duration of the trauma, peritraumatic dissociation, previous or comorbid psychiatric disorder, childhood abuse and neglect, and lack of family or social support (Gillespie et al., 2009a).

PTSD is the fifth most common of the major psychiatric disorders, with an overall lifetime prevalence rate of ~8% in the United States (Keane et al., 2009). PTSD is approximately twice as common in women, and prevalence rates correlate with trauma exposure rates (Pratchett et al., 2010; Trevillion et al., 2012). Prospective studies indicate that the majority of trauma victims experience the

cardinal symptoms of re-experiencing, avoidance and hyper-arousal immediately following trauma, but for many victims, these symptoms abate and eventually disappear (Rothbaum et al., 1992). For a significant minority, symptoms persist and develop into syndromal PTSD. Chronic PTSD is associated with significant comorbidity (e.g. major depression, substance and alcohol abuse, panic disorder), mortality (suicide, medical comorbidity, reduced life expectancy), as well as disability in daily activities, reduced vocational productivity and increased health care utilization (Brunello et al., 2001; Gillespie et al., 2009b; Weiss et al., 2011).

Over the last several years, there has been increased interest in PTSD genetics and epigenetics to identify genes that may suggest who will develop PTSD or how best to treat the disorder. Because of the complexity of defining PTSD for genetic studies, many rely on intermediate phenotypes (Meyer-Lindenberg and Weinberger, 2006) or endophenotypes (Gottesman and Gould, 2003), which may be more directly related to relevant gene action and thus enhance biologically robust gene discovery. Recently, neuroimaging has been leveraged as an intermediate phenotype with exceptional results. This article will review and summarize recent research on

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genetic approaches to understanding PTSD risk and resilience, including studies that employed epigenetics and/or neuroimaging methods.

Heritability

One of the most intriguing questions in PTSD is why only 20–30% of exposed subjects develop PTSD following trauma exposure. Like other medical and psychiatric disorders, it is clear that a component of this differential risk is genetic. Based on twin studies, heritability appears to account for 30–40% of the variance contributing to risk for PTSD (True et al., 1993; Xian et al., 2000; Stein et al., 2002b; Koenen et al., 2003, 2005). Notably, part of the variance contributed by gene-environment interactions is estimated as an environmental contribution. Thus, the overall genetic contribution to this disorder may be underestimated. Data from these studies suggest that temperament as well as other heritable factors contribute to increased risk of exposure to traumatic events. A growing number of twin studies are designed to more clearly identify and understand specific biological mechanisms underlying heritable risk and resilience to PTSD (Afifi et al., 2010).

Candidate gene studies

To date, genetic studies have focused primarily on candidate genes identified based on our current understanding of PTSD neurobiology. In general, these studies suggest a complex interaction between genetic and environmental factors. Further, many of the identified genetic polymorphisms are in promoter or other regulatory regions and not necessarily in coding regions of a gene (e.g. Poulton et al., 2008). Many reviews of candidate gene association studies for PTSD have been published to date (Broekman et al., 2007; Amstadter et al., 2009a; Norrholm and Ressler, 2009; Cornelis et al., 2010; Amstadter, 2012; Bomyea et al., 2012; Domschke, 2012; Mehta and Binder, 2012; Skelton et al., 2012; Digangi et al., 2013). Thus, this review will emphasize current findings on the genetics of PTSD, including genetic variants in the serotonergic and dopaminergic systems, hypothalamic-pituitary-adrenal (HPA) axis, and finally variants in other genes related to neurotransmission, neuromodulation and stress physiology (see below).

Serotonergic system candidate genes

Dysregulation of brain serotonergic systems has been implicated in the pathophysiology of PTSD (e.g. Southwick et al., 1994; Anger et al., 1999); indeed, this pathway represents the most studied candidate in PTSD. Among its many functions throughout the brain, serotonin regulates emotional responding and general emotionality; moreover, the serotonergic acting drugs

remain the first-line treatment for anxiety and depressive disorders and are the only currently available FDA-approved medications for PTSD.

Since the landmark study by Caspi et al. (2003), the most widely studied polymorphism in this system is located in the promoter region of the serotonin transporter (*SLC6A4*, rs25531, *5-HTTLPR*). The *5-HTTLPR* polymorphism contains two alleles, L (long) and S (short), and alters *SLC6A4* transcription; for instance, the S-allele reduces serotonin transporter gene expression and function leading to reduced serotonin uptake (Lesch et al., 1996). Though main effects of this polymorphism have been demonstrated (Lee et al., 2005; Thakur et al., 2009), most studies indicate that risk is associated with genotype (mainly S-allele carriers) and high trauma/stress (Kilpatrick et al., 2007; Grabe et al., 2009; Koenen et al., 2009; Xie et al., 2009, 2012; Kolassa et al., 2010b; Wang et al., 2011; Mercer et al., 2012). In contrast, several studies have reported no association (Mellman et al., 2009; Sayin et al., 2010). Complicating the issues of association studies with *5-HTTLPR* is that the polymorphism has been found to be tri-allelic ($L_A/L_C/S$) in that a third functional allele (L_C) has been identified (Nakamura et al., 2000); thus, earlier association studies may not reflect the full range of genetic variation (Kenna et al., 2012). Another variant in the serotonin system, the serotonin receptor 2A polymorphism (rs6311), has also been found to be associated with PTSD (Lee et al., 2007; Mellman et al., 2009).

Dopaminergic system candidate genes

Dysregulation of dopaminergic neurotransmission has also been implicated in the pathophysiology of PTSD (Yehuda et al., 1992; Hamner and Diamond, 1993). Dopamine is involved in attention and vigilance, arousal, and sleep, all systems that are dysregulated in PTSD. A polymorphism in the gene encoding the dopamine transporter (*SLC6A3* also known as DAT or DAT1) has a 40-base pair repeat located on chromosome 5p15 (Vandenberg et al., 1992). Since the seminal study of Segman et al. (2002), there have been several published reports replicating the association of the 9-repeat (9R) allele of *SLC6A3* with PTSD (e.g. Drury et al., 2009), and at least one reporting no association (Bailey et al., 2010). Recent publications reported carriers of the 9R allele had increased risk of PTSD when compared to those with the 10R allele (Valente et al., 2011b; Chang et al., 2012a). Furthermore, their preliminary report suggested an increased risk for PTSD might be mediated by high methylation of the *SLC6A3* promoter locus (CpG site cg13202751) in 9R allele carriers.

The association between the dopamine receptor D2 (*DRD2*) and PTSD has also been examined with inconsistent results. *DRD2* contains rs1800497 (also known as Taq1A), a single nucleotide polymorphism (SNP) with T (A1) and C (A2) alleles (Grandy et al., 1989).

In Caucasian war veterans, the *A1*-allele was associated with PTSD (Comings et al., 1996), and with PTSD and heavy alcohol consumption (Young et al., 2002), but this finding was not replicated (Gelernter et al., 1999). No association between PTSD diagnosis or symptom severity and the *A1*-allele of *DRD2* (or *SLC6A3*) was reported in a civilian Armenian sample after the Spitak earthquake (Bailey et al., 2010). However, a current study reported a gene-gene interaction between the *DRD2* Taq1A *1A*-allele and the valine (Val)-66 allele of *BDNF* (rs6265), but no direct association between either polymorphism and the severity of PTSD symptoms in a South African population (Hemmings et al., 2013).

Genetic variants in dopamine beta-hydroxylase (*DBH*) represent a likely candidate for examining genetic contributions to anxiety disorders because of the role this enzyme plays in converting dopamine to norepinephrine as part of catecholamine synthesis (Cubells and Zabetian, 2004). A polymorphism in *DBH* (-1021C/T; rs1611115) has been shown to account for 35–52% of the variation in plasma-*DBH* activity (Zabetian et al., 2001). However, Mustapic and colleagues reported no main effect of this polymorphism with PTSD, but they did find that war veterans with PTSD who carried the CC genotype of the *DBH*-1021C/T variant had lower plasma *DBH* activity (Mustapic et al., 2007). These findings were replicated in a civilian sample of African Americans (Tang et al., 2010).

Catechol-O-methyltransferase (*COMT*) is a critical enzyme involved in the breakdown of the catecholamine neurotransmitters including dopamine, norepinephrine and epinephrine. Thus, variation in the level of *COMT* activity is an important mediator in the regulation of these neurotransmitter systems, which are likely to play a role in the hyper-arousal symptoms of PTSD, including inattention, hyper-vigilance and sleep disruption. *COMT* contains a functional polymorphism at codon 158 (rs4680) that substitutes the amino acid Val for methionine (Met), and is associated with a significant reduction in enzyme activity (Lachman et al., 1996). The Met158 allele is also associated with a decreased ability to extinguish conditioned fear (Lonsdorf et al., 2009), a putative trait of PTSD. A significant association between one or more copies of the Met158 allele and PTSD has been reported (Valente et al., 2011a), in addition to a gene-environment interaction between the Met158 allele and the number of traumatic event types in predicting PTSD (Kolassa et al., 2010a). Moreover, a recent study examining the intermediate phenotype of fear inhibition in PTSD found that individuals with the Met/Met genotype demonstrated impaired fear inhibition, which may be mediated by higher methylation in the *COMT* promoter region (Norrholm et al., 2013). Thus, regulation of *COMT* and subsequent catecholamine neurotransmitter cascades may be an important factor in fear processing for those with PTSD and similar psychiatric disorders.

Hypothalamic-pituitary-adrenal axis candidate genes

PTSD is also characterized by dysregulation of the stress response system, such that activity of the hypothalamic-pituitary-adrenal (HPA) axis is altered and hyper-responsive to cortisol feedback (Yehuda et al., 1993; Yehuda, 2009). This stress dysregulation is thought to be associated with both physiological and psychological emotion dysregulation and stress hyper-responsiveness, which are common in PTSD. These HPA axis effects occur, in part, through enhanced sensitivity of the glucocorticoid receptor (GR)-mediated feedback mechanism that suppresses stress-induced cortisol release (van Zuiden et al., 2012). Two small studies reported associations between PTSD and cannabinoid receptor (*CNR1*) gene variants (NM_016083 and NM_033181; (Lu et al., 2008), and between a SNP in corticotropin-releasing hormone receptor-1 (*CRHR1*, rs12944712) and PTSD onset in paediatric injury patients (Amstadter et al., 2011). However, no significant associations were found between GR (*NR3C1*) polymorphisms (N363S and BclI) and PTSD diagnosis in a cohort of 118 Vietnam veterans (Bachmann et al., 2005).

The most promising candidate thus far is *FKBP5* (Binder et al., 2008; Xie et al., 2010; Mehta et al., 2011; Sarapas et al., 2011; Klengel et al., 2013), an important regulator of the stress system by altering GR sensitivity (Scammell et al., 2001). Binder and colleagues found that 4 SNPs in *FKBP5* (rs9296158, rs3800373, 1360780, rs9470080) interacted with child abuse severity to predict adult PTSD in a primarily African American civilian cohort (Binder et al., 2008). The initial interaction was partially replicated (rs9470080) in a population of African Americans with a history of childhood adversity (Xie et al., 2010). More recently, a polymorphism in *FKBP5* (rs1360780), that increases the risk of developing stress-related psychiatric disorders in adulthood, was found to be dependent on changes in DNA methylation occurring as a consequence of childhood trauma-dependent stress (Klengel et al., 2013).

Also regulating the stress response is the neuropeptide pituitary adenylate cyclase-activating polypeptide (*PACAP*), which functions in parts of the brain that mediate anxiety- and fear-related behaviours, and is directly involved in regulating corticotrophin releasing hormone (*CRH*) production (see review by Vaudry et al., 2009). Recently a genetic variant in the *PAC1* receptor (*ADCYAP1R1*; rs2267735) that disrupts a putative oestrogen response element has been found to be associated with PTSD in a primarily African-American cohort of women (Ressler et al., 2011). A follow-up study reported an interaction between genotype and total trauma load in a replicate sample of African-American females from the same population (Almli et al., 2013). Further, PTSD associates with alterations in peripheral blood DNA methylation and mRNA expression of the *ADCYAP1R1* transcript (Ressler et al., 2011). Although the association

with the *ADCYAP1R1* variant was not replicated among presumably less traumatized, African American and Caucasian populations (Chang et al., 2012b), an interaction between *ADCYAP1R1* genotype and childhood maltreatment may predict PTSD in females (Uddin et al., 2012).

The neurobiology of stress regulation, particularly with regard to the HPA axis and the regulation of CRH production and cortisol feedback, may underlie many of the symptoms of PTSD. Candidate gene studies targeting pathways within the HPA system have been productive, particularly with regards to the *FKBP5* pathway, which has been multiply replicated at the genetic, epigenetic, mRNA expression and protein levels of analysis.

BDNF candidate genes

Brain derived neurotrophic factor (BDNF) is involved in the neural plasticity underlying the extinction of fear (Chhatwal et al., 2006; Heldt et al., 2007; Soliman et al., 2010) and recovery from stress, both of which are disrupted in PTSD. Based on its role in hippocampal-dependent learning and the neurobiology of anxiety and depression, the *BDNF* gene has been studied in relation to anxiety disorders such as PTSD (see Andero and Ressler, 2012). A nonconservative amino acid substitution (Val66Met, rs6265) has been identified in the *BDNF* on chromosome 11p14.1 (Sen et al., 2003); however, most studies have found no association (Olf et al., 2005; Lee et al., 2006; Zhang et al., 2006; Valente et al., 2011b). As mentioned previously, a significant interaction between *DRD2* Taq1A (rs1800497) and Val66Met (rs6265) predicts PTSD severity (Hemmings et al., 2013). Interestingly, a recent study in humans and rats suggests that *BDNF* over-expression may be a critical stress response underlying PTSD by showing that the Val66Met allele confers vulnerability to PTSD via startle data and plasma BDNF levels (Zhang et al., 2013). Furthermore, *BDNF* polymorphisms may be associated with response to treatment (Felmingham et al., 2013), consistent with its known role in mechanisms of extinction of fear. Studies combining neuroimaging with genetics may shed more light on the association with BDNF and PTSD.

Additional candidate genes

Several other candidate genes have been studied in relation PTSD genetics, but with limited success. A recent review of the link between neuropeptide Y (NPY) and PTSD has been published (Sah and Geraciotti, 2012), and highlights research on this stress-resilience factor. *NPY* has been identified as a risk locus for anxiety and anxiety disorders (e.g. Kaabi et al., 2006), and it is thought that it has a direct role in decreasing fear states and enhancing fear extinction (Gutman et al., 2008). However, the one published genetic study did not find an association between a polymorphism in *NPY* (Leu7Pro; rs16139)

and PTSD in a population of Caucasian combat veterans (Lappalainen et al., 2002).

Monoamine oxidase B (MAO-B) catabolizes dopamine, tyramine, tryptamine and other monoamines that are involved in arousal, vigilance and attention, as outlined above (Oreland, 2004). The *MAOB* intron 13 polymorphism (a G/A substitution; rs1799836) has been studied in relation to PTSD because *MAOB* expression in platelets has been implicated in several psychopathologies and may represent a biomarker for vulnerability to psychiatric illness (Schalling et al., 1987; Oreland, 2004; Ruchkin et al., 2005). However, a study on a potential association between *MAOB* polymorphisms and PTSD has been inconclusive (Pivac et al., 2007).

The inhibitory neurotransmitter, γ -aminobutyric acid (GABA), has been implicated in animal studies of fear and anxiety (Delgado et al., 2006). Of many genes with differential expression levels depending on PTSD status (Segman et al., 2005), one GABA_A receptor gene has been studied in relation to PTSD. Three polymorphisms in the GABA_A receptor subunit alpha 2 (*GABRA2*) had significant interactions with childhood trauma to predict PTSD (Nelson et al., 2009).

Apolipoprotein E (ApoE), a 34 kDa protein that regulates the binding of lipoproteins to the low-density lipoprotein receptor, is most commonly known due to its role in cardiovascular and Alzheimer's diseases. As with many psychiatric disorders, however, ApoE may also play a role in neuronal and glial responding to stress dysregulation. The gene *APOE* is polymorphic with three major isoforms: *ApoE2* (cys130, cys176), *ApoE3* (cys130, arg176), and *ApoE4* (arg130, arg176) (Ghebranious et al., 2005). A significant association between the *ApoE2* allele and impaired memory and greater re-experiencing symptoms has been found in combat-exposed PTSD patients (Freeman et al., 2005).

Regulator of G-protein signalling 2 (*RGS2*) is part of a protein family that has been extensively implicated in neural plasticity associated with learning and memory, and thus may be critical for the dysregulated cognitive functioning associated with PTSD and in impaired recovery following trauma. Indeed, *RGS2* variants have been associated with anxiety (Leygraf et al., 2006; Smoller et al., 2008). An association with *RGS2* (rs4606) and PTSD was found under conditions of high stress and low social support (Amstadter et al., 2009b); further support of this association is found with neuroimaging (see below).

Overarching statements on the genetic underpinnings of PTSD through candidate gene studies are premature at this point, although several genes hold promise as potential biomarkers. Despite the increased number of studies on the genetics of PTSD over the years, there clearly have been limitations in study design and non-reproducibility of findings (Amstadter, 2012). Moreover, PTSD can be examined both categorically and continuously, and important confounding factors, such as sex,

race or trauma history are not consistently addressed in all studies making it difficult to draw conclusions. Interestingly, a method using a cumulative risk score showed that association with 4 or more risk alleles of candidate genes *FKBP5* (rs9470080), *COMT* (rs4680), and cholinergic receptor nicotinic alpha-5 (*CHRNA5*; rs16969968) conferred ~7 times the risk of PTSD (Boscarino et al., 2011). An additional study added *CRHR1* (rs110402) to the cumulative risk model and found both a main effect and interaction with level of trauma (Boscarino et al., 2012). Thus, it is clear across psychiatric disorders that these are not single gene disorders. Instead, they are complex, multi-genic disorders that will likely be best explained through multi-genic risk marker profiles of many identified gene pathways of small effect size (Psychiatric GWAS Consortium Coordinating Committee, 2009). The field still needs well-powered, hypothesis-neutral studies, such as large-scale, collaborative GWAS approaches, as described below, to identify more robust candidate genes and to identify the important neurobiological targets for research on understanding and treating PTSD. There is anticipation that as genetic markers are more clearly defined and replicated, we may eventually assign cumulative risk for PTSD based on biomarkers combined with trauma exposure, not unlike the medical determination of cardiovascular risk based on BMI, cholesterol, blood pressure, sedentary lifestyle and smoking history.

Genome-wide association studies

While candidate pathways that contribute to PTSD tend to be well supported in the literature, it is not trivial to select candidate genes or polymorphisms that can meet stringent definitions of association. Thus, a genome-wide association study (GWAS) can be employed to identify disease-associated variants independently of what is known about its pathophysiology.

The first GWAS of PTSD was recently published, and significant association with a variant in the retinoid-related orphan receptor alpha (*RORA*) was found (Logue et al., 2012). *RORA* is a particularly interesting candidate in light of its putative associations with attention-deficit hyperactivity disorder (Neale et al., 2008), bipolar disorder (Le-Niculescu et al., 2009), autism (Nguyen et al., 2010) and, most notably, depression (Garriock et al., 2010). In relation to PTSD, Logue and colleagues suggest that alterations in *RORA* levels, because of inherited genetic variation, may reduce the capacity of neurons to respond to the biochemical stressors (oxidative stress, steroid hormone elevations and inflammation) induced by traumatic stress (Logue et al., 2012). In a discovery sample of Caucasian US military veterans and their partners (295 cases and 196 controls), the authors found one SNP in *RORA* (rs8042149) that remained significant after correction for multiple testing and had an odds ratio over 2.0. Examination of this

SNP in African Americans from the same cohort (43 cases and 41 controls) did not replicate the association with rs8042149; however, other SNPs within *RORA* were nominally associated ($p < 0.05$) with PTSD. The association was not replicated with data from the Detroit Neighbourhood Health Study (100 cases and 421 controls; African Americans), but other nominally significant SNPs in *RORA* were found. Of note is that the original association between the *RORA* SNP rs8042129 and PTSD in a cohort of Florida hurricane survivors was recently published (Amstadter et al., 2013). These studies, including initial GWAS 'hit' and replication in external cohorts, are a promising first step in determining genetic risk for PTSD. GWAS studies of over 50000 subjects (including cases and traumatized controls) are ongoing in civilians and veterans cohorts, and a PTSD subgroup is actively being planned within the Psychiatric GWAS Consortium (<https://pgc.unc.edu/>).

Epigenetics

Epigenetic studies may also provide insight into the molecular mechanisms that associate with PTSD or potential targets for therapies. Much like sequence variants can influence the expression of a gene, epigenetic patterns dictate the timing and magnitude of gene expression by restricting areas of the genome available for transcription (Bonasio et al., 2010). However, some parts of the epigenome change in response to the environment and are potentially reversible (Feinberg, 2007; Feil and Fraga, 2011).

The field of epigenetics encompasses the study of covalent and non-covalent modifications of DNA, its associated proteins and RNA transcripts that regulate gene expression. To protect and organize DNA in the nucleus of a cell, it is wrapped around packaging proteins (histones), which can be modified to influence transcription, chromatin conformation and cofactor recruitment (Annunziato, 2008; Bannister and Kouzarides, 2011). Histone modifications often correlate with changes in methylation of DNA at the 5' carbon of cytosine in the context of a cytosine phosphodiester guanine (CpG) dinucleotide, commonly called a CpG site. DNA methylation patterns vary throughout a gene based on the genetic architecture of a region. Increased methylation of a promoter region often correlates with decreased expression of that gene (Bonasio et al., 2010) while intragenic or intronic methylation may regulate alternative promoters and enhancers that define alternative transcripts (Maunakea et al., 2010). DNA methylation is the most common epigenetic modification examined in studies of PTSD.

It is thought that the sensitization of the stress-response pathways is mediated by long-term epigenetic alterations of both histones and DNA. Animal studies that focus on epigenetic changes accompanying fear conditioning and extinction provide insight into PTSD, and this topic

has been recently reviewed (Zovkic and Sweatt, 2013). In humans, epigenetic mechanisms of stress-sensitization and PTSD have been studied in highly traumatized populations (e.g. Koenen et al., 2011). Studies have identified DNA methylation differences in multiple genes across the genome related to immune function and inflammation of those with PTSD compared to controls (Uddin et al., 2010; Smith et al., 2011). For example, Roth and colleagues reported that early maltreatment of rat pups produced increased methylation of *BDNF* that resulted in persistent decreases in gene expression in the adult prefrontal cortex (Roth et al., 2009) while Smith and colleagues reported increased methylation of a CpG site in *BDNF* and peripheral blood of adults with PTSD (Smith et al., 2011). Consistent with this, PTSD cases and controls can also be delineated by measuring genomic DNA methylation globally (Smith et al., 2011; Rusiecki et al., 2012). Together, these results suggest that psychosocial stress may alter global and gene-specific DNA methylation patterns potentially associated with peripheral immune dysregulation. Though it is not clear to what degree methylation changes in the blood correlate with those in the brain, a recent study suggests consistency of many genes (Davies et al., 2012).

Interestingly, stress experienced during prenatal development may also contribute to PTSD risk. Indeed maternal and neonatal cortisol levels correlate at delivery (Smith et al., 2011), but clinical investigations suggest that high levels of stress during pregnancy induce epigenetic changes in HPA axis genes that may contribute to psychopathology in offspring (Oberlander et al., 2008; McGowan et al., 2009). Along these lines, studies following the offspring of women who suffered traumatic events during pregnancy, such as the Dutch Hunger Winter or the September 11, 2001 attack on the World Trade Centre, report physiological and gene expression differences in the offspring (Yehuda et al., 2005, 2009; Roseboom et al., 2006; Stein et al., 2009) that may be mediated by epigenetic changes in the offspring (Heijmans et al., 2008).

A recent study revealed that maltreatment during childhood correlated with differences in DNA methylation and gene expression when PTSD subjects who were abused as children were compared to PTSD subjects with no history of abuse (Mehta et al., 2013). Similar differences in DNA methylation and gene expression were also observed based on age, gender, ethnicity, early-life socioeconomic status and psychosocial stress (Lam et al., 2012). These studies suggest that the epigenome responds to the environment and that there may be distinct and highly individualized biological pathways that promote PTSD. Given this phenotypic heterogeneity, genetic studies of intermediate phenotypes (i.e. neuroimaging), may be the most direct path to identifying genes that contributed to PTSD.

Neuroimaging genetics

In general, individuals with PTSD have been shown to exhibit specific patterns of information processing, including attentional biases for trauma-relevant cues (Bryant and Harvey, 1997; Dalgleish et al., 2003; Fani et al., 2012; Wald et al., 2013), and impairments in sustained attention, declarative and working memory as compared to individuals without PTSD (Bremner et al., 1993, 2004; Uddo et al., 1993; Yehuda et al., 1995; Vasterling et al., 1998, 2002; Gilbertson et al., 2001; Stein et al., 2002a; Koso and Hansen, 2006; Samuelson et al., 2006; Schweizer and Dalgleish, 2011; Dretsch et al., 2012). These phenomena may be relevant to particular patterns of neural response and structure that are characteristic of individuals with PTSD, including smaller hippocampal volumes (Bremner et al., 1995; Kitayama et al., 2005; Karl et al., 2006) and exaggerated amygdala response (Rauch et al., 2000; Armony et al., 2005; Shin et al., 2005; Bryant et al., 2008a,b). Together, these traits can be considered intermediate/endophenotypes. By characterizing gene-specific neurobiological traits associated with PTSD (Radant et al., 2001), neuroimaging genetics research may help identify intermediate phenotypes of PTSD that clarify the functional link between genes and disease phenotype (Glahn et al., 2007). An earlier review discusses structural MRI findings as related to PTSD (Damsa et al., 2009); however, we have summarized recent studies of neuroimaging data on candidate genes for PTSD and related phenotypes (see also recent reviews: Martin et al., 2009; Domschke and Dannlowski, 2010), which underscore the utility of the methodology for understanding potential mechanisms and therapy for psychiatric disorders such as PTSD (Table 1).

The growing neuroimaging literature relevant to intermediate phenotypes for PTSD has examined associations between allelic variations in *5-HTTLPR*, *BDNF*, *FKBP5*, *COMT*, and *NPY* genes, and brain structure and function in healthy populations and individuals with affective disorders. As noted earlier, these genes appear to play a role in PTSD pathogenesis, exerting effects on specific brain structures and their corresponding functions. Regarding function, a majority of fMRI studies relevant to PTSD intermediate phenotypes have employed paradigms that include emotionally salient stimuli, typically, photographs of facial expressions, to examine gene-specific responses to these stimuli in basic emotion processing circuits. Studies of brain structure have primarily focused on regions that have previously demonstrated dysfunction in PTSD populations: the hippocampus and amygdala; these regions have been implicated in the expression and extinction of learned fear, as well as explicit learning and declarative memory processes.

Studies of the serotonin transporter gene, *5-HTTLPR*, currently dominate this literature. Many of these studies have focused on SNP rs25531, largely indicating

heightened amygdala activation in S-allele carriers in response to cues that signal threat (Morey et al., 2011; Alexander et al., 2012; Drabant et al., 2012). Indeed, one study found this pattern of activation to be particularly apparent in males with SS genotype who reported higher exposure to potentially traumatic experiences (Alexander et al., 2012). Some structural studies have likewise indicated that the S-allele may represent 'risk' for lower hippocampal volume (Eker et al., 2011), particularly in combination with childhood abuse history (Frodl et al., 2010; Everaerd et al., 2012); however, this finding has not been uniform across all studies (Cole et al., 2011).

A number of neuroimaging studies have examined how allelic variants of *FKBP5*, *COMT* and *NPY* associate differentially with behavioral and neural responses to threat-relevant facial expressions; prior studies of PTSD have shown exaggerated limbic responses to these cues (Rauch et al., 2000; Armony et al., 2005; Shin et al., 2005; Bryant et al., 2008a,b). Two ROI-based studies indicate that heightened activation in the amygdala (White et al., 2012) and hippocampus (Fani et al., 2013) to threat cues in carriers of risk alleles for various *FKBP5* polymorphisms identified in previous studies (Binder et al., 2008). White et al. (2012) found these effects to be attributable to a gene by environment interaction; Fani et al. (2013) did not observe interactive effects, but found that, compared to individuals without the risk allele, *FKBP5* risk allele carriers (for SNP rs1360780) demonstrated an attentional bias toward threat cues and corresponding increases in hippocampal activation. Heightened amygdala responses to threat cues (angry and fearful faces) have also been observed in risk allele carriers for *COMT* (specifically, Val-allele carriers for SNP rs4680) (Domschke et al., 2012) and *NPY* (Domschke et al., 2010b).

Smaller hippocampal volumes represent putative structural endophenotypes for PTSD, as observed in MRI studies of *5-HTTLPR*, *BDNF*, and *FKBP5* (Gatt et al., 2009; Frodl et al., 2010; Eker et al., 2011; Everaerd et al., 2012; Carballedo et al., 2013; Fani et al., 2013), with some of these findings reflecting gene by environment (e.g. childhood maltreatment) interactions (Gatt et al., 2009; Everaerd et al., 2012; Carballedo et al., 2013). These structural differences between genotype groups are likely to have functional consequences, particularly with regard to learning and memory. In support of this, Gatt et al. (2009) found that Met-allele carriers for *BDNF* (rs2625) who were exposed to early life stress demonstrated poorer working memory in accordance with smaller hippocampal, as well as lateral prefrontal, volumes (Gatt et al., 2009).

The findings of these genetic neuroimaging studies have not been entirely consistent; this signals a need for replication in large samples, and likewise, examination of specific genetic effects among different demographic groups. For example, two statistically

well-powered studies did not observe associations between hippocampal volume and allelic variations in *5-HTTLPR* and *BDNF* among populations of healthy, depressed and anxious individuals (Cole et al., 2011; Mueller et al., 2013). Within studies of candidate genes, inconsistencies have also emerged between genotypes and patterns of neural structure and response, thus complicating the identification of a pure 'risk' genotype. In addition, it is likely that more than one gene influences the patterns of neural function and structure observed in these studies; thus, genome-wide and multiple candidate gene approaches may more precisely specify genetic associations with these phenomena. Causal inferences similarly cannot be made about findings in anxious/depressed populations; these cross-sectional studies cannot definitively extricate gene-related effects from disease sequelae. Further, a majority of extant studies have conducted statistical tests on specific regions of interest, particularly the hippocampus and amygdala; other prefrontal cortical regions, including aspects of the anterior cingulate, dorsolateral prefrontal cortex, are worthy targets for further exploration in neuroendophenotypic studies of PTSD. Complementary cognitive and behavioral data will also help shed light on the processes that are affected by functional and structural differences.

Conclusions

As with many psychiatric disorders, the risk for PTSD following trauma has moderate genetic heritability. Identifying and understanding the gene pathways leading to differential risk for PTSD will enhance our ability to dissect the different components of PTSD development and recovery. Furthermore, combining neuroimaging with genetics provides a novel approach to understanding how dysregulated gene pathways affect neural systems involved in stress and fear processing that are thought to underlie PTSD pathophysiology. New developments in large-scale genome-wide associate studies, whole genome sequencing, copy number variants, epigenetic and gene expression analyses will soon allow for convergent genomic approaches to further define, in a hypothesis-neutral manner, gene pathways critically involved in PTSD. Until then, the genetics of PTSD have relied mainly on candidate studies, which have met with some success, specific examples of which have been reviewed herein. PTSD provides a fascinating case in biological psychiatry, in which the neural circuits are moderately well understood, robust animal models are present and the fields of molecular learning and memory are complementary. Through classic and convergent genomic approaches, a mechanistic understanding of risk and resilience in PTSD is achievable, and with that, insight into targeted treatment and prevention approaches should follow.

Table 1. Select publications on neuroimaging genetics with post-traumatic stress disorder (PTSD) patients or intermediate/endophenotypes of PTSD and candidate genes

Reference	Subjects/ phenotype	Task	Method	Region(s) of interest	Gene	Findings
Alexander et al., 2012	Male controls (48)	Fearful face <i>vs.</i> fixation	fMRI		5-HTTLPR (rs25531)	– G×E: Amygdala activation and amygdala/hypothalamus connectivity: SS males with a history of stressful life events>other genotype and environment groups
Drabant et al., 2012	Female controls (48)	Stress exposure task/ threat of electric shock	fMRI		5-HTTLPR (rs75531)	– Activation to ‘safe’ trials <i>vs.</i> shock anticipation: widespread increase in activation throughout brain, SS>LS>LL – SS genotype: positive correlation between mPFC activation and anxiety – L-allele carriers: negative correlation between insula activation and perceived success at regulating anxiety
Morey et al., 2011	PTSD (22); trauma controls (20)	Working memory	fMRI	vIPFC, amygdala, fusiform gyrus, dlPFC, LPC	5-HTTLPR (rs16965628, rs25531)	– rs16965628: Diagnosis×gene interaction for vIPFC activation during exposure to trauma-relevant distractors; GG genotype: PTSD>TC – rs25531: L amygdala activation, S allele carriers: PTSD>TC
Cole et al., 2011	Depression (84) Controls (111)		MRI	Hippocampus	5-HTTLPR (rs25531)	– No gene or gene×diagnosis effects for shape or volume
Eker et al., 2011	Depression (44) Controls (43)		MRI	Hippocampus	5-HTTLPR (rs25531)	– Diagnosis×gene interaction for hippocampal volume; SS genotype: Depressed<controls
Everaerd et al., 2012	Controls (136 male, 221 female)		MRI	Hippocampus	5-HTTLPR (rs25531)	– G×E: within males, S-allele carriers: higher CA associated with lower volume – Gene main effects: females, hippocampal volume: S-allele carriers<L-allele carriers
Frodl et al., 2010	Depression (24) Controls (27)		MRI	Hippocampus+ whole brain	5-HTTLPR (rs25531)	– S-allele carriers: emotional neglect history associated with lower hippocampal volume – LL genotype: emotional neglect associated with larger dlPFC volume
Gatt et al., 2009	Controls (89)	Cognitive battery (administered outside of scanner)	MRI		BDNF (Val66Met)	– G×E: Met carriers with ELS: smaller hippocampus, amygdala, lateral PFC volumes, poorer working memory – Val/Val with ELS: greater amygdala volume associated with greater mPFC volume and higher anxiety

Carballedo et al., 2013	Depression (62) Controls (71)		MRI	Hippocampus	<i>BDNF</i> (Val66Met)	– G×E for hippocampal volume: Met carriers with ELS<Met carriers without ELS – Met carriers without ELS>Val/Val without ELS – No gene or gene×diagnosis effects for volume or shape
Cole et al., 2011	Depression (84) Controls (111)		MRI	Hippocampus	<i>BDNF</i> (Val66Met)	– No gene or gene×diagnosis effects for volume or shape
Mueller et al., 2013	Adolescents: anxiety disorder (39), Controls (63)		MRI	Hippocampus, amygdala, insula, ACC	<i>BDNF</i> (Val66Met)	– Diagnosis×gene interactions; R insula: anxious Met carriers<anxious Val/Val; ACC: anxious Val/Val<healthy Val/Val
White et al., 2012	Adolescent controls (139)	Face matching task (angry and fearful faces vs. shapes)	fMRI	Amygdala	<i>FKBP5</i> (multiple snps)	– G×E: greater amygdala activation in risk alleles carriers with history of emotional neglect (snps: rs9394309, rs7748266, rs1360780, rs9296158, rs3800373 rs9470080)
Fani et al., 2013	PTSD (15), controls (21), all female	Attention bias task (dot probe)	fMRI, MRI	Hippocampus	<i>FKBP5</i> (rs1360780)	–T (risk) allele carriers vs. CC genotype: greater attention bias towards threat, corresponding increases in hippocampal activation and differences in hippocampal morphology
Domschke et al., 2008	Panic disorder (12 female, 8 male)	Passive viewing of emotional facial expressions	fMRI	Amygdala, vmPFC, OFC, dlPFC, ACC	<i>COMT</i> (rs4680)	– Fearful vs. no faces: amygdala, L OFC, activation: Val-allele carriers> Met-allele carriers – Angry vs. no faces: vmPFC: AG/GG (risk genotypes)>AA – Happy vs. no faces: vmPFC: AG/GG (risk genotypes)>AA
Domschke et al., 2012	Controls (34 male, 51 female)	Face matching task (angry and fearful faces vs. shapes)	fMRI	Amygdala	<i>COMT</i> (rs4680)	– L amygdala activation in females: Val/val genotype>Met-allele carriers
Domschke et al., 2010a	Depression (35)	Passive viewing of emotional facial expressions	fMRI	Amygdala	<i>NPY</i> (rs16147)	– Angry vs. neutral faces, amygdala activation: C-allele carriers>TT genotype
Zhou et al., 2008	Controls (71)	Face matching task (angry and fearful faces vs. shapes)	fMRI	Amygdala, hippocampus	<i>NPY</i> (rs5574 haplotypes)	– Amygdala and hippocampus activation: low-NPY-expression (LL) diplotype>high-expression (HH) diplotype

Abbreviations: ACC, anterior cingulate cortex; BDNF, brain-derived neurotrophic factor; CA, childhood abuse; COMT, catechol-O-methyltransferase; dlPFC, dorsolateral prefrontal cortex; ELS, early life stress; FKBP5, FK506 binding protein 5; fMRI, functional magnetic resonance imaging; G×E, gene by environment interaction; LPC, lateral parietal cortex; L, left; MRI, magnetic resonance imaging; mPFC, medial prefrontal cortex; NPY, neuropeptide Y; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PTSD, post-traumatic stress disorder; R, right; 5-HTTLPR, serotonin-transporter-linked polymorphic region; TC, trauma controls; vlPFC, ventrolateral prefrontal cortex.

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