Invited review

Twin studies of posttraumatic stress disorder: Differentiating vulnerability factors from sequelae

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ABSTRACT

Posttraumatic stress disorder (PTSD) is defined by one's response to an environmental event. However, genetic factors are important in determining people's response to that event, and even their likelihood of being exposed to particular traumatic events in the first place. Classical twin designs can decompose genetic and environmental sources of variance. Such studies are reviewed extensively elsewhere, and we cover them only briefly in this review. Instead, we focus primarily on the identical co-twin control design. This design makes it possible to resolve the "chicken–egg" dilemma inherent in standard case-control designs, namely, distinguishing risk from sequelae. Abnormalities that are present in both the twin with PTSD and the unaffected co-twin suggest pre-existing vulnerability indicators. These include smaller hippocampal volume, large cavum septum pellucidum, more neurological soft signs, lower general intellectual ability, and poorer performance in the specific cognitive abilities of executive function, attention, declarative memory, and processing of contextual cues. In contrast, abnormalities in a twin with PTSD that are not present in the identical co-twin suggest consequences of PTSD or trauma exposure. These include psychophysiological responding, higher resting anterior cingulate metabolism, event-related potential abnormalities associated with attentional processes, recall intrusions, and possibly some types of chronic pain. Most co-twin control studies of PTSD have been small and come from the same twin registry of middle-aged male veterans. Consequently, there is a great need for replication and extension of the findings, particularly in women and younger individuals. The creation of new twin registries would do much toward accomplishing this goal.

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1. Introduction

An estimated 50–90% of individuals in the United States experience at least one traumatic event during their lifetime; however only a minority of trauma-exposed individuals develops posttraumatic stress disorder (PTSD) (Kessler et al., 1995; Roberts et al., 2011, in press). PTSD constitutes a response to trauma exposure that involves intense fear, helplessness or horror plus symptoms of persistent reexperiencing of the traumatic event, persistent avoidance of trauma-associated stimuli and numbing of responsiveness, and persistent increased arousal (American Psychiatric Association, 2000). Conditional risk of PTSD is highly variable by type of exposure, ranging from 80% among former prisoners of war (Engdahl et al., 1997) to about 50% among rape survivors and 8% among individuals exposed to natural disasters (Kessler et al., 1995). Despite gains in the psychosocial literature to identify variables related to vulnerability in the aftermath of exposure to a traumatic event (Brewin et al., 2000; Ozer et al., 2003), a large amount of variance remains unexplained. In this article, we review the literature on twin studies of PTSD with a particular focus on how twin designs can be used to distinguish between vulnerability factors for and consequences of the disorder. A recent, extensive review of twin studies of PTSD by Afifi et al. (2010) focused primarily on the classical twin design. Here we focus on studies that were not available at the time of that review, and primarily on the co-twin control design,

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which has led to valuable contributions to our understanding of vulnerability factors for the development of PTSD.

2. Twin designs

2.1. Classical twin design

Traditionally, the twin design was used to calculate the heritability of a phenotype, i.e., the proportion of the population variance explained by genetic factors. When heritability estimates are reported, they refer to the results of studies using the classical twin design. Basically, the twin method compares similarity between identical or monozygotic (MZ) pairs relative to similarity between fraternal or dizygotic (DZ) pairs. MZ twins share 100% of their genes as well as 100% of the common environment, which may include, but is not limited to, aspects of the family environment in which they were raised. DZ twins share roughly 50% of their genes and 100% of their common environment. If MZ twins are significantly more similar on a characteristic than DZ twins, then this *phenotype* (observed characteristic) is genetically influenced. The *heritability* estimate is estimated by the formula $2(rMZ - rDZ)$, where $r =$ the intraclass twin correlation (Plomin et al., 2001). For categorical phenotypes, such as PTSD, the tetrachoric correlation is used to calculate heritability. More precise estimates are obtained with maximum-likelihood-based structural equation modeling (Neale et al., 2004). Classical twin studies have made at least three important contributions to our understanding of the genetic etiology of PTSD: heritability estimates for exposure to traumatic events; heritability estimates for PTSD; and elucidating genetic and environmental factors underlying the comorbidity of PTSD and other conditions.

2.2. Co-twin control design

As with other disorders, examining abnormalities associated with PTSD presents a "chicken–egg" problem. How do we determine whether abnormalities were consequences of the disorder or were pre-existing? Something can only be a vulnerability factors if it has been shown to precede the disorder onset. In much PTSD research, traditional case-control designs are used to assess whether a given biological marker is more prevalent in individuals who already have PTSD compared to trauma-exposed controls who did not develop PTSD. Such studies show whether a biological factor is a correlate of PTSD. However, traditional case-control designs cannot determine whether the biological factor is a part of the disease process, also referred to as a 'PTSD sign,' or a risk factor for the disorder. This limitation is present even in prospective studies that test whether biological factors assessed in the acute aftermath of trauma exposure predict the development of PTSD. Biological factors assessed in the acute aftermath of trauma exposure that predict the development of PTSD may be early indicators of the emerging disorder rather than true risk factors.

The kinds of studies just noted are incapable of differentiating chicken and egg. They cannot fully resolve the question of whether an observed sign is a risk factor or a consequence of the disorder. In many ways, the ideal study would be to follow a large group of people prospectively, with assessments covering the periods before and after exposure to trauma. But not knowing if or when traumatic events will occur is, of course, a major practical limitation. The co-twin control design is, however, particularly well-suited to address this question.

The discordant MZ twin research design offers a strategy to determine whether a biological correlate of PTSD is a risk factor for the disorder or a sign of PTSD and related posttrauma sequela. The MZ-discordant design is similar to that used in other case-controls studies when individuals with and without PTSD are compared *across* twin pairs on a specific biological correlate to determine whether that marker is associated with the PTSD diagnosis. However, by allowing comparisons *within* MZ twin pairs discordant for trauma exposure, the MZ-discordant design offers the opportunity to examine whether the biological marker is a risk factor for PTSD or develops along with PTSD (i.e., a PTSD sign). These inferences are possible because MZ twin pairs share 100% of their genes and their family environment in youth and, therefore, are matched on a number of factors that would be impossible to control for in a non-twin sample. The design includes four participant groups: (1) trauma-exposed index twins who developed PTSD; (2) their "high-risk" trauma-unexposed co-twins who did not have PTSD. They are considered high-risk because their genetically identical twin developed PTSD when exposed to trauma; (3) trauma-exposed index twins with no PTSD; and (4) their trauma-unexposed co-twins who did not have PTSD. They are considered low-risk because their genetically identical twin did not develop PTSD when exposed to trauma.

The logic behind the MZ-discordant design is that if a biological marker associated with PTSD is an underlying familial risk or vulnerability factor for the disorder then it should meet the following criteria. First, it should be associated with PTSD across twin pairs. That is, it should be more prevalent in MZ twins with PTSD than in trauma-exposed MZ twins who did not develop PTSD. Second, it should be similarly prevalent in both MZ twins with PTSD and their high-risk co-twins. In essence, the high-risk co-twin is serving as a proxy for what his/her co-twin would have been like if she/he had never been exposed to trauma and developed PTSD. If the biological marker is equally prevalent in the high-risk co-twins and the MZ twins with PTSD then this suggests the marker existed prior to the development of PTSD. Third, the biological marker should be more prevalent in the high-risk co-twins than in the MZ control twins exposed to trauma who did not develop PTSD or their low-risk co-twins.

3. Findings from classical twin studies

3.1. Heritability of traumatic events

An important contribution of classical twin studies has been the recognition of genetic influences on environmental exposures. Organisms are not merely passive recipients of environmental experiences; rather, organisms often play an active role in selecting the environments to which they are exposed. This phenomenon has been referred to as gene–environment covariance, gene–environment correlation or genetic control of exposure to the environment (Kendler and Eaves, 1986). Selection of one's environment, and the subsequent potential for exposure to trauma, is partly determined by genetic factors (Kendler and Baker, 2007). For example, twin studies have demonstrated that genetic factors influence exposure to combat and violence. Lyons et al. (1993) studied members of the Vietnam Era Twin (VET) Registry and investigated variables indicative of combat-related trauma (e.g., volunteering for service in Southeast Asia, service in Southeast Asia, combat exposure, being awarded a combat medal). Heritability estimates ranged from 0.35 for Southeast Asia service to 0.54 for being awarded a combat medal. The common environment was not a significant influence on any of these combat-related variables. In a study of a sample of volunteer twins, Jang et al. (2001) reported a significant heritability for assaultive traumatic events and no significant heritability for non-assaultive traumatic events. The influence of the environment shared by twins was significant for non-assaultive traumatic events, but not for assaultive traumatic events. In another study using a sample that overlapped with that of Jang et al. (2001), Stein et al. (2002) reported that the best fitting model for

assaultive trauma indicated that genetic factors explained 20% of the variance, while the shared and non-shared environments explained 21% and 58% of the variance, respectively. The best fitting model for non-assaultive trauma did not include genetic effects; the shared environment explained 39% of the variance and the unique environment explained 61% of the variance. In a large sample of Dutch twins, Middeldorp et al. (2005) found evidence for familial influences on a wide range of stressful life events. However, for potentially traumatic events such as robbery, assault and traffic accidents they were unable to distinguish between genetic and common environmental influences.

In general, this relatively small number of studies supports the importance of considering the role that genetic factors play in influencing the probability that an individual will be exposed to traumatic experiences. The evidence is strongest for the role of genetic factors in exposure to assaultive trauma, particularly if one considers combat exposure to be "assaultive trauma." More work needs to be done to fully elucidate this phenomenon as combat-related trauma is almost certainly an admixture of assaultive and non-assaultive trauma. For example, one's most traumatic combat-related experience may be seeing others being killed or injured. Nevertheless, these studies indicate that influencing the individual's selection of his or her environment is one mechanism by which genetic factors influence the risk of experiencing a traumatic event, which in turn, influences the risk of developing PTSD.

3.2. Heritability of PTSD

Classical twin studies suggest that genetic influences explain a substantial proportion of vulnerability to PTSD even after accounting for genetic influences on trauma exposure. An early examination of the VET Registry twins reported that 30% of the variance in PTSD was accounted for by genetic factors, even after controlling for combat exposure (True et al., 1993). Similarly, a twin study of male and female civilian volunteers identified similar heritability of PTSD, with further variance accounted for by non-shared environmental factors (Stein et al., 2002). Taken together with family research designs using disaster-exposed samples (e.g., Goenjian et al., 2008), which are less vulnerable to the self-selection bias that may exist in samples exposed to military or assaultive violence, these findings suggest that genetic factors play an important role in vulnerability to developing PTSD.

3.3. Genetic influences on comorbidity with other psychiatric disorders

The classical twin design can be extended to examine the genetic and environmental architecture of the covariation of two or more phenotypes. For example, a recent reanalysis of data from the VET Registry suggests that, in fact, genetic influences on PTSD overlap with those for both the externalizing and internalizing disorders (Wolf et al., 2010). Bivariate and multivariate twin studies have shown that genetic influences on PTSD largely overlap with those for other mental disorders. Specifically, genetic factors that influence the risk of major depression account for the majority of the genetic variance in PTSD (Fu et al., 2007; Koenen et al., 2008). Genetic influences common to generalized anxiety disorder and panic disorder symptoms account for approximately 60% of the genetic variance in PTSD (Chantarujikapong et al., 2001) and those common to alcohol and drug dependence (Xian et al., 2000) and nicotine dependence (Koenen et al., 2005) account for over 40% of the variance associated with PTSD.

3.4. General cognitive ability and risk of PTSD

An inverse association between cognitive ability and PTSD has been well-documented in civilian (Breslau et al., 2006; Koenen et al., 2007) and military samples (Kremen et al., 2007; Macklin et al., 1998; Pitman et al., 1991). Although impaired cognitive ability has been proposed as a consequence of trauma and PTSD (De Bellis et al., 1999), work from our group using data from the VET Registry suggests lower general cognitive ability is present prior to trauma exposure (Kremen et al., 2007). These results are described in greater detail in the sections on co-twin control studies. Here we note, however, that we also performed classical bivariate twin analyses which suggest that the association between cognitive ability and PTSD is largely explained by common genetic influences (Kremen et al., 2007).

4. Findings from co-twin control studies

These studies indicate that several abnormalities that were originally assumed to be the sequelae of PTSD actually appear to be pre-existing risk or protective factors. Findings from these co-twin control studies are summarized in Table 1.

4.1. Support for pre-existing risk or protective factors

4.1.1. Abnormally large cavum septum pellucidum (CSP)
The CSP exists when the medial walls of the lateral ventricles in the brain fail to fuse, leaving a small cavity. The CSP is present at birth but is usually absent by 3–6 months of age. The prevalence of an abnormally large CSP is thought to be approximately 20% in adults and associated with abnormal limbic system development (Sarwar, 1989). In the MZ twin discordant design, an abnormally large CSP was found more often in those with PTSD and their high-risk non-combat-exposed co-twins than in combat-exposed veterans without PTSD and their low-risk co-twins (May et al., 2004). These results suggest an abnormal CSP serves as a risk factor for chronic PTSD.

4.1.2. Smaller hippocampal volume
Smaller hippocampal volume has been correlated with PTSD in several non-twin case-control studies (Bremner et al., 1995; De Bellis et al., 2001; Gurvits et al., 1996; Hedges et al., 2003; Villarreal et al., 2002). Two recent meta-analyses confirm the association between PTSD diagnosis and smaller hippocampal volume (Kitayama et al., 2005; Smith, 2005). The association between PTSD diagnosis and smaller hippocampal volume has been attributed to the adverse effects of stress hormones on the brain (Sapolsky, 2000), as animal models show hippocampal damage in response to extreme stress (Sapolsky, 1996; Sapolsky et al., 1990). However, an important study of hippocampal volume and PTSD using the MZ-discordant design found smaller hippocampal volume not only in combat veterans with chronic PTSD, but also in their non-combat-exposed co-twins as compared to combat veterans who did not develop the disorder (Gilbertson et al., 2002). These results suggest that small hippocampal volume is a risk factor for chronic PTSD (Gilbertson et al., 2002). In a non-twin study by Woodward et al. (2006), there was evidence suggesting that the association between PTSD and smaller hippocampal volume is present when there is comorbid alcohol dependence. This issue warrants further examination as many participants in the Gilbertson et al. study had histories of alcohol dependence. On the other hand, it is worth noting that the effect size—based on Cohen's d (1988)—for participants without alcohol dependence in the study of Woodward et al. was $d = 0.34$. This was similar to the effect found by Gilbertson et al., but it did not reach

Table 1
Co-twin control studies of factors associated with PTSD.

Study	Associated phenotype	Type of trauma
Pre-existing risk/protective factors for PTSD		
May et al. (2004)	Enlarged cavum septum pellucidum	Combat exposure
Gilbertson et al. (2002)	Reduced hippocampal volume[a]	Combat exposure
Gurvits et al. (2006)	More neurological soft signs	Combat exposure
Kremen et al. (2007)	General cognitive ability (g)	Mixed (combat exposure and other traumatic events)
Gilbertson et al. (2006)	Attention, verbal declarative memory, executive function	Combat exposure
Gilbertson et al. (2007)	Configural processing of contextual cues	Combat exposure
Sequelae of PTSD		
Gilbertson et al. (2006)	Recall intrusions[b]	Combat exposure
Kasai et al. (2008)	Reduced rostral anterior cingulate gray matter density (voxel-based morphometry)	Combat exposure
Milad et al. (2008)	Poorer extinction of conditioned fear	Combat exposure
Orr et al. (2003)	Increased heart rate response to sudden, loud tones	Combat exposure
Metzger et al. (2008)	Increased auditory P2 amplitude intensity slope	Combat exposure
Metzger et al. (2009)	Reduced auditory P3b amplitude	Combat exposure
Boscarino et al. (2010)	Rheumatoid arthritis[c]	Mixed
Wright et al. (2010)	Interstitial cystitis (urological pain)[c]	Mixed

[a] Some evidence suggests that hippocampal reductions may partially be a function of comorbid alcohol dependence.
[b] These appear to be due to trauma exposure itself, independent of PTSD.
[c] Results are consistent with these being sequelae of PTSD, but the study design does not allow for that direct conclusion.

statistical significance in the Woodward et al. study. Thus, smaller hippocampal volume may still be a risk factor, but one that is enhanced by comorbid alcohol dependence. The persistence of PTSD symptoms may also be a factor because studies that found smaller hippocampi in individuals with PTSD appear to have been those that included more chronic cases (Gilbertson et al., 2007).

4.1.3. Neurological soft signs

Neurological soft signs are assessed by neurological exam and represent subtle indices of neurological function that cannot be linked to a specific brain region. Neurological soft signs have been correlated with PTSD in several studies (Gurvits et al., 1997, 1993). Greater neurological soft signs are thought to represent "subtle cortical dysfunction" that confers vulnerability to developing chronic PTSD possibly via "failure of inhibitory control over conditioned emotional responses (p. 249)" (Pitman et al., 2006). In an MZ-discordant design, combat-exposed twins with PTSD had more neurological soft signs than those without PTSD. Moreover, the high-risk co-twins of the combat veterans with PTSD had more neurological soft signs than the low-risk co-twins of the combat veterans who did not develop PTSD, suggesting that neurological soft signs are a risk factor for PTSD (Gurvits et al., 2006).

4.1.4. Neurocognitive performance deficits

As discussed above, an inverse association between pre-trauma general intellectual ability and risk of PTSD has been well-documented in both veteran (Kremen et al., 2007; Macklin et al., 1998; Pitman et al., 1991) and civilian samples (Breslau et al., 2006; Koenen et al., 2007). In a modified co-twin control study with a large sample of both MZ and DZ twins, pre-trauma general intellectual ability was lowest in pairs concordant for PTSD, highest in pairs concordant for not having PTSD, and intermediate for PTSD-discordant pairs (Kremen et al., 2007). Closer examination of the PTSD-discordant pairs revealed that cognitive differences were accounted for by DZ, but not MZ, pairs. This finding suggests that the differences were due to genetic factors because that would preclude MZ twin differences. Findings from the MZ-discordant design also suggest other specific domains of neurocognitive performance that are commonly implicated in PTSD are actually familial risk factors for PTSD (Gilbertson et al., 2006). These include attention, verbal declarative memory, and executive function deficits. In a subsequent

study, Gilbertson et al. (2007) found that both MZ twins with PTSD and their co-twins were impaired in configural processing of contextual cues. These deficits, which were associated with hippocampal volume, are also related to deficits in context-based extinction of conditioned fear responses.

4.2. Features that are sequelae of PTSD or trauma exposure

Here we refer generally to deficits or abnormalities that are present only in MZ twins with PTSD but not in their co-twins or in control twins, or are present to a greater degree in the twins with PTSD.

4.2.1. Neurocognitive functions

Although the pattern of neuropsychological performance suggests that most deficits are risk factors for PTSD, recall intrusions—which may be associated with deficits in cognitive inhibition—followed a pattern suggesting that they are related to trauma exposure independent of PTSD (Gilbertson et al., 2006). It is also worth noting that there were small differences between combat-exposed twins with PTSD and their unexposed co-twins in verbal memory, attention, and general visual–spatial ability. Exposed twins performed more poorly, with effect sizes ranging from $d = 0.21$ to 0.27, although these differences were not statistically significant in these relatively small samples.

4.2.2. Brain structure and function

Reduced gray matter density in a voxel-based morphometry study was found in the rostral anterior cingulate in combat-exposed twins with PTSD compared with combat-exposed twins without PTSD (Kasai et al., 2008). Results of a positron emission tomography study suggested that higher resting metabolism in the anterior and mid-cingulate cortex is a familial risk factor for PTSD. The rostral anterior cingulate is considered to be the affective division of the cingulate cortex, whereas the anterior/mid-cingulate is thought to be important for conflict monitoring and response selection.

4.2.3. Psychophysiology/electrophysiology

Milad et al. (2008) conducted a study of reduced recall of fear extinction in PTSD using a discordant twin pair approach. They

studied 14 pairs of MZ twins discordant for combat exposure; half of the combat-exposed twins had PTSD. Participants were administered a fear conditioning and extinction paradigm. On the day following extinction, twins with PTSD demonstrated poorer extinction recall than their own co-twins without combat exposure and unrelated subjects with combat exposure, but without PTSD. Results indicated that deficits in the retention of extinction of a conditioned fear is the result of combat exposure leading to PTSD and does not represent a vulnerability to the development of PTSD given exposure to combat.

Large heart rate responses to sudden, loud tones were also found to be consequences of PTSD rather than a familial risk factor (Orr et al., 2003).

In co-twin control studies of auditory event-related potentials, results were consistent with both reduced P3b amplitude (Metzger et al., 2009) and increased P2 amplitude intensity (Metzger et al., 2008) being consequences of PTSD. P2 (200) and P3 (300) refer to families of positive wave components of event-related potentials. The P3 component is associated with voluntary attention to relevant (target) stimuli, and the P2 component is thought to be associated with inhibition and heightened central serotonergic activity. In these studies, P2 amplitude was defined as the most positive point between 140 and 230 ms after stimulus onset. P3 amplitude was defined as the most positive point between 300 and 500 ms after stimulus onset. P2 amplitude intensity slope was defined as the slope of P2 amplitudes in response to tones of increasing intensity. These findings do appear to be consistent with the consequences of a disorder of stress responsivity. However, Metzger et al. (2008) noted that the P2 finding was in the opposite direction of previous findings in male veterans, but consistent with findings in women and abused children.

4.2.4. Pain

Several lines of research indicate that PTSD also is significantly associated with physical health conditions. The bulk of that research has focused on the high comorbidity between PTSD and chronic pain conditions, and it is postulated that PTSD and chronic pain are mutually maintained (Sharp and Harvey, 2001) or that there are shared vulnerability factors that predispose individuals to both PTSD and chronic pain (Asmundson et al., 2002). In that regard, twin studies have been exceptionally useful in examining the potentially shared genetic and common environmental factors that may contribute to PTSD and a number of chronic pain conditions. The twin studies examining the comorbidity of PTSD and chronic pain have been, for the most part, co-twin control studies that control for the confounding effects of shared genetic and common environmental factors in examining the association between PTSD and chronic pain conditions such as temporomandibular disorders, chronic widespread pain, rheumatoid arthritis, and urological symptoms (Afari et al., 2008; Arguelles et al., 2006; Boscarino et al., 2010; Wright et al., 2010).

Boscarino et al. (2010) focused on the association of PTSD with rheumatoid arthritis in 3143 male twin pairs from the VET Registry. These investigators found that familial and genetic influences did not explain the relationship between PTSD and rheumatoid arthritis. Rather, those in the upper quartile of PTSD symptoms were 3.8 times more likely (95% confidence interval = 2.1–6.1) to have rheumatoid arthritis compared with those in the lowest quartile. This result is consistent with rheumatoid arthritis being a consequence of trauma exposure leading to PTSD.

Using the community-based University of Washington Twin Registry, Wright et al. (2010) examined the association of PTSD with pain symptoms of interstitial cystitis, a urological pain condition of unknown etiology that primarily affects women. Based on data from 1165 female twins, those with painful urological symptoms were almost 4 times more likely to report PTSD symptoms (95% confidence interval = 2.6–5.8) after adjusting for age and correlated twin data. This first set of findings confirms the link between PTSD and painful urological symptoms seen in clinical studies (Clemens et al., 2008; Goldstein et al., 2008). A second set of analyses examined the association of PTSD and urological symptoms only in twin pairs discordant for urological symptoms, and again found a significant association between PTSD and painful urological symptoms (odds ratio = 2.2; 95% confidence interval = 1.2–3.8). Given that the association remains significant in the within-pair analyses that are adjusted for familial influences, the authors concluded that the link between PTSD and painful urological symptoms is independent of familial influences. These results may also be consistent with urological pain being a sequelae of PTSD, but analyses will need to be conducted in twin pairs that are discordant for PTSD rather than discordant for urological pain in order to confirm that conclusion. Although there is a need for more research in this area, the pattern of findings in both of these studies suggests a move away from examining shared familial and genetic hypotheses and point to environmental risk factors that may contribute to the comorbidity of PTSD and chronic pain conditions.

5. Conclusions and outlook

Twin studies have provided valuable contributions to our understanding of PTSD. Classical twin studies have shown that genetic factors are important determinants of risk for PTSD following exposure to trauma, but the same studies also confirm the importance of environmental factors as well. The twin method also demonstrates that we cannot simply rely on "common sense" notions of what constitutes an environmental factor. Indeed, the studies of Lyons et al. (1993) and Stein et al. (2002) indicate that variation in exposure to a traumatic event—the one thing that may seem most clearly environmental—is, in part, accounted for by genetic factors. This outcome makes sense if one considers the fact that the events to which one is exposed are not entirely random. For example, genetic predispositions (e.g., personality traits, susceptibility to alcohol abuse) will influence the kinds of environments that a person tends to seek out. Classical twin studies have also shown that there is substantial overlap of genetic factors that predispose to other anxiety disorders, depression, and substance abuse with PTSD.

Co-twin control studies have shown that some important associated features of PTSD, such as cognitive impairments or hippocampal volume reductions, are pre-existing risk factors rather than consequences of PTSD. These same studies have suggested that aspects of psychophysiological responding, brain metabolism, brain electrophysiology, and pain are consequences of PTSD that tend to be altered only after exposure to trauma and development of the disorder. It was suggested that at least one cognitive process—recall intrusions—was also a sequelae of trauma exposure rather than a vulnerability indicator. There was also a suggestion, based on small differences between MZ twins within PTSD-discordant pairs, that in addition to being risk/protective factors, some cognitive processes may undergo further acquired impairment as a result of trauma exposure. In other words, abnormalities may be both risk factors and features that continue to be exacerbated post-onset.

Overall, the findings suggest possible neurodevelopmental risk factors for PTSD (e.g., CSP, neurological soft signs, general cognitive ability) as well as factors that may affect frontal-limbic circuitry. The latter is suggested by hippocampal and anterior cingulate findings as well as event-related potential and cognitive findings implicating executive, attentional, and episodic memory functions. A greater focus on prefrontal cortex is probably warranted. Evidence is also

accumulating from co-twin control studies suggesting the importance of a variety of chronic pain conditions as sequelae of PTSD. Thus, comorbid physical as well as psychiatric disorders are important, although twin studies suggest that they are often different with respect to being risk factors versus consequences.

Given the genetic overlap with other psychiatric disorders, one obvious avenue with regard to potential pharmacological treatment is, in part, the use of medications that are successful in treating those related disorders. Perhaps the next logical step would be to focus on medications aimed at treating aspects of PTSD that have been shown to be consequences of the illness. Behaviors associated with psychophysiological and electrophysiological abnormalities as well as chronic pain might be good initial targets.

On the other hand, much of the currently available data to which we just referred are at best suggestive. The vast majority of findings stem from only two samples: the VET Registry in which the focus is most often on combat-related trauma during the Vietnam war; and the Canadian twin sample of Jang, Stein and colleagues. Much of this work has also been conducted on men. It is also important to note that virtually all of the co-twin control studies have come from the same research group of Pitman and colleagues. These are valuable studies, but generalizability may be limited because all of the studies are of Vietnam era men who have been tested in the same laboratory, and because the sample sizes tend to be quite small.

Small sample size is a problem for many co-twin control designs because it is often difficult to find participants meeting the study criteria. Although large sample size is a positive feature of any study, the need for very large sample sizes for classical twin studies can be a drawback of twin research on PTSD. It is difficult to find adequately large twin samples with a large enough subset of participants with PTSD, and creating a new twin sample is particularly costly and time-consuming. The inability to identify specific genes is another commonly referred to limitation of the twin method. Ultimately, it will, of course, be important to identify key polymorphisms that are associated with risk for, or protection from, PTSD. It will also be important to clarify epigenetic changes that are associated with PTSD (e.g., changes in gene expression or DNA methylation). However, the problem of the missing heritability for so many phenotypes (Maher, 2008) clearly indicates that high-throughput methods allowing for the rapid examination of hundreds of thousands of single nucleotide polymorphisms or CpG sites has not provided a simple solution in the search for genes associated with PTSD or almost any other condition. The need to refine the definition of the phenotype and elucidate phenotypes that do or do not share genetic variance are two of the possible rate-limiting factors for gene identification. Twin methods are quite useful in this regard. Consequently, we think that twin methods provide a key complement to molecular genetic studies of PTSD and other conditions (Kremen and Lyons, 2010).

Clearly more twin studies are needed that focus on non-combat trauma and on women. This is beginning to change as there are studies in their early stages that focus on women in the University of Washington Twin Registry (Afari et al., 2006). There has not been another veteran twin registry since the VET Registry, which included male twins who served in the military at some time between 1965 and 1975 (Eisen et al., 1987). The creation of a new twin registry focused on younger veterans of the wars in Iraq and Afghanistan is something that could substantially enhance research in this area. Such a registry would be able to address cohort differences that may be due to lifestyle differences in the different generations and to the differences in the combat experiences of the different wars. Moreover, this new registry would include women and more ethnic minorities than the VET Registry.

Finally, it should be noted that genes are anonymous in the twin method. The design is not informative as to which specific genes are involved or how many. It can, nevertheless, be very useful for identifying optimal phenotypes for genetic association studies. Recent epigenetic studies also indicate that gene expression and DNA methylation (e.g., McGowan et al., 2009; Yehuda et al., 2009) are likely to be very important for understanding PTSD, and these would have obvious potential value for drug development. Twins, particularly MZ twins, can be extremely valuable in the study of gene expression or DNA methylation or histone acetylation. Many factors other than trauma can affect these processes and, thus, represent potential confounds. Using an MZ co-twin control design controls for many potential confounds and substantially reduces error because twins within a pair are genotypically identical and have also shared the same rearing environment. These features make this a powerful design for epigenetic studies. This is yet another way in which the twin perspective can continue to make important contributions and to complement non-genetic studies as well as genetic association studies of PTSD.

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