**Reduced glucocorticoid responsivity may represent a predisposing marker that leads to additional stress vulnerability traits**

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The phenomenon of posttraumatic stress disorder (PTSD) has puzzled clinicians and researchers for decades. Why is it that, following exposure to an apparently similar stressful event, a subset of individuals develops PTSD while others do not? What differentiates this subset of vulnerable individuals from the majority that exhibit a more resilient response profile? The answers to these questions may have substantial clinical potential, as they could enable the identification of biomarkers of stress vulnerability at close proximity or even prior to the trauma exposure.

Multiple predisposing markers differentiating vulnerable from resilient cohorts have been proposed over the years and across research domains. Previous preclinical and clinical behavioral studies suggested that vulnerability may stem from reduced ability to extinguish fear and to learn safety, as well as from impaired emotional regulation and contextual processing (1). Another domain that has received substantial attention is sleep, with numerous reports demonstrating that sleep disturbances can significantly increase the likelihood of PTSD development (2). Across studies, predisposing sleep disturbances include alterations of sleep architecture, elevated nocturnal arousal, and fragmentation of rapid eye movement (REM) sleep. Another crop of literature investigated the endocrine mechanisms of stress vulnerability, with the hypothalamic-pituitary-adrenal (HPA) axis attracting most of the attention due to its central role in regulating stress responsivity. Indeed, PTSD, as well as additional stress-related psychopathologies, has been repeatedly associated with aberrant HPA activity at baseline and in response to stress (3). Finally, a wealth of neuroimaging and neurobiological studies has explored the neural underpinnings of PTSD and stress vulnerability. The seminal work of Gilbertson et al. in monozygotic twins highlighted a smaller hippocampal volume as a putative neural predisposing vulnerability marker (4), although this issue is still under debate (5).

Despite these major discoveries, the identification of stress vulnerability prior to trauma exposure is not yet feasible. One of the major challenges preventing such a breakthrough is that most studies considered these vulnerability markers to be independent risk factors, with their possible interrelation left unclear. Along these lines, causal associations between vulnerability markers have yet to be adequately explored, and it is therefore still unknown whether any of these markers has the potential to contribute to the emergence of the other markers. In the article by Monari et al that appears in the current issue of *Biological Psychiatry*, the authors attempted to address exactly these critical points. Specifically, the authors leveraged a genetically selected rat model of reduced corticosterone responsiveness to stress (low-CR) to explore whether such a genetic predisposition influences and potentially even favors the above-mentioned vulnerability markers of impaired fear extinction, REM sleep disturbances, and reduced hippocampal volume (6).

The results revealed several interesting patterns. First, as hypothesized, low-CR rats indeed exhibited reduced corticosterone responsiveness to stress compared with rats with a predisposition toward normative (norm-CR) or high (high-CR) corticosterone stress responsiveness. Next, ex vivo MRI was used to demonstrate that both low-CR and high-CR rats exhibit a reduced hippocampal volume compared with the norm-CR group, with no overall effect on total brain volume. The possible additional association of reduced corticosterone responsiveness with impaired fear extinction was investigated by administering the animals an auditory tone paired with a foot-shock three times (conditioning) and then providing the tone again on the next day without the foot-shock (memory recall and extinction training). Measurement of freezing behavior when the animals were presented with the tone without the foot-shock on the subsequent day and 30 days later was used to assess the ability of the rats to retrieve recent and remote fear extinction learning, respectively. Low-CR male rats exhibited similar freezing behavior to norm-CR rats during the initial memory recall and extinction training sessions. Nevertheless, their freezing behavior was significantly more common during recent and remote extinction retrieval sessions, as well as in response to the tone in a recall session 24 hours after fear reinstatement. These results were interpreted to suggest that reduced corticosterone responsiveness to stress is associated with deficient consolidation of fear extinction and elevated susceptibility to fear relapse.

In the next set of studies, the authors took their investigation a step further by administering corticosterone to low-CR rats immediately after extinction training, thereby assessing the potential causal role of glucocorticoid enhancement in reversing fear extinction deficits. Interestingly, low-CR male rats injected with corticosterone post-extinction no longer exhibited increased freezing behavior during recent and remote extinction retrieval sessions compared to norm-CR rats. A second injection of corticosterone yielded further attenuation of freezing behavior at a more remote extinction retrieval session and blocked fear relapse after reinstatement. The specific causal role of blunted corticosterone in fear extinction impairments was further supported by the demonstration that injection of a corticosterone synthesis inhibitor or a glucocorticoid receptor blocker induced elevated freezing behavior during extinction retrieval in norm-CR and high-CR rats, respectively.

The final set of studies focused on sleep and used polysomnographic recordings. Here, it was found that low-CR rats spent less time in REM sleep and exhibited longer bouts of REM sleep compared to norm-CR rats. To further explore the neurobiological mechanism of these phenomena, fiber photometry was applied to assess the amount of norepinephrine release during sleep in the hippocampus, specifically in the dentate gyrus. The reduction in norepinephrine levels that accompanies the transition from non-REM to REM sleep was less pronounced in low-CR rats and took longer to occur compared to the norepinephrine dynamics found in norm-CR rats. As a final step that tied these findings together, the authors assessed the impact of corticosterone administration post-extinction on subsequent REM sleep and norepinephrine release in low-CR rats. Remarkably, low-CR rats injected with corticosterone post-extinction resembled norm-CR rats with respect to the time spent in REM sleep and number of REM bouts in the first 3 hours post-extinction, a time period that putatively supports the consolidation of fear extinction. Low-CR rats injected with corticosterone also no longer exhibited any difference from norm-CR rats in hippocampal norepinephrine dynamics during REM sleep.

What does it all mean? First, considering the decades-long effort comprising multiple preclinical and clinical studies of stress vulnerability, the notion that some of the most potent previously suggested predisposing vulnerability markers are biologically interconnected is, by itself, highly encouraging. The findings specifically indicate blunted glucocorticoid responsiveness to stress as a predisposing marker that is not just associated with but even causally leads to impaired fear extinction and REM sleep disturbances. These results should be considered in light of the notion that sleep disturbances and impaired fear extinction may reinforce each other, forming a cycle that promotes stress vulnerability (7). The current findings therefore may open a window of opportunity for the *a priori* detection of such a vulnerability cycle, by suggesting that it may originate from a genetic predisposition to blunted cortisol responsivity to stress. In addition to *a priori* vulnerability detection, these results also offer a putative path for therapeutic intervention at close proximity to post-trauma exposure, by showing that glucocorticoid enhancement post-extinction training may strengthen the consolidation of fear extinction during the subsequent sleep. This is in line with recent preliminary clinical evidence that hydrocortisone administration in the immediate aftermath of trauma exposure may reduce the likelihood of PTSD development (8). Also supporting the suggested mechanism, REM sleep after experimental trauma has been found to play a protective role in trauma memory formation and contribute to the adaptive reconsolidation of aversive autobiographical memories (9).

While representing a major step forward, the clinical translation of these findings is far from trivial given the complexity of PTSD. For example, PTSD patients tend to exhibit substantial behavioral impairments across multiple domains of their functionality. Indeed, this is the cornerstone of the clinical diagnosis. Hence, while impaired fear extinction is an important factor, behavioral assessments across distinct functional domains may provide valuable insights into stress vulnerability vs. resilience, as was recently nicely demonstrated (10). In addition, the impact of genetic predisposition may be particularly potent in the context of gene-by-environment interactions. For example, childhood adversity is a potent vulnerability factor for PTSD that has been shown to impact HPA functioning, sleep, and fear extinction (7). Thus, accounting for its contribution may increase the clinical validity of the suggested vulnerability markers. Furthermore, many additional vulnerability markers have been identified over the years, such as pro- and anti-inflammatory cytokines of the immune system, metabolic hormones, and autonomic nervous system responsivity patterns. Finally, all of the above-mentioned effects were found in low-CR male rats but not in female rats. This stands in contrast to the higher prevalence of PTSD in women (1) and thereby further supports the relevance of sex differences in stress vulnerability and the potential benefits of sex-dependent diagnosis and treatment protocols.

In conclusion, even if it does not depict the complete picture of stress vulnerability, the work performed by Monari et al provides compelling evidence to support the validity and connectedness of previously highlighted predisposing risk factors for PTSD, raising the possibility of a multi-trait stress vulnerability. Future preclinical and clinical studies in this domain could further contribute to ongoing efforts to identify and effectively treat stress-vulnerable individuals in order to increase their resilience and prevent them from developing PTSD.

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