

When the “Golden Chain” Breaks: Sleep Disturbance and the Vicious Cycle of Chronic Stress

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Sleep is the golden chain that ties health and our bodies together.

—Thomas Dekker

Sleep is a universal experience with profound, multifaceted implications for physical and mental health. When sleep is disturbed, it can quite quickly become a deleterious chronic stressor, increasing the risk for the onset, exacerbation, and maintenance of stress-related psychopathology, such as posttraumatic stress disorder (PTSD) (1,2). Though there is mounting evidence concerning the neurobiological underpinnings of PTSD (2) and recent work suggesting that sleep disturbances relate to structural and functional alterations in limbic and paralimbic brain regions implicated in PTSD (3), the neurobiology of sleep impairment in the context of stress exposure and trauma exposure is largely unknown. In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, exciting work from Seo *et al.* (4) adds to this body of literature. They report on several dimensional trauma-related and sleep-related factors' predictiveness on intrinsic network connectivity among 6 a priori-defined seeds—5 in the fear-processing regions of the salience network and 1 in the anterior default mode network—that are implicated in top-down fear regulation. Their findings suggesting that paralimbic and frontocortical functional connectivity is predicted by subjectively reported hyperarousal and select metrics of sleep architecture among recently trauma-exposed individuals are interesting and clinically relevant, though generalization may be somewhat limited given the characteristics of their trauma-exposed cohort. In our opinion, the primary benefit of this article is that it underscores the critical need to include sleep disturbance as a factor in neurobiological studies of PTSD given its ubiquitous and cardinal role in the vicious cycle of chronic stress pathology (CSP), to consider symptoms dimensionally, to carefully examine various metrics of sleep using multimethod assessment, and to fully detail experimental methods, as the authors did.

Chronic stress is a major component of many psychiatric disorders, and biomarkers suggestive of stress-related synaptic dysconnectivity (e.g., gray matter deficits) have been reported across many severe psychiatric disorders (2). In recent years, clinical neuroscience research has begun to unravel the unique dysconnectivity patterns through which CSP contributes to distinct clinical presentations, including PTSD, highlighting a triple network model of psychopathology (2,5). Traumatic stress interacts with predisposing factors (e.g., genetics/epigenetics, sex, poor social support) to precipitate

CSP, consistent with localized synaptic loss and gain, leading to behavioral disruptions that further exacerbate the CSP, and so on (2). While adequate sleep may act as a resiliency factor, impaired sleep may serve as a primary contributor to the vicious cycle of CSP (1).

Synaptic plasticity is suspected to be based on the growth or retraction of dendrites associated with alterations in synaptic connectivity patterns. Sleep is thought to influence structural plasticity in a bidirectional nature through its influence on the number and morphology of dendritic spines secondary to periods of adequate sleep or sleep loss (6). These neural alterations then affect functional output in metrics such as alertness, cognition, and mood, including emotion regulation and fear/threat processing (6). The synaptic homeostasis hypothesis proposes that “sleep is the price the brain pays for plasticity” (7) and suggests that learning about one's immediate circumstances and environment occurring during periods of wakefulness requires heightened and strengthened synaptic connections throughout the brain, increasing cellular needs for energy and decreasing signal-to-noise ratios (6,7). During periods of adequate sleep, regional and global synaptic strength is normalized and neural processes restore cellular homeostasis (6–9), a process of spontaneous neural activity that leads to synaptic downscaling that may explain, at least in part, the benefits of sleep on memory acquisition, consolidation, and integration (6–9). Taken together, it appears that the impact of sleep and sleep loss vary and may have differential implications both globally and within specific regions of the brain (6,7).

One of the primary findings of Seo *et al.* (4) is the association of greater connectivity between select regions of the salience network and fear-related seeds and longer periods of objectively measured sleep onset latency (4). More severe hyperarousal during periods of wakefulness was associated with less connectivity between fear-related seeds and anterior emotion regulatory regions, while increased percentage of slow wave sleep—a metric of sleep implicated in memory consolidation—was associated with more connectivity between these regions (4). The authors suggest that post-traumatic symptoms, including prolonged sleep onset latency, may reflect exaggerated activity in the salience network and lesser top-down control of this network by the prefrontal cortex (4). Frank (8) notes that “learning is a deceptively simple term for a complex set of neural events, often involving multiple brain areas and signaling pathways including long-term synaptic potentiation (LTP) and depression (LTD)-like synaptic alterations” (8). Extinction, for example, which can involve synaptic weakening, allows for changes to previously learned

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behaviors in light of new information, and behavioral flexibility or reversal learning supports shifting beliefs based on new information and also requires LTD-like mechanisms (8). When sleep is impaired, the opportunity for global and/or region-specific synaptic downscaling is hindered, and therefore physical, emotional, and cognitive restoration and normalization are stalled, incomplete, and imperfect. If there is no opportunity to reset, so to speak, and to engage in extinction and reversal learning, fear- and threat-related beliefs and accompanying behaviors will become more ingrained as each day passes with disordered sleep, further compounding the neurobiological and behavioral consequences—perhaps supporting Seo *et al.*'s focus on hyperarousal symptoms (4).

The authors also report an association of PTSD with decreased connectivity between fear-related seeds and emotion regulation systems, whereas improved slow wave sleep had increased connectivity between these regions—other sleep metrics did not show this same pattern (4). Improved sleep was associated with some but not all top-down fear regulation (4). Consistent with previous evidence suggesting discrepancies between measures of sleep in individuals with PTSD, the mixed findings of Seo *et al.*'s objective and subjective measures support the need to 1) better understand the neural correlates of these various sleep metrics and 2) to find some consensus in the field on which of these metrics are of the greatest clinical and investigative utility (1). Some but not all studies suggest that individuals with PTSD may self-report increased sleep disturbance relative to objective findings (1). However, it may be important to consider the method and metric of sleep assessment. Specifically, longitudinal methods, such as polysomnography, actigraphy, and sleep diaries, may be more congruent, while global assessments of sleep may be less consistent with these measures (1). Night-to-night sleep assessment may not allow for adequate time to capture the association between sleep and PTSD symptom severity, which supports the importance of using both objective and subjective measures, as well as consideration of time, in the assessment of sleep and PTSD (1).

When considering time in the evaluation of sleep and PTSD, two of the exclusion criteria in the Seo *et al.* study (4) are noteworthy. The first is that the individuals included in this study were exposed to trauma within the 2 years before participation, which suggests that overall symptomology and the associated/underlying neural alterations are in relative infancy. The authors note that a narrower window between the trauma exposure and assessment would improve confidence in the associations between the specific index trauma and sleep impairments, and future work will benefit from exploring both the acute effects of trauma exposure on sleep (and vice versa) and long-term, chronic, lifetime effects. The second criterion excluded individuals with a history of childhood trauma and/or a diagnosis of PTSD before the traumatic experience occurring in the 2-year duration of the study. It is the norm, rather than the exception, for trauma-exposed individuals to experience more than one traumatic event in their lifetime. Considerable evidence suggests that individuals with childhood trauma are at greater risk for traumatic exposure in adulthood as well as the onset or worsening of stress-related

psychopathology. In addition, early-life stress and trauma are implicated in a myriad of deleterious consequences, including disruption to circadian rhythm, functional and structural neural changes, and alterations in autonomic and emotional reactivity, as well as dysregulation of metabolic and immune systems, which have been identified as important risk factors for a chronically impaired homeostatic balance after early-life stress (10).

Seo *et al.* (4) make a solid addition to the literature in their own right and set the stage for important studies that intend to further characterize sleep disturbance and PTSD across trauma-exposed cohorts. Parsing the causal and consequential behavioral and neurobiological features related to impaired sleep, psychopathology, and brain dysfunction will be of significant benefit for precision psychiatry because it may allow for the identification of subtypes of these disorders that are mechanistically coherent and distinct, and it offers potential targets for prevention, resilience promotion, and intervention among millions across the world struggling with effects of CSP (9).

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Article Information

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