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POSTTRAUMATIC STRESS DISORDER – THE NEUROSCIENTIFIC BASIS OF EVIDENCE-BASED TREATMENTS*

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Posttraumatic stress disorder (PTSD) is a relatively common anxiety spectrum syndrome, in which memory of a triggering trauma becomes aberrantly linked to autonomic and emotional arousal. The recurrent, internally generated stress response can produce enduring behavioral and brain changes. Mechanistically, this may involve both dysregulation of the hypothalamo-pituitary-adrenal axis as well as degradation of the capacity of supramodal cortical areas to process and manage trauma-related emotional content. The optimal balance of information processing and hence behavioral reactivity shifts from the reflective prefrontal cortex in favor of the more emotionally reactive amygdala. Trauma-focused therapies exploit adaptive neuroplasticity to decouple the memory of the trauma from the aberrant emotional and behavioral responses, in effect reconfiguring brain networks. The effect-size of such psychological therapies is generally larger than that for pharmacological treatments which are currently limited to drugs repurposed for PTSD. Nonetheless, in a significant number of patients, some symptoms can be at least partially attenuated by selective serotonin reuptake inhibitors. In addition, the frequency and intensity of trauma-related nightmares can usually be lowered by adrenergic alpha-1 receptor agonists. Even as novel modalities continue to be developed, the judicious implementation of currently available evidence-based treatments for PTSD can target the underlying neurobiology, provide symptomatic relief, and promote psychosocial recovery.

Key words: *memory, prefrontal cortex, amygdala, autonomic, neural, network*

ПОСТТРАВМАТИЧНИЙ СТРЕСОВИЙ РОЗЛАД: НЕЙРОНАУКОВІ ОСНОВИ ДОКАЗОВОГО ЛІКУВАННЯ

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Посттравматичний стресовий розлад (ПТСР) – це досить поширений синдром тривожного спектру, за наявності якого пам'ять про психотравмівну подію стає аберантно пов'язаною з вегетативним та емоційним збудженням. Повторювана внутрішньо спровокована стресова реакція зумовлює виникнення тривких змін поведінки. Механічно в цьому процесі відбувається дизрегуляція осі гіпоталамус-гіпофіз-наднирники, а також деградація здатності асоціативних зон кори головного мозку адекватно обробляти інформацію, яка пов'язана з психотравмівними чинниками, та керувати емоційними проявами цих пережитих подій. Контроль над оптимальним балансом обробки інформації, а отже, й поведінковою реактивністю зміщується від раціональної префронтальної кори на користь більш емоційно лабільного мигдалеподібного тіла. Психотерапевтичний метод репроцесуалізації травми виробляє адаптивну нейропластичність головного мозку внаслідок ремодельовання міжнейронних синаптичних зв'язків, що уможливорює відокремлення спогадів про психотравмівну подію від

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непередбачуваних емоційно-поведінкових реакцій. Ефективність зазначеної психотерапії загалом вища, ніж фармакотерапії, що сьогодні обмежена застосуванням засобів, які впливають лише на окремі компоненти ПТСР. Втім у значній когорти пацієнтів деякі симптоми можуть принаймні частково послаблюватись прийомом селективних інгібіторів зворотного нейронального захоплення серотоніну. Крім того, $\alpha 1$ -агоністи адренорецепторів зазвичай знижують частоту виникнення розладів сну. Розсудливе застосування доступних, станом на сьогодні, методів лікування ПТСР, які ґрунтуються на принципах доказової медицини, разом з розробкою новітніх підходів, може впливати на нейробиологічні механізми патогенезу, забезпечуючи симптоматичне полегшення та сприяючи психосоціальній реабілітації пацієнтів.

Ключові слова: пам'ять, префронтальна кора, мигдалеподібне тіло, вегетативний, міжнейронні зв'язки.

Introduction

Posttraumatic Stress Disorder (PTSD) is an anxiety spectrum syndrome that was added to the International Classification of Diseases and Related Health Problems version 9 (ICD-9) in 1978 and to the Diagnostic and Statistical Manual – III (DSM-III) in 1980 (American Psychiatric Association, 1980; World Health Organization, 1978). As is the case for other psychiatric disorders, the nosology of PTSD is currently based in phenomenology, that is in the emergence and course of nonspecific and often variable symptoms and not in reproducible neurobiological indices (Kendler, 2009; Stephan et al., 2016). While diagnostic elements have varied over time, criteria common to DSM-5 and ICD-10 include a) exposure to a significant traumatic event, b) intrusive recollections, c) avoidant symptoms d) increased physiological arousal (in ICD-10, arousal may be replaced by element of amnesia for the traumatic event) (American Psychiatric Association, 2013; World Health Organization, 1993) (Table 1). The trauma must be significant, but can be experienced directly or indirectly (Table 2).

In the United States (US), the estimated lifetime prevalence of exposure to at least one qualifying trauma is 70-90%, with most people experiencing two or more traumatic events (Kilpatrick et al., 2013; Resnick et al., 1993). The estimated risk of developing PTSD after a single traumatic exposure is 10-30%, with a higher risk associated with violent (e.g. rape, combat) or repeated trauma (Breslau et al., 1998; Friedman et al., 2007a; Grinage, 2003; Kilpatrick et al., 2013). While the reported prevalence of PTSD varies with diagnostic criteria, the quality of data collection and particularly on the population sampled, PTSD is estimated to affect some 8-10%

of the adult civilian population in the US (Breslau et al., 1998; Grinage, 2003; Kessler et al., 2012; Kessler et al., 1995) and up to 16% of deployed personnel in the US Armed Forces (Gates et al., 2012). It is more common in women (Breslau et al., 1998; Kessler et al., 1995).

Neurobiology

Since the majority of individuals exposed to significant trauma do not develop PTSD, the disorder can be considered as a deviation from the normative course of recovery. The expected weakening of the association between the initial traumatic event(s) and the acute psychological and biological reactions does not occur. In addition, the autonomic and emotional concomitants become decoupled from the initial trauma and can subsequently be triggered either by external or internal stimuli. Mechanistically, this reflects a maladaptive neuroplasticity of synaptic connections.

Repeated stimulation increases the efficiency of synaptic transmission (Hebb, 1949). "Neurons wire together if they fire together" (Lowel and Singer, 1992). While numerous brain circuits are potentially available for activation at any given moment, the precise activation pattern is dynamically determined 'on the fly' by internally- and externally-driven demands (Cole et al., 2013). In the case of PTSD, the repeated activation of circuits linking the traumatic memory with emotional and behavioral responses, becomes excessively facilitated.

Under normal conditions, information about a given event enters the brain where it can be briefly retained in short-term memory and then, depending on other factors, may be encoded, consolidated and stored in long-term memory until it is retrieved (Figure 1) (Lewis, 1979).

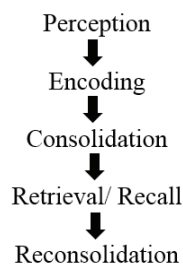


Figure 1: Stages of Memory

The full memory may integrate not just the facts about a given event (declarative memory - where and what happened) but also emotional value (pleasure, threat) and sensory concomitants (visual, olfactory, auditory, etc.). In PTSD, at least some of these elements become aberrantly linked to autonomic and other responses which initially cause and then are reinforced by chronic brain-based behavioral and cognitive changes (Figure 2).

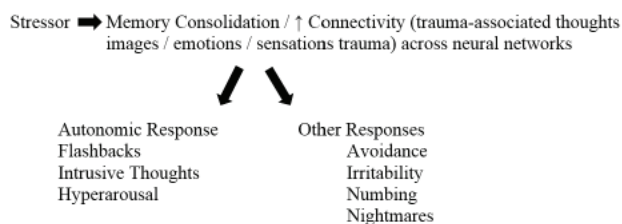


Figure 2: Development of PTSD

The human brain can be broadly conceptualized as having three phylogenetically, anatomically and functionally different systems, namely primary, limbic and neocortex; these interact at multiple levels (Figure 3).

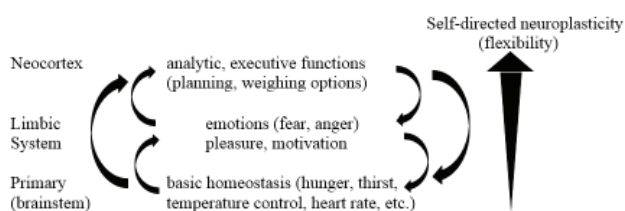


Figure 3: Functional Interactions in Mammalian Brain Systems

While all are neuroplastic, the complexity and responsiveness of their neuroplasticity to voluntary control increases from brainstem to neocortex. The neocortex is also distinguished by regional specialization for information processing (Benson, 1993). Executive function, that is the allocation of overall attention as well as integration of information from multiple brain levels, is mediated within the prefrontal

cortex (PFC). This phylogenetically unique region and particularly its layer III subserve enhanced information processing capabilities (Amatrudo et al., 2012) which constitute the most distinguishing functional feature of the human brain (Elston et al., 2006). Unfortunately, such specialization is accompanied by a heightened vulnerability to homeostatic imbalance.

Preclinical studies demonstrate that neurochemical changes induced by acute stress immediately degrade the ability of the PFC to provide executive function; repeated bouts of uncontrollable stress can lead to long-term structural changes such as impoverishment of the dendritic arbor and spines of PFC pyramidal cells, particularly those of layer III (Arnsten et al., 2015; McEwen and Morrison, 2013). A preliminary postmortem investigation has identified analogous structural and molecular changes in dendritic spines of pyramidal cells in the PFC of PTSD patients (Young et al., 2015). Converging high resolution imaging data suggest that trauma-related changes in frontal cortex gray matter correlate with certain domains of PTSD (Averill et al., 2017; O'Doherty et al., 2017; Wrocklage et al., 2017). PTSD-related changes in gray matter of amygdala and hippocampus have also been reported (Akiki et al., 2017; Pietrzak et al., 2015). Such structural changes would be expected to tip the balance for cognitive processing from the deliberative, reflective prefrontal cortex (PFC) in favor of more reflexive emotional and behavioral responses generated by subcortical regions such as the amygdala (Arnsten et al., 2015). Not surprisingly, patients with PTSD demonstrate atypical dynamic measures of connectivity across circuits involving the frontal cortex, hippocampus and amygdala (Abdallah et al., 2017; Etkin and Wager, 2007; Jin et al., 2017), resulting in excessive activity by the amygdala and an exaggerated perception of and response to threat (Etkin and Wager, 2007). Indirect transcriptome data suggest that low grade neuroinflammation may contribute to the brain changes (Breen et al., 2017).

Stress-induced autonomic arousal also activates the hypothalamo-pituitary-adrenal (HPA) axis (McEwen, 2007). Several groups have reported elevations of corticotrophin releasing factor or of cortisol in the cerebrospinal fluid of patients with PTSD (Baker et

al., 2005; Baker et al., 1999; Bremner et al., 1997) at times in the face of normal peripheral measures in plasma or urine (Baker et al., 2005; Baker et al., 1999). Despite the variability between studies, the overall data implicate enduring dysregulation of the HPA axis in at least some patients with PTSD.

Treatment

Currently, no pharmacological treatments specifically target either symptoms of PTSD (Table 3) or its suspected pathophysiology (Girgenti et al., 2017; Krystal et al., 2017). Serendipity and clinical experimentation have, however, resulted in the repurposing of several already available drug types. Clinicians familiar with the anxiolytic properties of tricyclic as well as monoamine-oxidase inhibitor (MAOI) antidepressants began using them in small numbers of patients with PTSD (Bleich et al., 1986; Burstein, 1984; Falcon et al., 1985; Hogben and Cornfield, 1981). Encouraging case reports prompted a randomized, double-blind, placebo-controlled clinical trial. In a preliminary sample of male veterans with PTSD related to their service during the Vietnam war, both phenelzine and imipramine were found to be superior to placebo in relieving distress related to intrusive phenomena (nightmares, flashbacks, recollections) but not in addressing non-specific anxiety or avoidance (Frank et al., 1988). The results were confirmed in the full patient sample with phenelzine showing a modest advantage over imipramine (Kosten et al., 1991). The potential side effects and dietary measures associated with MAOI use, however, limited the appeal of this drug class.

The emerging availability of serotonin reuptake inhibitors (SSRIs) with a more favorable side-effect profile and better tolerability prompted their *ad hoc* use in small groups of patients. Subsequently, in a seminal, double-blind, placebo-controlled 12-week trial, sertraline proved superior to placebo in attenuating avoidance and numbing, but was less effective against hyperarousal (Brady et al., 2000). Additional findings were that i) sertraline was generally well tolerated, ii) attendant symptomatic relief evolved slowly and iii) the placebo response (32%) was surprisingly large (Brady et al., 2000). Furthermore, while significantly more patients in the sertraline group reached predetermined criteria for treatment response (53%), overall the effects were quite modest and many pa-

tients showed incomplete symptom resolution (Brady et al., 2000). Comparable double-blind placebo-controlled trials demonstrated that paroxetine was also effective against several groups of symptoms (reexperiencing, avoidance/numbing, hyperarousal) (Marshall et al., 2001; Tucker et al., 2001). A relatively high placebo response rate and the persistence of significant symptoms in many patients were also noted (Tucker et al., 2001). The US Food and Drug Administration approved sertraline (1999) and paroxetine (2001) for the treatment of PTSD. Over the subsequent decade, other SSRIs as well as serotonin and norepinephrine uptake inhibitors (SNRIs) were similarly tested. A recent meta-analysis confirmed that while several of these drugs (fluoxetine, paroxetine, venlafaxine) are superior to placebo in attenuating PTSD symptoms, the effect size is rather small (0.23) and they are associated with significant side-effects, most commonly gastrointestinal distress, weight gain and sexual dysfunction (Hoskins et al., 2015). Furthermore, PTSD symptoms resulting from combat trauma as opposed to civilian trauma may be more resistant to SSRIs (Friedman et al., 2007b; Zohar et al., 2002).

Sleep problems are common and distressing features of PTSD. Recurring nightmares of the triggering event constitute one of several possible elements of intrusive recollection and contribute to sleep disturbances in some 70% of patients (Ohayon and Shapiro, 2000). Early case reports on the salutary effects of prazosin, an α_1 -adrenergic receptor antagonist (Raskind et al., 2000), prompted a larger, retrospective study. In combat veterans, prazosin significantly reduced the intensity and frequency of severe nightmares associated with chronic PTSD (Raskind et al., 2002). This was confirmed in a placebo-controlled 20-week double-blind crossover protocol (Raskind et al., 2003) and a later placebo-controlled, 8 week, parallel design trial (Raskind et al., 2007). The data unequivocally demonstrated that if prazosin were introduced at a dose of 1 mg/HS and elevated gradually at the rate of 1 mg/HS/week until either adequate symptom relief was achieved or untoward side effects (most commonly sedation or hypotension) limited further increases, the medication was generally well-tolerated, reduced traumatic nightmares, restored normal dreaming and could improve other PTSD symptoms as well as functional status (Raskind et al., 2000;

Raskind et al., 2007; Raskind et al., 2003; Raskind et al., 2002). The minimum recommended target dose of 6 mg/d was well below the mean doses achieved (13 mg/d) in some studies (Raskind et al., 2007). Unfortunately, despite this consistent body of data and the large treatment effect size (~ 1.0) (Raskind et al., 2007), prazosin remains underutilized even in clinical settings familiar with PTSD. A review of a computerized record system in a large US veteran's hospital showed that 20% of patients with PTSD-associated nightmares never filled their initial prazosin prescription and that only 14% of patients attained the minimum guideline recommended dose of 6 mg/d (Alexander et al., 2015).

Pharmacological responsiveness of symptoms may provide clues about underlying neurobiology. The receptor profiles of SSRIs, SNRIs and prazosin have prompted investigations of the serotonergic and adrenergic systems. In comparison to controls, subsets of patients with PTSD were found to be more sensitive to the anxiogenic effects of an intravenously administered serotonin type 2C receptor ($5HT_{2C}$) agonist or an adrenergic α_2 receptor antagonist (Southwick et al., 1997). This raised the possibility that certain PTSD symptoms in patient subgroups were mediated by hypersensitive $5HT_{2C}$ receptors; downregulation of these receptors could potentially provide symptomatic relief (Southwick et al., 1997). Analogously, since presynaptic α_2 receptors inhibit efflux of noradrenaline, their dysregulation could contribute to excessive activation of postsynaptic α_1 receptors in other patient subsets (Kelmendi et al., 2016). This could explain the efficacy of α_1 -adrenergic receptor antagonists against nightmares. Of course, many other potential contributors to sleep disturbances (e.g. poor sleep hygiene, gastroesophageal reflux syndrome, restless leg syndrome, sleep apnea) should be identified and treated as well (Table 4). The quality of sleep in PTSD can also be improved through cognitive behavioral therapy (Ho et al., 2016).

Several psychotherapies have been developed based on an emerging understanding of how memories are formed and integrated with emotional and behavioral responses. The association between a stimulus and these responses usually weakens during the process of extinction (Pavlov, 1927). In PTSD, this extinction fails. It had long been known that memory consolidation, the process converting

information from short term memory to long term memory (Figure 1) depends on protein synthesis (Flexner et al., 1962). It was also believed, however, that initially consolidated memories were relatively fixed. Later preclinical studies demonstrated that with each retrieval of a stored memory, the relevant information had to be reconsolidated via a protein synthesis-dependent mechanism (Debiec et al., 2002; Duvarci et al., 2008; Nader et al., 2000). In other words, storage of a given memory is not necessarily a unique event but rather a process repeated after each retrieval of that memory. As a result, retrieval renders the associative links of a given memory temporarily available for modification at the cellular and systems level (Nader, 2015). Memory itself can be designated as a treatment target.

An astute clinical psychologist observed that that recurring, distressing thoughts in PTSD could be permanently attenuated, if the subject's eyes were automatically moving in a multi-saccadic manner while the disturbing thought was being held in consciousness (Shapiro, 1989, 1996). The declarative or explicit memory, that is the facts of the traumatic event, was not abolished, but its intrusive nature and attendant autonomic and emotional concomitants were removed. This catalyzed the development of Eye Movement Desensitization and Reprocessing therapy (EMDR) (Bisson et al., 2007; Jeffries and Davis, 2013). It is thought to exploit the limited capacity of the brain to process information at any given point in time. By deliberately focusing on a sensory stimulus during retrieval of the memory, the individual is less able to attend to its distressing associations. Repetition of this process presumably weakens the links between the declarative memory and its previously distressing autonomic and emotional concomitants. Although the declarative memory remains and can be retrieved at will, it becomes progressively less intrusive and no longer evokes distress.

Analogous neurobiological mechanisms are likely operative in other trauma focused cognitive behavioral therapies (TFCBTs) (Bisson et al., 2007). Stimulus generalization (Pavlov, 1927) for example, may allow irrelevant or neutral stimuli to involuntarily trigger circuits (fear, fight or flight) that generate a maladaptive response (Figure 3). Some psychotherapeutic approaches focus on encouraging patients to rationally examine their symptom

triggers and thus gradually to circumscribe the range of triggering stimuli (Figure 4).

During an evening stroll with his father, a toddler was fatally stung by a black and red snake. The father now fears:

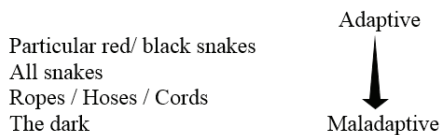


Figure 4: Stimulus Generalization

Due to their relatively large effect sizes (~ 1.0), tolerability and favorable side-effect profile (Cusack et al., 2016) EMDR and TFCBTs have been designated as first line treatments for PTSD, ahead of pharmacological approaches (Tol et al., 2014). It is particularly exciting that in preliminary studies, successful EMDR and TFCBTs measurably changed memory-driven activation of brain circuits implicated in emotional processing (Fonzo et al., 2017a; Fonzo et al., 2017b; Malejko et al., 2017; Thomaes et al., 2016) and promoted normalization of cortical gray matter (Boukezzi et al., 2017). In other words, when successful, these psychotherapeutic approaches may partially reverse or otherwise mitigate PTSD-induced brain changes that mediate symptoms and disability.

Such analyses inform treatment in other ways. Increasing data support a bi-directional relationship between PTSD and sleep disturbances. Suboptimal quality and quantity of sleep is a non-specific brain stress; even a few days of sleep deprivation or circadian misalignment affect metabolism, appetite, autonomic tone and various inflammatory biomarkers (McEwen and Karatsoreos, 2015). Sleep-disordered breathing is independently associated with changes in the functional connectivity of brain regions (Park et al., 2016) as well as with reductions in brain regional cortical volume (Shi et al., 2017). Such anti-trophic effects on the brain would be expected to augment or even synergize with the primary pathophysiology in PTSD. In turn, PTSD is itself associated with a markedly increased risk of sleep-disturbances (Alexander et al., 2016; Harvey et al., 2003; Ohayon and Shapiro, 2000) including sleep-disordered breathing (e.g. obstructive sleep apnea) (Krakow et al., 2015; Lettieri et al., 2015). This can set up a negative-feedback loop. On the one hand, sleep-disturbances may increase the risk for de-

veloping PTSD, exacerbate resulting symptoms and lower the effectiveness of therapies, while on the other hand undertreated PTSD can either cause or exacerbate a host of sleep problems (Gilbert et al., 2015; Short et al., 2017). Conversely, successful pharmacological as well as non-pharmacological treatments of insomnia, nightmares and/or sleep disordered breathing can improve other dimensions and psychosocial outcome in PTSD, perhaps by attenuating hyperarousal, lowering depression and elevating levels of trophic factors (Figure 5) (El-Solh et al., 2017; Krystal et al., 2016; Raskind et al., 2007; Rusch et al., 2015; Vandrey et al., 2014).

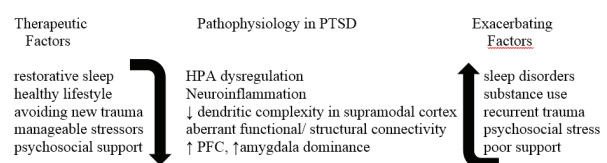


Figure 5: Interactions Between Pathophysiology and Contributing Factors in PTSD

A similar self-reinforcing interaction is seen with substance use disorders; these are both more prevalent in PTSD (Duncan et al., 1996; Pietrzak et al., 2011; Wisco et al., 2016) and associated with chronicity and poor treatment response (McCauley et al., 2012). Some data suggest that initiation and maintenance of substance use may represent a maladaptive attempt to deal with a PTSD-associated symptoms (Vandrey et al., 2014). Concomitant treatment of both disorders should be considered (Flanagan et al., 2016).

Summary

The pathophysiology of PTSD is complex but involves genetic, neurohumoral and neurochemical mechanisms as well as neuroinflammatory processes that change the brain at the molecular, structural and functional levels. As is the case for other psychiatric disorders, PTSD is mediated by brain networks rather than by any single neurotransmitter system (Insel, 2010). Suboptimal integration of factual, emotional and other types of information across brain networks results in heterotypical functional connectivity between declarative memories and their autonomic and emotional content. In chronic PTSD, the information-processing capacity of deeper layers of the PFC in particular may become compromised. As a general rule, interventions that promote adaptive neuroplasticity can mitigate or reverse this brain-based pathophysiology and promote

symptomatic as well as functional recovery (Figure 5). While we await the development of more effective treatments for PTSD (Girgenti et al., 2017), it behooves us to fully integrate and exploit interdisciplinary, evidence-based treatments that are currently available. These include psychotherapeutic approaches such as EMDR and judicious use of psychotropic drugs. When economic, systemic or individual factors (e.g. medication side effects, reluctance to

engage in psychotherapy) impede implementation of multimodal approaches, even limited and highly circumscribed efforts (e.g. sleep hygiene to treat sleep disorder, substance use treatment) can prove helpful in most patients. The critical tasks include i) identifying contributing factors and potential treatment targets, ii) determining which treatments are practical under given conditions, iii) continually assessing outcome and adapting treatment efforts.

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