

Development of an Amygdalocentric Neurocircuitry-Reactive Aggression Theoretical Model of Emergence Delirium in Posttraumatic Stress Disorder: An Integrative Literature Review

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The purposes of this integrative literature review were to (1) present a synopsis of current literature describing posttraumatic stress disorder (PTSD), the amygdalocentric neurocircuitry, emergence delirium, reactive aggression, and the interaction of general anesthetics and the amygdalocentric neurocircuitry; (2) synthesize this evidence; and (3) develop a new theoretical model that can be tested in future research studies. Over the past decade, a dramatic rise in PTSD among veterans has been reported because of recent combat deployments. Modern anesthetics alter the function of the amygdalocentric neurocircuitry to produce amnesia and sedation. The etiology of emergence delirium is poorly understood, and the condition is uncommon outside the pediatric population. Emergence delirium among patients with PTSD, however, has been

reported by military nurse anesthetists. To date, there have been no scientific studies conducted to identify the cause of emergence delirium in combat veterans with PTSD. This new theoretical model may explain why noxious stimuli at the time of emergence may stimulate the thalamus, leading to activation of an uninhibited amygdalocentric neurocircuitry. Because of the loss of top-down inhibition, the hyperactive amygdala then stimulates the hypothalamus, which is responsible for creating an increase in excitatory activity in the unconscious patient, resulting in emergence delirium.

Keywords: Amygdalocentric neurocircuitry, emergence delirium, posttraumatic stress disorder, reactive aggression, veteran.

Over the past decade, the Department of Veterans Affairs (VA) hospital system has seen a dramatic rise in posttraumatic stress disorder (PTSD) among veterans because of recent combat deployments called Operation Enduring Freedom in Afghanistan and Operation Iraqi Freedom in Iraq. It is estimated that approximately 10% to 18% of combat troops that served in Afghanistan and Iraq may have PTSD following their deployment.¹ Therefore, a greater number of veterans with PTSD may require anesthesia for surgical procedures to repair injuries and/or treat medical conditions associated with combat service. Little is known, however, about the possible interactions between PTSD and general anesthesia administered in surgical procedures.

Of particular interest is the possible association between PTSD and the development of emergence delirium (ED). In a recent publication, McGuire and Burkard² discussed PTSD as a potential risk factor for ED among active-duty service members and identified the need for scientific research in this area of inquiry. McGuire and Burkard identified, after an extensive review of sociologi-

cal, psychological, neurobiological, and anesthesia literature, that there has been little research investigating the interaction between surgery and PTSD. To our knowledge, no research studies published to date support a possible link between PTSD and ED. However, there has been literature published regarding ED, PTSD, reactive aggression, general anesthesia, and the amygdalocentric neurocircuitry (AN) that may explain this relationship. Therefore, the purposes of this integrative literature review were as follows: (1) present a synopsis of current literature describing PTSD, the amygdalocentric neurocircuitry, ED, reactive aggression, and the mechanism of action of drugs used in general anesthesia and their interaction with the amygdalocentric neurocircuitry; (2) synthesize this evidence; and (3) develop a new theoretical model that can be tested in future research studies.

Review of the Literature

A review of literature was conducted using the following databases: Cumulative Index to Nursing & Allied Health Literature, National Center for PTSD's PILOTS, and Google Scholar. The search criteria were limited to

the English language and included published articles from 1996 to 2012. Each database was searched using a combination of the following primary search key terms: *PTSD, emergence delirium, delirium, agitation, reactive aggression, amygdala, hippocampus, prefrontal cortex, combat veterans, and general anesthesia.*

• **Posttraumatic Stress Disorder.** Posttraumatic stress disorder is an incapacitating psychological disorder affecting individuals across the lifespan. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, PTSD is composed of 3 symptoms: (1) persistent reexperiencing of the traumatic event, (2) persistent avoidance of stimuli associated with the trauma, and (3) numbing of general responsiveness and persistent symptoms of increased arousal.^{3(p463)} Current diagnostic guidelines require that symptoms associated with PTSD must be present for more than 1 month and must cause substantial distress or impairment in normal functioning.³

The pharmacologic treatment of PTSD is a continually evolving field of study. Recommended pharmacologic treatment modalities by the VA/Department of Defense Clinical Practice Guidelines for monotherapy are serotonin reuptake inhibitors (sertraline and paroxetine), serotonin norepinephrine reuptake inhibitors (venlafaxine), tricyclic antidepressants, and monoamine oxidase inhibitors.⁴ Prazosin, an α_1 -antagonist, has been shown to increase the performance of the prefrontal cortex and decrease amygdala function, decreasing the incidence of nightmares, nonnightmare distressed awakenings, and insomnia in patients with PTSD.^{5,6} Topiramate, an anticonvulsant, improves symptoms related to PTSD by potentiating the inhibitory activity of γ -aminobutyric acid (GABA) receptor activity.⁷

General Anesthesia Effects on the Amygdalocentric Neurocircuitry

The importance of acknowledging the potential adverse effects of drugs used in general anesthesia in patients with PTSD is demonstrated by their pharmacologic properties and interaction with the AN. According to Rauch and associates,⁸ the interactions between the amygdala, medial prefrontal cortex (mPFC), and hippocampus comprise the AN. Both GABA and *N*-methyl-D-aspartic acid (NMDA) receptors are abundantly located in the AN.⁹ The amygdala, hippocampus, and mPFC are the primary regions responsible for producing amnesia under general anesthesia.¹⁰ The amygdala, however, has recently been identified as the region most likely to cause amnesia during administration of benzodiazepines, propofol, and volatile anesthetic inhalation agents.^{11,12} Activation of GABA_A receptors in the basolateral amygdala decreases the expression of activity-regulated cytoskeleton proteins in the hippocampus.¹¹ Inhibited formation of these proteins in the hippocampus prevents

the storage of memories, producing amnesia.¹¹

Increased glucocorticoid and glutamatergic tone during chronic stress can cause dendritic remodeling of the mPFC and hippocampus, resulting in decreased benzodiazepine binding sites on GABA_A receptors. The antianxiety effects of benzodiazepines remain effective; however, they do not provide a reduction of hyperarousal in patients with PTSD.¹³ Bremner and associates¹⁴ found a decreased amount of benzodiazepine receptor binding sites in the mPFC of combat veterans. The alteration of GABA_A receptor function in patients with PTSD may prevent volatile anesthetics from decreasing hyperarousal during general anesthesia, resulting in an increase in dysregulation of the hippocampus, mPFC, and amygdala.

Description of Amygdalocentric Neurocircuitry

• **Loss of Amygdala Control in Posttraumatic Stress Disorder.** The primary area of the prefrontal cortex associated with inhibition of the amygdala is the mPFC.¹⁵ The prefrontal cortex is associated with executive functions that include cognitive behaviors, personality, and decision making.¹⁶ The amygdala is associated with the transmission of feeling fear and excitation to the brainstem and hypothalamic areas.¹⁶ The mPFC and amygdala communicate primarily via GABA-mediated neurons. The GABA-mediated neurons in the mPFC inhibit activation of the central amygdala by activation of postsynaptic GABA_A receptors present on the basolateral amygdala.¹⁷

Studies using functional magnetic resonance imaging (fMRI) have shown a decrease in anterior cingulate volume of the mPFC and a decreased responsiveness of the mPFC among individuals with PTSD.¹⁸ The decreased mPFC inhibitory control over the amygdala allows an unopposed hyperresponsive amygdala to transmit feelings of fear and excitation to the brainstem and hypothalamic areas.¹⁷ Patients with PTSD also present with widespread impairment of GABA_A-ergic, short-latency, intracortical inhibition in the right hemisphere and right-sided impairment of presynaptic GABA_A-mediated modulation.¹⁹ In addition, patients with PTSD had a marked increase in glutamatergic intracortical facilitation in the right hemisphere.¹⁹ The increased glutamatergic tone may be responsible for the decrease in mPFC volume. In a retrospective study of patients with burns, those who were treated with ketamine, an NMDA receptor antagonist, had a decreased risk of experiencing PTSD.²⁰ In rats, NMDA receptor blockade prevented the ability of glutamate to cause stress-induced dendritic changes in the mPFC.²¹

• **Hippocampus and Posttraumatic Stress Disorder.** The hippocampus is a region of the cerebral cortex that is located in the ventral part of the cerebrum.²² The hippocampus is responsible for the encoding and storage of episodic memories²³ and for allowing the retrieval of information to determine the context of the situation.²⁴ The ventral hippocampus decreases behaviors related

to anxiety by having an inhibitory effect on the lateral amygdala.²⁵ The hippocampus is responsible for the activation of the hypothalamic-pituitary-adrenal axis.²⁶

Reduced hippocampal size has been suggested to increase the risk of PTSD.²⁷ Hippocampal volume decrease due to dendritic remodeling in the hippocampus has been associated with chronic stress and with PTSD.¹⁸ A decrease in hippocampal volume is also associated with memory distortion in patients who have a diagnosis of PTSD.²⁸ Hayes and colleagues²⁸ used fMRI and found that patients with PTSD who have a reduction in left hippocampal activity also demonstrated an increased presentation of irritability, outbursts of anger, hypervigilance, and an exaggerated startle response.

Spivak and colleagues²⁹ measured an increase in circulating neuroactive steroids, (dehydroepiandrosterone and dehydroepiandrosterone sulfate) in patients with combat-related PTSD. These steroids possess inhibitory activity at GABA_A receptors, producing a decreased GABAergic tone and causing an increased glutamatergic tone and suppressed activity of the hypothalamic-pituitary-adrenal axis regulated by the hippocampus.³⁰ The decreased function of the hippocampus and inability to accurately transmit neuronal impulses to the amygdala prevents the application of appropriate contextual information to afferent stimuli and thus perpetuate the conditioned fear response associated with the afferent stimuli.³¹ The inability to properly identify stimuli as being benign vs dangerous further potentiates the excitability of the amygdala. This deficiency of hippocampal control over the amygdala may increase the risk of overreacting to a benign stimulus (ie, noise, pain, tactile stimulation) as being dangerous, and it may increase the risk of reactive aggression.

Emergence Delirium

Emergence delirium can occur only on discontinuation of inhalation and intravenous drugs used during sedation and general anesthesia.³² Emergence delirium manifests in approximately 4.7% to 21.3% of patients and involves frequent nonpurposeful psychomotor movements, agitation, and overt physical aggressiveness.³² The most prevalent risk factors that have been reported for ED are preoperative administration of benzodiazepines and untreated postoperative pain.³² Emergence delirium is associated with many adverse outcomes: self-extubation, removal of intrabody tubes and lines, causing harm to patient and staff, and longer stays in the postanesthesia care unit.³²

- **Auditory Stimulation During Emergence.** During emergence from anesthesia the first sense to return is the sense of hearing, as measured by the middle latency auditory evoked response.³³ This auditory evoked response measures the response to noise by the brainstem, auditory cortex, and associated areas of the cortex.³⁴ Auditory stimulation activates areas of the acoustic thalamus,

which synapses with the lateral nucleus of the amygdala, or lateral amygdala (LA).³⁵ The thalamo-LA synapse is responsible for auditory fear conditioning and increased risk of inappropriate response to auditory stimuli.³⁵ The heightened response may result from the acute and chronic stress associated with PTSD, which causes a downregulation of large-conductance Ca²⁺-activated potassium channels (BKCa) located in the LA.^{36,37} Under normal function, activation of BKCa channels are responsible for decreasing stress-induced behavior. The decrease in BKCa channels is associated with an increase in excitatory activity evoked by NMDA postsynaptic potentials at the thalamo-LA synapse.³⁶

Increased amygdala activity related to auditory stimulation may also be increased because of dysfunctional innervations between the hippocampus and amygdala, and inappropriate retrieval of a traumatic memory associated with similar sounds heard during emergence.²⁵ Activation of the thalamus with an increase in regional cerebral blood flow was observed during a PTSD flashback provoked by combat sounds while undergoing single-photon emission computed tomography.³⁸ Similarly, the authors postulated that retrieval of a fear-conditioned response may also occur when the sense of smell and tactile stimulation return during emergence, resulting in aggression and agitation.³⁸

- **Reactive Aggression.** Reactive aggression, or impulsive aggression, is a reaction to a threat that is perceived as being dangerous.³⁹ Reactive aggression results from a deficiency of top-down control (mPFC and hippocampus) and increased bottom-up control (amygdala and insula).^{39,40} This basic reaction to a threatening stimulus is initiated by activation of the amygdala.³⁹ The dysfunction of the mPFC, more specifically the anterior cingulate cortex, to inhibit the exaggerated response of the amygdala and insula, results in a lower tolerance for activation of the motoric aggressive response to external stimuli, that is, noise.³⁹ Similar to the observations (flailing arms, attempts to escape, and directed harm to self and others) made during ED, they are also associated with motoric aggressive responses related to reactive aggression.³⁹ The impulsive reaction to this threat involves a state of rage directed at the source of what is being perceived as being dangerous.³⁹

Posttraumatic stress disorder has been found to be closely related to aggression. Teten et al⁴¹ investigated the type of aggression found primarily in veterans with PTSD. In that study, 136 veterans completed the Impulsive Premeditated Aggression Scale and the Buss Perry Aggression Questionnaire. Impulsive aggression was found to be present in 70% of veterans with PTSD.⁴¹ Veterans with diagnosed severe PTSD were found to have higher total aggression scores on the Northeast Program Evaluation Center survey after a comprehensive treatment program.⁴² According to Berenz et al,⁴³ persons who ex-

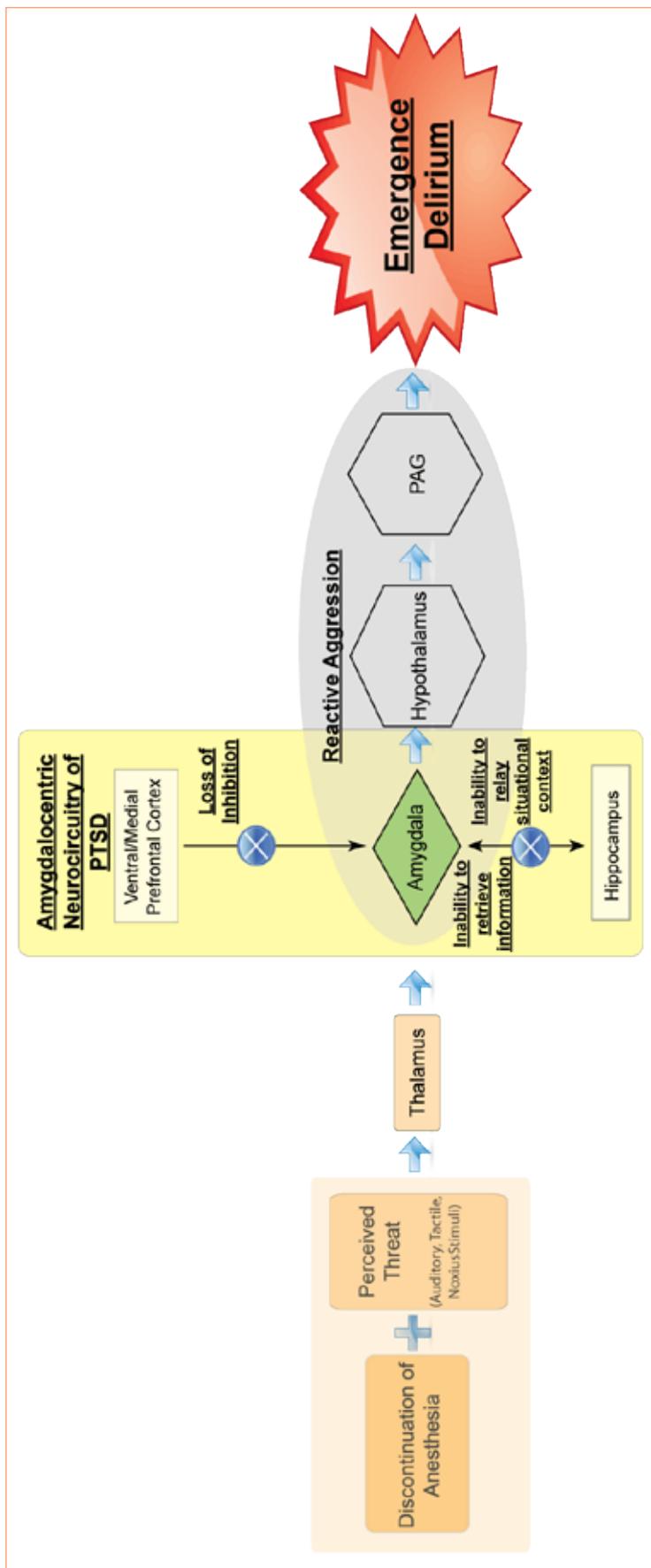


Figure. Theoretical Model of Amygdalocentric Neurocircuitry-Reactive Aggression

Progression of a perceived threat's stimulus through abnormal amygdalocentric neurocircuitry, activating the reactive aggression pathway, being displayed as emergence delirium. (Adapted from Rauch et al.⁶)

Abbreviations: PAG, periaqueductal gray matter; PTSD, posttraumatic stress disorder.

perience higher sensitivity levels to anxiety may also have more intense PTSD symptoms. Increased levels of anxiety are related to higher levels of aggression.³⁹

Model Development Through Synthesis of the Literature

The development of PTSD is associated with neurologic changes in the AN. Sedation and amnesia produced by volatile anesthetics, propofol, and benzodiazepines depend on their action on the different regions of the AN.^{9,10} Discontinuation of the drugs used during anesthesia for sedation and amnesia causes redistribution of the drug away from their target receptors on the amygdala, mPFC, and hippocampus. During emergence from general anesthesia, the patient's sense of hearing is the first sense to return.³⁴ Sounds in the operating room may cause activation of the acoustic thalamus.^{34,35} Activation of the thalamo-LA synapse allows for increased activation of the amygdala through NMDA receptor activation due to decreased inhibitory innervations and downregulation of BKCa channels.³⁴⁻³⁶ The increased auditory, tactile, and nociceptive stimulation increases the activity in the amygdala. The amygdala, uninhibited by the mPFC and hippocampus, transmits signals via the stria terminalis to the hypothalamus.⁴⁰ The hypothalamus sends impulses to the dorsal part of the periaqueductal gray matter.^{39,40} Activation of the periaqueductal gray matter increases motor activity by stimulation of neurons in the brainstem and spinal cord.⁴⁰ Increased motor activity may result in flailing of arms, attempt to escape, and uncooperative behavior, all of which are indicative of what anesthesia providers describe as ED. Thus, it can be hypothesized that during the emergence from general anesthesia there is increased amygdala activity along with decreased activity in the mPFC and hippocampus related to PTSD, which can lead to an increased risk of ED (Figure).

Implications for Theory Development, Research, and Practice

The only apparent published study that identified the risk factors for ED among combat veterans identified PTSD as a risk factor, but it was not statistically significant as an independent predictor of ED.⁴⁴ McGuire⁴⁴ used a cutoff score of greater than 50 on the Posttraumatic Checklist–Military (PCL-M) to make a positive diagnosis of PTSD. Bliese et al⁴⁵ demonstrated that using a score of 30 to 34 on the PCL-M maintained high specificity (0.9) and sensitivity (0.7) in the diagnosis of PTSD. Further studies are encouraged to use a PCL-M cutoff score of 30 to 34 to decrease the possibility of a false-negative PTSD diagnosis. The risk of experiencing PTSD following combat exposure can increase by 300%,⁴⁶ and it is essential to identify combat veterans who may have undiagnosed PTSD.

The proposed theoretical model (see Figure) is based on the assumption that external stimuli activate the amygdala, leading to ED. Interventions to decrease stimulation during emergence from anesthesia may decrease the onset of ED. Further research is encouraged to identify interventions that may be used to decrease stimuli during emergence, such as instituting a “quiet time” during emergence. The alterations to neurologic regions that are responsible for producing the effects of general anesthesia may prevent an appropriate depth of anesthesia for surgery. Research is recommended that investigates use of anesthesia adjuncts to augment volatile anesthetics during anesthesia and thus decrease the incidence of PTSD.

Dexmedetomidine, an α_2 -adrenergic agonist, has been shown to decrease the incidence of ED in children.⁴⁷ Administration of anticonvulsant medications (ie, topiramate) preoperatively could lead to a decrease in ED by increasing GABAergic neurotransmission,⁷ which is normally lost during emergence from anesthesia.³³ In an effort to decrease noxious stimuli such as postoperative pain, a comparison study that will examine the differences of ED occurrence following an opioid-based general anesthetic, general anesthesia combined with regional anesthesia, and regional anesthesia techniques alone may help to identify the anesthetic plan most suitable for patients with PTSD.

Conclusion

The purpose of this integrative literature review was to review and synthesize recent literature and data to increase the understanding of ED and PTSD, and to develop a theoretical model that identifies cerebral regions capable of increasing the risk of ED in patients with PTSD. The theoretical model is based on research from multiple disciplines in the scientific community. The belief that PTSD is a pseudopsychological disorder has been disproved by numerous research studies that have identified specific changes that occur as a result of a

traumatic experience.^{17-19,27,28} The authors of this article hope that there will be an increased interest in research in an area that has been neglected for many years. The lack of research among this vulnerable population should be alarming to the anesthesia community. With a major increase in veterans returning from combat operations who will undoubtedly require surgery, it is important to create a greater understanding regarding the interaction between anesthesia and PTSD.

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