

Posttraumatic Stress Disorder as a Function of Failed, Hippocampally Driven
Memory Consolidation:
The Therapeutic Value of a Good Night's Sleep

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Abbreviated title: Hippocampally-Based Theory for Treating PTSD

Text pages: 47

Figures: 0

Tables: 5

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Grants: NIH MH48161 and NS41582 to WBL

Key Words: nefazodone, hippocampus, amygdala, declarative memory, replay, teachback, CA3

Abstract

Recent studies establish the efficacy of the drug nefazodone in treating posttraumatic stress disorder (PTSD). Although this drug is prescribed as an antidepressant, we believe that its actual efficacy in treating PTSD lies elsewhere. To interpret this drug's beneficial effects in PTSD, this paper integrates contemporary literature on memory consolidation, including the computational literature and current theories of amygdala function. The result is a specific theory of PTSD that leads to a strong, apparently novel understanding of nefazodone's efficiency. Instead of assuming that PTSD is a pathological state of a brain with an overactive amygdala, we postulate that PTSD reflects a normally functioning brain driven to an extreme state, including an overly active amygdala, and then is stalled in this undesirable state. As the normal engine of episodic memory consolidation, the hippocampus appropriately drives the amygdala when attempting to store a traumatic episode. What results from this drive are the major symptoms of PTSD, especially the characteristic nightmares. These nightmares prevent normal sleep and thus, by hypothesis, prevent full episodic memory consolidation, including the downgrading of hippocampally stored memories. Nefazodone, and now perhaps two other drugs facilitate recovery from PTSD because they allow the traumatized victims to sleep through their nightmares; this effect is almost entirely independent of the antidepressant action of the drug.

Introduction

The alleviation of posttraumatic stress disorder (PTSD) is important because it currently affects 13-17% of Vietnam veterans (Davidson and Fairbank, 1992) and possibly 8% of the general adult population (Kessler et al., 1995). PTSD arises in these patients after exposure to catastrophic stress such as rape, torture, war, or assault (Spitzer et al., 1994). This anxiety disorder is characterized by an amygdala-based, hyperfear response associated with a specific traumatic event (Spitzer et al., 1994; Davis et al., 1997). Additionally, victims seem to display over-generalized fear responses for an undefined period following the trauma and habitually have nightmares and/or flashbacks for the event (for review see Pitman, 1997). We hypothesize that PTSD symptoms can be explained by a memory consolidation hypothesis. Specifically, hippocampal region CA3 teachback/replay primes and drives the amygdala and neocortex, leading to the list of symptoms, shown in Table 1, that are the diagnostic criteria for PTSD.

Table 1 here.

While the link between the symptomatology of PTSD and memory consolidation has previously been hypothesized (Van der Kolk et al., 1997), biological bases and theories of PTSD emphasize the amygdala rather than the hippocampus (for review see Pitman, 1997). As a result of this emphasis, there is a trend to design treatments of the symptoms rather than one particular symptom and the disease itself.

The theory presented here combines clinical observations with observations in the experimental neuroscience and cognitive literature. Because of the explicit neuroscientific

arguments advanced here, our theory suggests animal models of PTSD specifically focusing on a novel drug class.

The de facto, unsuspected prototype of this class is nefazodone (commercial name: Serzone, Bristol-Meyers Squibb, New York, NY), and it now seems to be joined by two other drugs, Mirtazapine and Trimipramine. We propose that the effectiveness of these drugs arises not from their antidepressant effect (Kaplan and Sadock, 1995) but from an antifear effect that operates particularly well on the irrational and overwhelming fear which characterizes nightmares. However, even though the amygdala is the presumed substrate and provocateur of this fear, our theory centers on hippocampal formation and episodic memory encoding as the critical issues for understanding the basis of PTSD and its ultimate cure.

Nefazodone has been shown to speed the cure of PTSD (Davidson et al., 1998; Hertzberg et al., 1998; Hidalgo et al., 1999; Zisook et al., 2000), and the theory presented here posits that this may be a true cure – not merely symptom alleviation – in the case of patients whose symptomatology emphasizes nightmares and lack of sleep. In one study (Zisook et al., 2000), there was a reduction in the frequency and intensity of symptoms among the fifteen veterans who completed the study. We suggest that alleviation of PTSD arises from nefazodone's ability to increase rapid eye movement (REM) sleep (Rush et al., 1998, demonstrated in depressed patients) and to allow for the normal REM sleep cycle that is necessary to complete the memory consolidation process and the weakening of memories stored in the hippocampal formation.

Linking memory consolidation and PTSD contrasts the recent theories of hippocampal pathology and PTSD. Specifically, we hypothesize that there are no abnormal processes occurring in any part of the brain during the early stages of the disease. Rather, the psychologically agonizing symptoms and the disruption of normal cognitive function and

emotional well being are caused by *normal* functions pushed to an *extreme*, as opposed to the creation of a pure pathological state. These normal functions, which depend on hippocampal-neocortical interactions, are part of declarative memory consolidation and are prevented by the associated emotional potency of the memory. This emotional potency and the normal mechanisms of memory consolidation produce most of the common PTSD symptomatology. By downgrading the autonomic, fear response of a nightmare, we hypothesize that nefazodone-like drugs produce symptom alleviation which accompanies a good night's sleep. This does not mean that the patient's nightmares are absent, only that the patient is now able to remain asleep during those nightmares. Thus, such a patient experiences the full sleep cycle which allows for memory consolidation and the downgrading of the hippocampal memory store, including its emotionally potent component.

1.1 Hypotheses Defined

Central Hypothesis: The primary symptomatology of PTSD arises as a result of the hippocampus attempting to perform its assigned job: producing neocortically stored, episodic memory. The key to explaining this disease, and nefazodone's alleviation of its symptoms, is understanding the normal function of the hippocampus in memory consolidation. Supplementing this brief analysis of memory consolidation will be several somewhat novel hypotheses concerning the functioning of hippocampal region CA3. First, there exists a queue priority for replaying each hippocampally-stored intermediate-term memory (ITM), and second, emotionally charged memories receive higher priority.¹ Third, for such strongly encoded memories, there exists a specific requirement for downgrading the strength of such a

¹ Note that we distinguish short-term memories—on the order of tens of seconds and prefrontally-based—from intermediate-term memories which are of greater longevity and, in the case of episodic memory, require the hippocampus.

hippocampally-based memory; this specific downgrading depends on the successful and correct neocortical encoding of the hippocampally stored episode. These ideas are derived from current theoretical and experimental work on hippocampal function and allow a more complete understanding of PTSD's relationship with memory consolidation. A fourth critical hypothesis states that memories can be stored in the hippocampus while remaining non-declarative.

1.2 Overview of the hypotheses

The problem of explaining the biological basis of cognition or of mental diseases is often not in generating new ideas, but rather in appropriately emphasizing and cointegrating the right set of experimentally substantiated ideas. Here we introduce four ideas and one corollary (see Table 2) to explain nefazodone's curative action in a manner consistent with contemporary neuroscience. An in-depth presentation begins at section 3.

First, the hippocampus serves as an intermediate-term memory store necessary for the consolidation of long-term memories as declaratively accessible memories, and these long-term declarative memories ultimately reside in the neocortex (Milner, 1972; Cohen and Squire, 1980). The declarative aspects of hippocampally-stored memory are equivalent to the contextual and episodic aspects of the encoded event. Thus, in the case of PTSD, the contextual and episodic aspects are the detailed description of the time, place, and surrounding details of the traumatic incident.

Table 2 here.

Second, the role of the amygdala is multifaceted (for review see Medina et al., 2002 and Richter-Levin and Akirav, 2000). Two subregions partially reflect this multifaceted nature: (a)

the basolateral group, composed of the lateral, basolateral, and basomedial nuclei and (b) the central group, composed of the central medial and central lateral nuclei. The multifaceted role of the amygdala is further complicated by the effect of the basolateral amygdala on the hippocampus at the encoding stage. In the case of highly emotional episodes, basolateral amygdala activation correlates with the strongest, longest lasting forms of synaptic modification in the hippocampus formation. Thus, PTSD requires amygdala activation at the hippocampal encoding stage, and it requires amygdala-mediated fear and agitation when the pathology exists.

Third, the formation of long-term episodic memory in the neocortex requires an interplay between the hippocampus and neocortex. This progressive interplay produces successively more precise and more declaratively accessible encodings. Eventually, such encodings can come to exist in the neocortex essentially independent of the hippocampus (as in the case of H.M., Scoville and Milner, 1957). The first stage of this interplay occurs during slow wave sleep (SWS) when the hippocampus replays (or teaches back) an earlier episodic experience. The second stage occurs during REM sleep as the neocortex tries to repeat this information, which it has received from the hippocampus.

An important corollary to this third concept is prioritized teachback/replay. Prioritized teachback/replay posits a type of competition between the CA3-localized ITM encodings: there will be a multiplicity of stored episodes in the hippocampal formation. But only one, or a fraction of one, can replay at a time. If one stored episode dominates in terms of many more encoding neurons and the greatest net excitatory synaptic-strength interconnecting these neurons, then this episode will dominate the competition for replay. In this way, a teachback/replay queue of encoded episodes can be functionally prioritized.

To say it another way, CA3-stored memories compete with each other to be replayed via a *biased random* process. The experienced emotionality and the longevity of an actual episode control the bias for replay. Here at the encoding stage (i.e., during the traumatic event and immediately after), the amygdala plays a pivotal role once again. The emotional experience during the episode strongly activates the basolateral amygdala and, as a result, the hippocampally-encoded episodic memory is better able to withstand decay, erasure, and the normal overwriting processes that are studied in the laboratory as long-term depression (LTD, e.g., Levy and Steward, 1979). Thus, there is a range of memory strengths determined by the associated emotionality, and memory strength determines queue priority.

Fourth, the conditions needed for achieving erasure are critical and nontrivial in the case of PTSD. When the fully associated, long-term neocortical encoding of the traumatic episode agrees with its hippocampal teacher, then and only then can erasure occur in the hippocampus. That is, erasure is episode specific. This fourth idea is the most critical idea of the theory relative to patient suffering and cure. **Specifically, this erasure is the process of synapse-specific LTD in CA3. Because queue priority depends on synaptic strength, this LTD is equivalent to a demotion of queue priority and, thus leads directly to symptom alleviation and cure.**

Before drawing out the basic neuroscience motivating these hypotheses, we summarize the exciting and insightful clinical research that inspires the entire presentation.

2.0 Hypothesis: nefazodone-like drugs improve PTSD symptoms, speeding cure by allowing patients to sleep through their nightmares.

Most posttraumatic stress disorder patients relive their traumatic experiences during sleep as intense, vivid nightmares (Ross et al., 1989). Because strong negative emotions are part of the

episode, their dreams should, if dreaming is related to memory storage, contain heightened fear. However, the arousing effects of these strong negative emotions, namely the fear that defines a nightmare, wakes the dreamer. Presumably amygdala-produced, somatic fear causes the patients to wake up in the middle of their dreams. Such awakening would disrupt a neocortical-hippocampal dialogue (see section 3.5) which is a normal part of memory consolidation.

The sleep deficits and disturbances of the regular sleep pattern (for review see Mellman, 1997) seem to correlate with deficits in learning and memory; 67-100% of military veterans with PTSD are reported to have poor memory of the traumatic episode. Moreover, this memory deficit includes memory of new events (Archibald and Tuddenham, 1965; Burnstein, 1985). Recent studies continue to point to memorial dysfunction as a major symptom of PTSD (Vasterling et al., 1998) and to nefazodone as a cure for this dysfunction. These observations of poor memory for new events are consistent with the traumatic event affecting hippocampal function.

Multiple studies point to the effective treatment of PTSD with nefazodone (Davidson et al., 1998; Hertzberg et al., 1998; Zisook et al., 2000). One such study, Davis et al., (2000), tested nefazodone for treatment of chronic, combat-related PTSD among Vietnam War veterans. The study found high improvement rates in the symptoms of the veterans, mainly in the first four weeks of treatment (compare this rapid effect with the timelag of antidepressant action). Another study by Davidson et al. (1998) *demonstrated a decrease in nightmares and sleep disturbances*, in addition to the usual decrease of symptoms seen, when patients were treated with nefazodone.

Recent experiments have confirmed the REM-preserving effect of nefazodone. Such studies also confirm that the drug produces a decrease in the time course of recovery from PTSD

(Davidson et al., 1998) and has positive effects on sleep (Sharpley et al., 1992; Sharpley et al., 1996; Armitage et al., 1997). Zisook et al. (2000) focused on nefazodone's effects on sleep and ensuing symptom alleviation. Patients reported an increase in total sleep hours, greater ease in falling asleep, a decrease in nightmares and sleep disruptions, and a more positive evaluation of their sleep. Thus, in the clinical literature, there is already some implicit appreciation of the theory we present below, and the above echoes the clinical observations and insights. These studies point to nefazodone-like drugs as a more effective treatment for PTSD. But how might nefazodone alleviate PTSD symptoms?

First, we want to emphasize the observations that argue against nefazodone's selective serotonin reuptake inhibitors' (SSRI) antidepressant effects as producing a cure. While fluoxetine and nefazodone have been shown equally efficient at reducing depressive symptoms, nefazodone's effects on sleep differ significantly from fluoxetine.

Nefazodone increases total REM sleep, increases sleep efficiency, and decreases awakenings (Rush et al., 1998). Fluoxetine either does not do this or has the opposite effect (Rush et al., 1998). Even more importantly, like the negative effects of fluoxetine on sleep, **the positive effects of nefazodone on sleep appear to be almost immediate.** Rush et al. (1998) noted this when describing the data from just the second night of nefazodone treatment:

The analysis of data from night-2... a significant effect (pre- to posttreatment change) was found between nefazodone and fluoxetine on sleep efficiency, number of awakenings, percent AMT, percent stage 1, percent stage 2, percent REM, and REM latency when all subjects were included (all $p < 0.01$).

Combining these observations with the textbook fact (Murray and Kelly, 2001) that fluoxetine and the other antidepressants in its class take two to four weeks to take effect forces us to

conclude that nefazodone is in two drug classes: it is an SSRI antidepressant (albeit a rather weak member), and it is the first representative of a new class of drugs affecting nightmares. The different effects on sleep by nefazodone, as compared with fluoxetine, suggest that compounds may exist that affect nightmares without being antidepressant drugs.

Patients, particularly those who amended their nefazodone regimen in order to increase sleep time, suggest a focus on sleep disruption. In one study concerning nefazodone's alleviation of PTSD symptoms, at least three of the patients violated protocol by taking their medications before bedtime, instead of the instructed regimen (Zisook et al., 2000). These patients justified their infringement of the explicit instructions by stating that they were trying to manage both their nightmares and their insomnia. Based upon the decrease in PTSD symptoms in these patients, this procedure was then successfully adopted for the treatment of three other individuals. We propose that rather than eliminating nightmarish dreams, nefazodone allows such dreams to occur without the excessively heightened fear response that would normally cause awakening. Moreover, and especially in contrast to alcohol, barbiturates, minor tranquilizers, and SSRIs, nefazodone does not decrease the amount of dream sleep (see Sharpley et al., 1996; Rush et al., 1998; Vogel et al., 1998; Hicks et al., 2002). Thus, we can conjecture that nefazodone decreases nightmare-associated agitation by specifically affecting the physiology occurring in, or controlled by, the amygdala during dream sleep.

As we interpret the clinical effects of nefazodone, we arrive at the core of our theory. The second part of the hippocampal-neocortical dialogue, REM sleep, is critical to the downgrading of the traumatic memory and to completing the integration of the traumatic episode with other memories in the neocortex (see Table 2, hypothesis four). Without sufficient REM sleep, the episodic memories persist in the hippocampus where they have the highest priority in

the replay queue (see section 3.4). Subsequent sleep episodes re-elicite the hippocampal replays, biasing dreams again for the same nightmares, causing further awakenings and further failure of the normal sleep cycle necessary for consolidation and erasure within the hippocampus.

3.0 The Basic Science Underlying the Four Hypotheses and One Corollary

This section is divided into five major subsections delineating the four hypotheses and one conjectured corollary (Table 2). The first four sections concern memory consolidation and episodic encoding as a neocortical phenomenon dependent on the hippocampal formation. The fifth section relates to the downgrading of the hippocampal memory strength.

3.1 Role of the Hippocampus in Declarative Memories

As stated above, our first hypothesis concerns the hippocampus and its role in long-term memory (LTM) storage. The hippocampus plays a central role in the consolidation of declarative memories. It **is necessary** for the consolidation of declarative memory (Scoville and Milner, 1957; Cohen and Squire, 1980; Cohen and Eichenbaum, 1993), and this is uncontroversial. But, based upon recent research described below, hippocampal encoding is **not sufficient**. That is, declarative memory is not synonymous with hippocampal memory. This distinction between hippocampally dependent storage and a hippocampally stored memory is important here because this distinction describes the status of episodic memory for the suffering PTSD victim.

The view that hippocampal storage can occur without declarative accessibility is new and not without controversy (Manns and Squire, 2001). However, recent studies (Chun and Phelps, 1999; Greene et al., 2001) and perhaps the PTSD patients themselves argue otherwise. Early on, PTSD patients appear to be amnesic for the traumatic event but eventually they may remember

the episode. Thus, we hypothesize that the memory for the traumatic event remains intact but is inaccessible to the prefrontal, cortical, declarative memory system until the patients begin to recover (Van der Kolk et al., 1997), suggesting that their hippocampal-dependent memory is not yet declarative.

A relevant example of what is arguably a non-declarative hippocampal memory was recently produced in our lab (Greene et al., 2001). We used a learning task requiring a normally functioning hippocampus (Dusek and Eichenbaum, 1997; Nagode and Pardo 2002). Subjects were trained and tested using the five-item transitive inference task in which Hiragana letters replaced the letters in the following hierarchy $A > B > C > D > E$. Training consisted of only adjacent pairs (i.e., AB, BC, CD, DE), and the relevant group of subjects was not told about the transitivity relationship. That is, from training experience with $B > C$ and $C > D$ (using essentially meaningless Hiragana symbols rather than Roman letters), the subjects were tested on the pair BD, a pairing of symbols which they had never seen during training. The key finding of this experiment was that accuracy on the inferential judgment task (i.e. $B > D$) did not depend on awareness of the hidden hierarchy among the individual symbols (Greene et al., 2001). In other words, the subjects who said they were guessing answered the BD transitivity question correctly 87.5% of the time. With sufficient training, more than 95% of the subjects became aware of the transitivity relationship (unpublished results). To say it more simply, in one paradigm over half the subjects said they were guessing yet their success equaled those subjects who could verbally explain (i.e. declare) the transitive nature of the task.

The Greene et al. (2001) results have implications pertinent to PTSD victims. Particularly for episodes far removed from past experiences, these results suggest that an intermediate-term, hippocampally-localized memory is inaccessible to the working memory

system of prefrontal cortex. Therefore, such hippocampal memories do not register as declarative memories. Recent imaging studies indirectly support this idea. In one fMRI study, verbal associations that were mainly completed unconsciously were accompanied by activation in the medial temporal lobe (Hunkin et al., 2002). Indeed, one could guess this inaccessibility from the neuroanatomy, given that there are no direct connections between Broca's area or prefrontal areas 46/9 and the entorhinal cortex, much less the hippocampus proper (for review of neural connections see Suzuki, 1999; Lavenex and Amaral, 2000). This lack of direct connectivity contrasts with the direct and reciprocal connections between dorsolateral prefrontal cortex (i.e., areas 46/9) and the major neocortical association regions of the temporal and parietal cortices (for review of neural connections see Petrides and Pandya, 1999; Barbas, 2000; Lavenex and Amaral 2000). Therefore, considering that the prefrontal cortex lacks direct access to the intermediate-term memories stored in the hippocampus, it is not surprising that these memories are unavailable for verbalization until they are consolidated permanently in the neocortex where direct connections exist. Thus the anatomical and experimental evidence is beginning to support the theory that hippocampal and declarative memory are not equivalent.

The inaccessibility of certain new, strange memories appears to explain many of the symptoms of PTSD, including the absence of declarative memory/narrative ability for the traumatic event as noted in Table 2. We suggest that the traumatic experience, particularly the associated affective information characteristic of PTSD-inducing episodes, are largely foreign to all previous memories. As a result, previously encoded memories, which are in fact specific neocortical connectivities, are not sufficiently compatible with the new experience. That is, the neocortical synapses and their strengths (including neocortical-basolateral amygdala interconnections) that define previously encoded experiences are inappropriate for the new

memory. As defined in hypothesis 3, this extreme novelty leads to a traumatic event “staying in” the hippocampus longer.

This differentiation between hippocampal-dependent declarative memory and declarative memory itself is critical to our hypothesis. A hippocampal ITM that is not yet declarative occupies a central role in our explanation of certain memorial symptoms occurring in PTSD patients (for review of memory deficits in PTSD see Wolfe and Schlesinger, 1997; Layton and Krikorian, 2002). Thus, a specific prediction of the present theory is that the declarative amnesia associated with extreme cases of PTSD is not caused by hippocampal damage (as discussed by Bremner et al., 1999), but rather arises from the memory’s declarative inaccessibility and its hippocampal occupation that denies new episodes access to this ITM storage device.

Rather than serving as a declaratively accessible store, the ITM stored in the hippocampal system can be pictured as directing a neocortical linking of smaller memory fragments dispersed across neocortex and basal amygdala. That is, as the hippocampus directs the formation of the appropriate, specific connectivity between these memory fragments, and when these directions are followed, declarative accessibility occurs. Clinical observations indicate that this neocortical storage is a gradual process in the case of prolonged, severely traumatic episodes (Van der Kolk et al., 1997). The traumatic experience of the PTSD patient is initially remembered as a somatosensory flashback experience with little narrative content of the traumatic event. As time progresses (and, we hypothesize, as the memory becomes consolidated in the neocortex), narrative ability gradually increases to almost 100%.

3.2 Hippocampal Memory and the Amygdala

The amygdala appropriately dominates current theories of the neural substrate of posttraumatic stress. Thus, it is important to relate our theory to the amygdala-based theories. The critical idea is this: **even though neuronal representations in the hippocampus are anhedonic and contextual (Hirsh, 1974; Kesner and Hardy, 1983; Nadel and Willner, 1980), the appropriate neural firing in the hippocampus leads to amygdala activation that is, in essence, internally-generated fear.** This idea comes via Fanselow's research that discerns context-generated fear versus simple stimulus-generated fear; with this insight, we will connect our hypothesis with the current amygdala-based theories of PTSD. That is, certain types of hippocampal memories should be expected to activate the amygdala and thus bias amygdala activation to produce stress and fear. We will then consider the role played by the amygdala in the hippocampally localized storage of the traumatic episode itself.

The amygdala and the hippocampus are intimately interconnected, and these connections are important to our theory from multiple perspectives. Most importantly, memories in the hippocampal formation can produce fear (Fanselow, 2000), and there is a sensible circuitry that would mediate such learned fear. The efferent connections from the hippocampus and hippocampal formation to the amygdala include direct connections to the central nucleus as well as particularly strong connections to the basolateral group, which itself projects to the central group (Pitkanen et al., 2000). Thus, replay of the hippocampally stored memory of a traumatic event can be expected to activate the amygdala. Second, the basolateral nucleus of the amygdala can be analogized to high-order association cortex, like several regions in the temporal lobe. That is, just like the reciprocal connections between the entorhinal cortex and visual association cortices and between the entorhinal cortex and auditory association cortices, the connections between the basolateral nucleus and the entorhinal cortex are reciprocal and excitatory (Suzuki

and Amaral, 1994; Stefanacci et al., 1996; Pitkanen et al., 2002). This analogy is further supported by the fact that the basolateral amygdala develops from the same tissue as neocortex (Meynert, 1867 as cited by Swanson, 1995), and in the theory presented here and based on its interactions with the hippocampal formation, the basolateral group is best viewed as part of the neocortex. Under our presumption that the hippocampus is the associator of last resort which helps higher-order association cortex find appropriate associative encodings (Levy, 1989), the discovered associations of the hippocampal formation are in a position to drive specific linkages between these visual and auditory association cortices and the basolateral amygdala.

In contrast to the basolateral amygdala, the central nucleus of the amygdala develops from the same tissue that gives rise to the striatum (Johnston, 1923). The central group is conceptually part of the ventral striatum (Heimer et al., 1999) and mediates the autonomic responses associated with fear in behaving animals (Davis, 1997) and, by inference, the autonomic response that accompanies the fear component of nightmares. Despite this difference, both the central nucleus and basolateral amygdala play roles in memory as related to fear conditioning. Historically, the role of the amygdala in mediating fear is well established (Kluver and Bucy, 1937). More recent studies (LeDoux et al., 1988; Petrovich et al., 1996; for review see LeDoux, 2000) allow us to further distinguish the critical roles of the two main nuclei: the basolateral nucleus and the central nucleus as mentioned earlier and noted in Table 2. The central nucleus is critical in mediating autonomic aspects of the fear response while the basolateral amygdala plays a critical role in mediating many types of learned fear. Such a view of amygdala-based learning is argued by Fanselow and LeDoux (1999) who point to the important role of the basolateral group in mediating long-term storage of fear-based memories. More to the point here, the work of Fanselow (for review, see Fanselow, 2000) emphasizes the

critical role of the hippocampus in context-based fear. This context-associated fear memory then activates the amygdala, whereas the work of LeDoux (for review see LeDoux, 2000) highlights the central nucleus as vital for association of fear to simple monosensory stimuli.

From our perspective (which seems derivative of Fanselow's), the connections mediating recall of episodic fear are the neocortical-archicortical pathways (including the hippocampus via the subiculum and entorhinal cortex) that can activate the basolateral nucleus which, in turn, activates the central nucleus (Petrovich et al., 1996). Thus, the concept that the hippocampal formation efferents mediate contextual/episodic fear by activating the amygdala helps explain multiple symptoms of PTSD.

The fragmented nature of PTSD victims' memory and its resolution, which seems to coincide with recovery (see e.g., Butler & Spiegel, 1997), are striking in their similarity to Fanselow's observations (for review see Fanselow 2000). These observations distinguish amygdala versus hippocampal memory for an unpleasant event. For the PTSD victim, the early stage is sensory – fear with no context – based on an amygdala-localized memory. Later, as the victim becomes declarative about the traumatic event, they are in fact demonstrating the recovery of context – they remember the place where the event occurred and the details of the event.

In addition, although amygdala activations lead to fear and hyperarousal, this activation is at the behest of hippocampal driving. This hippocampal-aspect to amygdala-mediated fear memory also explains why hippocampal teachback/replay – and subsequent neocortical activity – would lead to nightmares. Neocortical and basolateral amygdala neural activity, biased to reactivate by teachback/replay during SWS, would be exactly those neurons which were temporally associated during the traumatic episode. The basolateral contingent of neurons

would, in turn, activate the central nucleus, producing an autonomic fear response during a nightmare.

3.3 Sleep: From PTSD to the Neurophysiology of Teachback/Replay in the Hippocampus

Sleep can be divided into many phases, but for our purposes we need only consider two: slow-wave sleep and vivid, dream-associated REM sleep.

3.3.1 The Experimental Neurophysiology of Teachback/Replay

Important gains in our knowledge of the neurophysiology of memory consolidation have occurred in the last few years. The multisingle unit methods developed by McNaughton and Barnes (for review see Pennartz et al., 2002) have produced the strongest evidence for interpreting hippocampal messages during sleep as replay of earlier learning. Such single-unit observations easily combine with the work of Buzsaki and colleagues (for review see Buzsaki, 1998). They demonstrate the existence of spontaneous events of massive cell firing during SWS. These events originate within the CA3 region of the hippocampus, and by correlation, this cell firing must be part of the teachback/replay events documented by McNaughton and Wilson.

The biological observations suggesting the relationship between sleep, memory, and hippocampal-neocortical interactions can be traced back to the 1950s. The macroscopic neurophysiological observations of Green and Arduini (1954) determined that there is a complementary correlate of gross hippocampal activity, in addition to the well-known neocortical characteristics of sleep and wakefulness. During wakefulness, the active neocortex displays fast-desynchronized activity while hippocampal activity is relatively sluggish and synchronized. They also observed the same orthogonal relationship during REM sleep. However, during slow-wave sleep and drowsiness, the correlate reversed: neocortical low-

frequency, synchronized activity now correlated with hippocampal high-frequency, desynchronized activity. Thus, the activity patterns of the neocortex and the hippocampus are perfectly out of phase with each other (see Table 3). Years later, Buzsaki (Nadasdy et al., 1999 and for review see Buzsaki, 2002) elaborated upon the nature of this high-frequency hippocampal activity during neocortically defined, slow-wave sleep.

Table 3 here.

Buzsaki observed high-amplitude, high-frequency population discharges during SWS, which he termed sharp waves. Important to the theory here, these sharp waves are the refiring of many CA3 neurons in a time period that is less than 200 msec. The spontaneous cell firings originate from within hippocampal area CA3 and occur sporadically across each SWS cycle. More importantly (see below), the groups of neurons whose activity comprises the sharp wave are not random.

From the viewpoint of PTSD symptoms, it is interesting that region CA3 sometimes produces sharp waves during wakefulness. These times include the very situations when an awake animal would not need region CA3 or even an intact hippocampus, e.g., during washing/grooming, eating, and presumably during simple, familiar motor learning (Chrobak and Buzsaki, 1994) when no episodic information is accumulated. Thus, if the hippocampal-to-neocortical teachback process is the root cause of PTSD symptoms, then we have a mechanism for priming daytime flashbacks. Specifically, the daytime symptoms of PTSD, including spontaneous recollections, flashbacks, and anger, occur when the hippocampus drives the amygdala. The intense anger (noted by Hertzberg et al., 1998) arises when spontaneous daytime hippocampal firing unconsciously triggers the emotional memory of the traumatic episode.

However, strong hippocampal activity at appropriate times is not enough for our theory. To find credible the selectivity of hippocampal replay requires research comparing neurons firing during sleep versus during wakefulness. Such studies originated with the work of Pavlides and Winson (1989) and were brought to fulfillment by Wilson, McNaughton, and their colleagues (Wilson and McNaughton, 1994; Lee and Wilson, 2002). Recording from one neuron at a time, Pavlides and Winson observed that neurons, whose firing was driven by a daytime experience, had a higher probability of firing during sleep than neurons not driven by the same episode. The implication is that something related to – or perhaps something that is exactly – a recently stored memory is reactivated during sleep. Recent studies in humans have obtained a similar result (Staba et al., 2002).

Recordings from multiple single neurons produce the strongest case that episodic memories are replayed. Because episodes are constructed of temporally and spatially correlated perceptions, the temporal and spatial aspects of episodic memory require simultaneous recordings from a multiplicity of neurons that encode the neuronal correlates of such memories. These are exactly the results of McNaughton and colleagues (Wilson and McNaughton, 1994; Skaggs and McNaughton, 1996; for review see Hoffman and McNaughton, 2002). Thus Pavlides and Winson's result is replicated, but more importantly, McNaughton and colleagues discovered that the qualitative temporal ordering of daytime, episodic neural firing is preserved during replay. Thus, the evidence for spontaneous replay of episodic memory and therefore hippocampal driving of the PTSD synptomology seems even more than plausible.

Hypothesis: the replay (Wilson and McNaughton 1994, Pavlides and Winson 1989) that clearly exists during SWS and during REM are essentially different. The replay during SWS originates from within hippocampal region CA3 (Buzsaki 1998, 2002) and is a temporally

compressed version (Wilson and McNaughton 1994, August & Levy 1997, 1999). However, the replay seen in the hippocampus during REM sleep is, by hypothesis, originating in neocortex.

Therefore we predict that EC inactivation during REM sleep will prevent the replay in the hippocampus during REM but not during SWS.

So much for the idea that hippocampal refiring activates neocortical and basolateral neurons during SWS. But what about vivid REM dream sleep when nightmares occur? Before we can discuss this issue, we must consider one more aspect of hippocampal SWS replay – queue priority.

3.4 The Corollary: Prioritized replay and the physiology of biasing the replay process

There is a problem with the SWS-replay scenario: the lack of time during a full night's SWS to replay all of daytime experience. Common things must be jammed together, but since they are common, they are easier to encode in the neocortex because the appropriate connectivity largely exists, and little time thus needs to be devoted, even on-line encoding seems possible in such cases. The storage of the important and the novel requires more time. Thus, there must be a replay biasing mechanism that can select the more important and more novel over the less so.

The neurophysiological data show that replay is biased. Hippocampal neurons that were active during recent experiences that occupied significant periods of time are more likely to be refired (Wilson and McNaughton, 1994). Computational research indicates that replay of such episodic experiences arises from the potentiated, recurrent connections of CA3 driven by randomness (August and Levy, 1997, 1999). Because the computational model is defined by the dynamics of unstable attractors, it follows that the more neurons that are devoted to a particular

episodic memory, then the more likely the replay of that particular memory versus another memory. Because any episode occurs over time, the sequence-learning characteristic of CA3 (Levy, 1989, 1996) encodes the episode as a changing pattern of neuronal firing. When this changing pattern leads back onto itself – as would be the case of a prolonged, repetitive traumatic event – then the sequential neuronal firing patterns tend to reproduce portions of themselves. This strong attractor is a strong memory with high priority in the teachback/replay queue.

In sum (see Table 4), queue priority is a stochastic concept that is the inevitable result of a replay mechanism that is random and occurs infrequently compared to the amount of time occupied by wakeful episodic experiences.

Table 4 here.

3.4.1 The Neuroscience of Queue Priority

The queue priority hypothesis relies on the idea that episodic memory strength can vary as a function of the episode. The neuroscience relevant to queue priority is the research that manipulates memory strength at the behavioral level and synaptic strength at the level of experimental neurophysiology. First, we will present the psychobiological evidence concerning prioritized replay.

Historically, the story begins with electroconvulsive shock therapy in the 1930s, when clinicians noted the effects of electroconvulsive shock therapy on memory. Experimental science eventually noted these clinical observations and began to use such manipulations to study memory consolidation. The idea of memory consolidation was strongly supported by the

work of McGaugh and colleagues (for review see McGaugh, 2000) who introduced post-training manipulations. Their studies established reliable pharmacological methods for memory manipulations — administered during or even briefly after training. For example, post-training norepinephrine can strengthen memory while protein synthesis blockade can disrupt memory consolidation (for review, see McGaugh, 2000). Such manipulations can be considered a model for the effects of emotion on memory strength in the hippocampus.

The importance of emotionality in strengthening memory has been shown in both human (Hamann et al., 1997) and laboratory animal studies (for reviews, see Ferry et al., 1997; McGaugh & Roozendaal, 2002). (The animal studies have particularly strong relevance to humans, the hippocampus is essentially identical across all mammalian species, as are the nuclei of the amygdala.) One laboratory experiment simulated the effect of an overactive amygdala via stress hormone treatments, e.g. stress associated hormones, such as epinephrine and glucocorticoids. These treatments affected memory storage via the amygdala (McGaugh et al., 1996). Specifically, the hormones strengthened memories, making them seemingly immune to overwrite, erasure, and decay. The training procedures of these experiments are particularly relevant to the topic at hand because they involve associating a strongly negative emotional event with a particular place, i.e. the context that defines an episode. The similarities of PTSD traumatic events — rapes, friendly fire incidents, etc, — are precisely those events where a place and a context are associated with an overwhelmingly emotional episode.

The neurophysiology of hippocampal memory storage begins with the study of long-term potentiation (LTP) (Bliss and Lomo, 1973) and its associative nature (Levy and Steward, 1979; McNaughton et al., 1978). Here we shall point to pharmacological manipulations of LTP and its

complement, long-term depression (LTD), which explain how emotionality is integrated into synaptic memory.

As a function of post-trial emotional experiences, studies of LTP longevity produce particularly powerful arguments for stronger and longer lasting memories; moreover, studies in awake behaving animals substantiate the amygdala's effect on the longevity of hippocampal LTP. Post-conditioning stimuli of positive emotional valence, i.e. allowing water-deprived rats to drink, and stimuli of negative valence, i.e. electrical foot shock, each strengthen LTP induced directly in the dentate gyrus of unrestrained rats (Seidenbecher et al., 1997), and this strengthening was not to produce a larger response. Rather, such post-conditioning emotional experiences slowed the decay of LTP. LTP levels were 70% and 43%, respectively, above control 24 hours after LTP induction whereas the controls had returned to a baseline level. Because there is no indication of any decay between 8-24 hours (the longest interval observed) and with the caveat that later measurements were not adequate, these data are consistent with LTP that has the potential to last indefinitely. Thus affective experiences can enhance the longevity of synaptic encoding.

Frey et al. (2001) expanded the Seidenbecher et al. (1997) study. Here, behavioral stimuli, i.e. drinking and shock, were replaced by basolateral amygdala stimulation. The results are completely consistent with Seidenbecher et al. (1997), the ideas of McGaugh and colleagues, and the ideas presented here. Post-conditioning amygdala stimulations enhanced the longevity of LTP in the hippocampus. These results give strong evidence supporting the emotional control of memory strength in the hippocampus as required by our queue priority-based theory.

A second group of studies looks at the biochemical pharmacology of LTP. They consistently show that LTP is greater in magnitude or longer lasting when monoamines or

cAMP-like substances, which monoamines produce, are introduced into the bathing medium of hippocampal slices (e.g., Stanton and Sarvey, 1985). A combination of these monoamines appears to control the cAMP levels that in turn regulate protein synthesis, which has long been implicated in memory (Flexner et al., 1971, for review see Davis and Squire, 1984) and the modulation of LTP (Davis and Squire, 1984; Stanton and Sarvey, 1984). Most recently, the behavioral consolidation experiments are supported by more detailed biochemical correlates of synaptic LTP (for review see Kandel, 2001). In conclusion, three different systems, i.e. behavioral, neural and behavioral, and neural alone, are all enhanced by norepinephrine and disrupted by a decrease in protein synthesis.

Lastly, observations based on experimental manipulations and functional imaging studies support the idea of memory strength is controlled by emotional experience mediated by amygdala activation. Multiple studies have shown a direct correlation between emotional content and enhanced memory (Cahill and McGaugh, 1990; Cahill et al., 1996; Cahill and McGaugh, 1998; Hamann et al., 1997, 1999) and hippocampal, or medial temporal lobe, activity. Using positron emission tomography imaging, Hamann et al. (1999) demonstrated a positive correlation between amygdala/hippocampal activity and declarative memory. Equally important, they used a behavioral study to demonstrate a positive correlation between emotional content and spontaneous recall memory, i.e. hippocampally dependent declarative memory. Together, these studies make clear that the strength of memories stored in the hippocampus – and those headed for neocortical declarative status – depends on emotional experience and the amygdala both at the time of encoding and just after.

3.5 Dream Sleep and Erasure

We finally arrive at the fourth hypothesis. It has been previously hypothesized that dreaming would be the time to erase memories in the hippocampus (Crick and Mitchinson, 1983). Motivation for such a hypothesis grows out of the fact that intermediate-term memory systems presumably have a low capacity, and certainly this is true of our hippocampal model (Levy and Wu, 1996). Thus some erasure of earlier episodes is necessary either before or during the encoding of a new episode if this new episodic experience is to be stored (and this explains anterograde memory deficits in PTSD). Although the Crick and Mitchinson hypothesis does not seem necessary given that daytime overwriting can occur (or at least such overwriting occurs in most computational models, including ours), their hypothesis begins to make sense if such overwriting does not occur in the case of strongly encoded memories. That is, highly emotional episodes may not be overwritten by the less emotional, episodic experiences typical of day-to-day life which is exactly our interpretation of Seidenbecher et al. (1997) and Frey et al. (2001).

But even more must be considered if such a hard-to-erase, predeclarative storage of an emotional episode is to be most useful for future decision making. Specifically, erasure must be both controlled and specific. That is, erasure should be postponed until declarative accessibility is achieved. Simply put, nonspecific erasure during sleep is counterproductive.

It is our explicit hypothesis that dream sleep must activate the **appropriate** neuronal patterns in the hippocampus to produce an active, LTD-like erasure. An active process requires the appropriate cell-firing pattern to cause LTD at the appropriate synapses. Thus, the occurrence of such specific, localized LTD would change the teachback/replay queue priority, allowing new memories to come to the front of the teachback/replay line. Based on experimental observations, we believe that erasure of memory is an active process (e.g., Levy and Steward, 1979), and this idea is supported by more recent experiments. Long-lasting LTP in the

hippocampus (McNaughton, 1982) presumably requires an active process mediated by NMDA (N-methyl-D-aspartate) receptors (Villarreal et al., 2002). Because NMDA receptors require depolarization to function, removing long-lasting LTP requires an active process. Villarreal et al. (2002) discuss LTP decay as active, stating that LTP is actively reversed by the activation of NMDA receptors. They demonstrated that NMDA receptor blockage caused long-lasting LTP, and therefore conjectured that there was an active process of LTP erasure occurring. It logically follows that the appropriate pattern of neurons must be activated to produce the appropriate synapse-specific erasure conditions under physiological conditions.

The fact that a specific activity pattern is required for LTD of strongly encoded memories is actually a fail-safe, noise-free way to design erasure of the teachback system of ITM. Such a procedure is reminiscent of a specialized form of human communication: when precise communications are of extreme, i.e., life-and-death, importance. For example, consider communication between a pilot and the control tower. The control tower gives a heading and the pilot *repeats it back* for verification. Likewise, shipboard particularly on submarine, every bridge command is repeated for verification. In such cases, the information is repeated to confirm that the originally transmitted information was exactly received. Thus, it seems perfectly appropriate that, for the most emotional events in one's life – the ones of greatest importance, the ones involving negative reinforcement, the ones that can kill you – that such a fail-safe procedure would have evolved because it will preserve life and limb in the future. Specifically, for episodic memories of high emotional content: the neocortical cell firing that mediates dreaming is an attempt to confirm exactly the encoding instructions received by the neocortex and amygdala during hippocampal replay.

We are now at the heart of understanding of the difficulty in curing posttraumatic stress. It is only when the neocortex, including basolateral amygdala, has 1) received, 2) appropriately encoded, and 3) returns back the appropriate neuronal firing patterns, does there result the therapeutically desirable demotion in the teachback/replay queue of the traumatic memory.

4.0 Hippocampal Degeneration with PTSD

The current theory easily incorporates the hippocampal degeneration seen in some PTSD victims without positing that this shrinkage is the cause of the illness. That is, the theory here holds that the damage to the hippocampus occurs as a secondary aspect of the disease. During the natural process of teachback, the amygdala would be strongly activated leading to glutocorticoid secretion, just as in any stressful situations (McGaugh *et al* 1996; McGaugh and Roozendaal 2002). And as discussed by Sapolsky, it is this steroid that causes the cellular degeneration in the hippocampus (for review see Sapolsky 2001). Thus, hyperactive amygdala function generates corticosterone production with a deleterious effect on the hippocampus and dentate gyrus (McGaugh and Roozendaal 2002, McGaugh *et al.* 1996, Davis 1997). We hypothesize that early treatment with nefazodone will help prevent this secondary effect of PTSD by helping to demote the traumatic episode from the replay queue.

Table 5 here.

5.0 Conclusion

It is our main conjecture that the pathologies of posttraumatic stress disorder arise from a very strong memory of the traumatic event stored in hippocampal region CA3 and that cure will be affected when the excitatory synapses mediating this memory are weakened. The argument

for this theory brings together experimental neuroscience that is decades old and as fresh as Kandel's Nobel prize. The link between memory consolidation and PTSD symptoms precedes through a unifying conceptualization of the role played by the key components of the consolidation process. The theory is speculative because some of the biology is controversial (see Table 5); however, all these ideas are plausible and amenable to further experimental testing. The central, novel conjecture is that hippocampal teachback\replay biases dream content for the traumatic event. This biased content includes an evocation of fear, not in the hippocampus, but evoked by hippocampal priming of amygdala activation. Therefore, nightmares, the hallmark of PTSD (Ross et al., 1989), would be an inevitable experience during sleep for a traumatized individual. Awakening by a nightmare prevents erasure or downgrading of the hippocampally-stored traumatic memories as well and it prevents the final consolidation phases in the neocortex. With a few exceptions, medicine currently prescribed for PTSD (see Di Perri et al., 1986; Monti, 1989; Nofzinger et al., 1995) often allows the patients to sleep, but does not allow for REM sleep (Montgomery et al., 1983; Mouret et al., 1988; Vogel, 1990). As a result, such treatment hinders consolidation and hinders cure even though it is palliative in other regards. If the theory presented here is correct, such treatments are a major error.

Nefazodone treatment is an exception. It should facilitate rather than hinder neocortical memory consolidation accompanied by a cell- and synapse-specific LTD in the hippocampus. In terms of practical importance, this single effect of nefazodone's action defines a new class of drugs easily distinguished from the other SSRI's. The physiology and biochemical pharmacology of this particular pharmacological action deserves further experimental attention including basic neuroscience studies that would further define this new drug class.

Acknowledgements

This work was supported by NIH MH48161 and NS41582 to WBL, and by the Department of Neurosurgery. WBL also thanks Gary Lynch (UC Irvine) for bringing the importance of Green and Arduini to his attention. We appreciate Scott D. Moore's (Duke University) comments on an earlier version of the manuscript.

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<i>Type of Criteria</i>	• <i>Criteria</i>
Re-experiencing	<ul style="list-style-type: none"> • Recurrent, intrusive, and distressing recollections • Recurrent, distressing dreams • Flashbacks • Intense psychological distress at exposure to events that symbolize or resemble the traumatic event • Physiological reactivity to cues that symbolize or resemble the traumatic event
Avoidance	<ul style="list-style-type: none"> • Inability to recall an important aspect of the trauma • Avoiding activities or situations associated with the acute event
Arousal	<ul style="list-style-type: none"> • Insomnia • Irritability or outbursts of anger

Table 1: Some major symptoms of PTSD grouped to aid in the diagnosis (Spitzer et al., 1994).

<i>Key Component</i>	<i>Functional Description</i>	<i>PTSD Relevance</i>
1. Hippocampus: ITM store	<ul style="list-style-type: none"> • Necessary for the encoding of long-lasting declarative memories in the neocortex • Not sufficient for declarative memories 	While declarative amnesia persists in PTSD, the details of the traumatic event remain in the ITM store of the hippocampus.
2. Multifaceted Amygdala	<ul style="list-style-type: none"> • Central Nucleus: Mediates fear response to emotionally painful experiences. • Basolateral Nucleus: Indirectly modulates strength of episodic memories and fear conditioning and bridges hippocampal activation to central amygdala activation. 	Hippocampally primed nightmares and spontaneous recollections result from the hippocampus driving the amygdala and neocortex. Amygdala mediates anxiety and fear but is not spontaneously active.
3. Teachback/ Replay	<ul style="list-style-type: none"> • Hippocampal region CA3 drives neocortical encoding of long-lasting declarative memories (consolidation) by replaying hippocampally stored episodes • Chance of replay (queue priority) determined by emotional content of episodes 	Replay primes the amygdala and thus drives PTSD symptoms: nightmares, flashbacks, and possibly anger.
4. Erasure/Queue Demotion	<ul style="list-style-type: none"> • Weakens, with high specificity, the relevant hippocampally stored memories • Demotion in the replay queue depends on successful encoding 	A normal, uninterrupted sleep cycle is required for successful neocortical encoding and the accompanying synaptic encoding in the hippocampus. It is also required for erasure and queue demotion. PTSD symptoms will continue as long as queue priority of the traumatic event is high. There is poor declarative encoding of new events because the ITM store and replay are dominated by the earlier traumatic event and therefore erasure is necessary

Table 2: Hypothesized Regional Brain Functions Relevant to PTSD. The table summarizes the link between the four key ideas and PTSD symptomatology. The functional description of each describes its normal function and helps to elucidate abnormal complications related to PTSD.

<i>Sleep Stage</i>	<i>Neural Activity in the Hippocampus</i>	<i>Neural Activity in the Neocortex</i>
Awake	Low	High
Slow wave sleep	High	Low
REM sleep	Low	High

Table 3: Neural firing during three stages of the arousal/sleep continuum. Three stages of sleep – awake, slow wave sleep, and REM sleep – are correlated with neural activity in the hippocampus and neocortex at that time (for review, see Pavlides and Winson (1989) and Noda et al. (1970)). The inverse relationship between hippocampal and neocortical firing is relevant to the relationship between sleep, memory, and hippocampal-neocortical interactions.

<i>Queue Priority</i>
<ul style="list-style-type: none">• Each replay can only encapsulate a single (perhaps fractional) episode• Such a brief event implies a queue-like situation because not more than one episodic memory may be transmitted back to the neocortex at a time. That is, each memory must await a turn at being replayed• Replay is a biased, random process• High queue priority derives from strong and pervasive, long-lasting long-term potentiation• A highly emotional experience leads to long-lasting long-term potentiation

Table 4: Key Concepts Concerning Queue Priority. Queue priority is a critical hypothesis of the theory. This competition for replay between CA3-stored memories is probabilistic where the rank of such probabilities is called queue priority.

- The hippocampus is necessary but not sufficient for declarative memory (section 3.1)
- There is competition for replay during SWS (i.e., queue priority, section 3.4.1)
- The outcome of the competition is determined by a biased random process that depends on the longevity and emotionality of the stored event (section 3.4.1)
- Hippocampal replay biases dream content via short term LTP in neocortex and amygdala (section 3.5)
- Erasure in CA3 is memory specific and requires appropriate cell firing patterns (section 3.5)
- Sleeping through a nightmare is necessary for this memory specific weakening process in CA3 (section 3.5) and memory strengthening in neocortex.
- Nefazodone downgrades the autonomic fear generated by nightmares so the nightmares do not cause awakening (section 2.0)
- There is a new drug class that suggests further research to develop drugs of greater specificity within this class.

Table 5. The major innovations of the theory.