PSYCHOPHYSIOLOGICAL RESPONSES TO AUDITORY STIMULI DURING SLEEP IN POST-TRAUMATIC STRESS DISORDER

by

Peter Lloyd Franzen

A Dissertation Submitted to the Faulty of the

DEPARTMENT OF PSYCHOLOGY

In Partial Fulfillment of the Requirements
For the Degree of

DOCTOR OF PHILOSOPHY

In the Graduate College

UNIVERSITY OF ARIZONA

2003
As members of the Final Examination Committee, we certify that we have read the dissertation prepared by Peter Lloyd Franzen entitled PSYCHOPHYSIOLOGICAL RESPONSES TO AUDITORY STIMULI DURING SLEEP IN POST-TRAUMATIC STRESS DISORDER and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

John J. B. Allen, Ph.D.
Alfred Kastn, Ph.D.
Mary L. Menk, Ph.D.
Hal Arkowitz, Ph.D.

Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copy of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

Richard R. Bootzin, Ph.D.
STATEMENT BY AUTHOR

This dissertation has been submitted in partial fulfillment of requirements for an advanced degree at The University of Arizona and is deposited in the University Library to be made available to borrowers under rules of the Library.

Brief quotations from this dissertation are allowable without special permission, provided that accurate acknowledgment of source is made. Requests for permission for extended quotation from or reproduction of this manuscript in whole or in part may be granted by the head of the major department or the Dean of the Graduate College when in his or her judgment the proposed use of the material is in the interests of scholarship. In all other instances, however, permission must be obtained from the author.

SIGNED: [Signature]
ACKNOWLEDGEMENTS

I would first like to thank my advisor, Richard Bootzin, Ph.D., without his support and encouragement throughout my entire graduate school career this work would not have been possible. Dick is great. He has been a treasure to work with all these years. Also critical in the completion of my dissertation project were my two collaborators in California. Ian Colrain, Ph.D., of SRI International and University of Melbourne, Australia, has been a second mentor to me and has been a pleasure to work with. Steven Woodward, Ph.D. of the National Center for PTSD, Palo Alto Healthcare System, provided access to a sleep laboratory and patient population; he was crucial in assisting with data collection and reduction. My thanks and appreciation goes to them as well.

Numerous colleagues, friends, and family provided the friendship and support indispensable to the completion of this study. I am particularly indebted to draft readers, Anne Germain, Ph.D., Dick Bootzin, Ph.D., Ian Colrain, Ph.D., Chris Larson, Ph.D., Sheryl Reminger, Ph.D., Jason Barker, Ph.D., and Dave Towers, M.A. I would also like to specifically thank my parents, Wayne and Janet Franzen; internship colleagues, and last but certainly not least, all of my friends and colleagues that have helped and supported me during graduate school and the completion of this project. Thanks also go to the staff at the National Center for PTSD, Sleep Laboratory for their logistical assistance with some aspects of this dissertation project: Lorrie Stewart, Wendy Stegman, and Ned Arsenault. Finally, thanks go to the Vietnam veterans who without their participation this study would not have been possible.

This study was funded in part by the National Center for PTSD.
TABLE OF CONTENTS

LIST OF FIGURES ................................................................. 6
LIST OF TABLES ................................................................. 7
ABSTRACT ........................................................................... 8
INTRODUCTION ...................................................................... 10
  Sleep in PTSD ................................................................. 12
  Hyperarousal During Sleep in PTSD ................................. 16
  Information Processing During Sleep ................................. 19
  Summary of Prior Research .............................................. 24
  Objectives and Hypotheses for the Present Study ................. 26

METHODS ........................................................................... 28
  Participants ....................................................................... 28
  Procedure ......................................................................... 32
  Stimuli ............................................................................. 32
  Psychophysiological Measures ........................................... 34
    Electroencephalogram (EEG) ........................................... 34
    Electrooculogram (EOG) .................................................. 34
    Electromyogram (EMG) .................................................... 34
    Electocardiogram (ECG) ................................................... 34
    Respiration (RESP) .......................................................... 34
  Oxymetry .......................................................................... 34
  Recording Apparatus, Data Acquisition, and Data Reduction  35
  Psychophysiological Variables ........................................... 36
    Evoked K-complex identification and trial average ............... 36
    Cortical Arousal ............................................................... 37
    Heart Rate ........................................................................ 38

RESULTS ................................................................................ 40
  Probability of K-Complex Elicitation ................................... 40
  Evoked K-complex: N550 Amplitude and Latency ................. 41
  Cortical Arousal ................................................................. 42
  Heart Rate ......................................................................... 46

DISCUSSION .......................................................................... 50
  Information Processing is Disturbed in PTSD ....................... 50
  A Unique Response to Traumatic Stimuli not Evident in the PTSD Group 52
  PTSD is Associated with Tonic but Not Reactive Hyperarousal  53
  Limitations and future directions ........................................ 55

APPENDIX A ........................................................................ 58
REFERENCES ....................................................................... 59
LIST OF FIGURES

Figure 1. Mean probability and standard error of the mean (SEM) for K-complex elicitation to a stimulus. ................................................................. 41
Figure 2. Mean N550 latency and standard error of the mean (SEM) in milliseconds. .. 42
Figure 3. Difference scores (post-stimulus - baseline) of estimated mean power ratio in response to stimulus and whether a K-complex was evoked. ................. 44
Figure 4. Difference scores (post-stimulus - baseline) of estimated mean (untransformed) beta power in response to stimulus and whether a K-complex was evoked. ... 46
Figure 5. Example of mean HR change following stimulus onset (in this case, for all tone trials that evoked a K-complex), showing an initial bradycardic response peaking around 1.5 s following stimulus onset, and a longer tachycardic response peaking approximately 5 s following stimulus onset. ...................... 48
Figure 6. Estimated mean change in heart rate deceleration (bradycardia) and acceleration (tachycardia) for stimulus type and K-Type across all participants. .......... 49
LIST OF TABLES

Table 1. Patient demographic information .................................................. 29
Table 2. Patient comorbid diagnoses ............................................................ 30
Table 3. Patient inventory results ............................................................... 31
Table 4. Psychophysiological recording settings ........................................... 35
Table 5: F-values, degrees of freedom, and probabilities for power ratio repeated measures ANOVA ................................................................. 43
Table 6: F-values, degrees of freedom, and probabilities for beta-band analyses .... 45
ABSTRACT

Sleep complaints are common in people who develop Post Traumatic Stress Disorder (PTSD). PTSD-related information processing abnormalities evident during wakefulness might continue into sleep. A group of Vietnam veterans with and without PTSD (patients and combat-controls) were studied to examine psychophysiological responses to auditory stimuli during stage 2 NREM sleep. Three stimuli (500 ms) categories were presented in an oddball paradigm: pure tones (standard, 60% probability of occurring), trauma-related (i.e., combat sounds) and affectively neutral, environmental stimuli (20% each). The effects of stimulus presentation on evoked K-complexes, heart rate (HR), and cortical activity (power spectra ratio of fast to slow EEG activity, and beta-band power) were examined; the impact of evoking a K-complex (KC+ and KC- trials) on these last two measures was also examined. Significantly fewer K-complexes were elicited in patients; there were no within group differences in the proportion of K-complexes elicited between tone and trauma stimuli. Patients unexpectedly produced significantly more K-complexes to neutral stimuli. Examination of the N550 component of the evoked K-complex revealed significantly longer latencies in the control group, who also had longer latency for trauma stimuli relative to tone and neutral stimuli. There were no findings on N550 amplitude. Cortical arousal results ran contrary to predictions. Rather, controls demonstrated modest increases in overall cortical activity post-stimulus, while patients demonstrated decreases that were even more pronounced for KC+ trials. Beta activity was marginally higher in controls, and for KC+ trials for both groups. The smallest beta power increase was to trauma stimuli for both groups; in controls, beta activity increased
most to neutral stimuli. Tonic heart rate was found to be (marginally) elevated in patients. There was no impact on initial HR decelerations, but analysis of the ensuing HR acceleration revealed a main effect of K-complex type (greater HR increases for K+ trials) and stimulus type (significantly higher increases to neutral stimuli). Results suggest sleep-related information processing is altered in PTSD and conflicting evidence for cortical and autonomic hyperarousal during sleep in PTSD, although further research is necessary to establish the generalizability to other populations (such as acute PTSD or other anxiety disorders).
INTRODUCTION

Exposure to a traumatic event – usually those that involve death or serious assault, such as rape – certainly takes a toll on a person’s coping resources. The acute stress reaction that follows is natural and expected. That many trauma-exposed individuals eventually fully recover from such events underscores the remarkable adaptability of the human spirit. A significant portion of people exposed to traumatic events, as much as 25% by some estimates (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Rothbaum, Foa, Riggs, Murdock, & Walsh, 1992), will continue to experience traumatic stress reactions for many months and often years afterward. Three symptom clusters characterize such reactions and comprise the syndrome of Post Traumatic Stress Disorder (PTSD): intrusions (e.g., flashbacks and nightmares), avoidance (e.g., emotional numbing), and hyperarousal (e.g., sleep disturbances, exaggerated startle, and concentration difficulties). See Appendix A for the full DSM-IV-TR diagnostic criteria (American Psychiatric Association, 2000). Objective and subjective sleep complaints occurring early after traumatic exposure have been shown to predict who will develop PTSD (Koren, Aronon, Lavie, & Klein, 2002; Mellman, Bustamante, Fins, Pigeon, & Nolan, 2002). It may be that sleep disruption reflects a core dysfunction of PTSD (Ross, Ball, Sullivan, & Carroff, 1989).

Although the nature of this dysfunction within sleep has yet to be identified, the waking literature on PTSD suggests that information processing is disrupted in this population. Abnormalities of information processing identified to date, such as attentional biases toward trauma-related stimuli, larger startle responses that are less likely to
habituate, and memory impairments, are suggestive of automatic processing biases in PTSD (for review see Buckley, Blanchard, & Neill, 2000; McNally, 1998). As Buckley and colleagues stated "automatic processing biases may underlie the hyperarousal symptoms of PTSD such as hypervigilance and exaggerated startle response. In addition, automatic processing biases may be responsible for the involuntary re-experiencing symptoms of the disorder. If PTSD subjects preferentially scan the environment for trauma-specific threatening stimuli, then identification of such stimuli, may involuntarily activate trauma networks to a level above conscious awareness and produce intrusive recollections, flashbacks, and nightmares" (Buckley, et al., 2000, p. 159). In turn, such dysregulation of automatic information processing may also predispose PTSD patients to be more sensitive to external stimulation during sleep, thus resulting in sleep disturbances.

Persistence of hyperarousal in sleep has been poorly described in PTSD, and to date there have been no investigations specifically looking at information processing in sleep and PTSD. Abnormal information processing during sleep may be directly relevant to self-reports of severe sleep disruption in people who have PTSD. The goal of the present study was to understand how people with PTSD respond to auditory stimuli during sleep, so that we may better understand how the sleeping brain processes and responds to external stimulation, as well as to provide some insight into pathophysiological processes involved in the sleep symptoms characteristic of PTSD.
Sleep in PTSD

Sleep symptoms -- difficulty initiating and maintaining sleep and nightmares (which also lead to unwanted awakening) -- comprise two of the diagnostic criteria for PTSD. People with PTSD report difficulties both falling asleep and maintaining sleep (i.e., from disrupted sleep and also waking from nightmares). Recent epidemiological assessments of sleep complaints in PTSD range from 70% to 91% (Ohayon & Shapiro, 2000; Roszell, McFall, & Malas, 1991). Nightmare disturbance has been found to be quite durable and chronic. A recent survey found that 80% of World War II veterans with PTSD continue to report recurrent distressing dreams (Engdahl, Eberly, Hurwitz, Mahowald, & Blake, 2000). Given the large percentage of people with PTSD who endorse at least one of the diagnostic sleep criteria, do polysomnographic studies corroborate these subjective sleep complaints?

When objective sleep is studied in PTSD using polysomnography or actigraphy, few findings emerge. Studies on people recently traumatized have largely found little to no impact on objective measures of sleep (i.e., using polysomnography; Mellman, 1996; Klein, Koren, Arnon, & Lavie, 2002; or actigraphy; Dagan, Zinger, & Lavie, 1997; Klein, Koren, Arnon, & Lavie, 2003). Some investigators, however, have found immediate manifestations of PTSD effects on sleep. Schlosberg and Benjamin (1978) reported severely disrupted sleep during the acute phase of war-related PTSD (Schlosberg & Benjamin, 1978). Also, in a prospective study of sleep in motor vehicle accident victims, those who went on to develop PTSD could be discriminated by less self-reported total sleep and increased motor activity, suggesting a more restless sleep
(Klein, Aron, Koren, & Lavie, 1997). By retrospective report, sleep appears to be disrupted during the acute phase of traumatic exposure. In a sample of elderly war veterans who had developed PTSD from their participation in World War II, most participants and their spouses “gave clear accounts of grossly disturbed sleep in the years following discharge from the military, disturbances that diminished with time” (Engdahl, Eberly, Hurwitz, Mahowald, & Blake, 2000, p. 524). Understanding the impact of PTSD on objective sleep measures is complicated by the time since traumatization (i.e., acute versus chronic PTSD), and psychiatric comorbidities (Leskin, Woodward, Young, & Sheikh, 2002). It is rare to find a person who meets diagnostic criteria solely for PTSD and no other disorder. Other common comorbid diagnoses include panic disorder, generalized anxiety disorder, major depressive disorder, and substance abuse (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; McFarlane, 1986; Sierles, Chen, McFarland, & Taylor, 1983); each of these disorders are independently known to affect sleep as well (for review see Bootzin, Manber, Loewy, Kuo, & Franzen, 2001). The effects of comorbid diagnoses on sleep disturbances in PTSD from the National Comorbidity Survey (Kessler, et al., 1994) found no significant differences in the percentage of sleep complaints among PTSD alone or PTSD comorbid with substance abuse, generalized anxiety, or major depressive disorders. About 80% of the aforementioned sample had sleep complaints regardless of comorbidity, with the exception of much higher percentages for people with PTSD and comorbid panic disorder – 100% complained of insomnia and 96% complained of frequent nightmares (Leskin, et al., 2002).
The lack of consistent and specific polysomnographic abnormalities\(^1\) in studies of PTSD sleep needs to be interpreted with caution, however. Because subjective sleep complaints are so universal in people with PTSD, it is quite likely that the traditional macrostructural sleep variables (e.g., sleep onset latency, percentages of sleep stages, awakenings) are not sensitive enough to identify objective evidence of sleep disruptions in PTSD. Thus, we can not conclude that the lack of objective sleep differences to date rules out the possibility of PTSD-specific pathophysiological abnormalities that affect sleep processes. For example, researchers have observed that it is extremely rare to record a nightmare in the laboratory setting, even in those people who complain of multiple nightmare episodes per week (Woodward, Arsenault, Murray, & Bliwise, 2000). This does not imply that traumatized people only subjectively feel as if they have nightmares, but are not actually having them. Perhaps the very nature of being observed causes nightmares to cease, or perhaps it is because traumatized individuals feel safe in such a setting (PTSD participants have reported a high degree of security and comfort from being in a controlled and observed setting; Woodward, 1995). Thus, it may be that sleep disturbances in PTSD normalize in a controlled laboratory setting. Alternatively, sleep disturbances that are present may not be detected with current sleep assessment techniques.

Insomnia is another disorder in which the traditional objective measures (i.e., polysomnography or actigraphy) seem not to capture the degree of subjective complaint.

---

\(^1\) It is important to note, however, that the most consistent polysomnographic finding in PTSD sleep involves early REM latency, a typical abnormality also noted in depression, and increased REM density (Mellman, Bustamante, Fins, Pigeon, & Bruce, 2002; Mellman, Nolan, Hebding, Kulick-Bell, & Dominguez, 1997; Dow, Kelsoe, & Gillin, 1996 Ross, et al., 1994).
regarding sleep disturbance. Sleep state misperception is the term used to describe people who drastically under-report the amount of sleep that they objectively demonstrate (American Sleep Disorders Association, 1997). The majority of people, however, who complain of primary insomnia (i.e., not the result of another medical or psychiatric problem) are considered to have psychophysiological insomnia. However, they too underestimate their sleep (i.e., latency, total sleep time, number of awakenings) compared to objective measures (Borkovec & Weerts, 1976; Carskadon et al., 1976; Rosa & Bonnet, 2000). It has been proposed that this results from increased access to cognitive rumination during sleep (Perlis, Giles, Mendelson, Bootzin, & Wyatt, 1997), possibly resulting from hyperarousal, which has been found in both psychophysiological and sleep state misperception insomnia (Vgontzas & Chrousos, 2002; Bonnet & Arand, 1997, 1995; Terzano & Parrino, 1992).

Thus, while the sleep state itself might not be abnormally changed in PTSD, polysomnographic measures of sleep do not provide any information about arousal fluctuations or information processing which may be driving the subjective complaints. As in psychophysiological insomnia, it may be possible that their subjective complaint is simply a misperception that one is awake when one is actually sleeping. More likely, however, the problem lies within the mechanisms (neurophysiological and/or neurochemical) that generate and maintain the sleep state. Increased arousal, which is typical of PTSD, could lead to dysregulation of thalamocortical hyperpolarization during sleep, thereby decreasing inhibition of sensory information that reaches the cortex. Thus,
cognitive activity itself may be increased via the enhanced sensory information processing that results from anxiety-related hyperarousal.

**Hyperarousal During Sleep in PTSD**

Clinical research has supported the idea that psychopathology is sometimes associated with hyperarousal that is maintained into the sleep state. Less is known about the extent of hyperarousal evident during sleep in PTSD. Hyperarousal during sleep has been found in a number of other populations. Perlis and colleagues have reported elevated levels of tonic beta and gamma activity, fast frequencies in the electroencephalogram (EEG) that are related to cognitive processing, during sleep in psychophysiological insomnia compared to controls (Perlis, Andrews, Orff, Smith, & Giles, 2001; Perlis, Kehr, Smith, Andrews, Orff, & Giles, 2001). Evidence that insomniacs show hyperarousal during sleep as well as across the 24-hour period is shown by measures of metabolic rate and physiological arousal (Arand, 1998; Bonnet & Arand, 1995). Other populations in which evidence of hyperarousal during sleep have been found include depression (Ho, Gillin, Buchsbaum, Wu, Abel, & Bunney, 1996; Nofzinger, et al., 2000) and panic disorder (Roy-Byrne, Mellman, & Uhde, 1988).

Few studies, however, have assessed hyperarousal within the sleep state in PTSD, and there are no known studies specifically addressing information processing. Germain & Nielsen (in press) report more nocturnal awakenings in a PTSD group with frequent nightmares compared to a group of non-PTSD individuals also with frequent nightmares, and healthy controls, which they interpret as supporting the hypothesis of hyperarousal in sleep in PTSD. Woodward, Murburg, & Bliwise (2000) were the first to report on central
and autonomic arousal within the sleep state using a population of combat PTSD inpatients and healthy controls. They found no differences in heart rate (HR) during Non-Rapid Eye Movement (NREM) sleep or Rapid Eye Movement (REM) sleep, which they interpret as supporting the previous waking studies that baseline HRs do not differ in PTSD when anticipatory anxiety is removed. HR was averaged across all of NREM sleep; it is possible that difference might emerge between the stages of NREM sleep (i.e., stages 1, 2, and 3/4 or slow wave sleep) or tonic REM versus phasic REM (i.e., when rapid eye movements and phasic muscle bursts are evident). Their study, however, did find evidence of increased cortical arousal in PTSD during sleep (as measured by electroencephalogram (EEG) power across various bands): delta- and theta-band power (.2 to 7.8 Hz) was significantly reduced during slow wave sleep (for those participants who achieved slow wave sleep), and there was a trend toward faster EEG frequencies across the entire NREM state. A surprising finding was the positive relation between sigma-band (12 - 15.8 Hz) EEG power and hyperarousal scores on the Clinician Administered PTSD scale (CAPS; Blake, et al., 1995). Sigma activity is related to sleep spindles -- synchronized activity evident in the EEG that stems from the activity of the reticular nucleus of the thalamus (Contreras, Destexhe, Sejnowski, & Steriade, 1997; Steriade, 1994), which plays a large role in the gating of thalamocortical information flow (i.e., sensory inputs) via strong inhibition of thalamic relay neurons. The author’s interpretation of the sigma findings is that more severe hyperarousal is associated with stronger gating of thalamocortical information flow during sleep. This increased sigma activity may reflect the blocking of external or internal stimuli as a compensatory
mechanism to minimize the disruption of sleep (Dagan, Lavie, & Bleich, 1991). This is consistent with reports of elevated arousal/waking thresholds during slow wave sleep in PTSD (Dagan, Lavie, & Bleich, 1991; Lavie, Katz, Pillar, & Zinger, 1998; Schoen, Kramer, & Kinney, 1984). Such results are counterintuitive given complaints of extreme arousability reported by individuals with PTSD. Thus, the extent and the role of hyperarousal during sleep in PTSD are far from being well understood.

Hyperarousal and hyperresponsiveness, particularly to trauma-based information, are major characteristics of PTSD in the waking state, and thus might continue into the sleep state as well. It is reasonable to expect hyperarousal to continue into the sleep state in PTSD as has been found in a number of psychiatric disorders as described above, and associations have been found between increased arousal and disrupted information processing during sleep. Sleep-related information processing abnormalities, if substantiated in PTSD, may provide an understanding of the basis for subjective complaints of sleep disturbances in PTSD despite the lack of specific polysomnographic abnormalities.

Obviously, the typical cognitive tasks used to study information processing during the day, in particular those that involve verbal or other complex behavioral responses, are not appropriate for the sleeping subject. The next section will describe the literature on information processing during sleep in normal controls, and what these findings suggest as to how to measure processing during sleep in PTSD.
Information Processing During Sleep

The function of sleep remains a mystery, despite attempts over the past few decades to address this question. It is clear, however, that sleep is an important behavior, as we spend one third of our life doing it. When we do not get enough sleep, we are more vulnerable to accidents, poor decision making, and other impairments. Even when under pressure to stay awake for long periods of time, such as in combat or studying for exams, sleep becomes impossible to resist. Contrary to popular opinion, however, our brains do not "turn off" when we go to sleep. Neuronal activity and firing patterns do change dramatically (e.g., thalamocortical cells become hyperpolarized and large populations of neurons fire in sequence); however, this does not equate with being 'unconscious' when we are sleeping. It may be more appropriate to refer to sleep as a state of 'lesser consciousness.' While a person's ability to process, attend, and react to the outside world is markedly dampened during sleep, we are not simply cut off from our environment when we are asleep. People are responsive to external provocation in a number of ways, as evidenced by phasic changes in cortical activity (i.e., an evoked K-Complex, an arousal, or a change in the stage of sleep), behavioral responses (i.e., signaling with a button push or making eye movements as in the case of lucid dreaming), or termination of the sleep state itself (i.e., awakening).

In 1939, Loomis, Harvey, and Hobart were the first to identify an EEG response to a stimulus during sleep. They observed that the presentation of an external stimulus produced an immediate large negative deflection, followed by a positive deflection, and then a return to baseline, which they termed the K-complex. It was soon reported that the
K-complex can also occur spontaneously (i.e., without any apparent external stimulation) in the sleep recording. Early investigations into the K-complex found that they are easily evoked by auditory stimuli; other stimuli, such as visual and tactile stimuli, as well as painful shock, evoke a morphologically equivalent response (Roth, Shaw, & Green, 1956). More recently, Colrain and colleagues have reported the elicitation of K-complexes using inspiratory occlusion stimuli (Afifi, Guilleminault, & Colrain, 2002; Colrain 1999; Gora, Colrain, & Trinder, 1999, 2001; Webster & Colrain, 1998).

Although coming from an outside source (experimental occlusion of breath technically outside the subject), the 'stimulus' is effectively internal (likely from activity of muscle spindle receptors in the diaphragm (Davenport, Thompson, Reep, & Freed, 1985) or intercostal muscles (Davenport, Shannon, Mercak, Reep, & Lindsey, 1993) – reflecting some interoceptive process. Such data fits with the suggestion that spontaneous K-complexes are in fact elicited by stimuli inside the body.

Reports of the morphology of the K-complex have been variable (Ujszaszi & Halasz, 1986; 1988), and Paiva and Rosa (1991) proposed six different variations in the morphology of a spontaneous K-complex. The impact of concurrent processes that contribute to the background EEG on the morphology of an individual K-complex is unknown. Individual K-complexes are embedded within the ongoing EEG signal, and background EEG amplitude varies as a function of sleep stage (100 μV or more during stage 2, and 200 to 400 μV during slow wave sleep). This background activity likely affects the appearance of a K-complex for any individual occurrence, leading Bastien and Campbell (1992) to propose the use of signal averaging to extract the pure K-complex.
response from the unrelated EEG activity in the background, a technique commonly employed in the recording of evoked potentials or event-related potential (ERP). During wakefulness, the averaging of successive trials is critical in ERP studies, as stimulus responses are not visible in the raw EEG tracing because they are embedded within the 'noise' of the background signal. By averaging successive trials together, such noise (presumably from random activity) should average out, leaving a characteristic waveform related to the cortical processing of the information presented to the subject.

During NREM sleep, large EEG responses (i.e., the K-complex and vertex sharp waves) to an individual stimulus can be seen in the raw EEG (i.e., without the necessity of averaging together successive trials). These responses will therefore have a marked impact on any averages that include trials where such a large response/event occurs. Research investigating evoked potentials during sleep has led to the conclusion that the K-complex is largely responsible for the N550 component of the sleep ERP. This has implications as to whether all trials should be included, or subdivided as to whether a K-complex occurred. Averaging all trials together will result in lower N550 amplitudes from the inclusion of all trials in which a K-complex did not occur, as the N550 is markedly reduced or absent for trials in which K-complex is absent. By averaging only those trials in which a visible K-complex occurs in response to a stimulus the evoked response of K-complex will reveal the 'pure' evoked K-complex response (Bastien, Crowley, & Colrain, 2002).

The K-complex has been shown to be a sensitive marker of information processing. The probability of evoking a K-complex as well as the amplitude of the N550
component can be manipulated by various stimulus characteristics and experimental paradigms. Bastien and Campbell (1992) found more K-complexes to stimuli at 80 dB SPL than to 60 dB SPL, although N550 amplitude was invariant. Cambell, Bell and Duncan-Elliot (1985) reported larger N550 amplitudes for stimuli present with a fast rise time (1 and 10 ms) compared to slower rise times (20 to 40 ms). The K-complex has been found to show initial habituation to repeated stimuli, and the probability of eliciting a K-complex varies as a function of the time between stimuli (i.e., inter-stimulus interval; ISI) as first reported by Firth (1973). Bastien and Campbell (1994) studied the impact of variation in ISI on K-complex production by varying the ISI between 5 s, 10 s, and 30 s. The 30 s ISI produced more K-complex responses and the corresponding N550 amplitude was larger. Rare stimuli evoke more K-complex responses and larger N550 amplitudes compared to frequent stimuli presented in an oddball paradigm (Bastuji, Garcia-Larrea, Franc, & Mauguiere, 1995; Colrain, Webster, & Hirst 1999; Niiyama, Fujiwara, Satoh, & Hishikawa, 1994). These findings have led some to propose that the N550 reflects endogenous processing -- recognition that a stimulus is a target-- during NREM sleep (Niiyama, Fushimi, Sekine, & Hishikawa, 1995). Alternatively, stimulus specific habituation may explain these findings if different populations of neurons are activated by the different stimuli, consistent with Salisbury and Squires' (1993) finding that N550 amplitude increased as a function of pitch difference between target and standard stimuli. Colrain, Di Parsia, and Gora (2000) tested this hypothesis by presenting an oddball paradigm (standard tone for 60% of trials and targets for 20% of trials) during wakefulness to establish target status for the deviants. During the night, a third deviant
tone was introduced also at 20% probability. N550 amplitude was larger for both of the rare averages, compared to the standard the rare amplitudes did not differ from each other; the authors concluded that N550 amplitude is more sensitive to stimulus probability than stimulus relevance.

It is generally assumed, however, that stimulus relevance (or salience) also impacts K-complex production. An early study found more K-complexes evoked by the subject's own name than by subject's name backward or other names (Oswald, Taylor, & Treisman 1960). Replications include finding more K-complexes to one’s own name than other name or tone (Voss & Harsh, 1998), and more K-complexes to conditioned stimuli than unconditioned stimuli (McDonald, et al., 1975). However, a failure to replicate this was reported by McDonald and colleagues (1975) where another’s name evoked the most K-complexes (60%) compared to one’s own name (52%) and tone (38%).

Thus, the K-complex can be evoked by stimuli presented in a variety of modalities (e.g., auditory, respiratory, tactile), and both evoked components and probability of elicitation are subject to stimulus effects. There is debate, however, as to the functional significance of the K-complex. Originally, it was thought that the K-complex represented an arousal response, because they occur in response to external provocation (e.g., Ehrhart, Ehrhart, Muzet, Schieber, & Naitoh, 1981; Halasz, 1983; Johnson & Karpan, 1968; Oswald, Taylor, & Treisman, 1960; Roth, Shaw, & Green, 1956). An alternative position, however, is that the K-complex represents a sleep protective response or an attempt by the sleeping brain to maintain sleep. In the face of increasing stimulation, such as increasingly louder environmental sounds, there will be an
eventual shift to a light stage of sleep and/or wakefulness, an ability that would surely be adaptive in potentially dangerous situations. At the same time, however, sleep is clearly important, and it would be quite maladaptive to wake to every environmental sensation. There is evidence that the K-complex is an electrophysiological representation of a brain state where arousals are less likely to occur (see Bastien, Crowley, & Colrain, 2002, for review).

Two recent studies provide strong evidence to support the hypothesis that the K-complex reflects a sleep maintenance or protective response. Nichols, Colrain, and Trinder (2002) manipulated sleep drive by fragmenting sleep, thereby increasing sleep drive. They reported that both spontaneous and evoked K-complexes increased on the night immediately following the sleep fragmentation night. Peszka and Harsh (2002) also manipulated sleep drive by having a nap at their normal bedtime where they measured K-complexes in response to a two-tone presentation. Subjects were kept awake until their typical bedtime the following night. The two-tone presentation was repeated, and the proportion of evoked K-complexes significantly increased from the first baseline night. Thus, interventions that increase sleep drive and decrease arousability lead to brain states more conducive to K-complex production.

Summary of Prior Research

In summary, some primary features of PTSD include hyperarousal, hypervigilance, and sleep disturbance (in the form of insomnia and nightmares). Traditional objective sleep measures, i.e., polysomnography, have failed to adequately document the typical sleep complaints in PTSD. While information processing is known
to be dysfunctional in PTSD during the waking state, it has yet to be examined during the sleep state. Studies of information processing and sleep in healthy subjects have demonstrated that as we fall asleep, and across the different stages of sleep, we are still capable of sensing, attending, and responding -- both electrophysiologically and behaviorally, e.g., taking a deep breath or depressing a microswitch to terminate a tone -- (Harsh, Badia, O’Rourke, Burton, Revis, & Magee, 1987; Williams, Morlock, & Morlock, 1966) to the outside world. The evoked K-complex is a reasonable measure with which to investigate information processing during sleep in PTSD, as it is a well-described response that relates to information processing of stimuli during the sleep state in healthy subjects. While there is evidence that the K-complexes are linked to information processing in response to sensory stimuli in healthy subjects, little is known about the K-complex role in information processing during sleep in people with PTSD. Further, previous findings that the K-complex is sensitive to relevant stimuli suggest that this would be a sensitive measure of how trauma-related information is processed during sleep. Examinations of heart rate and cortical activity can provide insights into autonomic and central nervous system arousal levels during sleep in response to external provocation, as well as the opportunity to assess the impact of an evoked K-complex on these measures. The present study attempts to identify an objective index of sleep–enhanced information processing during sleep, assumed to be due to hyperarousal -- that might capture PTSD-related sleep disturbances.
Objectives and Hypotheses for the Present Study

The goal of the present study was to investigate how PTSD may impact sleep-related processing by examining psychophysiological responses to different types of auditory stimuli during stage 2 sleep. In addition, a PTSD population allows for the study of how personally relevant or meaningful stimuli are processed as compared to less meaningful stimuli. This was achieved by having a pure tone stimulus condition and a trauma-related stimulus condition. Because trauma-based auditory stimuli are environmental sounds, they are therefore more complex than a pure sign sound wave as in the tone condition. Therefore, an additional, affectively neutral stimulus condition was used to control for sound complexity.

It was hypothesized that the hyperarousal and hypervigilance common in PTSD during wakefulness will persist into the sleep state, and thus, information processing during sleep will be enhanced compared to non-PTSD participants. People with PTSD were predicted to show enhanced psychophysiological responses to all auditory stimuli presented during sleep relative to control participants; with relatively greater enhancement to trauma-related stimuli. Thus, it was predicted that cortical arousal (i.e., faster EEG activity relative to slower activity) and heart rate changes would be greater in the PTSD group compared to the control group.

Predictions about K-complex elicitation were based on Oswald and colleague’s (1960) hypothesis that more K-complexes are evoked to relevant stimuli. Thus, it was hypothesized that trauma stimuli should evoke more K-complexes than other types of stimuli, particularly for the PTSD group. Because the trauma and neutral trials were rarer
than tone trials, both groups were predicted to elicit more K-complexes to the rare stimuli, as evidenced by larger averaged N550 amplitudes.
METHODS

This dissertation is an analysis and report of data collected at the National Center for PTSD, Palo Alto VA Health Care System, Menlo Park Division, Sleep and EEG Laboratory under the direction of Steven H. Woodward.

Participants

There were 24 male Vietnam veterans (mean age = 54 years, range = 48 to 59) who consented to participate in the study. All participants had combat experience during the war (i.e. trauma-exposed). All participants received equal compensation for their participation in the study. Of this sample, 14 participants had an active diagnosis of PTSD (patients) and 10 participants (combat controls) were free from psychiatric disorders. An additional 6 participants (3 patients and 3 controls) participated, but were excluded from the study due loss of data from technological complications. An additional patient was withdrawn from the study during the night by the experimenter/lab technician because he would awaken to every stimulus presented while he was sleeping.

Controls were screened using the Clinician-Administered PTSD Scale (CAPS; Blake, et al., 1995) and the Structured Clinical Interview for DSM-IV Axis I Diagnoses (First, Spitzer, Gibbon, & Williams, 1997). They were recruited from the community and had participated in previous studies conducted at the National Center for PTSD. Patients were recruited from a residential treatment program for PTSD run by the National Center for PTSD at the Palo Alto VA Medical Center, Menlo Park Division. All patients in the sample complained of having difficulty sleeping (i.e., either initiating and/or maintaining sleep) during recruitment, though they were not selected on this basis. There was a large
degree of psychiatric comorbidity in the patient group. In particular, depression, alcohol, and other substance abuse were prevalent among the patients. Patients were free from substance use/abuse for at least five months prior to their participation in the study. See Tables 1, 2, and 3 for a listing of patient characteristics.

Table 1. Patient demographic information.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Education (years)</th>
<th>Alcohol Use (years)</th>
<th>Alcohol Intoxication (years)</th>
<th>Polysubstance Abuse (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT001</td>
<td>49</td>
<td>12</td>
<td>35</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>PT002</td>
<td>56</td>
<td>14</td>
<td>44</td>
<td>44</td>
<td>10</td>
</tr>
<tr>
<td>PT003</td>
<td>51</td>
<td>13</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PT004</td>
<td>48</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PT005</td>
<td>56</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PT006</td>
<td>56</td>
<td>13</td>
<td>39</td>
<td>39</td>
<td>4</td>
</tr>
<tr>
<td>PT007</td>
<td>51</td>
<td>12</td>
<td>36</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>PT008</td>
<td>52</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT009</td>
<td>54</td>
<td>18</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PT010</td>
<td>55</td>
<td>12</td>
<td>30</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>PT011</td>
<td>52</td>
<td>13</td>
<td>23</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>PT012</td>
<td>51</td>
<td>13</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>PT013</td>
<td>54</td>
<td>14</td>
<td>6</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>PT014</td>
<td>54</td>
<td>12</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Mean</td>
<td>52.8</td>
<td>13.4</td>
<td>23.3</td>
<td>15.2</td>
<td>9.5</td>
</tr>
<tr>
<td>(SD)</td>
<td>(2.6)</td>
<td>(1.6)</td>
<td>(15.8)</td>
<td>(16.3)</td>
<td>(11.7)</td>
</tr>
<tr>
<td>Patient</td>
<td>DSM-IV Diagnoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT001</td>
<td>Major Depressive Disorder, Alcohol Abuse, Cannabis Abuse, Cocaine Dependence, Adult Antisocial Behavior</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT002</td>
<td>Major Depressive Disorder, Specific Phobia, Alcohol Dependence, Sedative, Hypnotic, and Anxiolytic Dependence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT003</td>
<td>Major Depressive Disorder, Adult Antisocial Behavior</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT004</td>
<td>Major Depressive Disorder, Opiod Abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT005</td>
<td>Major Depressive Disorder, Panic Disorder with Agoraphobia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT006</td>
<td>Depressive Disorder NOS, Psychotic Disorder NOS, Alcohol Dependence, Polysubstance Dependence, Panic Disorder with Agoraphobia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT007</td>
<td>Major Depressive Disorder, Alcohol Dependence, Opiod Dependence, Cocaine Dependence, Social Phobia, Specific Phobia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT008</td>
<td>Major Depressive Disorder, Alcohol Dependence, Cocaine Dependence, Cannabis Abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT009</td>
<td>Major Depressive Disorder, Panic Disorder with Agoraphobia, Cannabis Abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT010</td>
<td>Dysthymic Disorder, Anxiety Disorder NOS, Alcohol Dependence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT011</td>
<td>Major Depressive Disorder, Alcohol Dependence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT012</td>
<td>Major Depressive Disorder, Alcohol Dependence, Cocaine Dependence, Cannabis Abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT013</td>
<td>Major Depressive Disorder, Dysthymic Disorder, Alcohol Abuse, Cannabis Dependence, Amphetamine Dependence, Cocaine Abuse, Hallucinogen Abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT014</td>
<td>Major Depressive Disorder, Alcohol Dependence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Patient inventory results.

<table>
<thead>
<tr>
<th>(Possible Range)</th>
<th>BDI Score (0 - 63)</th>
<th>CES Score (0 - 35)</th>
<th>CAPS Reexperiencing Score (0 - 20)</th>
<th>CAPS Avoidance/ Numbing Score (0 - 28)</th>
<th>CAPS Hyperarousal Score (0 - 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT001</td>
<td>33</td>
<td>5</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>PT002</td>
<td>34</td>
<td>33</td>
<td>5</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>PT003</td>
<td>26</td>
<td>26</td>
<td>5</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>PT004</td>
<td>50</td>
<td>32</td>
<td>4</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>PT005</td>
<td>26</td>
<td>29</td>
<td>2</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>PT006</td>
<td>34</td>
<td>23</td>
<td>5</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>PT007</td>
<td>27</td>
<td>23</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>PT008</td>
<td>16</td>
<td>18</td>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>PT009</td>
<td>24</td>
<td></td>
<td>4</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>PT010</td>
<td>25</td>
<td>17</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>PT011</td>
<td>30</td>
<td>28</td>
<td>4</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>PT012</td>
<td>13</td>
<td>23</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>PT013</td>
<td>28</td>
<td>27</td>
<td>4</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>PT014</td>
<td>5</td>
<td>29</td>
<td>1</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Mean</td>
<td>26.5</td>
<td>27.5</td>
<td>3.8</td>
<td>6.9</td>
<td>5.1</td>
</tr>
<tr>
<td>(SD)</td>
<td>(10.7)</td>
<td>(6.6)</td>
<td>(1.3)</td>
<td>(2.8)</td>
<td>(1.8)</td>
</tr>
</tbody>
</table>

Note: BDI = Beck Depression Inventory; CES = Combat Exposure Scale; CAPS = Clinician Assessed PTSD Scale, Current ratings
Procedure

Participants arrived at the sleep laboratory at either 7:30 pm or 9:30 pm. The experiment was explained, and informed consent was obtained. They were familiarized with the laboratory environment, and then changed into their night clothes. Auditory thresholds for each ear were assessed using 1000 Hz and 4000 Hz pure tones using an Audio-Scout Bell Tone portable audiometric system in a standardized manner, using the same earphones used during their overnight sleep recordings. E-A-RTONE 3A insert earphones (i.e., placed into the ear canal) were used. Next, physiological sensors were attached. This entire procedure took approximately two hours. Afterward, participants were free to go to bed when feeling sleepy, which was usually right away. Once participants achieved at least 15 minutes of consolidated stage 2 sleep, auditory stimuli were presented.

Stimuli

Three types of stimuli were presented to participants during stage 2 sleep: pure tones (tone condition); 5 affectively neutral sounds (neutral condition); and 5 combat-related sounds (trauma condition). The tones consisted of a 1000 Hz pure tone; neutral sounds consisted of a crow, telephone ring, piano note, bell, and trumpet; trauma sounds consisted of gun shots and explosions that were used in previous studies of PTSD in Vietnam veterans, and were developed by Steven H. Woodward.

All stimuli were normalized to have equivalently fast rise times and be equally loud (73 dB on average), and were 500 ms in duration; the only quality in which the stimuli differed was faster rise times for the tone stimuli (5 ms). The stimuli were
presented in an oddball paradigm with a randomized inter-stimulus interval (ISI) of 15 to 30 seconds, as the probability of K-complex production has been shown to be maximized at this ISI (Bastien & Campbell, 1994; Campbell, Bell, & Deacon-Elliot, 1985). Tones were most frequent, occurring 60% of the time, while neutral and trauma stimuli each occurred 20% of the time. A random order for stimulus presentation was generated, and this same list was used for all participants (i.e., all participants heard the same stimuli in the same order).

Upon detection of an arousal to stage 1 sleep, wakefulness, movement arousal, or REM sleep, the presentation of stimuli was manually halted. Stimulus presentation was resumed once a participant achieved at least five minutes of uninterrupted stage 2 sleep. Trials that were presented during any other stage of sleep were discarded. Trials were presented throughout the entire night of recording. The total number of stimuli presented to each subject was dependent on their sleep quality and continuity. The number of stimuli presented to participants ranged from 89 to 506 (grand mean number of trials presented = 239; controls = 233, patients = 243; differences between the groups was not significant). Participants were allowed to awaken naturally in the morning, or at a time they specified they night before. No participants had an adverse reaction to the auditory stimuli presented during sleep. Stimuli presentations were stopped during the night for one patient, as he would wake to every stimulus presented, and he was allowed and able to sleep for the remainder of the night. Another patient woke in the night with significant anxiety, likely a nocturnal panic attack, but this was during a time in which stimuli were not being presented; he was able to calm down and return to sleep.
Psychophysiological Measures

**Electroencephalogram (EEG).** EEG was measured at the following sites, using the international 10-20 system (Jasper, 1958): F7, F8, F3, F4, Cz, P3, and P4, each referenced to linked ear lobes A1/A2.

**Electrooculogram (EOG).** EOG was measured with two electrodes, each referenced to linked earlobes (A1/A2), near upper right eye and lower left eye.

**Electromyogram (EMG).** Chin muscle activity for sleep stage scoring was recorded using a bipolar reference from among three electrodes attached over the mentalis and submentalis muscles.

**Electrocardiogram (ECG).** Heart rate was measured using bipolar leads placed near the right collar bone and lower left rib cage.

**Respiration (RESP).** Respiration was measured using a conventional piezo-electric strain-gauge placed across the abdomen to screen for apnea.

**Oxymetry.** Blood oxygen levels were measured using an oximeter placed on the index finger. This signal was used to ensure participants were not having significant desaturations (less than 85%) and was not digitized.

Refer to Table 4 for amplifier and filter settings.
Table 4. Psychophysiological recording settings.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Low Frequency</th>
<th>Sensitivity</th>
<th>High Frequency</th>
<th>60 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOG</td>
<td>0.1 μV</td>
<td>50</td>
<td>100</td>
<td>in</td>
</tr>
<tr>
<td>Chin EMG</td>
<td>30 μV</td>
<td>7.5</td>
<td>300</td>
<td>in</td>
</tr>
<tr>
<td>EEG</td>
<td>0.1 μV</td>
<td>20</td>
<td>100</td>
<td>in</td>
</tr>
<tr>
<td>ECG</td>
<td>1 MM</td>
<td>2</td>
<td>30</td>
<td>in</td>
</tr>
<tr>
<td>RESP</td>
<td>0.1 μV</td>
<td>7.5</td>
<td>100</td>
<td>in</td>
</tr>
</tbody>
</table>

**Recording Apparatus, Data Acquisition, and Data Reduction**

Gold cup electrodes were used to collect EEG, EOG, and EMG signals. EEG electrodes were affixed to the scalp with either Grass 10-20 paste or tape (for those sites in which hair was not present) following abrasion. Impedances were measured to ensure they were below 5 KOhms. ECG was collected with disposable electrodes. Auditory stimuli contained a pulse that was sent to a data channel when presented to participants; pulses were later used to extract trials from the continuous recording. Signals were amplified using analog amplifiers (Grass-Telefactor, Warwick, RI), and then digitized at sampling rate of 400 Hz. Calibrations were conducted at the beginning of each subject’s recording; these were used to correct the data amplitudes prior to data processing. Trials were extracted from the overnight data files by down sampling to 200 HZ for data storage considerations, and were epoched into windows that began 20 s prior to stimulus onset and extended 10 s following the stimulus. Data collection and reduction software was
written by Steven Woodward, Ph.D. at the National Center for PTSD using Matlab software (Mathworks, Inc., Natick, MA).

**Psychophysiological Variables**

**Evoked K-complex identification and trial average.** K-complex scoring was done blind to the participant’s PTSD status and order of stimulus presentation. Ambiguous trials were reviewed and a consensus reached with a second rater for 18 of the participants. Inter-rater agreement was greater than 90% in K-complex identification for four participants. K-complexes were identified in frontal recording leads (i.e., F3 and F4) using the standard Rechtschaffen and Kales’ (1968) criteria: a large negative sharp wave followed by a positive component that is at least .5 s in duration.

To be considered an evoked K-complex, the peak of the negative component also had to satisfy the following criteria: amplitude of -75 μV or greater, measured at F3 or F4, and occurring between 400 and 1000 ms from stimulus onset. The evoked window in the present study is longer than typical due in part to the longer stimuli duration of stimuli used in the present study, as well as the older age of our participants; older individuals have been shown to have both longer N550 latencies and smaller N550 amplitudes (Crowley, Trinder, & Colrain, 2002). Trials in which a movement arousal, delta burst, or other artifact occurred immediately before a stimulus presentation were rejected and not used in the averaging procedure. All trials that were to be included in the averaging
process were classified into two response types on the basis of visual inspection of each epoch. The two response types were trials that contained K-complexes (KC+) and trials in which a K-complex did not occur (KC-). Grouped trials were averaged relative to stimulus type (tone, neutral, and trauma) for each subject. These produced average evoked potential files for each of the response types.

Amplitude and latency of the N550 component was determined by identifying the most negative value (amplitude) that occurred between 400 ms and 1000 ms on the averaged KC+ files. N550 was measured at Fz – estimated by averaging F3 and F4 -- where the N550 component has previously been shown to be maximal (Colrain, Webster, & Hirst, 1999; Cote, de Lugt, Langley, & Campbell, 1999; Crowley, Trinder, & Colrain, 2002; Gora, Colrain, & Trinder, 1999, 2001; McCormick, Nielsen, Ptito, & Montplaisir, 1997; Niiyama, Fushimi, Sekine, & Hishikawa, 1995).

Cortical arousal. Cortical arousal was measured using spectral analysis of the EEG in two ways: absolute power (microvolts-squared/Hz) in the beta-band (16 to 30 Hz) and by calculating a ratio of absolute power in the fast activity range over slow activity (power ratio: alpha, sigma, and beta [8 to 30 Hz]/theta and delta [1 to 7.5 Hz]). Cortical arousal was operationalized as increases in these measures of cortical activity following the stimulus. Change in cortical activity was assessed by comparing these power measurements over a 4 s baseline period (immediately preceding stimulus onset)

--

2 Typically, stimuli used in studies investigating the evoked K-C use brief stimuli (i.e., 50 ms) with fast rise times. Because we wanted to use to be able to compare recognizable stimuli that were personally meaningful to affectively neutral and tone stimuli, our stimuli were longer than typical (i.e., 500 ms). To investigate whether the long duration of the stimuli also evoked K-Cs (but later), 'late' K-complexes were also scored using an evoked window of 1000 to 1400 ms post-stimulus. There were far fewer late evoked
and a 4 s post-stimulus period (beginning one second after stimulus onset). The immediate 1 s period following stimulus onset was not included to reduce overrepresentation of delta frequency that would result from those trials in which a K-complex was evoked. Each 4 second epoch was transformed into the frequency domain using a classic Welch periodogram spectral analysis (nFFT = 200 samples with 50% overlapping Hamming window segments). Absolute power of the beta range (16 to 30 Hz) was examined, as well as a ratio of fast. Because there were no a priori hypotheses regarding differences among the various EEG sites, the data were analyzed at Cz. Beta power was found to have a skewed distribution as is common, and was subsequently log transformed.

Each trial was also scored for the presence of a microarousal -- sub-awakening arousal responses that are scored during sleep -- if one occurred within 10 seconds following stimulus onset. Too few microarousals were identified to analyze differences between group or stimulus type.

**Heart rate.** Inter-Beat-Interval (IBI) was determined by identifying the time in milliseconds between the R-wave of each heart beat. These data were resampled to real time to produce average IBIs for each 500 msec of data across the 30 s sampled epoch (i.e., stimulus onset was extracted such that each trial occurred at second 20). Baseline IBIs were averaged from the 20 s prior to stimulus onset. The proceeding 10 s were used to determine the time course of IBI changes following a stimulus. To determine post-

K-complexes (only about 10%), and no apparent differences between the groups; as a result, these data were not further analyzed.
stimuli HR changes, IBI was then converted to $HR^3$. To analyze the data, the bradycardic response was calculated by subtracting the baseline from minimum heart rate; the tachycardic response was calculated by subtracting the minimum heart rate from the maximum heart rate for the first 6.5 s following stimulus onset.

\[ HR \text{ (beats per minute)} = \frac{1}{IBI} \times 60,000 \]
RESULTS

Repeated measures analyses of variance (ANOVAs) were used to compare differences between patient and control groups on K-C proportion, amplitude, and latency, cortical activity/arousal, and heart rate in response to the three types of auditory stimuli (tone, neutral, and trauma). Both cortical arousal and HR analyses were conducted by also comparing trials in which a K-complex was elicited (K+ trials) to those where a K-complex (K- trials) was absent. A level of $p < .05$ was used as a test for significance, although results within the range of $p = .10$ were considered marginally significant and also reported. Where appropriate, simple effects ANOVAs and post-hoc t-tests were used to assess differences within significant interactions for comparisons of interest.

Probability of K-Complex Elicitation

A 2 x 3 (Group X Stimulus Type) repeated measures ANOVA of proportion of K-C elicitation revealed a main effect of group, $F(1,22) = 17.54, p = .0004$ and stimulus type, $F(2,44) = 6.19, p = .0043$. The interaction between Group and Stimulus Type was also significant $F(2,44) = 3.97, p = .026$; see Figure 1. Controls evoked significantly more K-complexes than patients, 55% to 35% on average, respectively. There were no differences in rate of K-complex production between the tone and trauma stimuli (and across all three stimuli types in the control group). Post-hoc paired sample t-tests demonstrated that within the patient group K-complex elicitation rate was significantly higher for neutral stimuli than tone or trauma stimuli; there was no difference between
tone and trauma stimuli. Post-hoc independent sample t-test demonstrated no difference between the controls and patients on K-complex elicitation rate for neutral stimuli.

Figure 1. Mean probability and standard error of the mean (SEM) for K-complex elicitation to a stimulus.

Evoked K-complex: N550 Amplitude and Latency

A 2 x 3 (Group X Stimulus Type) repeated measures ANOVA of N550 amplitude revealed no statistical differences between group, stimulus type, or their interaction. A 2 x 3 (Group X Stimulus Type) repeated measures ANOVA of N550 latency revealed a main effect of group, $F(1,22) = 4.323, p = .0495$, and a marginally significant effect of stimulus type, $F(1,22) = 3.05, p = .057$. The interaction between group and stimulus type was also marginally significant, $F(1,22) = 2.603, p = .085$, see Figure 2. Patients had significantly longer N550 latencies relative to controls. Patients had significantly longer N550 latencies across all stimulus types relative to the controls. Within the control group,
post-hoc paired sample t-tests demonstrated significantly longer N550 latency to trauma stimuli than to tone or neutral stimuli; there was no difference on latency between tone and neutral.

Figure 2. Mean N550 latency and standard error of the mean (SEM) in milliseconds.

Cortical Arousal

Two measures of cortical arousal – the power ratio and beta-band power – were independently assessed to determine if baseline (pre-stimulus) power differed between subject groups and across condition (i.e., stimulus type and K-complex type). A repeated measures ANOVA failed to show any differences at baseline. Difference scores (seconds 1 to 5 following stimulus onset minus baseline) in EEG power change were calculated and analyzed with a 2 x 3 x 2 (Group X Stimulus Type X K-Type) repeated measures ANOVA. Significant main effects and interactions are listed in Tables 5 and 6; see Figures 3 and 4.
The striking observation of the impact of auditory stimuli on cortical arousal as defined by EEG power ratios (fast relative to slow activity) was an opposite response pattern between patients and controls (see Figure 3). Patients demonstrated a decrease in power ratio for all stimulus types, which was more marked in the KC+ trials and in particular to neutral stimuli (although not significantly different from tone or trauma). The exception to small increases in the control group occurred in KC- trials, with a slight decrease to trauma and strong increase in neutral stimuli.

Table 5: F-values, degrees of freedom, and probabilities for power ratio repeated measures ANOVA.

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>F-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>1, 22</td>
<td>14.251</td>
<td>.001</td>
</tr>
<tr>
<td>Stimulus Type</td>
<td>2, 44</td>
<td>4.214</td>
<td>.021</td>
</tr>
<tr>
<td>K Type</td>
<td>1, 22</td>
<td>11.530</td>
<td>.003</td>
</tr>
<tr>
<td>Group * Stimulus Type</td>
<td>2, 44</td>
<td>10.535</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Stimulus Type * K Type</td>
<td>2, 44</td>
<td>9.683</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Group * Stimulus Type * K Type</td>
<td>2, 44</td>
<td>5.823</td>
<td>.006</td>
</tr>
</tbody>
</table>
Figure 3. Difference scores (post-stimulus - baseline) of estimated mean power ratio in response to stimulus and whether a K-complex was evoked. K+ are trials in which a K-complex was elicited by a stimulus and K- are trials in which a K-complex was not elicited.

Beta power showed larger increases across all conditions in the controls as compared to the patients, and both groups had more beta activity for trials in which K-complex was evoked (see Figure 4). Post-hoc paired sample t-tests of beta increase in the patient group for KC+ trials demonstrated that there was significantly smaller beta increases post-stimulus than for tone or neutral stimuli; tone and neutral stimuli did not differ from each other. In the control group, beta increases were most pronounced for neutral stimuli regardless of K-complex elicitation, and beta activity was slightly higher for tone stimuli than trauma stimuli.
Table 6: F-values, degrees of freedom, and probabilities for beta-band analyses.

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>F-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>1, 22</td>
<td>3.556</td>
<td>.072*</td>
</tr>
<tr>
<td>Stimulus Type</td>
<td>2, 44</td>
<td>10.401</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>K Type</td>
<td>1, 22</td>
<td>37.258</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Group * Stimulus Type * K Type</td>
<td>2, 44</td>
<td>5.823</td>
<td>.080*</td>
</tr>
</tbody>
</table>

*Marginally significant
Figure 4. Difference scores (post-stimulus - baseline) of estimated mean (untransformed) beta power in response to stimulus and whether a K-complex was evoked. K+ are trials in which a K-complex was elicited by a stimulus and K- are trials in which a K-complex was not elicited.

Heart Rate

HR responses showed a typical, initial bradycardia response (about 1.5 s), followed by a tachycardia response consistent with orienting responses (see Figure 5). Comparison of baseline heart rate between patients and controls was assessed with a 2 X 3 X 2 (Group X Stimulus Type X K-Type) repeated measures ANOVA, which revealed a main effect of group that approached significance, $F (1,22) = 3.989$, $p = .058$. On average, baseline HR was 8.3 beats per minute faster in patients than controls (mean =
55.2 and 63.5 beats per minute, respectively. A 2 X 3 X 2 (Group X Stimulus Type X K-Type) repeated measures ANOVA on heart rate deceleration (i.e., bradycardia) post-stimulus (minimum HR – baseline HR) revealed no significant main effects or interactions. The repeated measures ANOVA on heart rate acceleration (tachycardia) post-stimulus did not reveal a significant main effect of group, however, there was a significant main effect of Stimulus Type and K-Type, \( F (2,44) = 6.754, p = .003 \) and \( F (1,22) = 9.939, p = .005 \), respectively (see Figure 6). Heart rate increases were significantly larger for K+ trials compared to K- trials. Stimulus Type also affected HR increase irrespective of K-complex elicitation. Tone trials showed the largest increase, followed by trauma, and then neutral. Pairwise comparisons of Stimulus Type revealed that the increase in HR for tones was significantly higher in neutral than for tone \((p=.001)\) or trauma \((p=.032)\), \( F (2,21) = 7.823, p = .003 \). The difference in HR increase between tone and trauma was not significant.
Figure 5. Example of mean HR change following stimulus onset (in this case, for all tone trials that evoked a K-complex), showing an initial bradycardic response peaking around 1.5 s following stimulus onset, and a longer tachycardic response peaking approximately 5 s following stimulus onset.
Figure 6. Estimated mean change in heart rate deceleration (bradycardia) and acceleration (tachycardia) for stimulus type and K-Type across all participants. K+ are trials in which a K-complex was elicited by a stimulus and K- are trials in which a K-complex was not elicited.
DISCUSSION

The primary goal of the present study was to explore central and autonomic nervous system responses during sleep in PTSD. PTSD is known to affect arousal, vigilance, and information processing during wakefulness, but less is known about how these processes operate during the sleep state in PTSD. Additionally, there are no known studies that have specifically assessed sleep-related information processing in this population.

The primary information processing difference found in the present study between combat veterans with and without PTSD was that those with PTSD had fewer and smaller physiological responses to stimuli presented during sleep than the combat controls. Results in the present study showed that the PTSD group had fewer K-complexes, and were less aroused cortically following the presentation of a stimulus regardless of stimulus type.

Information Processing is Disturbed in PTSD

The findings suggest that information processing is disturbed in the PTSD group studied, however not with the expected pattern. As compared to controls, patients were generally less responsive in terms of K-complex elicitation. In response to tone and trauma stimuli, patients demonstrated K-complexes less frequently, but demonstrated equivalent K-complex responses to the neutral stimuli. Thus, patients exhibited overall dampened responsiveness, but this effect was variable across stimulus conditions.

Oswald and colleague’s (1960) hypothesis that K-complexes are evoked to salient stimuli was not supported. Neither group, both of whom were trauma-exposed,
demonstrated within group differences between the most meaningful and the most meaningless stimuli (combat sounds and pure tones, respectively). That is, there was no difference in K-complex responses to essentially information-free stimuli (tones) and information-rich, highly salient stimuli (trauma). Furthermore, results from the present study highlight the all-or-nothing nature of the K-complex. When they were elicited, K-complexes tended to be the same size (i.e., amplitude), regardless of stimulus type or subject group.

One explanation for the findings that the PTSD sample had fewer and smaller responses (i.e., lower K-complex elicitation rate, decrease in EEG power) might result from alcohol and substance use evident in the patients but not the controls. Long-term alcohol abuse correlates cortical atrophy, and a recent study found lower K-complex elicitation rate and smaller N550 amplitudes in long-term alcohol abusers (Nicholas, Trinder, & Colrain, 2002). The present findings that the response rate to neutral stimuli did not significantly differ between the PTSD group and control group, and that N550 amplitudes across all stimulus types also did not differ between the groups, argues against this explanation.

An alternative interpretation to the unexpected findings is a psychological one. The chronic sequelae of the trauma may lead to a psychological phenomenon where responses to stimuli are blunted as the reflection of long term consequences to the trauma that they experienced, which does not occur in trauma-exposed individuals without PTSD. This may develop as a compensatory mechanism to accommodate for severe sleep disruption that occurs immediately following a traumatic experience. Some evidence
shows that those who have disrupted sleep following a trauma are more likely to go on to
develop PTSD (e.g., Mellman, et al., 2002). Other mechanisms that might cause blunted
responses are deregulatory effects of stress responses resulting from traumatic situations.
For example, the HPA axis (hypothalamic-pituitary-adrenal axis) can become altered
under conditions of an extreme stress response (for review, see Bremmer, 1999;
Sapolsky, 1996), which can lead to a number of effects, including neuronal death and
lowered sensitivity to cortisol, a hormone released during stress.

A Unique Response to Traumatic Stimuli not Evident in the PTSD Group

Individuals with PTSD have been shown to be hyperreactive to traumatic cues
during wake, even when those cues are presented outside of awareness (i.e., subliminally
processed; for review, see Buckley, Blanchard, & Neill, 2000; McNally, 1995, 1998).
The PTSD sample in this study did not show hyper-responsivity to combat sounds
presented while they were asleep. Instead, there was an expected finding of increased
responsiveness to neutral stimuli, in that patients were more likely to evoke a K-complex
in response to a neutral stimulus than to either a trauma or tone stimulus.

Although the neutral condition was originally added to the study design in an
attempt to control for sound complexity, it is also possible that the neutral sounds were
indeed more complex than the trauma stimuli. Trauma stimuli were comprised of combat
sounds (i.e., gunshots and explosions), which have less spectral variation than other types
of environmental sounds. In addition, or perhaps more likely, is that the increased
response rate to neutral stimuli was a novelty effect. Condition-wise, neutral and trauma
stimuli had the same likelihood of occurring (20% each). The neutral stimuli, however,
came from different ontological categories. Thus, each independent neutral sound was more ‘rare’ than the trauma sounds (i.e. 4% chance of occurring compared to 20%). With this interpretation, the patients appeared to be hyperresponsive to stimulus novelty rather than stimulus relevance.

The differential response of the PTSD group to neutral stimuli was not found in the controls. This may be due to a ceiling effect obscured detectable differences in their responses to the three types of stimuli in the control group. The particular stimuli and design in the present study (e.g., long ISI, fast rise times, etc.) may have maximized the total number of K-complexes possible. However, evoked K-complex rates greater than the 55% rate found in the present study for the control group have been reported in the literature which argues against this interpretation. For example, Nicholas, Trinder, & Colrain (2002) reported a 67% K-complex response rate for controls compared to 51% for a chronic alcohol sample (mean age 59 and 63, respectively).

**PTSD is Associated with Tonic but Not Reactive Hyperarousal**

Predictions that hyperarousal as measured by cortical arousal would be evident in the sleep state in PTSD were not supported. Baseline levels of cortical arousal and beta activity did not differ between the controls and the patients. Rather, patients exhibited less cortical arousal as compared to the controls following the presentation of an auditory stimulus as measured by both power ratio and beta power. When evaluating the relation of fast to slow EEG frequencies for trials in which a K-complex was evoked, patients had relatively less fast and more slow EEG activity, while controls demonstrated modest increases in fast relative to slow EEG activity. While the magnitude decrease observed in
the patient’s power ratios for KC- trials was less than KC+ trials, when considered in combination with the change in beta activity following KC- trials, there is relatively little to no change in activity or arousal level. The data suggest that when there is no K-complex response, the stimuli are not recognized on the cortical level.

In contrast to findings on cortical arousal, there was heart rate evidence that autonomic hyperarousal extended into the sleep state for the PTSD group. Baseline heart rate in the patients was higher than baseline heart rate in the controls suggesting tonic hyperarousal within stage 2 sleep in the PTSD population sampled. Unlike measures of cortical hyperarousal, cardiac reactivity did not differ between the PTSD and control group. It is interesting to note, however, that since the type of stimulus presented had an impact on HR increase post-stimulus (largest for neutral), the HR response was a sensitive marker of stimulus discrimination during sleep in the present study. This is especially true if viewed within the interpretation that the differences detected by the sleeping brain are due to stimulus novelty. The addition of a non-combat control group to the present study would have helped to determine if the similar HR changes seen in the patients and controls was related somehow to combat experience.

There is converging evidence to suggest that sustained high levels of cortisol have a neurotoxic effect on hippocampal cells, which are important to memory and in regulation of the HPA axis and therefore the stress response in general. Thus, chronic stress conditions, such as occurs in PTSD, may lead to a deregulation in HPA axis function resulting in a decreased ability to mount a stress response.
Finally, differences found between the PTSD group and the combat controls could be due to other factors, such as life-long psychopathologies in the patient group, including other comorbid diagnoses, or other aspects of their experience (e.g., trouble succeeding in life, service connected disability).

Limitations and future directions

Additional work is needed to bring greater clarification to the impact of PTSD on sleep, and the role, function, and consequence of information processing abnormalities evident on sleep symptoms and daytime function. Study findings are limited in part by a relatively small sample size. The present findings are further complicated by a number of factors common to research with psychiatric populations, such as comorbid diagnoses, extensive substance abuse histories, and use of psychotropic medications in the PTSD sample. More homogeneous PTSD samples (e.g., Vietnam veterans with a current diagnosis of PTSD without substance abuse problems or depressive disorders), are difficult to obtain and may be less clinically relevant. The use of other control samples would have been useful in the design of the present study and merit consideration in future studies, such as age-matched groups of (a) non-traumatized individuals, (b) individuals matched for alcohol use/abuse-matched but free from PTSD, and (c) psychopathology comparison groups, such as individuals with depression and/or anxiety. Lastly, the use of a recently traumatized sample, such as veterans from the Somalia Theater or Gulf War Theater, would have provided an ideal comparison of acute versus chronic PTSD. However, these samples are difficult to obtain and require wide resources in terms of participant recruitment and data collection.
Although guided by logistical considerations, another study limitation was the lack of an adaptation night. Participants only spent one night in the lab -- certainly a novel environment, including a plethora of electrodes and constant monitoring by the experimenter -- which raises the possibility of the impact of 'first night effects' on the present findings. Findings of elevated tonic HR in the patient group and responsiveness to complex, novel stimuli, may have been confounded by first night effects. While the inclusion of an adaptation night is a fairly standard design feature in polysomnographic studies, the overall impact of such effects on the sleep record appears to be generally weak.

Data interpretation is also complicated by potential medication effects from the various psychotropic agents (e.g., antidepressants) being taken by the patient population. The effect of such agents on sleep-related information processing is unknown. These medications are known to sometimes improve sleep (although some are known to disrupt sleep), and as such they may impact the processing of sensory stimulation during the sleep state. Additionally, the physiological impact of such medications on autonomic system, such as heart rate, confounds the measurement of hyperarousal in the study population. Nonetheless, most people who have an active and current diagnosis of PTSD will almost invariably be on some kind of psychotropic medication, and so exclusion due to use of psychotropic medication would decrease clinical relevance.

The relationship between information processing and sleep in PTSD could be elaborated upon with further research. Functional neuroimaging techniques, such as PET or fMRI, may clarify the underpinnings of disturbed information processing during sleep.
in PTSD. Likewise, systematic study of information processing during REM sleep may yield useful information, as specific REM abnormalities have been noted (i.e., early REM latency and increased REM density), reexperiencing of the traumatic event occurs in the form of nightmares during this state, and cortical activity is distinctly different than during NREM (i.e., much more like the wake state, which is also reflected in more wake-like evoked response potentials; Takahara, Nittono, & Hori, 2002; Kote & Campbell, 1999). By sampling arousal measures across both wake and sleep, relative change in arousal across state can be assessed within the same study sample.

In the present study, individuals with PTSD responded differently than the controls as measured with a variety of psychophysiological markers. The study of PTSD reactivity during sleep can be a useful way to investigate issues of hyperarousal, hypervigilance, automatic processing biases in PTSD, and potential pathophysiological processes involved in PTSD-related sleep disturbance.
APPENDIX A

Diagnostic criteria according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 2000).

A. The person has been exposed to a traumatic event in which both of the following were present:
   1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of the self or others
   2) the person's response involved intense fear, helplessness, or horror. Note: In children, this may be expressed instead by disorganized or agitated behavior.

B. The traumatic event is persistently reexperienced in one (or more) of the following ways:
   1) recurrent and intrusive distressing recollections of the event
   2) recurrent distressing dreams of the event
   3) acting out or feeling as if the traumatic event were recurring (includes a sense of reliving, illusions, hallucinations, and dissociative flashbacks)
   4) intense psychological distress at exposure to internal or external cues representing the event
   5) physiological reactivity on exposure to cues representing the event

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness as indicated by three or more of the following:
   1) efforts to avoid thoughts, feelings, or conversations associated with the trauma
   2) efforts to avoid activities, places, or people that arouse recollections of the trauma
   3) inability to recall an important aspect of trauma
   4) markedly diminished interest or participation in significant activities
   5) feelings of detachment or estrangement
   6) restricted range of affect
   7) sense of foreshortened future

D. Persistent symptoms of increased arousal, as indicated by two or more of the following:
   1) difficulty falling or staying asleep
   2) irritability or outbursts of anger
   3) difficulty concentrating
   4) hypervigilance
   5) exaggerated startle response

E. Duration of disturbance is more than 1 month.

F. The disturbance causes clinically significant distress or impairment.
REFERENCES


Nicholas, C. L., Trinder, J., Colrain, I. M. (2002). Increased production of evoked and spontaneous K-complexes following a night of fragmented sleep. *Sleep*


beta EEG power and regional cerebral glucose metabolism during NREM sleep. 
*Psychiatric Research, 98*, 71-91.


