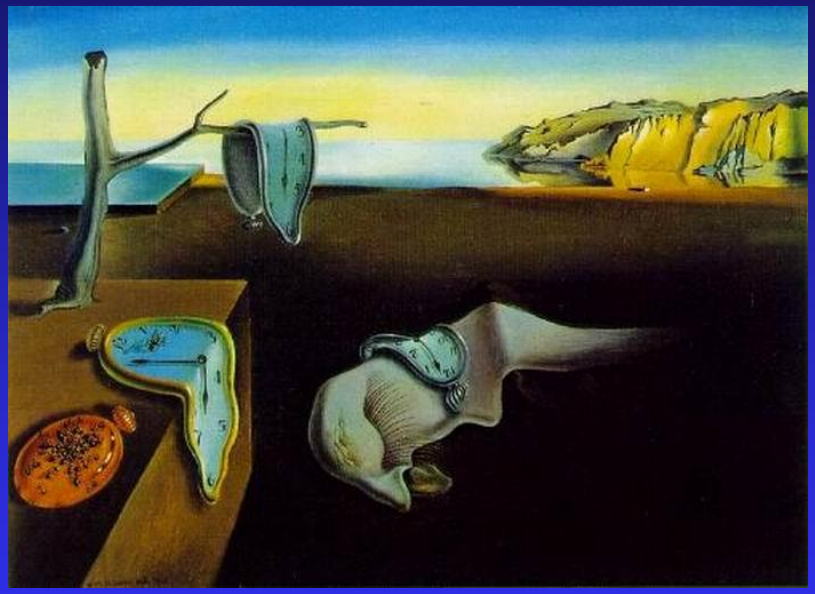
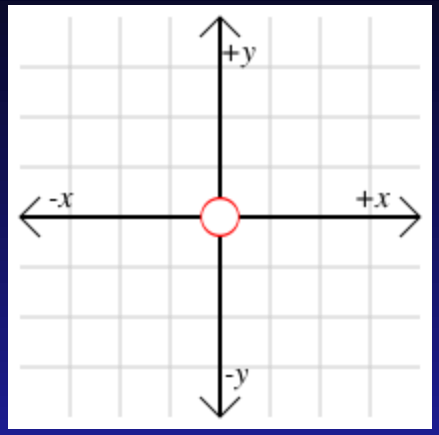
THE NEUROCOGNITIVE MODEL

10 AND 4 YEARS ON





1) MOVE BEYOND THE PRESENTING COMPLAINTS OF

CAN'T FALL ASLEEP

CAN'T STAY ASLEEP.

2) TO OPERATIONALLY DEFINE WHAT IS MEANT BY

"HYPERAROUSAL"

3) TAKE INTO ACCOUNT OTHER ESSENTIAL FEATURES OF INSOMNIA

FEATURES THAT MAY SPEAK TO THE ETIOLOGY AND PATHOPHYSIOLOGY OF THE DISORDER.

INSOMNIA IS A DISORDER OF HYPERAROUSAL

Q: IN CHRONIC INSOMNIA

IS THE LEVEL OF AROUSAL ENOUGH TO INTERFERE WITH SLEEP INITIATION OR MAINTENANCE ?

DOES THE AROUSAL LEVEL COMPARE TO THIS ?!

RE: OTHER ESSENTIAL FEATURES

WHEN “AWAKE” THERE IS THIS PROBLEM

WHEN “ASLEEP” THERE IS THIS PROBLEM

THERE IS THE PERCEPTION

When you have insomnia, you're never really asleep and you're never really awake.

– Chuck Palahniuk
(Portland Native)
Fight Club

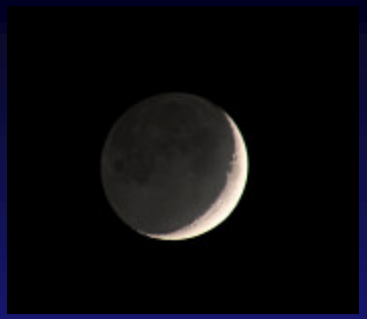
Compliments Rebecca Bernert

THERE IS THE RECOLLECTION

"I am sure, [and] many times too,
that I slept without knowing it -
but I never slept knowing it."

-- Ernest Hemmingway

Compliments of Paul Shaw



IN BRIEF

- When Awake: Enhanced Exterio and Interioception
- When Asleep: Enhanced Exterio and Interioception
- Following Sleep: Enhanced Episodic Memory

The consequences:

Sleep is difficult to initiate and maintain;

Sleep is perceived as shallow,
as “in between state”, or as not sleep

THE SPECIFICS OF THE MODEL

J. Sleep Res. (1997) 6, 179–188

Psychophysiological insomnia: the behavioural model and a neurocognitive perspective

M. L. PERLIS[1], D. E. GILES[1], W. B. MENDELSON[2], R. R. BOOTZIN[3] and J. K. WYATT[4]

[1]Department of Psychiatry, University of Rochester, [2]Department of Psychiatry, University of Chicago, [3]Department of Psychology, University of Arizona and [4]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, USA

Accepted in revised form 29 May 1997; received 6 January 1997

SUMMARY A number of paradoxes are apparent in the assessment and treatment of psychophysiological insomnia and sleep state misperception. Three of these paradoxes exist as discrepancies between polysomnographic (PSG) measures and the subjective impressions regarding sleep quality and quantity. The remaining incongruity exists largely within the objective domain. In the case of subjective–objective discrepancies, patients with insomnia: (1) frequently identify themselves as having been awake when awakened from PSG defined sleep; (2) tend to overestimate sleep latency and underestimate total sleep time as compared with PSG measures; (3) appear to derive more benefit from pharmacotherapy that can be explained by objective gains. The remaining paradox pertains to the observation that hypnotic medications, by and large, do not normalize sleep architecture or produce a more 'sleep-like' EEG. In this paper, we review possible explanations for these various paradoxes, introduce a new perspective and suggest possible research avenues. The model introduced is based on the observation that beta and/or gamma activity (which have been found to be associated with cognitive processes) is enhanced in insomnia at or around sleep onset. We propose that this kind of high frequency EEG activity may interfere with the normal establishment of sleep onset-related mesograde amnesia. As a result, the patient with insomnia maintains a level of information and/or memory processing that blurs the phenomenological distinction between sleep and wakefulness and influences retrospective judgments about sleep initiation and duration.

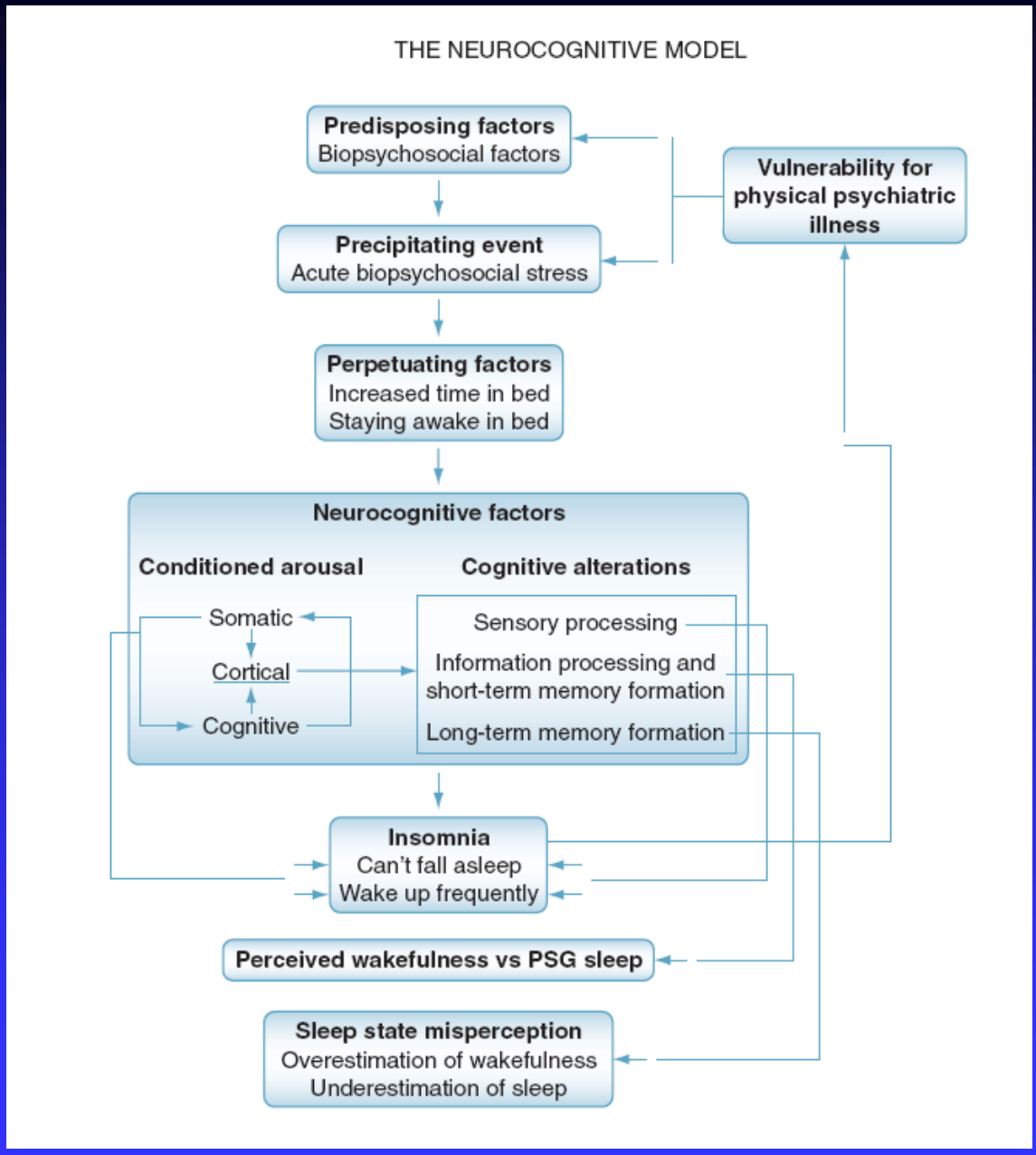
KEYWORDS behavioural model, beta activity, gamma activity, insomnia, subjective/objective discrepancies

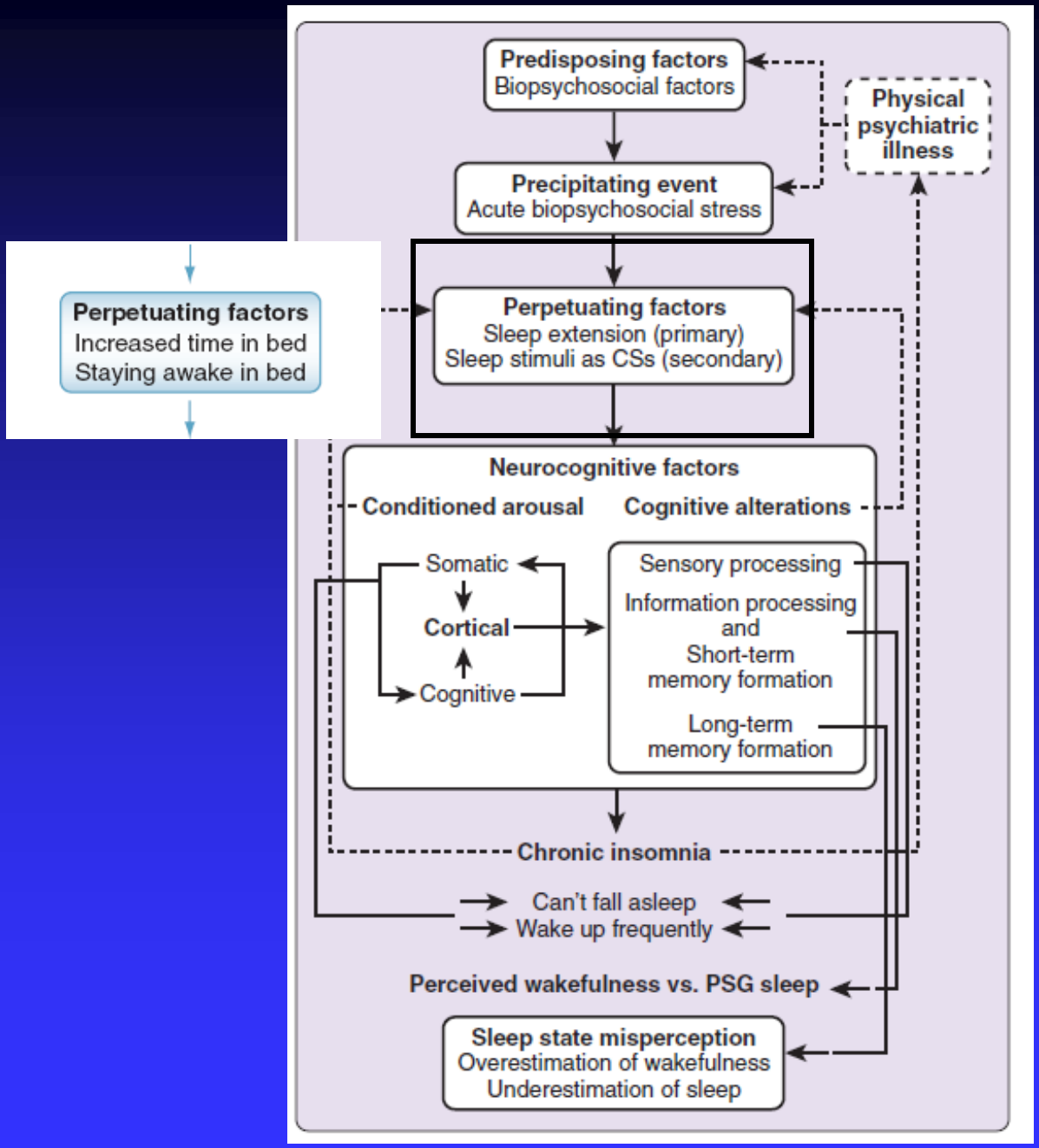
INTRODUCTION

As many as one in four adults around the world have been reported to have problems with sleep initiation, sleep maintenance and/or non-restorative sleep (Angst *et al.* 1989; Janson *et al.* 1995; Silva *et al.* 1996). In the United States, approximately 26 million people or 10% of the population suffer from insomnia (Hammond 1964; Bixler *et al.* 1979; Institute of Medicine 1979; Karacan *et al.* 1983; Mellinger *et al.* 1985; Ford and Kamerow 1989; Gallup Organization 1991). Each year millions of prescriptions for hypnotic medications are prescribed to ameliorate such symptoms (Institute of Medicine 1979; Mellinger *et al.* 1985; Shader *et al.* 1991; Pharmacy Times 1996). Despite the magnitude of the problem and the costs of treatment (Stoller 1994), little is known about the pathophysiology of insomnia, the mechanisms of action of hypnotic medication and how both relate to the experience of insomnia.

The complaint of insomnia may be symptomatic of a variety of disorders. Insomnia may be related to other sleep disorders such as nocturnal myoclonus or sleep apnoea, to pain associated with medical conditions, to medical conditions themselves, or to psychiatric disorders such as major depression (American Sleep Disorders Association 1990; Bootzin and Perlis 1992; Buysse and Perlis 1996). When contributing disorders such as

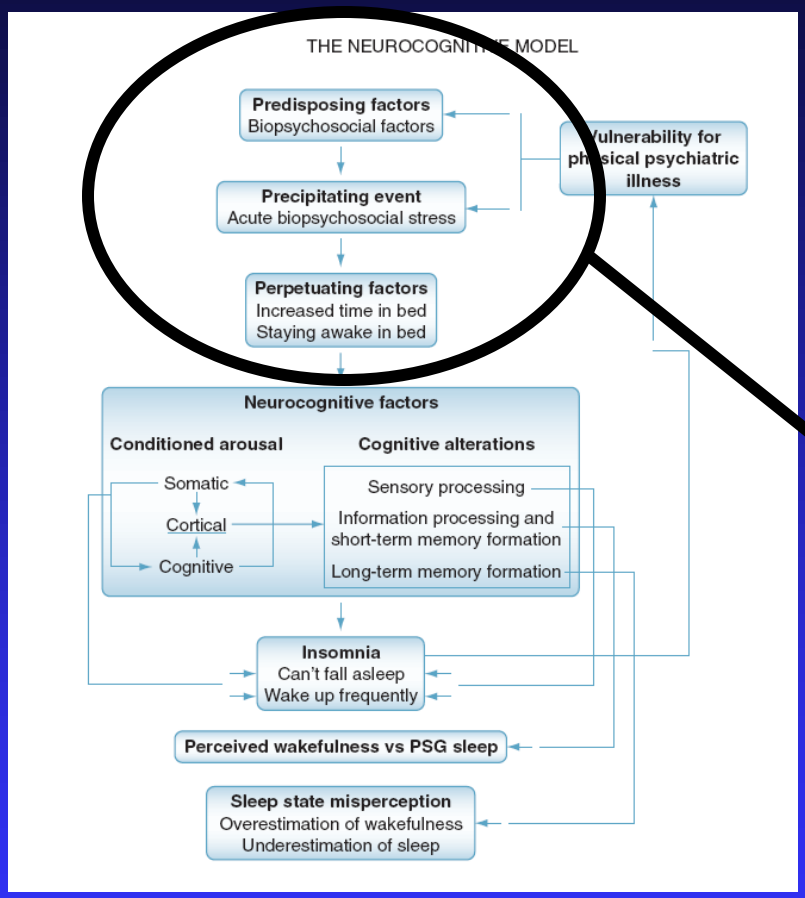
Correspondence: Michael L. Perlis, Department of Psychiatry, University of Rochester, 300 Crittenden Blvd., Rochester, NY 14642, USA. e-mail: mperlis@obgyn.rochester.edu

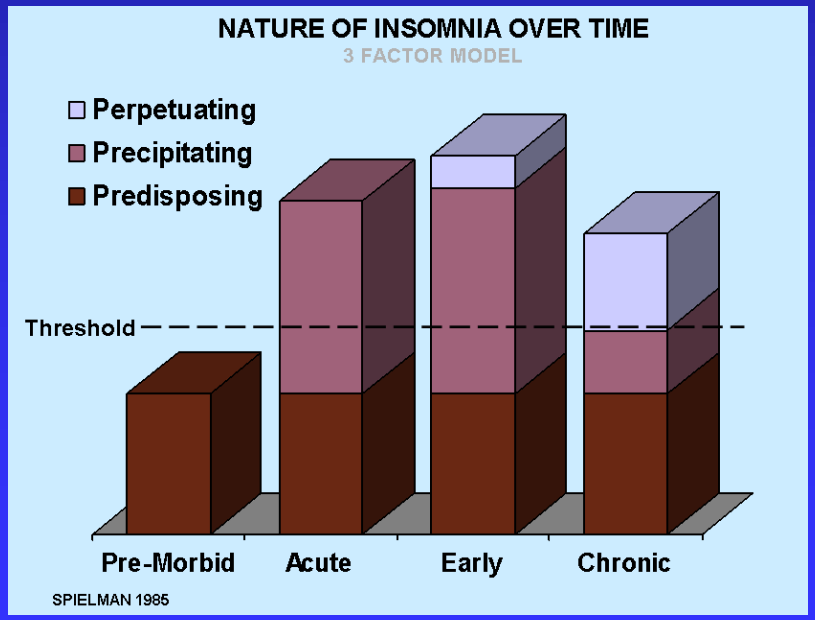

THE NEUROCOGNITIVE MODEL
Predisposing factors
Biopsychosocial factors
Vulnerability for physical psychiatric illness
Precipitating event
Acute biopsychosocial stress
Perpetuating factors
Increased time in bed
Staying awake in bed
Neurocognitive factors
Conditioned arousal
Cognitive alterations
Somatic
Cortical
Cognitive
Sensory processing
Information processing and short-term memory formation
Long-term memory formation
Insomnia
Can't fall asleep
Wake up frequently
Perceived wakefulness vs PSG sleep
Sleep state misperception
Overestimation of wakefulness
Underestimation of sleep


Predisposing factors
Biopsychosocial factors
Physical psychiatric illness
Precipitating event
Acute biopsychosocial stress
Perpetuating factors
Increased time in bed
Staying awake in bed
Perpetuating factors
Sleep extension (primary)
Sleep stimuli as CSs (secondary)
Neurocognitive factors
Conditioned arousal
Cognitive alterations
Somatic
Cortical
Cognitive
Sensory processing
Information processing and Short-term memory formation
Long-term memory formation
Chronic insomnia
Can't fall asleep
Wake up frequently
Perceived wakefulness vs. PSG sleep
Sleep state misperception
Overestimation of wakefulness
Underestimation of sleep

THE NEUROCOGNITIVE MODEL OF INSOMNIA

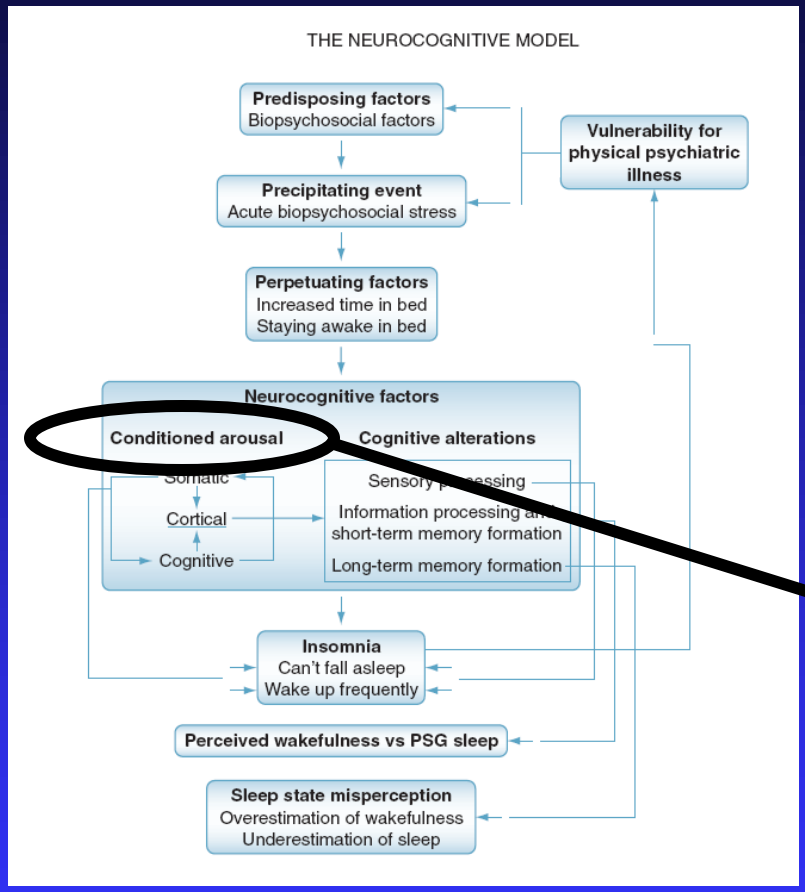
BASED ON THE BEHAVIORAL MODEL

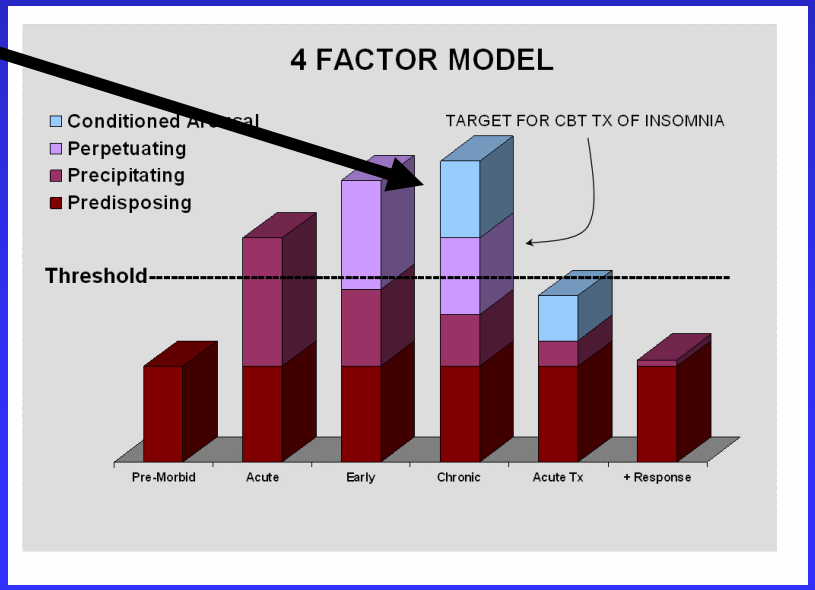




THE NEUROCOGNITIVE MODEL OF INSOMNIA

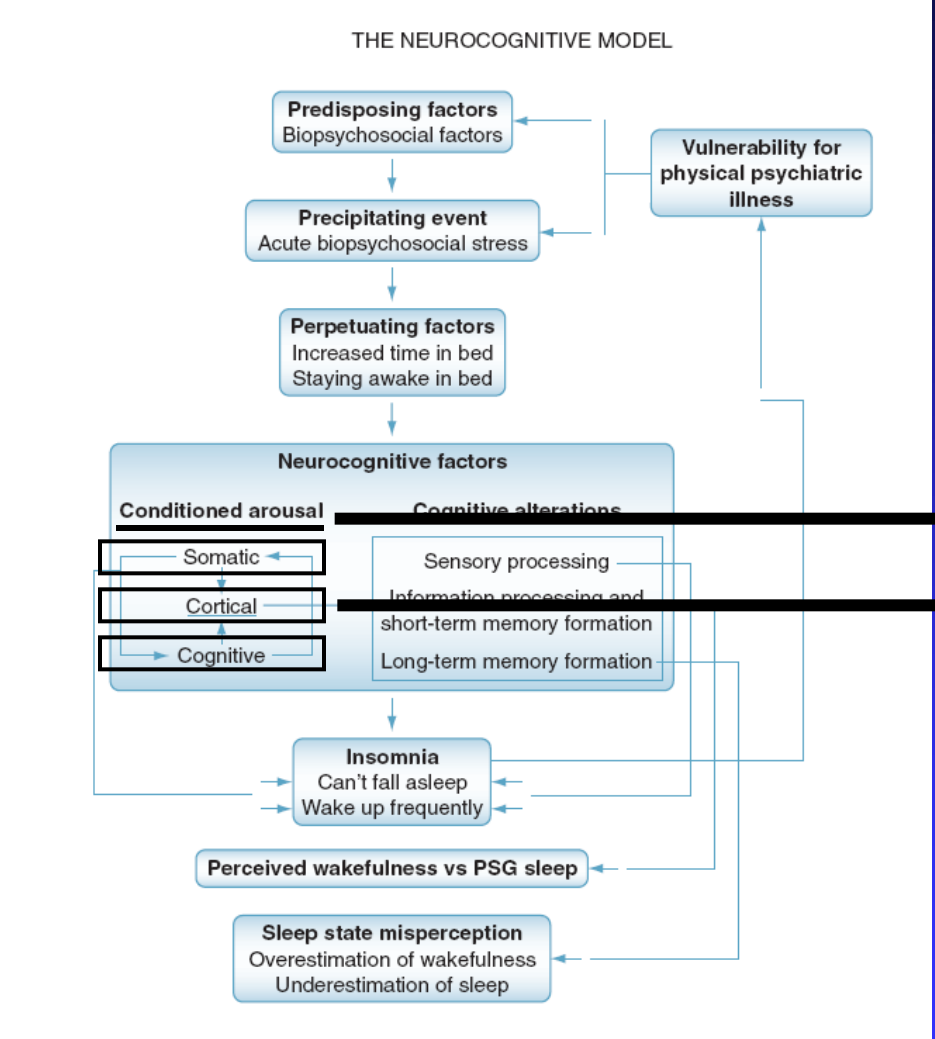
EXTENSION OF BEHAVIORAL MODEL





THE NEUROCOGNITIVE MODEL OF INSOMNIA

EXTENSION OF PHYSIOLOGIC MODEL – SANS ASSUMPTIONS



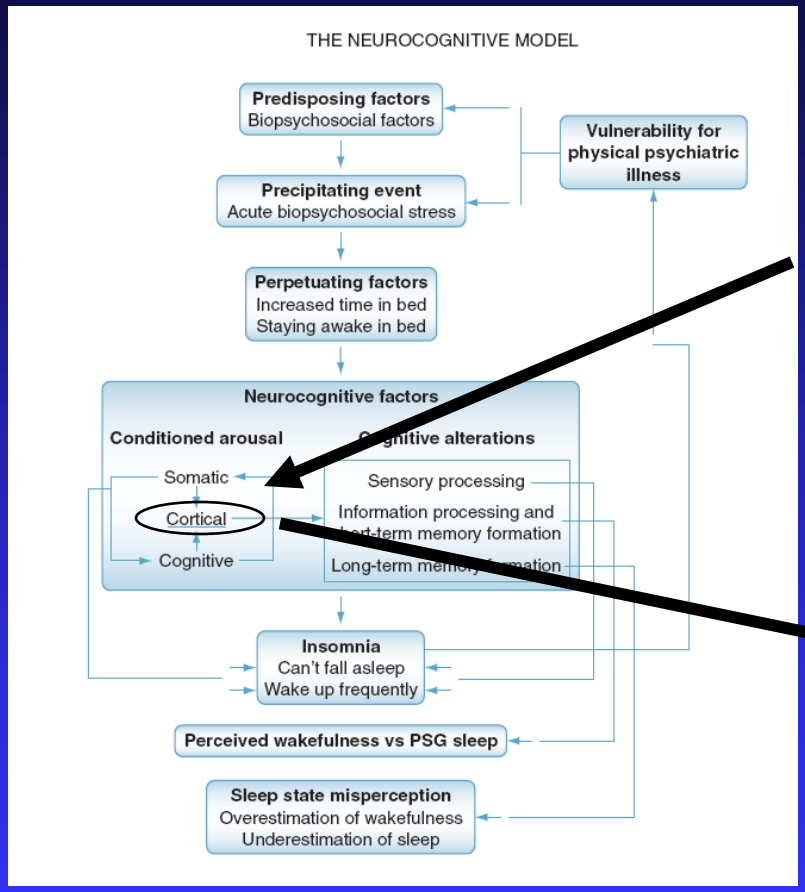
NOT NECESSARY TO ASSUME THAT AROUSAL IS AROUSAL

CONDITIONED VS. ELICTED

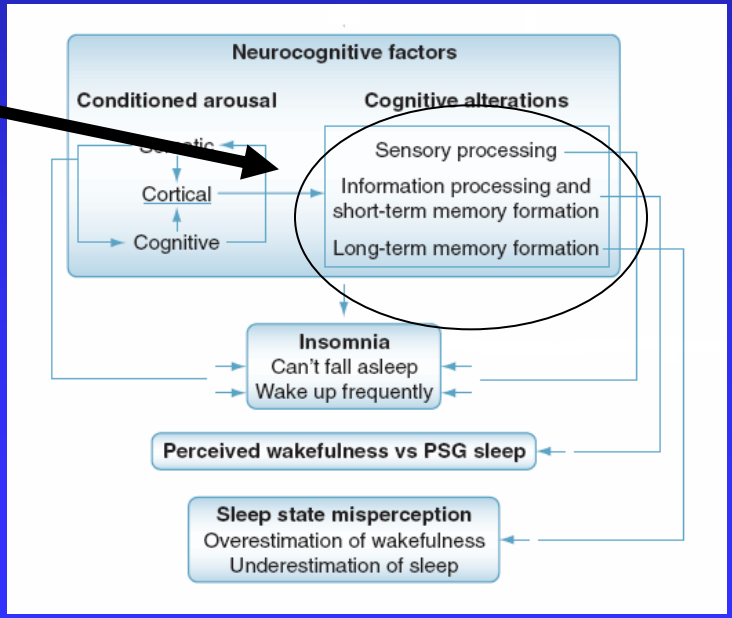
ARRAYED IN 3 DOMAINS

THE NEUROCOGNITIVE MODEL OF INSOMNIA

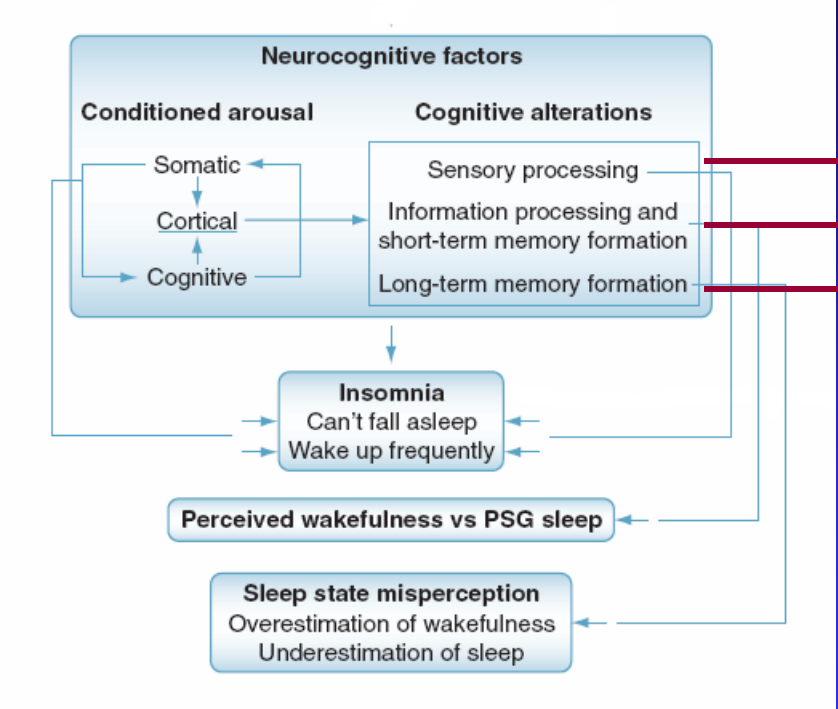
EXTENSION OF PHYSIOLOGIC MODEL – SANS ASSUMPTIONS



NOT NECESSARY TO ASSUME THAT AROUSAL AND SLEEP ARE MUTUALLY EXCLUSIVE



THE NEUROCOGNITIVE MODEL OF INSOMNIA

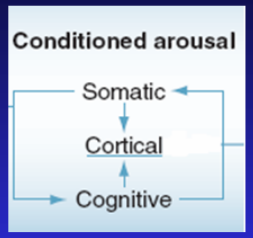


STARTLE & ORIENT

IDENTIFY & RESPOND

REMEMBER

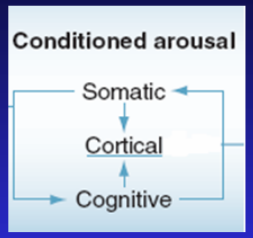
HOW MIGHT ONE ASSESS THE MODEL ?



HOW MIGHT ONE MEASURE CORTICAL/COGNITIVE AROUSAL ??

SLEEP RELATED COGNITIVE AROUSAL COULD BE MEASURED BY MEMORY & PERCEPTION TASKS

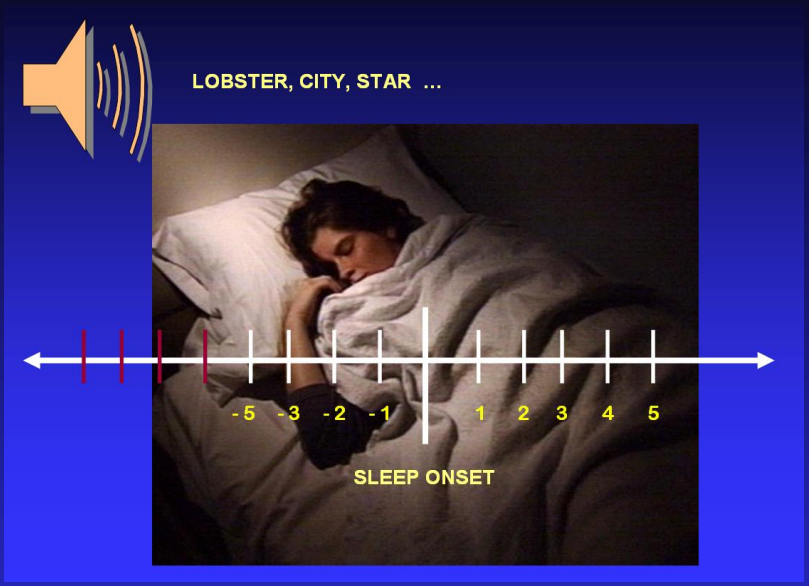
SLEEP RELATED CORTICAL AROUSAL COULD BE MEASURED BY
QEEG
ERPs
FUNCTIONAL IMAGING

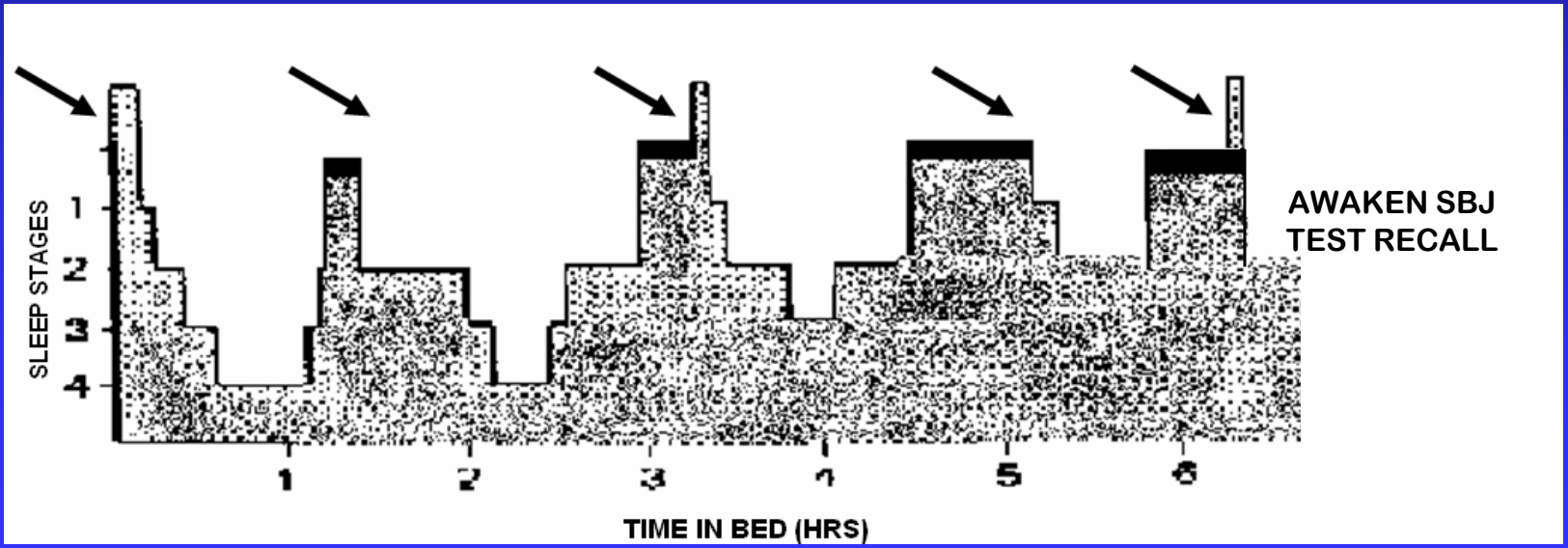


HOW MIGHT ONE MEASURE
CORTICAL/COGNITIVE AROUSAL ??

MEMORY & PERCEPTION TASKS

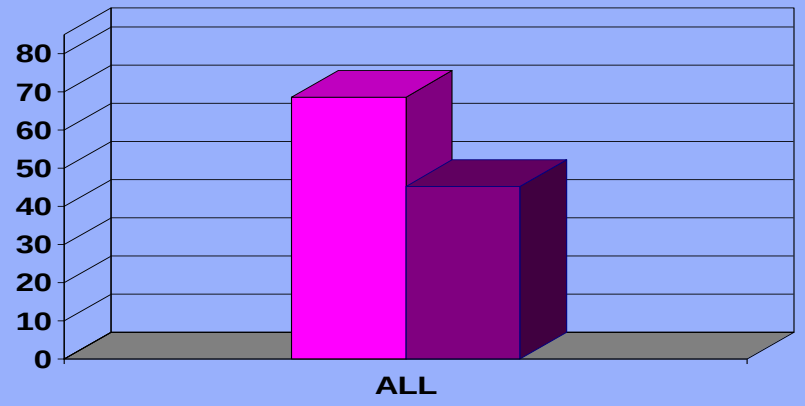
LOBSTER, CITY, STAR …

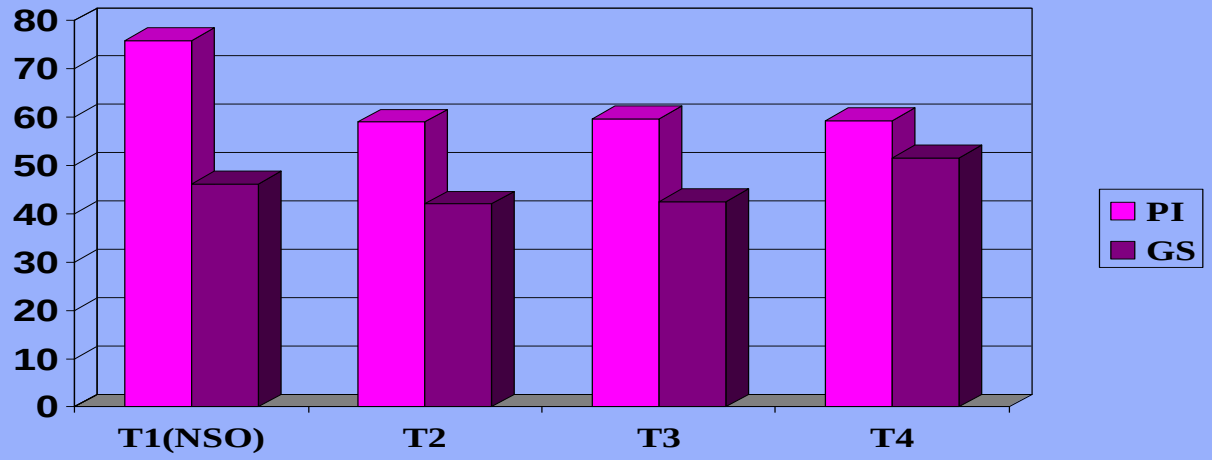

LOBSTER, CITY, STAR ...
-5 -3 -2 -1 1 2 3 4 5
SLEEP ONSET


SLEEP STAGES
1
2
3
4
1
2
3
4
5
6
TIME IN BED (HRS)
AWAKEN SBJ
TEST RECALL

LONG TERM MEMORY FOR WORD STIMULI

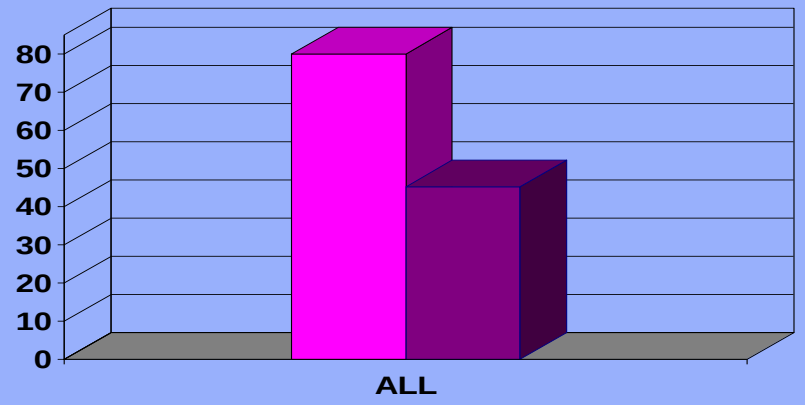
LONG TERM MEMORY = RECOGNITION
WORD STIMULI PRESENTED AT 5 SLEEP ONSETS: NSO & 4 FORCED AWAKENINGS

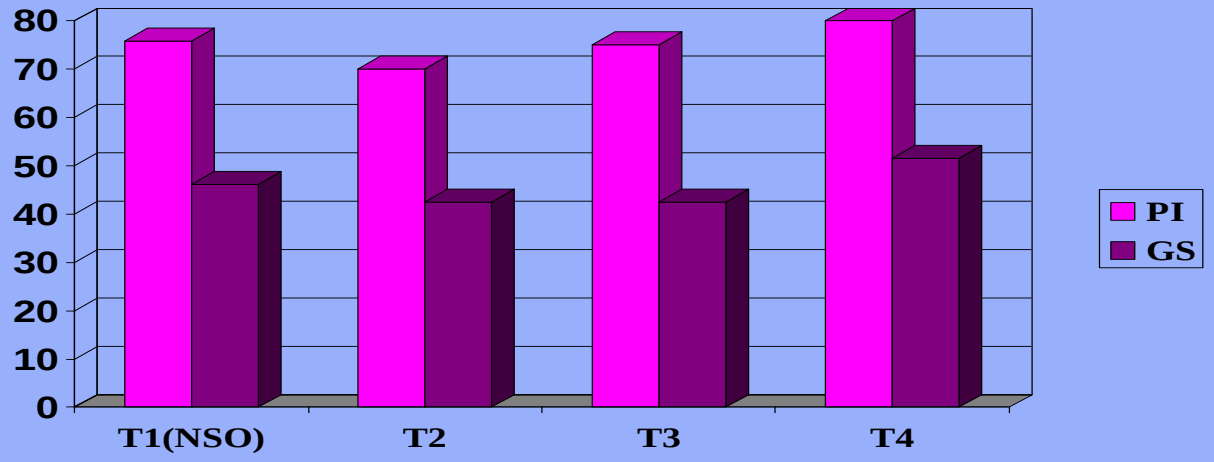




WHY DIDN'T THE DATA LOOK LIKE THIS ?

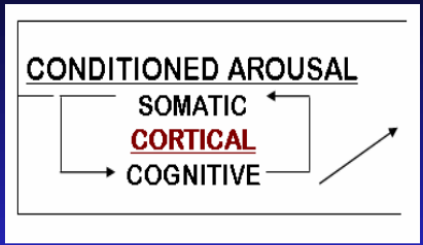
LONG TERM MEMORY = RECOGNITION
WORD STIMULI PRESENTED AT 4 SLEEP ONSETS: NSO & 3 FORCED AWAKENINGS





ISSUES

WILL THE EXPLICIT VS IMPLICIT MEMORY BE RELEVANT ?



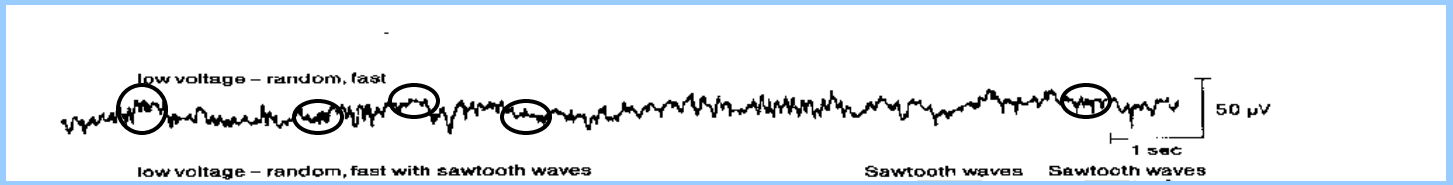
HOW MIGHT ONE MEASURE
CORTICAL/COGNITIVE AROUSAL ??

QEEG

HIGH FREQUENCY EEG

BETA (β) EEG

AWAKE - ALERT

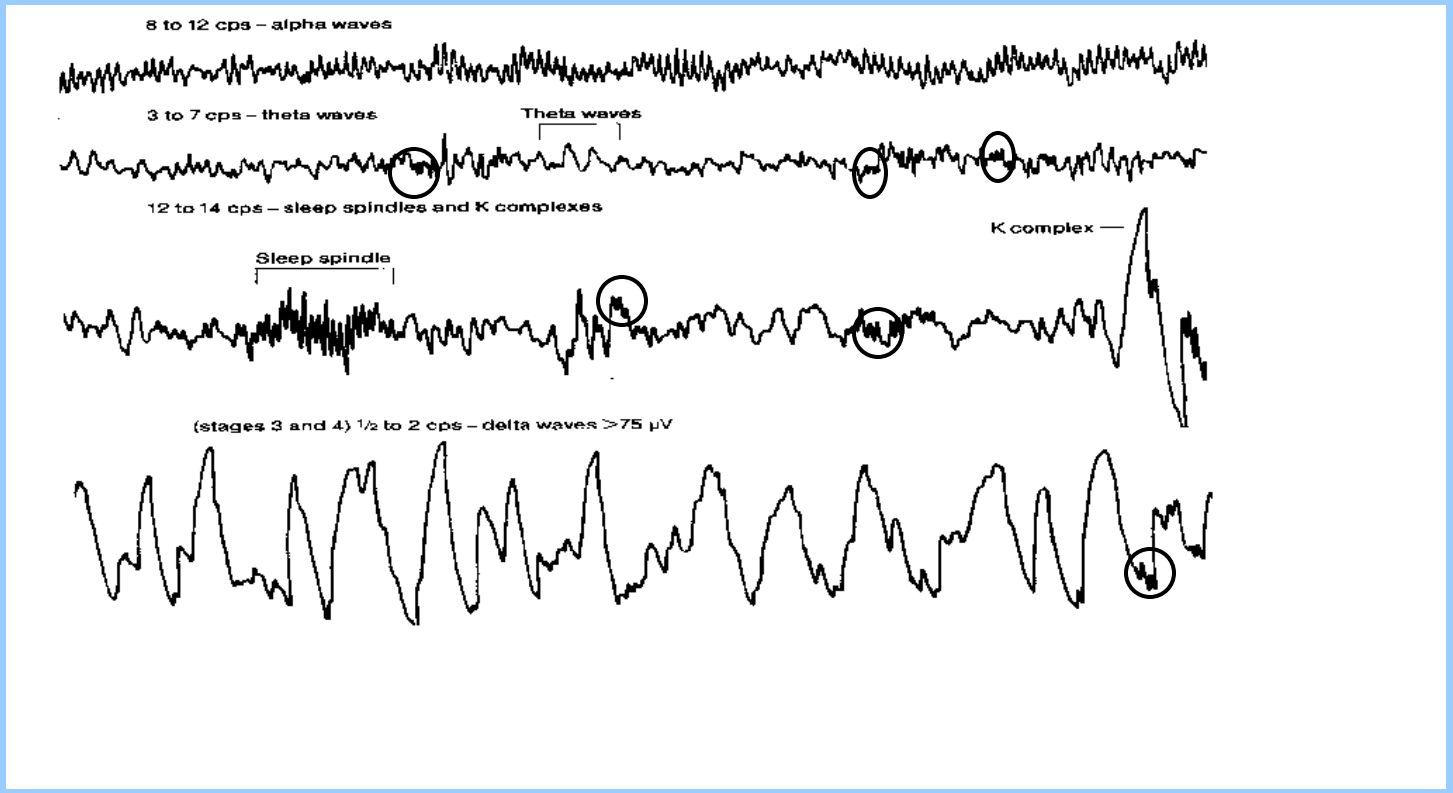


AWAKE - ALPHA

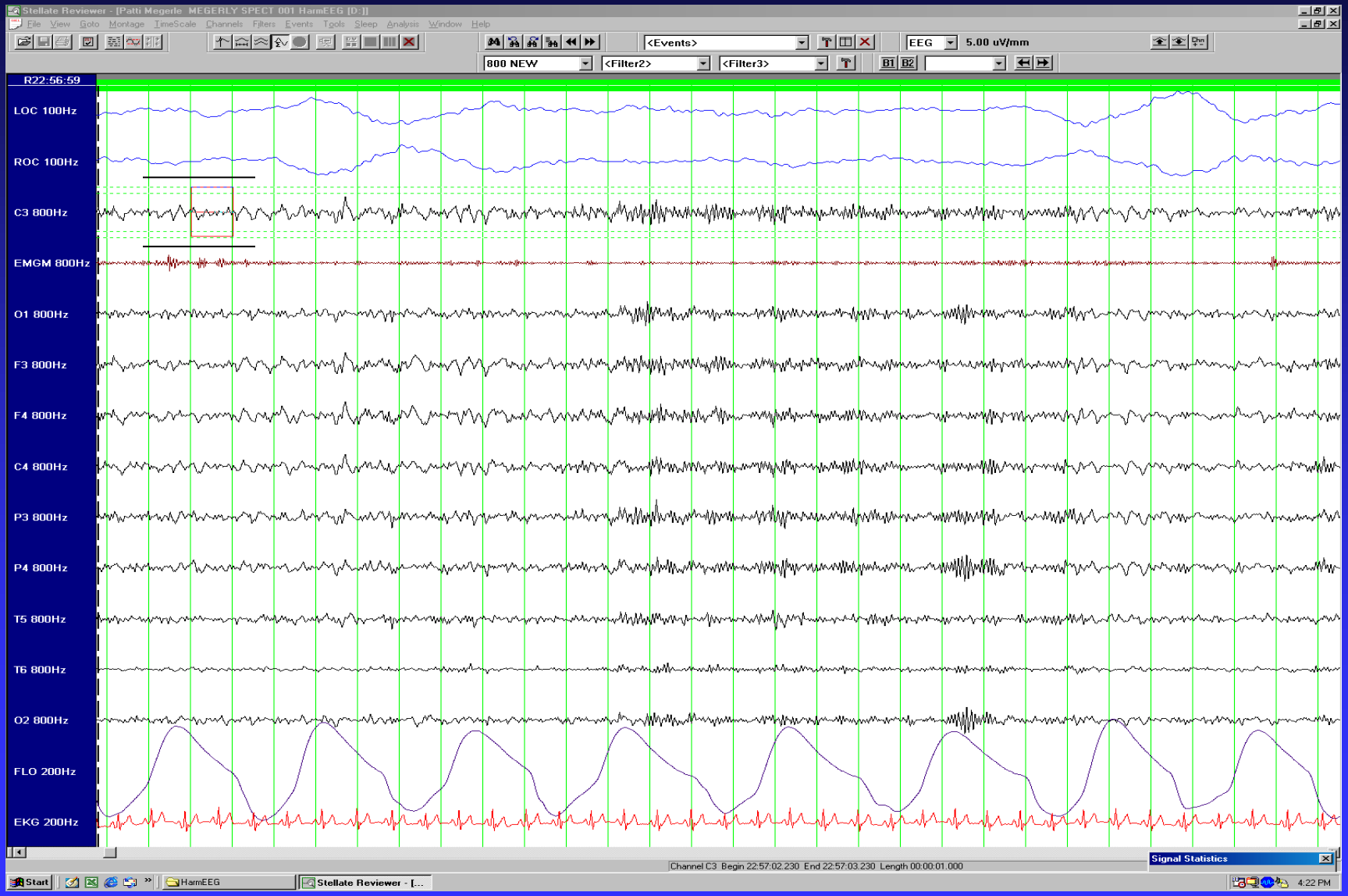
STAGE 1 SLEEP

STAGE 2 SLEEP

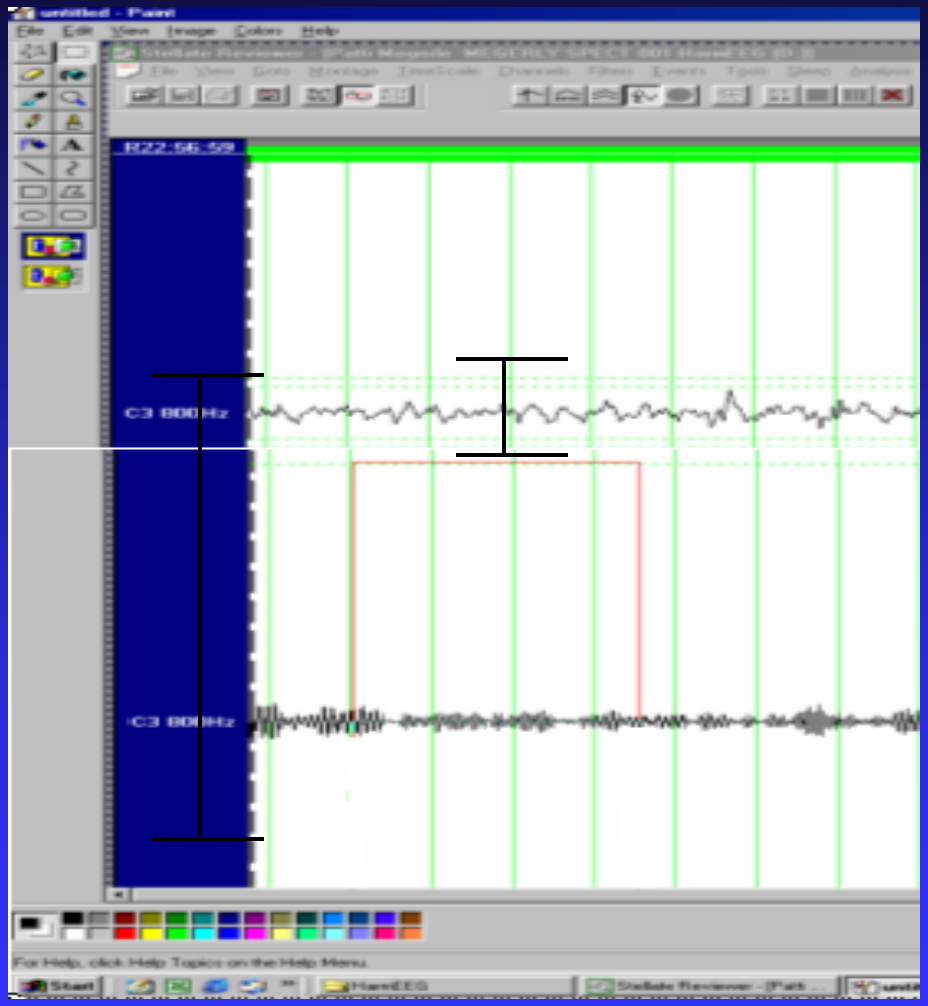
STAGES 3 & 4 (SWS)



STANDARD PSG TRACING (NORMAL GAINS & FILTERS)



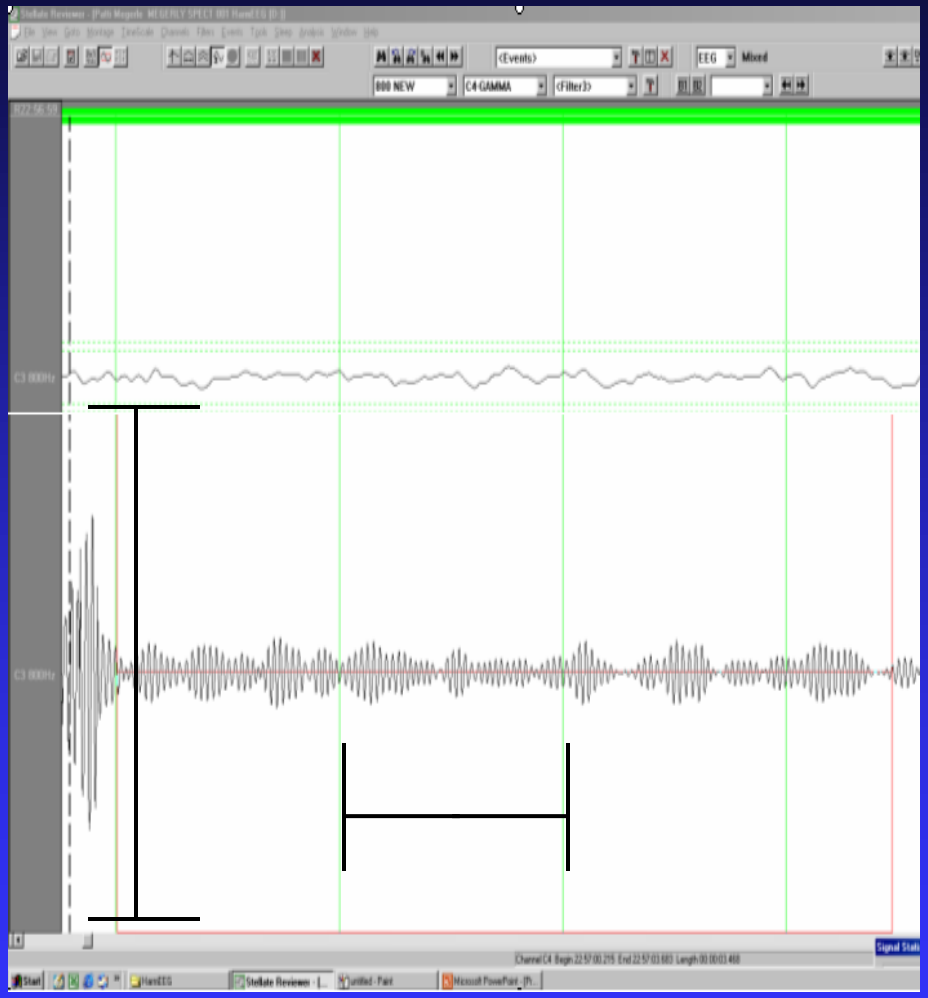
PSG TRACING (2ND CHANNEL WITH γ GAINS & FILTERS)



NORMAL TRACE (0.3 - 20 Hz)
STAGE 1 AT 5 µv / mm

γ TRACE (35 - 45 Hz)
STAGE 1 AT 0.001 µv / mm
VOLTAGE = 1.3 µv

PSG TRACING (2ND CHANNEL WITH γ GAINS, FILTERS & TIME BASE)

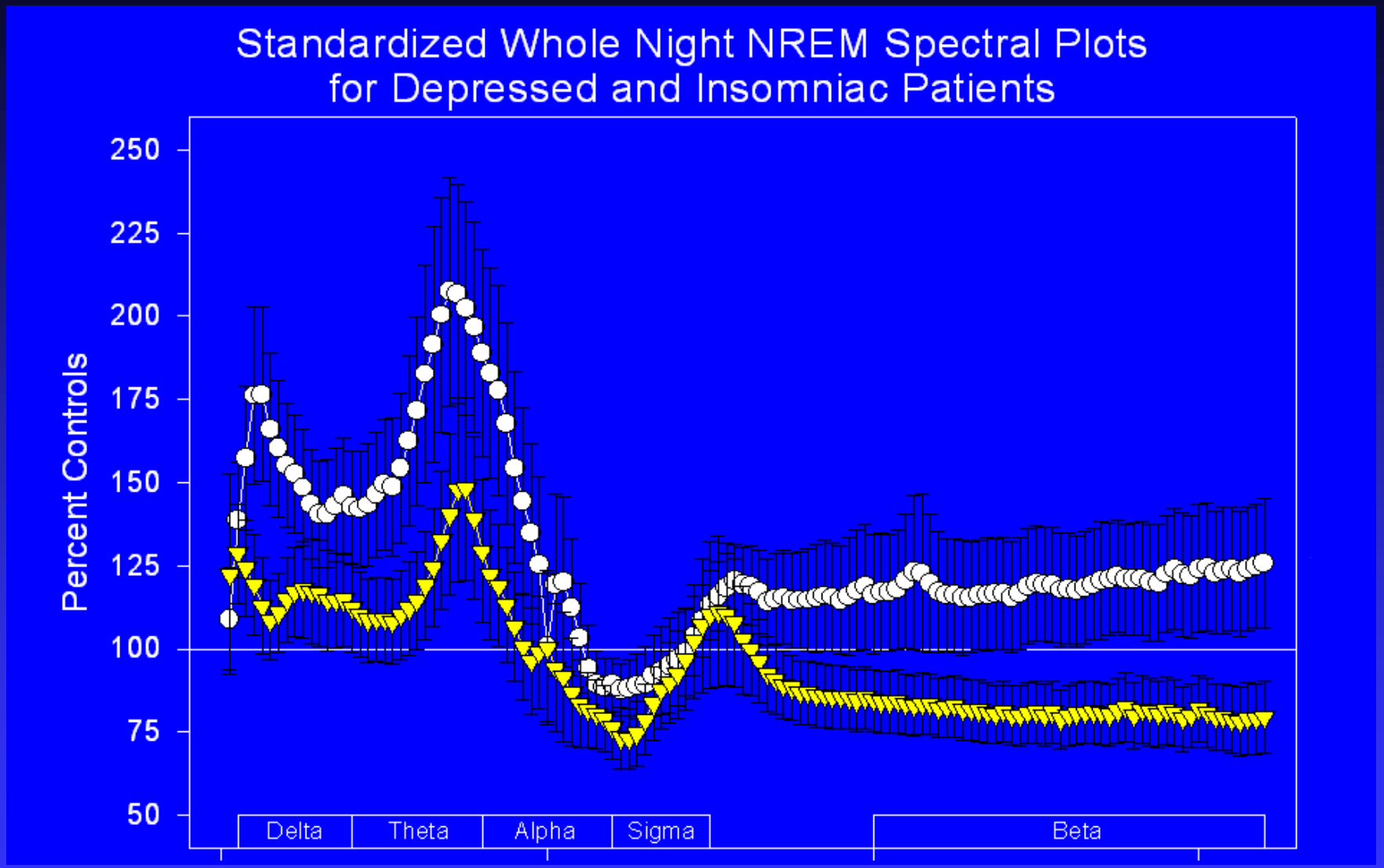


NORMAL TRACE (0.3-20 Hz)
STAGE 1 AT 5 µv / mm

γ TRACE (35-45 Hz)
STAGE 1 AT 0.001 µv / mm
VOLTAGE = 1.3 µv

"10" STUDIES HAVE FOUND EVIDENCE OF CNS AROUSAL IN INSOMNIA IN TERMS OF INCREASED BETA EEG

Freedman et al., 1986	EEG & Clin Neurophy 63: 408-413
Merica & Gaillard, 1991	Physiol.Behav. 52: 99-204
Jacobs & Benson, 1993	Behavior Therapy 24: 159-174
La Marche & Oligivie, 1997	Sleep. 20: 724-733
Merica & Gaillard, 1998	Europ. J. of Neurosc. 10: 1826-1834
Nofzinger et al., 1999	Sleep. 22 supp 1: S99-S99
Perlis et al., 2001	Sleep, 24(1):110-117
Perlis et al., 2001	J. Sleep Research,10:93-104
Krystal et al., 2002	Sleep, 25(6): 630-640
Buysse et al., 2008	Sleep, 31 (12): 1673-1682

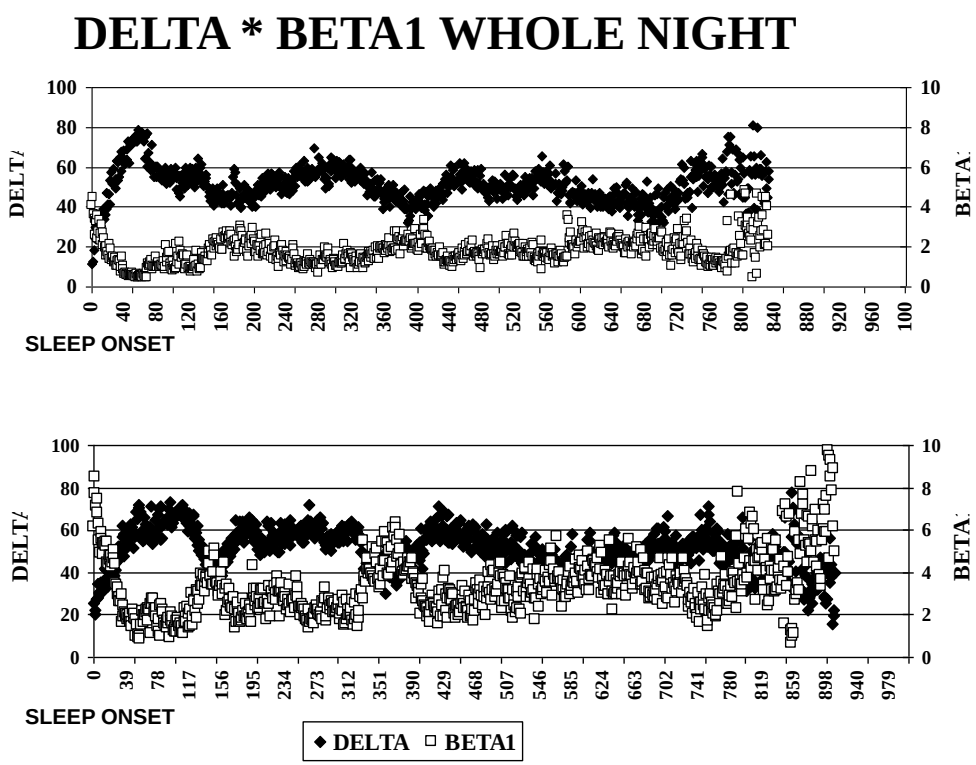


Unpublished Data – Nofzinger - UPITT

CNS AROUSAL IN INSOMNIA IN TERMS OF BETA EEG

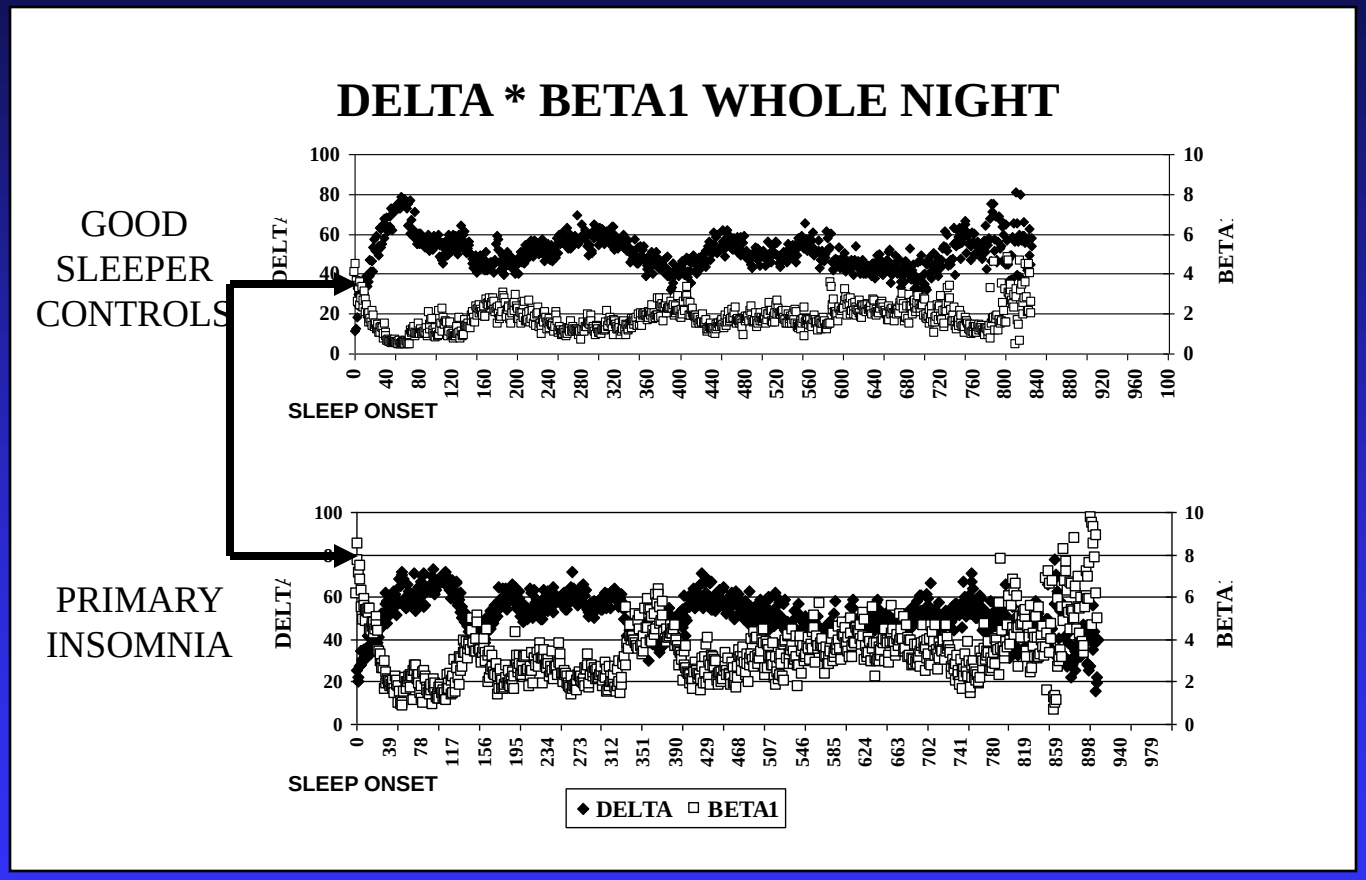
GOOD SLEEPER CONTROLS

PRIMARY INSOMNIA



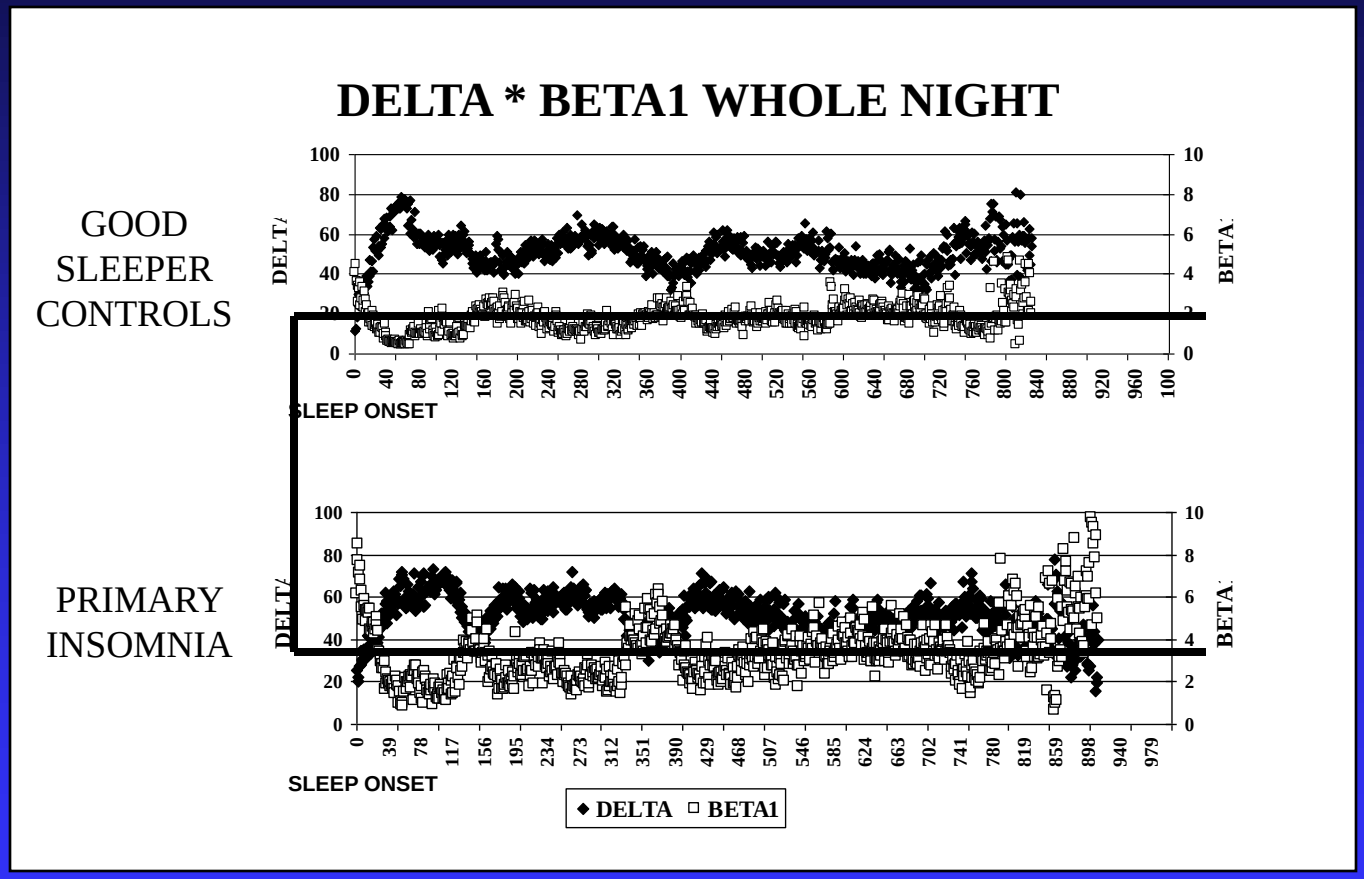
Perlis et al., 2001. J. Sleep Research,10:93-104

CNS AROUSAL IN INSOMNIA IN TERMS OF BETA EEG



Perlis et al., 2001. J. Sleep Research,10:93-104

CNS AROUSAL IN INSOMNIA IN TERMS OF BETA EEG

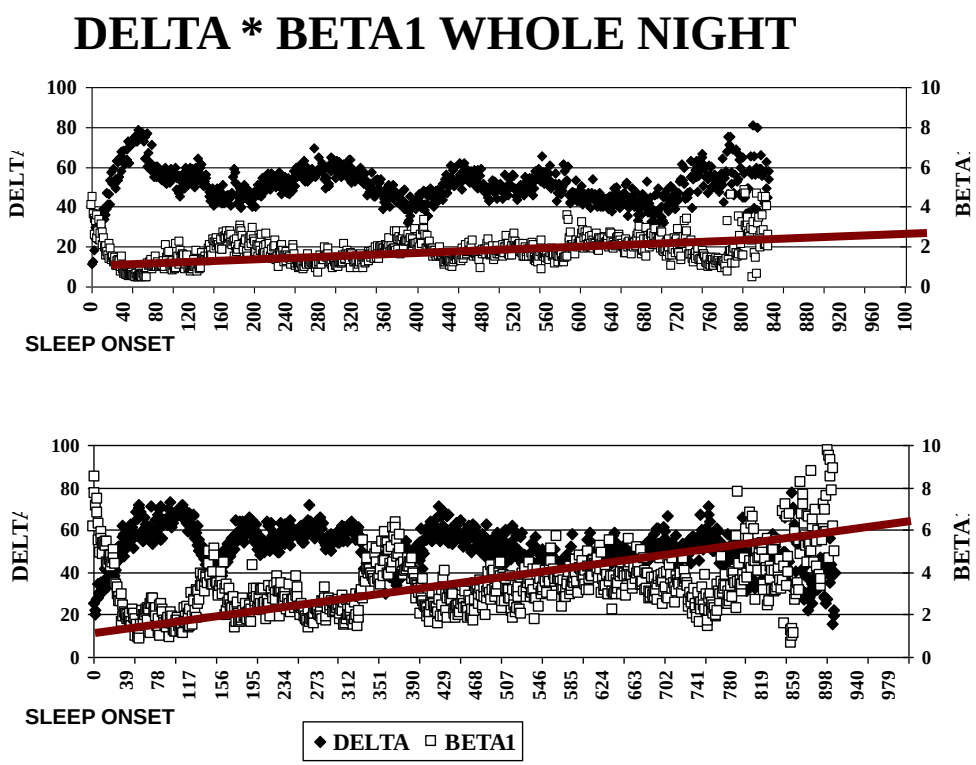


Perlis et al., 2001. J. Sleep Research,10:93-104

CNS AROUSAL IN INSOMNIA IN TERMS OF BETA EEG

GOOD SLEEPER CONTROLS

PRIMARY INSOMNIA

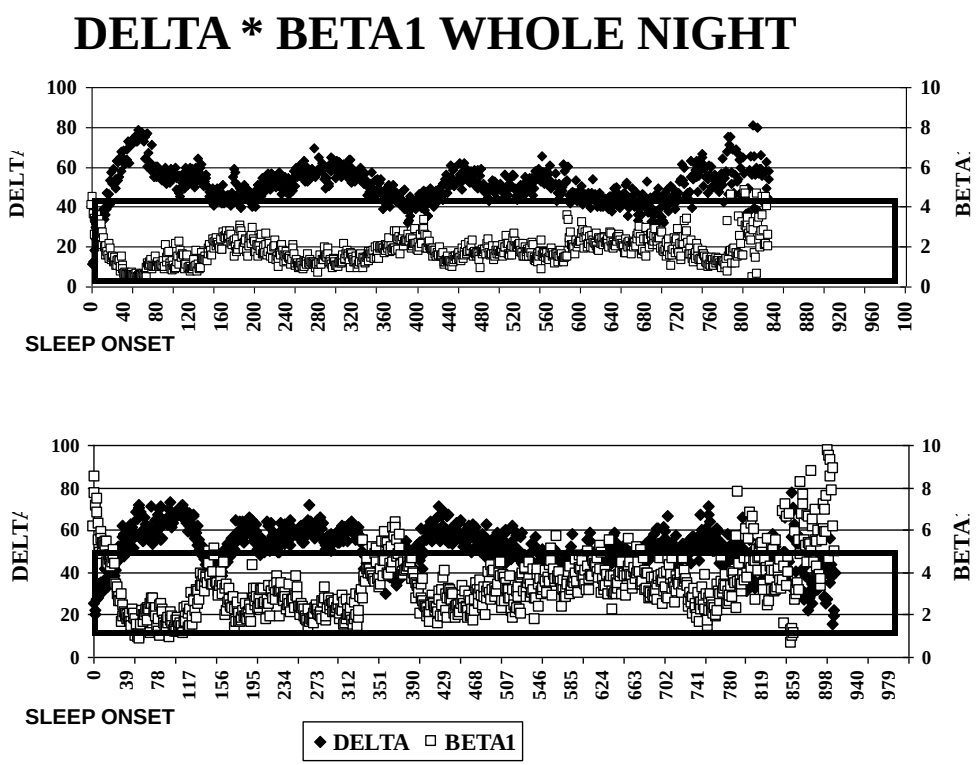


Perlis et al., 2001. J. Sleep Research,10:93-104

CNS AROUSAL IN INSOMNIA IN TERMS OF BETA EEG

GOOD SLEEPER CONTROLS

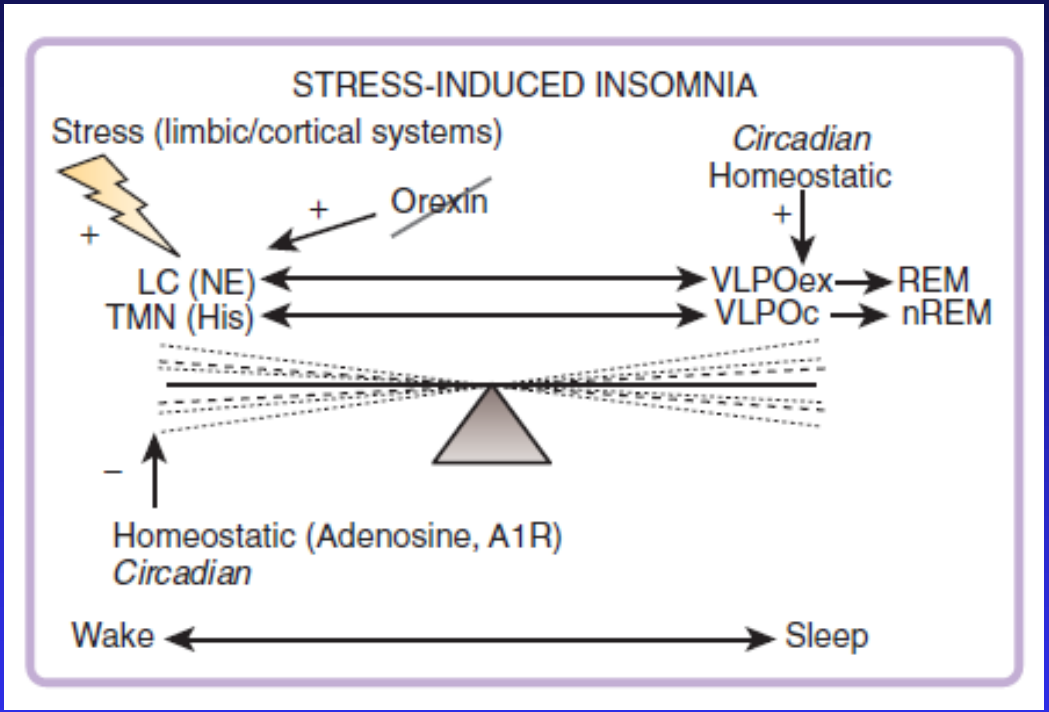
PRIMARY INSOMNIA



Perlis et al., 2001. J. Sleep Research,10:93-104

THE RODENT MODEL OF ACUTE INSOMNIA

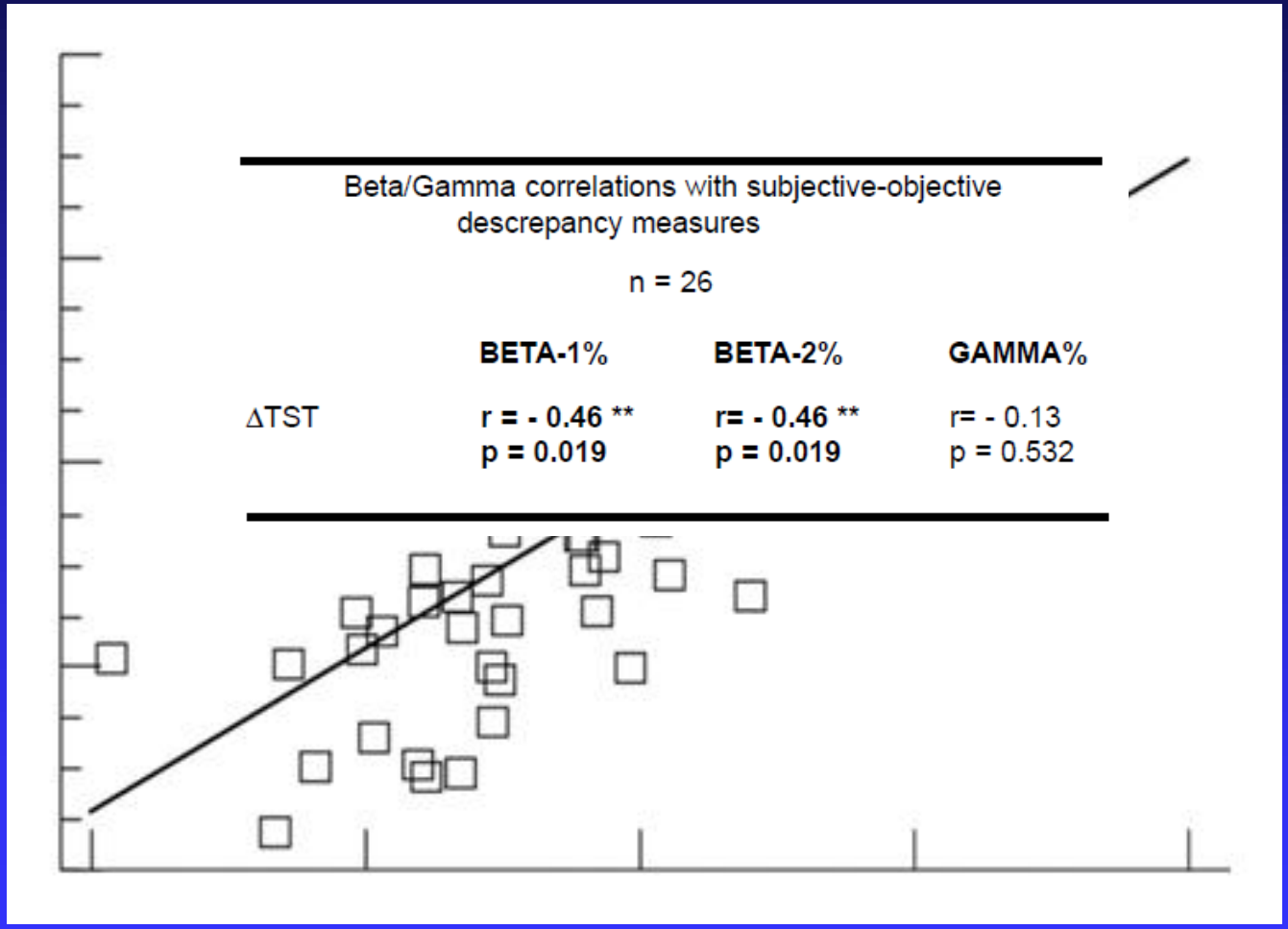
Basic Description



In stress-induced insomnia the sleep–wake switch is forced into an unstable position, allowing the emergence of an intermediate state in which both sleep and wake circuitries are activated simultaneously,

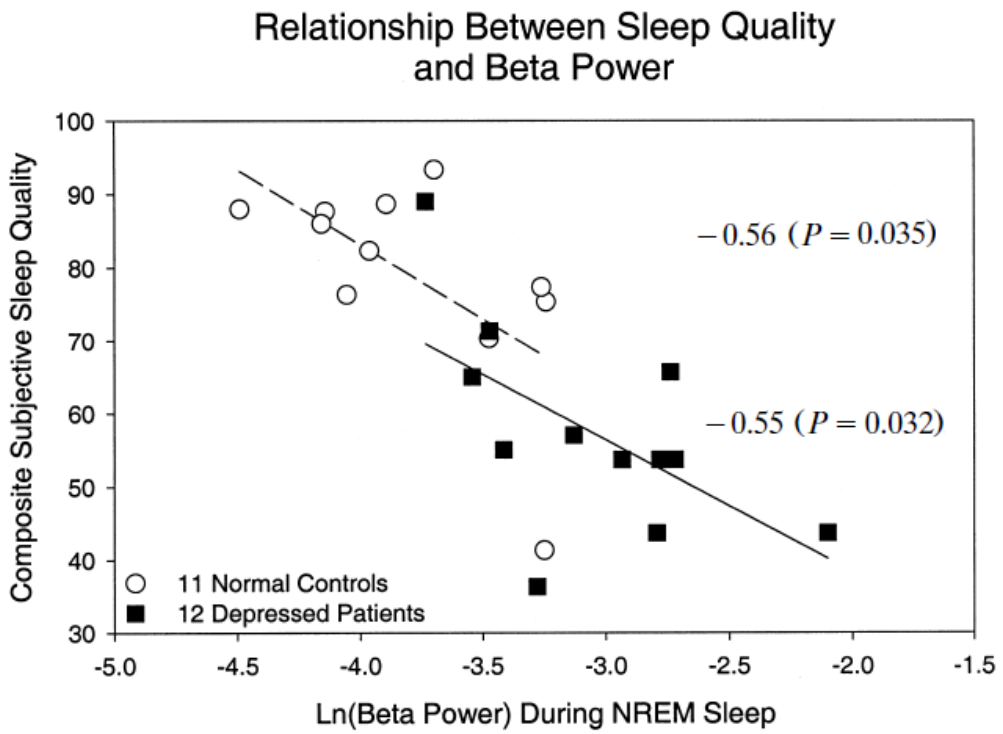
IS INCREASED BETA/GAMMA RELATED TO THE SUBJECTIVE EXPERIENCE OF SLEEP ?

INCREASED BETA EEG IS ASSOCIATED WITH SLEEP STATE MISPERCEPTION

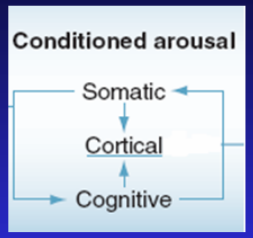


Perlis et al., 2001. Sleep,24(1):110-117

INCREASED BETA EEG IS ASSOCIATED WITH POORER SUBJECTIVE SLEEP QUALITY



In both healthy and depressed subjects, beta power negatively correlated with subjective sleep quality.



HOW MIGHT ONE MEASURE CORTICAL/COGNITIVE AROUSAL ??

ERPs

INSOMNIA

ERP Evidence of Enhanced Excitatory and Reduced Inhibitory Processes of Auditory Stimuli During Sleep in Patients With Primary Insomnia

Chien-Ming Yang, PhD[1]; Hsiao-Sui Lo, MD[2]

[1]Department of Psychology and The Research Center for Mind, Brain, and Learning, National Chengchi University, Taipei, Taiwan; [2]Department of Neurology, Chung Shan Medical University, Taichung, Taiwan

Study Objectives: Increased information processing around the onset of sleep and during sleep has been suggested as an important factor for the pathogenesis of insomnia. The purpose of the present study was to examine the processing of auditory information during sleep in patients with insomnia through the recording of event-related potentials (ERPs).

Design: A mixed design was used in which subject group was a between-subject factor and sleep stage and type of tone presented were within-subject factors.

Participants: Fifteen patients with primary insomnia and 15 normal sleepers (controls) were studied.

Measurements and Results: An odd-ball paradigm was conducted to evoke ERPs throughout the night. Patients with insomnia showed larger N1 and smaller P2 to rare tones, smaller N350 to standard tones, and slower P900 to both tones during the first 5 minutes of continuous stage 2 sleep. No consistent ERP differences were detected between the 2 groups when the waveforms were averaged across the whole night.

Conclusions: Patients with insomnia showed an enhancement in attention and a reduction in the inhibitory process that normally facilitates sleep onset in the beginning part of sleep. The results partially support the hyperarousal theory, ie, enhanced information processing during the initiation of sleep is a contributing factor for insomnia.

Keywords: ERP, insomnia, Information Processing

Citation: Yang CM, Lo HS. ERP Evidence of Enhanced Excitatory and Reduced Inhibitory Processes of Auditory Stimuli During Sleep in Patients With Primary Insomnia. *SLEEP* 2007;30(5):585-592

PATIENTS WITH INSOMNIA OFTEN REPORT AWARENESS OF ENVIRONMENTAL ACTIVITIES FOR AN EXTENDED PERIOD OF TIME WHILE LYING IN BED TRYING TO FALL asleep.[1-3] They also tend to report that they are still awake even though polysomnographic recording indicates sound sleep status.[4] Therefore, patients who complain of insomnia often overestimate their sleep-onset latency and underestimate theirtotal sleep time.[5-7] Perlis and his colleagues have proposed a hyperarousal hypothesis for insomnia from a neurocognitive perspective that offers a possible explanation of the above phenomenon.[8] This model hypothesizes that the difficulties in sleep initiation and/or sleep maintenance in patients with primary insomnia may be associated with increased information processing around the onset of sleep. Accordingly, patients with insomnia may have an elevated degree of cortical or cognitive arousal that corresponds to enhanced information processing during polysomnography-defined sleep. Thus, they tend to perceive wakefulness even though the electroencephalogram (EEG) indicates sleep. This point of view is primarily supported by the demonstration that high-frequency EEG power (beta range: 14-35 Hz; gamma range: 35-45 Hz) prior to and during sleep are elevated in patients with insomnia, as compared with normal controls.[9-11] Furthermore, their beta power during sleep correlates with the discrepancies between subjective and polysomnography-defined sleep.[11] After treatment with cognitive behavioral therapy, beta activities have been found to decrease significantly.[12,14] Because high-frequency EEG has been reported to be associated with increased cognitive activities, these findings support the hypothesis that information processing during sleep is increased in patients with insomnia.

Although-high frequency EEG is usually thought to be associated with higher mental activities, there are alternative explanations of these findings. Bonnet and Arand have pointed out that increased muscle tension can also contribute to high-frequency EEG.[15] They have shown that high-frequency EEG power can be elevated simply by having the subjects engage in some mild physical activities, such as standing up and sitting down or walking around. Therefore, the elevated high-frequency EEG observed in insomniacs is not necessarily associated with increased cortical activities. In addition, even if the high-frequency EEG reflects increased mental activities in insomniacs, it is not necessarily associated with enhancement of processing of environmental stimuli. High-frequency EEG, in fact, could reflect heightened anxiety, rumination, or both.

The present study was undertaken to further evaluate information processing during sleep in patients with insomnia with the recording of event-related potentials (ERPs). ERPs can reflect the neurophysiologic activities elicited by sensory stimulation and do not require behavioral responses or conscious awareness. It is therefore an ideal technique to study information processing during sleep. Previous studies on the ERP changes during sleep have shown an attenuation of the N1 and an enhancement of the P2 (also called P220) as a person falls asleep.[16,17] Also, several ERP components have been reported to appear during non-rapid eye movement (NREM) sleep, including N350, P450, N550, and P900.[18-20] The N1 has been suggested to be associated with the formation of auditory feature traces and an automatic switching of attention toward novel stimuli, whereas the P2 has been related to inhibition of sensory interferences. The attenuated N1 and enhanced P2 reflect decreased cortical excitability and

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Address correspondence to: Hsiao-Sui Lo, Chung Shan Medical University, Department of neurology, No. 110, Sec. 1, Chien-Kuo N. Road, Taichung, 402, Taiwan; E-mail: hsiaosui@yahoo.com

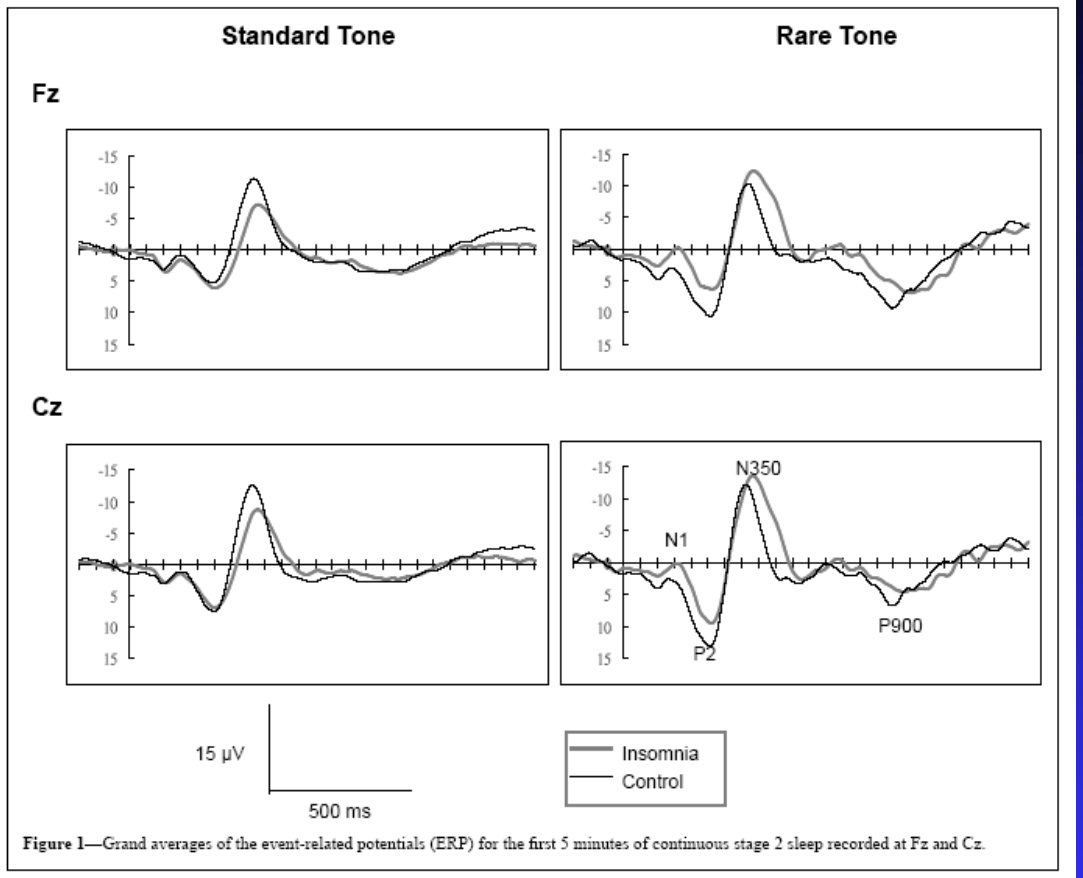

Figure 1—Grand averages of the event-related potentials (ERP) for the first 5 minutes of continuous stage 2 sleep recorded at Fz and Cz.

Patients with insomnia showed an enhancement in attention and a reduction in the inhibitory process that normally facilitates sleep onset in the beginning part of sleep. These results partially support the hyperarousal theory, i.e., enhanced information processing during the initiation of sleep is a contributing factor for insomnia. (Chien-Ming Yang, 2007).

INSOMNIA

Chronic Psychophysiological Insomnia: Hyperarousal and/or Inhibition Deficits? An ERPs Investigation

Célyne H. Bastien, PhD[1,2]; Geneviève St-Jean, BA[1,2]; Charles M. Morin, PhD[3]; Isabelle Turcotte, BA[1,2]; Julie Carrier, PhD[3]

[1]École de psychologie, Université Laval, Québec, Québec, Canada; [2]Laboratoire de neurosciences comportementales humaines, Centre de recherche Université Laval-Robert Giffard, Québec, Québec, Canada; [3]Département de psychologie, Université de Montréal, Chronobiology Laboratory Sleep Center, Montréal, Québec, Canada

Study Objectives: Chronic primary insomnia has been hypothesized to result from conditioned arousal or the inability to initiate normal sleep processes. The event-related potentials (ERPs) N1, P2, and N350 are useful indexes of arousal. The objective is to compare these ERPs in primary chronic psychophysiological insomniacs (INS) and good sleepers (GS) during multiple recordings.

Participants: Participants were 15 INS (mean age = 46 years, SD = 7.5) and 16 GS (mean age = 37 years, SD = 10.1).

Methods and Procedure: Following a multistep clinical evaluation, INS and GS participants underwent 4 consecutive nights of PSG recordings (N1 to N4). ERPs were recorded on the 3rd and 4th nights in the sleep laboratory (N3 and N4). ERPs recordings were made during wake on both nights (in the evening and upon awakening), with the addition of sleep-onset recordings on N4. Auditory stimuli consisted of "standard" and "deviant" tones.

Statistical Analysis: Repeated measures ANOVAs were computed for each ERP for each recording for each type of stimulus.

Results: The amplitude of P2 and N350 was greater for the deviant than for the standard stimulus in both groups. The amplitude of N1 was larger in INS than GS in the morning and the evening. While the amplitude of N350 was larger in GS than in INS at sleep onset, the amplitude of P2 was greater in INS than in GS at that time.

Conclusion: Signs of greater cortical arousal in psychophysiological insomnia individuals are observed, especially upon awakening in the morning. However, at sleep onset, difficulties from disengaging from wake processes and some inability at initiating normal sleep processes appear also present in individuals with insomnia compared to good sleepers.

Keywords: Psychophysiological insomnia, arousal, inhibition, event-related potentials, wake, sleep onset, sleep

Citation: Bastien CH, St-Jean G, Morin CM, Turcotte I, Carrier J. Chronic psychophysiological insomnia: hyperarousal and/or inhibition deficits? An ERPs investigation. *SLEEP* 2008;31(6):887-898.

RECENT EPIDEMIOLOGICAL REVIEWS INDICATE THAT BETWEEN 30% AND 48% OF ADULTS COMPLAIN OF INSOMNIA SYMPTOMS,[1] WHILE CLOSE TO 10% SUFFER of an insomnia syndrome (severe and chronic insomnia complaints).[2] Although many precipitating factors[3] and maintaining factors[4] have been suggested, the underlying cortical mechanisms linked to the perpetration of chronic insomnia remain poorly understood.

The neurocognitive model[5] suggests that insomnia sufferers developed conditioned cortical arousal from the association of sleep related stimuli and encountered sleep difficulties. High cortical arousal would be present at the peri-onset of sleep and persist during sleep and be one of the perpetrating factors of chronic insomnia. Providing empirical evidence to this theory, recent studies using spectral analysis (PSA) have shown that β activity is increased in primary insomnia relative to good sleepers, both around the sleep-onset period and during NREM sleep.[6-8] These findings, which are not always correlated with impairments of the macrostructure of sleep, are nevertheless consistent with psychological findings that insomniacs are hypervigilant and ruminative at night[9-12] and with the presumed contributing role of attentional processes and information processing factors to insomnia.[13]

On the other hand, a second theory, the psychobiological model, put forward by Espie,[14] suggests that high cortical arousal in insomnia sufferers may not be sufficient to maintain sleep difficulties. Rather, processes such as the inhibitory influence of attention and intention on "normal sleep processes" would deregulate and breach the automaticity of normal unattended sleep initiation. Alternatively, it would be an inability to *de-arouse* or disengage from active wake processing that interferes with the normal initiation of sleep processes in insomnia sufferers. Thus higher cortical arousal might be present at any time before sleep onset and during the night, but another process, inhibition of arousal, might be absent or deficient as insomnia sufferers attempt to fall asleep or return to sleep during the night. Although high cortical activity, as measured with PSA, has been reported in chronic insomnia sufferers, less is known about the hypothesized possible de-arousal deficiency in insomnia sufferers.

Few experimental designs have been aimed at eliciting or measuring on-going arousal and/or inhibition processes, in individuals with insomnia. Studies have generally failed to find differences between insomnia individuals and good sleepers

Disclosure Statement

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Address correspondence to: Célyne H. Bastien, PhD, École de Psychologie, Université Laval, Québec, Québec, Canada, G1K 7P4. Tel: (418) 656-2131, Ext: 8344; Fax: (418) 656-3646, E-mail address: Celyne.bastien@psy.ulaval.ca

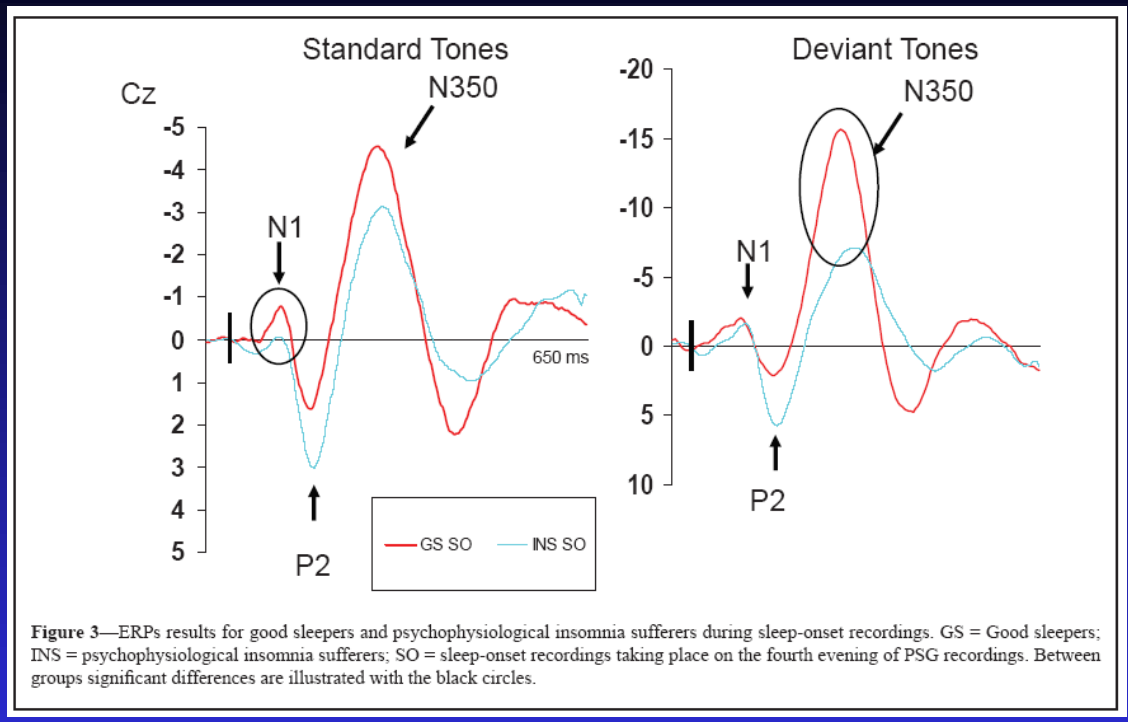
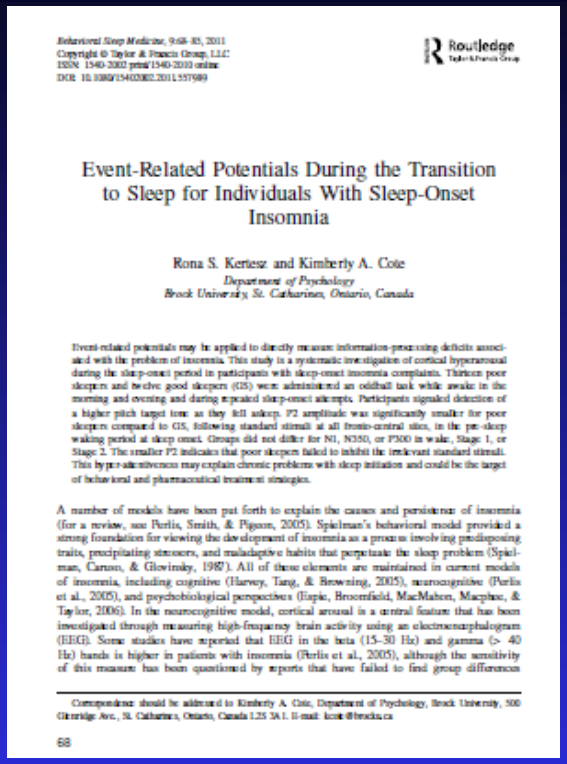


Figure 3—ERPs results for good sleepers and psychophysiological insomnia sufferers during sleep-onset recordings. GS = Good sleepers; INS = psychophysiological insomnia sufferers; SO = sleep-onset recordings taking place on the fourth evening of PSG recordings. Between groups significant differences are illustrated with the black circles.

The sleep onset data confirm the hypothesis that patients with insomnia "have difficulties inhibiting cortical arousal" as indicated by smaller N350 components. (Bastien et al. 2008).



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Routledge
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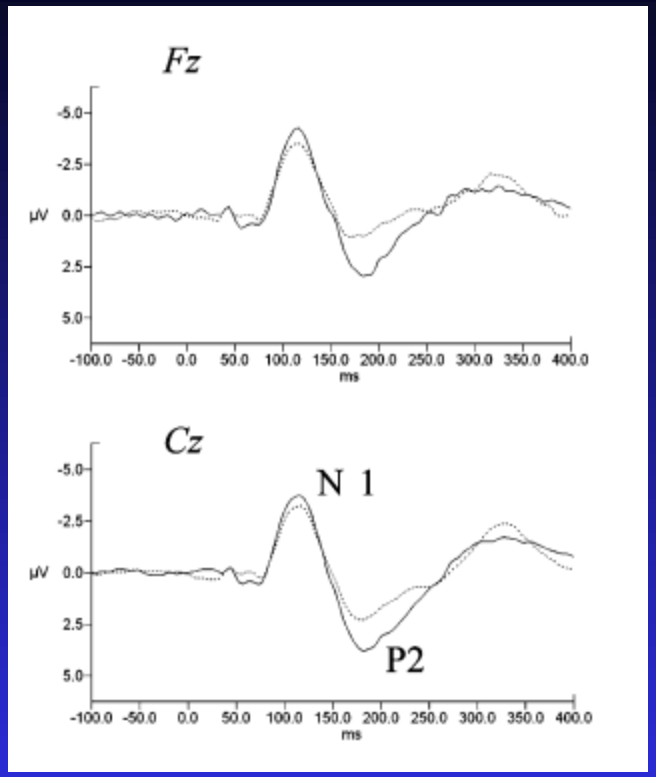
Event-Related Potentials During the Transition to Sleep for Individuals With Sleep-Onset Insomnia

Rona S. Kertesz and Kimberly A. Cote
Department of Psychology
Brock University, St. Catharines, Ontario, Canada

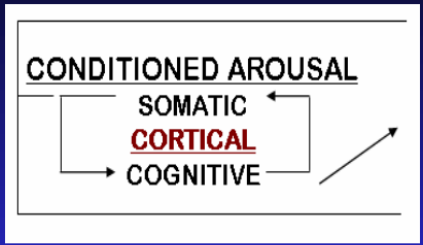
Event-related potentials may be applied to directly measure information-processing deficits associated with the problem of insomnia. This study is a systematic investigation of cortical hyperarousal during the sleep-onset period in participants with sleep-onset insomnia complaints. Thirteen poor sleepers and twelve good sleepers (GS) were administered an oddball task while awake in the morning and evening and during repeated sleep-onset attempts. Participants signaled detection of a higher pitch target tone as they fell asleep. P2 amplitude was significantly smaller for poor sleepers compared to GS, following standard stimuli at all fronto-central sites, in the pre-sleep waking period at sleep onset. Groups did not differ for N1, N350, or P300 in wake, Stage 1, or Stage 2. The smaller P2 indicates that poor sleepers failed to inhibit the irrelevant standard stimuli. This hyperattentiveness may explain chronic problems with sleep initiation and could be the target of behavioral and pharmaceutical treatment strategies.

A number of models have been put forth to explain the causes and persistence of insomnia (for a review, see Perlis, Smith, & Pigeon, 2005). Spielman's behavioral model provided a strong foundation for viewing the development of insomnia as a process involving predisposing traits, precipitating stressors, and maladaptive habits that perpetuate the sleep problem (Spielman, Caruso, & Glovinsky, 1987). All of these elements are maintained in current models of insomnia, including cognitive (Harvey, Tang, & Browning, 2005), neurocognitive (Perlis et al., 2005), and psychobiological perspectives (Espie, Broomfield, MacMahon, Macphie, & Taylor, 2006). In the neurocognitive model, cortical arousal is a central feature that has been investigated through measuring high-frequency brain activity using an electroencephalogram (EEG). Some studies have reported that EEG in the beta (15–30 Hz) and gamma (> 40 Hz) bands is higher in patients with insomnia (Perlis et al., 2005), although the sensitivity of this measure has been questioned by reports that have failed to find group differences

Correspondence should be addressed to Kimberly A. Cote, Department of Psychology, Brock University, 500 Glenridge Ave., St. Catharines, Ontario, Canada L2S 3A1. E-mail: kcot@brocku.ca



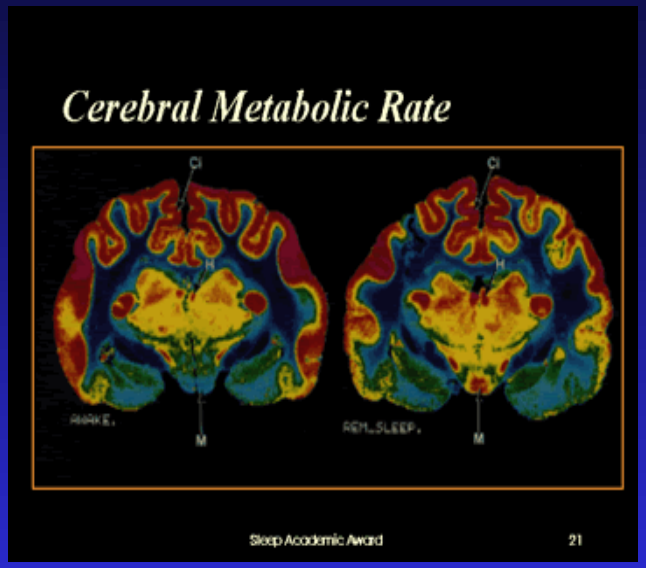
Participants with insomnia had smaller P2 amplitudes compared to GS at all frontal and central sites recorded during the pre-sleep waking period of sleep onset. The smaller P2 reflects a failure to inhibit or block out stimuli during attempts to fall asleep in the poor sleeper group. This failure to inhibit stimuli was specific to the standard, non-pertinent stimuli in the oddball task. These results are consistent with neurocognitive and psychobiological perspectives of insomnia… (Kertesz & Cote, 2011)



HOW MIGHT ONE MEASURE
CORTICAL/COGNITIVE AROUSAL ??

FUNCTIONAL IMAGING

FUNCTIONAL IMAGING OF SLEEP IN INSOMNIA



2 SPECT STUDIES BY THE ROCHESTER GROUP

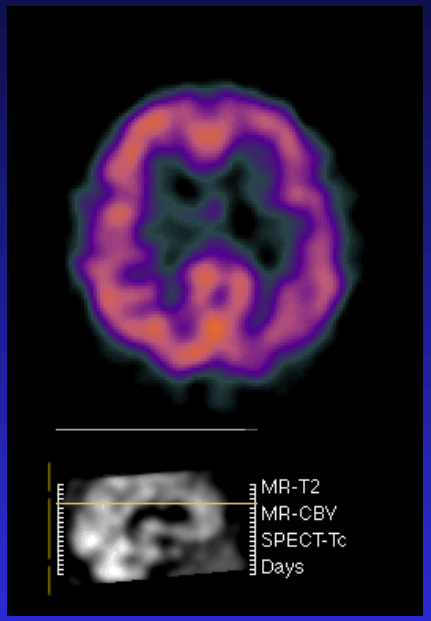
INSOMNIA VS GOOD SLEEPERS

PRE-POST TX IN PATENTS WITH INSOMNIA

1 PET STUDY BY THE PITTSBURGH GROUP

INSOMNIA VS GOOD SLEEPERS

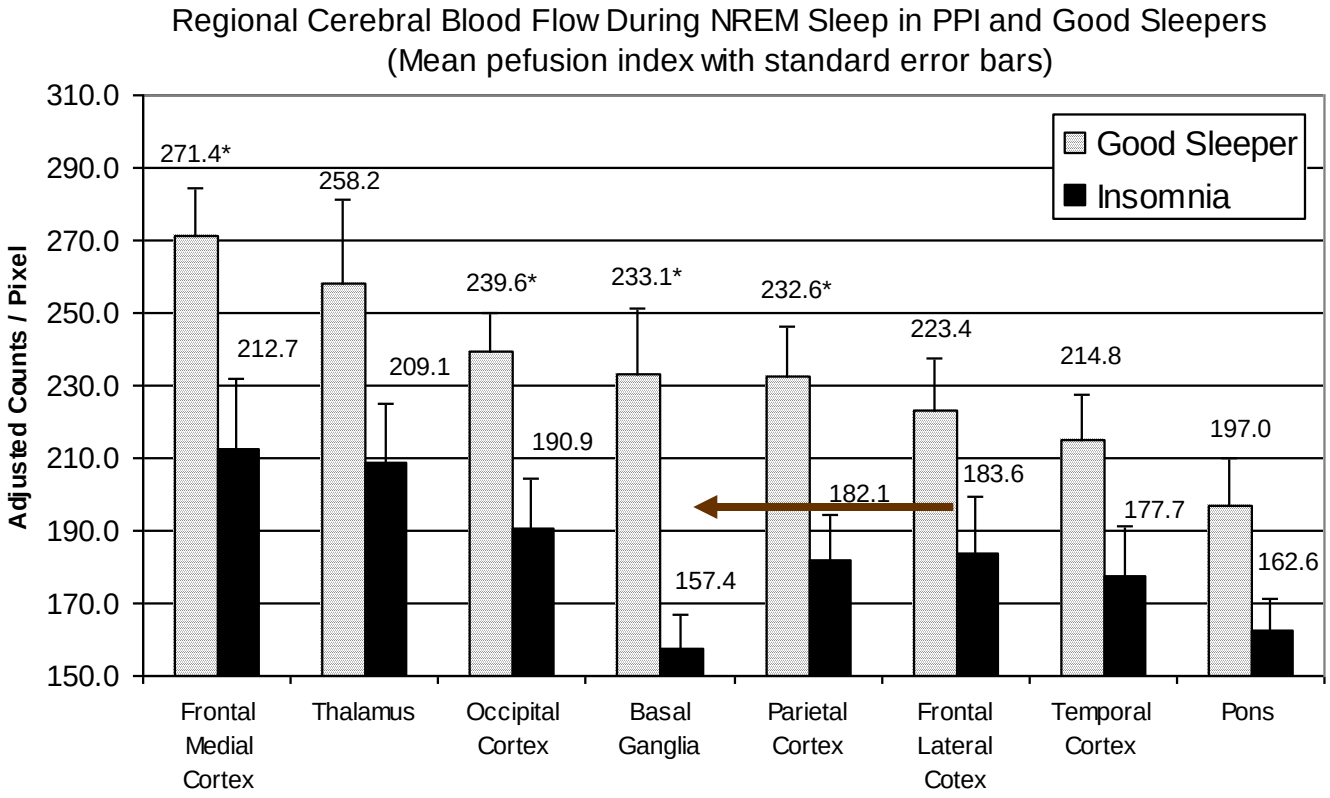
THE ROCHESTER STUDY



WHAT DID THE SPECT ASSESSMENTS SHOW ?

THE SPECT DATA

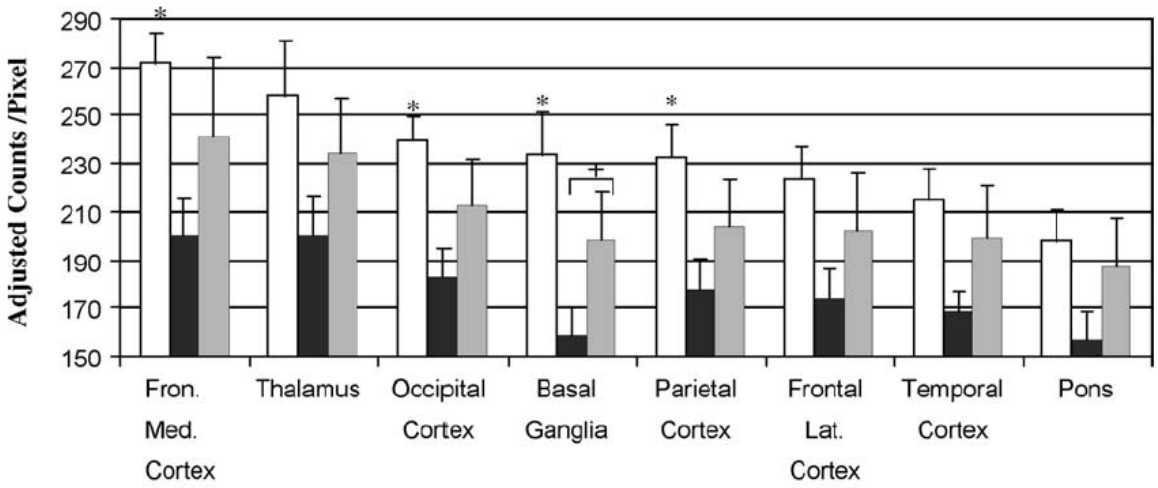
FIGURE 1



Smith, Perlis, et al., 2002 American Journal of Psychiatry

SPECT PRE-POST CBT- I

Letter to the Editor / Sleep Medicine 6 (2005) 93–94



Note: Good sleeper data is from Smith et al (2002b). Neuroimaging of NREM sleep in primary insomnia: A tc 99-HMPAO Single Photon Emission Computed Tomography study. *Sleep* 25(3), 325-335

Fig. 1. rCBF during NREM sleep before and after cognitive behavior therapy for insomnia compared to matched good sleeper controls.

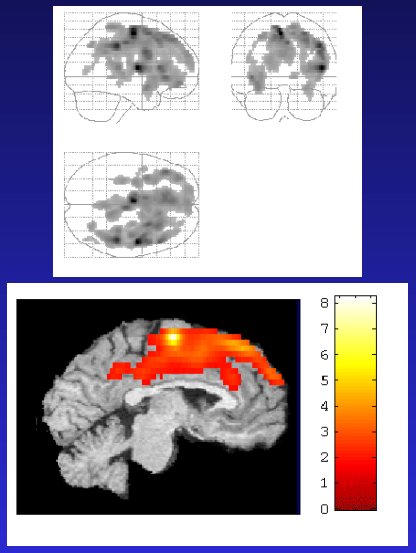
Smith, Perlis, et al., 2005 Sleep Medicine

THE SPECT DILEMMA

HOW CAN CNS HYPERAROUSAL BE rCBF-CHARACTERIZED AS A HYPOMETABOLIC STATE ?!

ASK ME ABOUT THIS DURING THE QnA –
BUT IT'S NOT AS MESSED UP AS WE THOUGHT

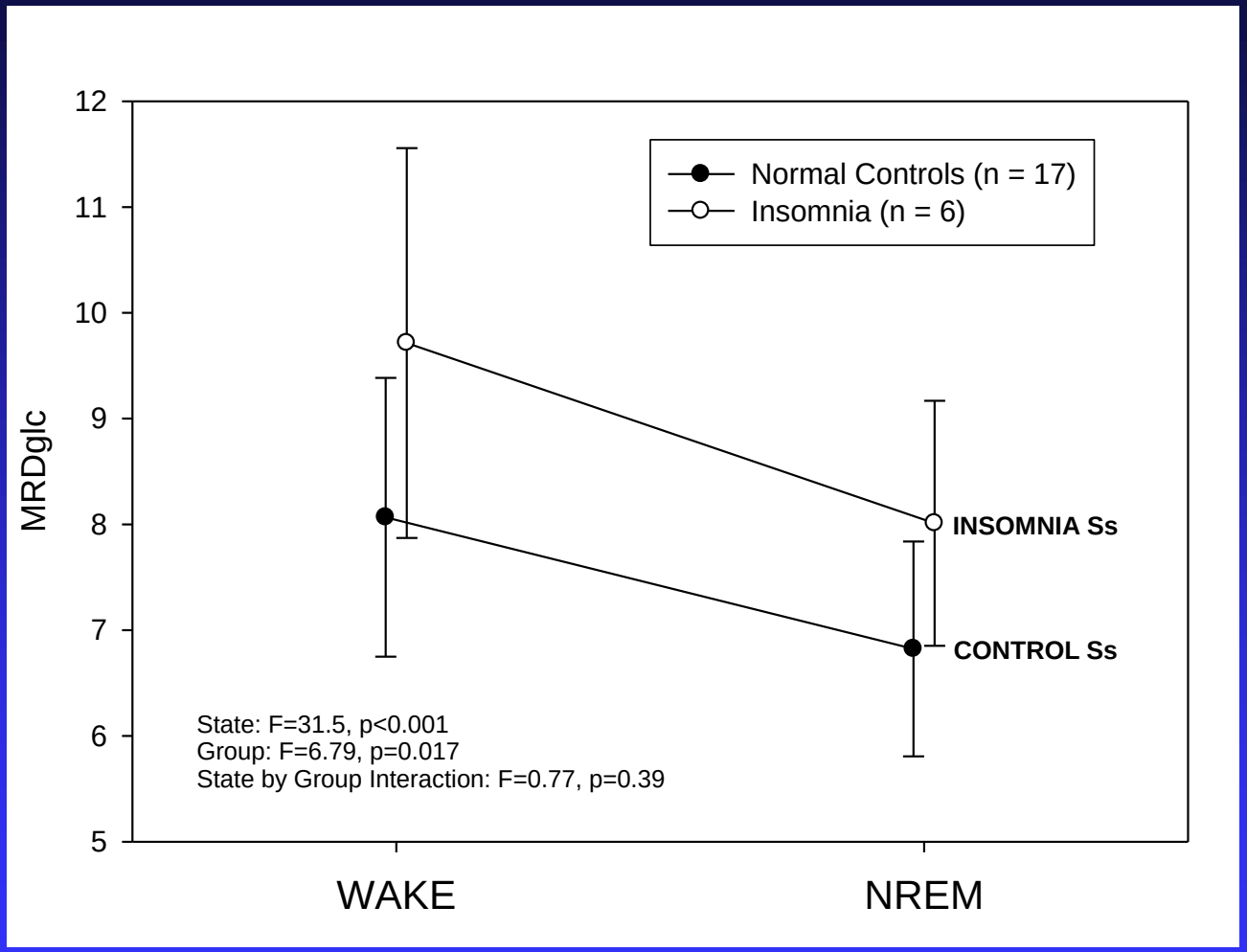
THE PITTSBURGH STUDY



WHAT DID THE PET ASSESSMENT SHOW ?

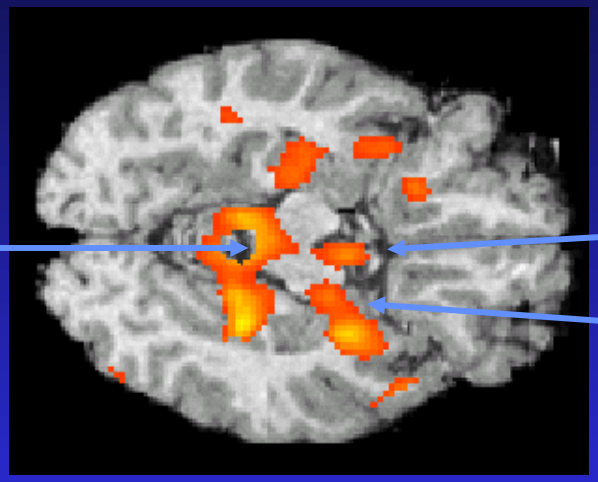
HYPERMETABOLISM IN INSOMNIA PATIENTS

Whole brain metabolism



Original Slide Provided By Eric Nofzinger – University of Pittsburgh

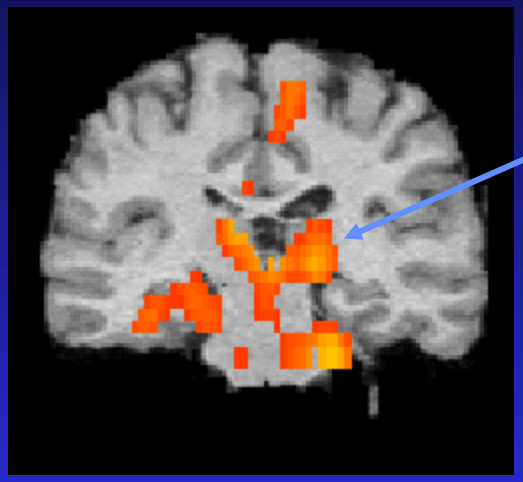
AROUSAL SYSTEMS IN INSOMNIA SUBJECTS THAT DEACTIVATE LESS FROM WAKING TO SLEEP



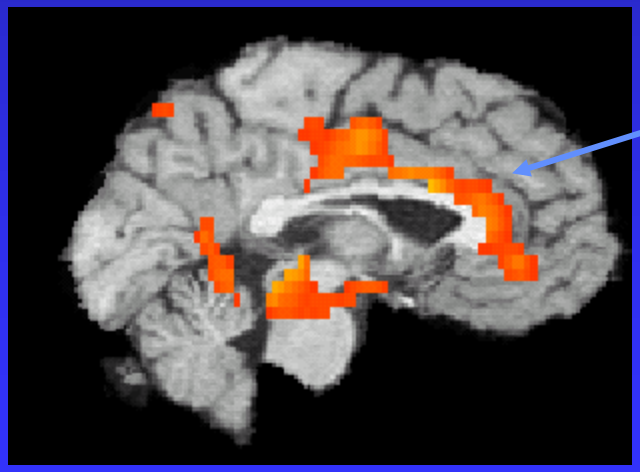
ARAS

Hypothalamus

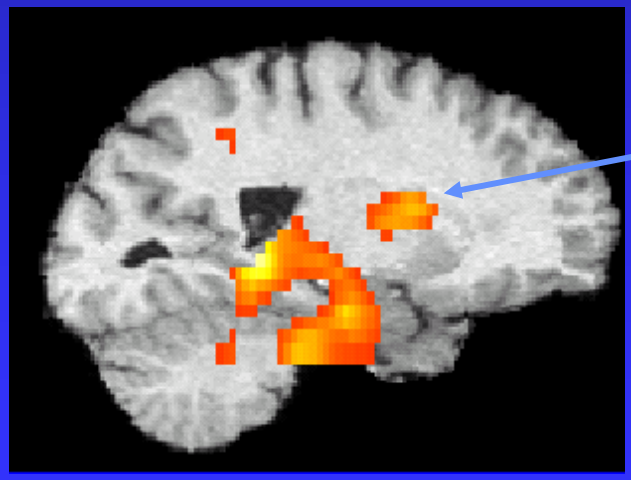
Mesial temporal cortex



Thalamus

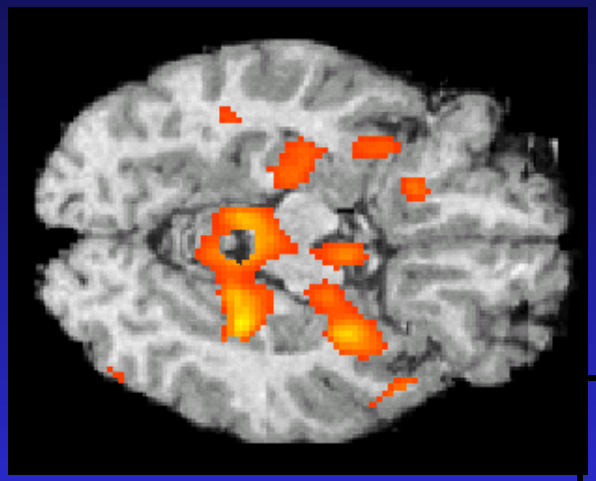


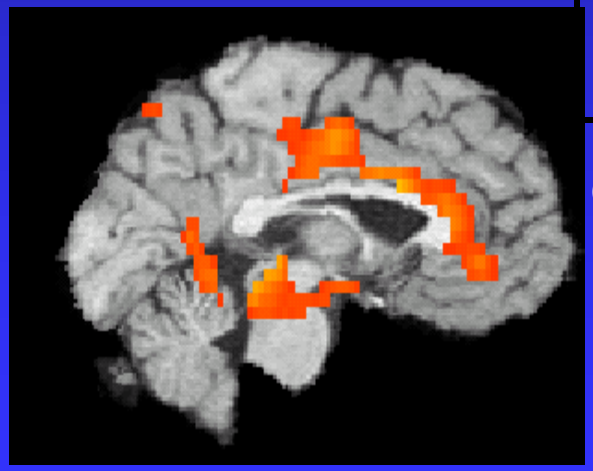
Cingulate



Insular cortex

DOES IT MAKE SENSE THAT THESE PARTICULAR AREAS ARE “HOTTER” ?





ARAS → Activates and deactivates the cerebral cortex and is involved in maintaining alertness

Hypothalamus → Regulates sleep and wakefulness, exerts control over the occurrence of consolidated sleep and wakefulness, and may have a role in sleep homeostasis.

Thalamus → Regulates sensory processing and the activation and deactivation of the cortex.

Mesial Temporal Cortex → Plays a role in memory formation and novelty detection (damage results in anterograde amnesia)

Cingulate → Plays an excitatory role in emotions and in motivated behavior.

Insular cortex → Plays a role in the perception of disgust and pain.

THE ISSUE OF FAILURE TO INHIBIT WAKEFULNESS

RAPID PUBLICATION

Reduced Brain GABA in Primary Insomnia: Preliminary Data from 4T Proton Magnetic Resonance Spectroscopy (1H-MRS)

John W. Winkelman, MD, PhD[1,3]; Orfeu M. Buxton, PhD[1]; J. Eric Jensen, PhD[2,3]; Kathleen L. Benson, PhD[1]; Shawn P. O'Connor, BA[1]; Wei Wang, MA[1]; Perry F. Renshaw, MD, PhD[2,3]

[1]Division of Sleep Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, MA; [2]Brain Imaging Center, McLean Hospital, Belmont, MA; [3]Department of Psychiatry, Harvard Medical School, Boston, MA

Study Objectives: Both basic and clinical data suggest a potential significant role for GABA in the etiology and maintenance of primary insomnia (PI). Proton magnetic resonance spectroscopy (1H-MRS) can non-invasively determine GABA levels in human brain. Our objective was to assess GABA levels in unmedicated individuals with PI, using 1H-MRS.

Design and Setting: Matched-groups, cross-sectional study conducted at two university-based hospitals.

Participants: Sixteen non-medicated individuals (8 women) with PI (mean age = 37.3 +/- 8.1) and 16 (7 women) well-screened normal sleepers (mean age = 37.6 +/- 4.5).

Methods and Measurements: PI was established with an unstructured clinical interview, a Structured Clinical Interview for DSM-IV (SCID), sleep diary, actigraphy and polysomnography (PSG). 1H-MRS data were collected on a Varian 4 Tesla magnetic resonance imaging/spectroscopy scanner. Global brain GABA levels were averaged from samples in the basal ganglia, thalamus, and temporal, parietal, and occipital white-matter and cortex.

Results: Average brain GABA levels were nearly 30% lower in patients with PI (.18 +/- .06) compared to controls (.25 +/- .11). GABA levels were negatively correlated with wake after sleep onset (WASO) on two independent PSGs (r = -0.71, p = 0.0024 and -0.70, p = 0.0048).

Conclusions: Our preliminary finding of a global reduction in GABA in non-medicated individuals with PI is the first demonstration of a neurochemical difference in the brains of those with PI compared to normal sleeping controls. 1H-MRS is a valuable tool to assess GABA in vivo, and may provide a means to shed further light on the neurobiology of insomnia.

Keywords: primary insomnia, magnetic resonance spectroscopy, polysomnographic sleep measures

Citation: Winkelman JW; Buxton OM; Jensen JE; Benson KL; O'Connor SP; Wang W; Renshaw PF. Reduced brain GABA in primary insomnia: preliminary data from 4T proton magnetic resonance spectroscopy (1H-MRS). *SLEEP* 2008;31(11):1499-1506.

CHRONIC INSOMNIA AFFECTS ROUGHLY 10% OF ALL ADULTS IN INDUSTRIALIZED COUNTRIES AND IS THE MOST COMMON SLEEP DISORDER. IT IS ASSOCIATED with high comorbidity with a variety of medical disorders,[1] impaired quality of life,[2] and consistent evidence of an increased risk of incident mood disorders.[3] In the absence of an adequate understanding of its pathophysiology, insomnia is divided into primary and comorbid forms, the latter diagnosed when coexisting medical, sleep or psychiatric disorders are present. Roughly 25% of those with insomnia are considered to have primary insomnia (PI).

Three distinct lines of evidence point to a potential significant role of GABA in the etiology and/or persistence of PI: 1) benzodiazepine receptor agonists (BzRAs), which are efficacious in the treatment of insomnia, increase activity at GABA neurons, the most prevalent inhibitory neurotransmitters in the CNS[4]; 2) physiological, neuroimaging, and cognitive methods demonstrate hyperarousal in PI, which may relate to an imbalance of excitatory and inhibitory CNS influences, in which GABA may potentially play a role[5]; and 3) neurons in the ventrolateral preoptic nucleus (VLPO), which contain GABA, promote sleep in lower animals through suppression of CNS arousal systems in the tuberomammillary nucleus (TMN) and the brainstem monoaminergic systems.[6]

Recent progress in the non-invasive evaluation of GABA levels in human brain has been achieved by means of proton magnetic resonance spectroscopy (1H-MRS).[7-12] These methods estimate the relative concentrations of brain neurotransmitters and metabolites from their resonance spectra in stimulated brain areas. Due to the low concentration of these metabolites in brain tissue, 1H-MRS averages spectra from larger anatomical areas than MRI to increase the signal:noise ratio.

We now report the results of the first study of in vivo GABA levels in unmedicated individuals with PI, using 1H-MRS.

METHODS

Subjects

Young and middle-aged (25-55 years) subjects were recruited from advertisements for a study of glucose metabolism and neuroimaging in DSM-IV defined PI (307.42) at Brigham and Women's Hospital and McLean Hospital from January 2007 to May 2008. Insomnia subjects had to have had greater than 6 months of difficulty initiating or maintaining sleep with resulting daytime distress or dysfunction. Specifically, they had to report a total sleep time ≤ 6.5 hrs and a) sleep onset latency > 45 minutes or b) wake after sleep onset > 45 minutes or c) total wake time during the sleep period (sleep latency + wake after

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Address correspondence to: John W. Winkelman, MD, PhD, Division of Sleep Medicine, Brigham & Women's Hospital, Harvard Medical School, 1505 Commonwealth Avenue, Brighton, MA 02135; Tel: (617) 783-1441; Fax: (617) 663-6192; E-mail: JWWinkelman@partners.org

Decreased Brain GABA in Primary Insomnia vs. Controls

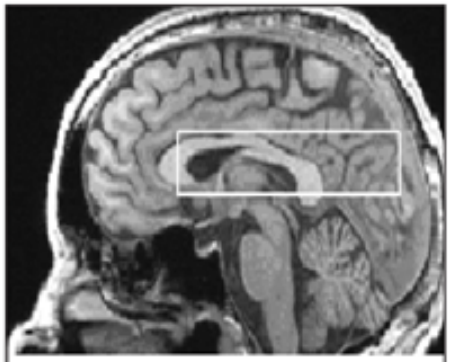


Figure 1—Sagittal image at 4 T depicting the placement of the 30mm thick MRSI slab.

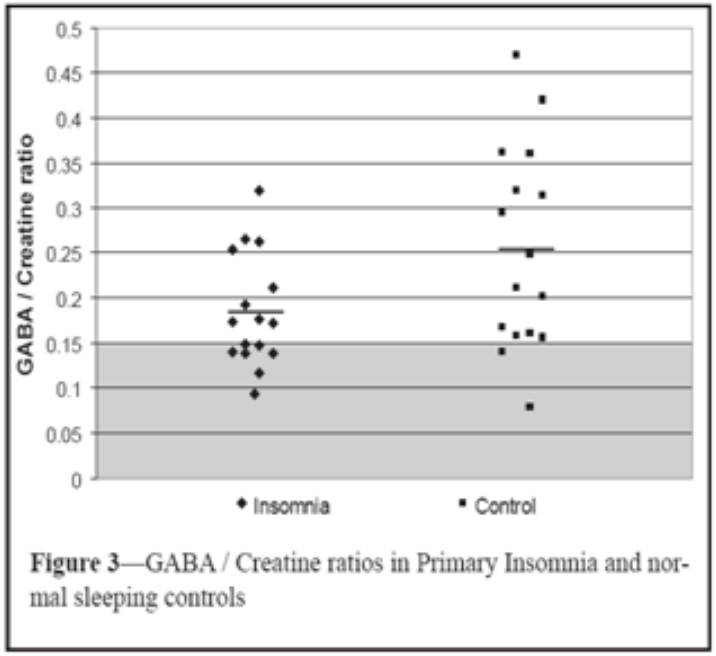


Figure 3—GABA / Creatine ratios in Primary Insomnia and normal sleeping controls

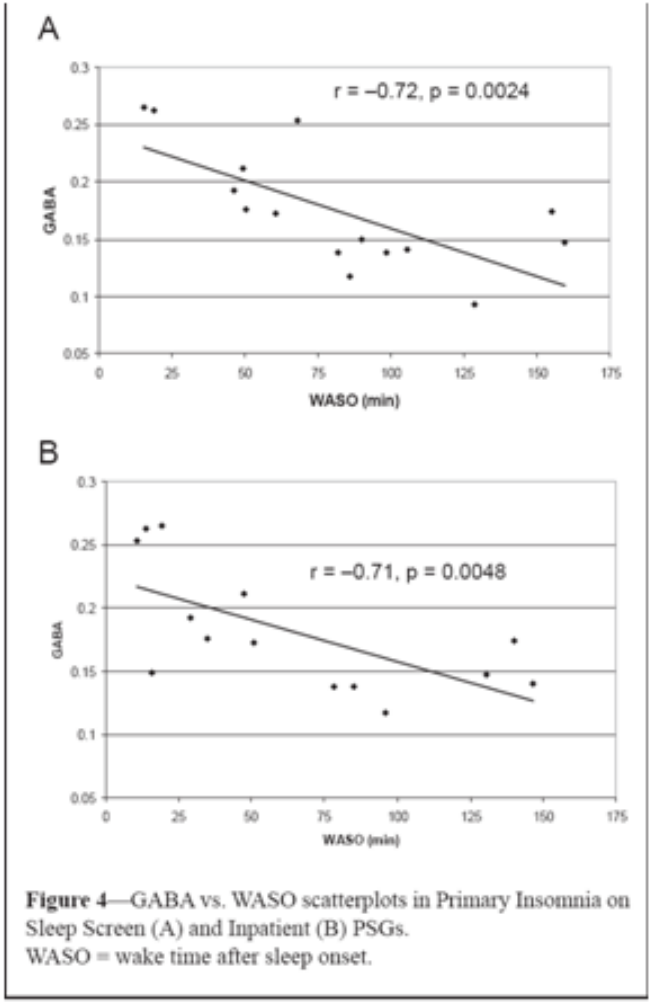
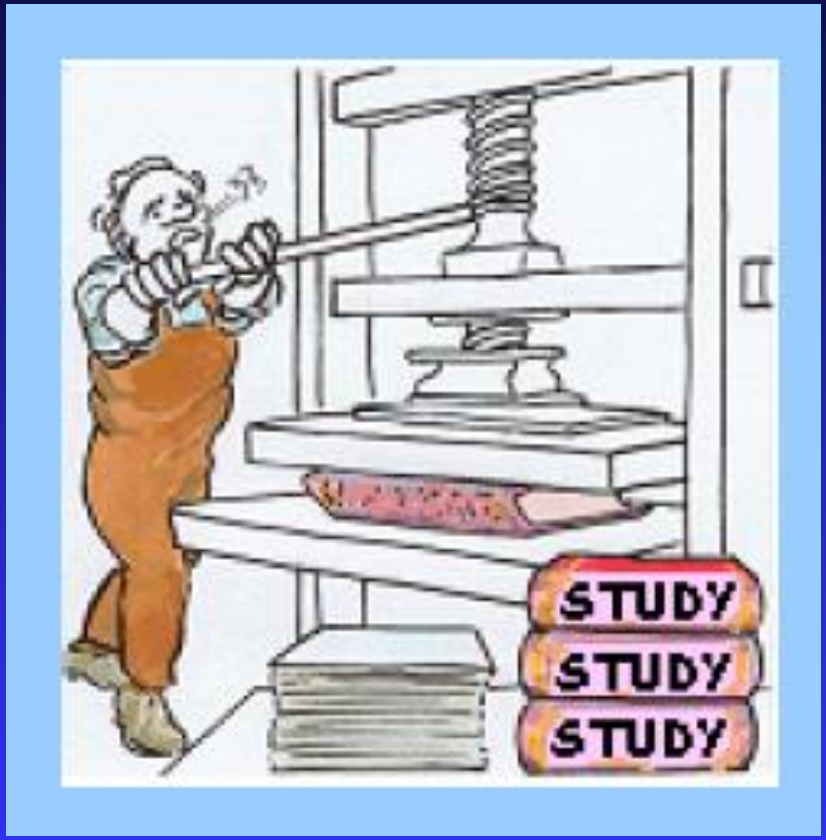


Figure 4—GABA vs. WASO scatterplots in Primary Insomnia on Sleep Screen (A) and Inpatient (B) PSGs.
WASO = wake time after sleep onset.

Winkelman et al., Sleep. 2008

SUMMARY



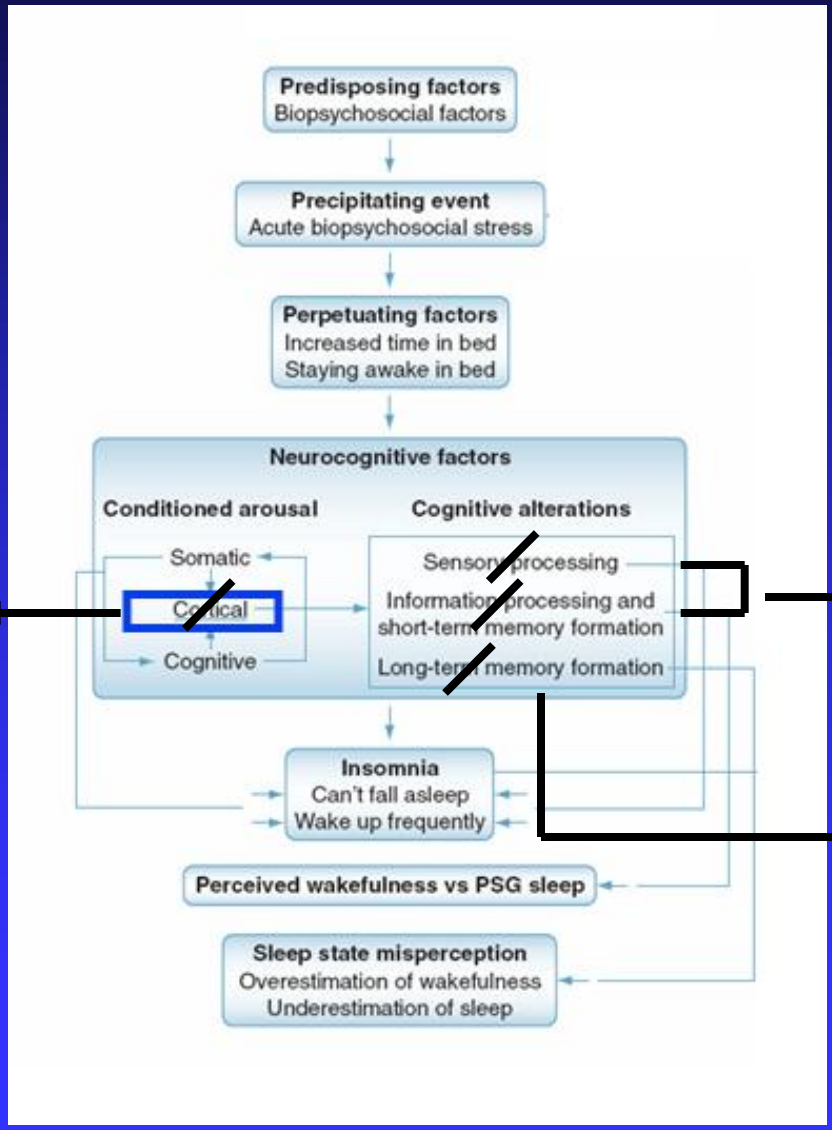
WHAT WE KNOW SO FAR

Patients with Chronic Insomnia exhibit

- an attenuation of the normal mesograde amnesia of sleep.
- increased cortical arousal as measured in terms of Beta and Gamma EEG
- an association between cortical arousal (Beta & Gamma EEG) and 1) subjective sleep quality and 2) magnitude of sleep state misperception.
- increased cortical arousal as measured in terms of glucose utilization (PET)
- an enhancement in attention and a reduction in the inhibitory process at sleep onset (ERPs).

WHAT IS THE CLINICAL RELEVANCE OF ALL THIS ?

SRT
ISR
BZs / BZRAs
NEUROFEEDBACK ?
DA ANTAG. ?
GABA AGON. ?
5HT2A ANTAG. ?



SRT
ISR ?
BZs / BZRAs

SRT
BZs
ACH ANTAG.
NMDA ANTAG

WHAT IS THE NAME OF THIS PAINTING ?

WHY IS IT RELEVANT ?

BREAK

The University of Pennsylvania

Michael Perlis PhD
Director, Upenn Behavioral Sleep Medicine Program
mperlis@upenn.edu