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?!
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
Psychophysiological insomnia: the behavioural model and a neurocognitive perspective


Department of Psychiatry, University of Rochester, Department of Psychology, University of Chicago, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, USA

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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 impression regarding sleep quantity and quality. The remaining inconsistency 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 gamma activity (which have been found to be associated with cognitive processes) is enhanced in insomniacs 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 monograde insomnia. 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-rhythmic sleep (Armitage et al. 1980, Simonds et al. 1993, Silva et al. 1996). In the United States, approximately 26 million people or 10% of the population suffer from insomnia (Hammond 1964, Stoker et al. 1979, Institute of Medicine 1979, Karasu et al. 1985, Mullan et al. 1985, Ford and Kamarou 1989; Gallup Organization 1991). Each year millions of prescriptions for hypnotic medications are prescribed to

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

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BASED ON THE BEHAVIOR MODEL AN EXTENSION OF THE BEHAVIORAL MODEL AN EXTENSION OF THE PHYSIOLOGIC PERSPECTIVE SANS ASSUMPTIONS NEUROBIOLOGIC CONCOMITANT OF WORRY
THE NEUROCOGNITIVE MODEL

Predisposing factors
Biopsychosocial factors

Precipitating event
Acute biopsychosocial stress

Perpetuating factors
Increased time in bed
Staying awake in bed

Vulnerability for physical psychiatric illness

Neurocognitive factors

Conditioned arousal
Somatic
Cortical
Cognitive

Cognitive alterations
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
THE NEUROCOGNITIVE MODEL OF INSOMNIA
EXTENSION OF BEHAVIORAL MODEL

THE NEUROCOGNITIVE MODEL

- Predisposing factors
  - Biopsychosocial factors
- Precipitating event
  - Acute biopsychosocial stress
- Perpetuating factors
  - Increased time in bed
  - Staying awake in bed

- Vulnerability for physical psychiatric illness

Neurocognitive factors
- Conditioned arousal
  - Symptom
    - Cortical
    - Cognitive
- Cognitive alterations
  - 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

4 FACTOR MODEL

- Conditioned Arousal
- Perpetuating
- Precipitating
- Predisposing

TARGET FOR CBT TX OF INSOMNIA

Threshold

Pre-Morbid, Acute, Early, Chronic, Acute Tx, + Response
THE NEUROCOGNITIVE MODEL OF INSOMNIA

EXTENSION OF PHYSIOLOGIC MODEL – SANS ASSUMPTIONS

THE NEUROCOGNITIVE MODEL

Predisposing factors
Biopsychosocial factors

Precipitating event
Acute biopsychosocial stress

Perpetuating factors
Increased time in bed
Staying awake in bed

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Sleep state misperception
Overestimation of wakefulness
Underestimation of sleep

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

Neurocognitive factors
- Conditioned arousal
  - Somatic
  - Cortical
  - Cognitive
- Cognitive alterations
  - 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

STARTLE & ORIENT
IDENTIFY & RESPOND
REMEMBER
HOW MIGHT ONE ASSESS THE MODEL?
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 ??
HOW MIGHT ONE MEASURE CORTICAL/COGNITIVE AROUSAL??

MEMORY & PERCEPTION TASKS
SLEEP ONSET

- 5 - 3 - 2 - 1  1  2  3  4  5

LOBSTER, CITY, STAR ...
LONG TERM MEMORY FOR WORD STIMULI

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

ALL

LONG TERM MEMORY FOR WORD STIMULI
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)
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)
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)
“10” STUDIES HAVE FOUND EVIDENCE OF CNS AROUSAL IN INSOMNIA IN TERMS OF INCREASED BETA EEG

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal/Volume/Publication Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedman et al., 1986</td>
<td>EEG &amp; Clin Neurophy 63: 408-413</td>
</tr>
<tr>
<td>Merica &amp; Gaillard, 1991</td>
<td>Physiol. Behav. 52: 99-204</td>
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<td>Jacobs &amp; Benson, 1993</td>
<td>Behavior Therapy 24: 159-174</td>
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<td>La Marche &amp; Oligivie, 1997</td>
<td>Sleep. 20: 724-733</td>
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<td>Nofzinger et al., 1999</td>
<td>Sleep. 22 supp 1: S99-S99</td>
</tr>
<tr>
<td>Perlis et al., 2001</td>
<td>Sleep, 24(1):110-117</td>
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<tr>
<td>Perlis et al., 2001</td>
<td>J. Sleep Research, 10: 93-104</td>
</tr>
<tr>
<td>Krystal et al., 2002</td>
<td>Sleep, 25(6): 630-640</td>
</tr>
<tr>
<td>Buysse et al., 2008</td>
<td>Sleep, 31 (12): 1673-1682</td>
</tr>
</tbody>
</table>
Standardized Whole Night NREM Spectral Plots for Depressed and Insomniac Patients

Unpublished Data – Nofzinger - UPITT
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

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CNS AROUSAL IN INSOMNIA IN TERMS OF BETA EEG

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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
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

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
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).
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).
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
WHAT DID THE SPECT ASSESSMENTS SHOW?
FIGURE 1
Regional Cerebral Blood Flow During NREM Sleep in PPI and Good Sleepers
(Mean perfusion index with standard error bars)

The SPECT data
Smith, Perlis, et al., 2002 American Journal of Psychiatry
SPECT PRE-POST CBT- I

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

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 ?!

WHAT THE HECK?
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

State: F=31.5, p<0.001
Group: F=6.79, p=0.017
State by Group Interaction: F=0.77, p=0.39

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

John W. Winneke, MD, PhD,1 Orion M. Burton, PhD,2 J. Eric Jensen, PhD,2 Kathleen L. Rensel, PhD,2 Deane P. O'Connor, BA,1 Wei Wang, MA,1 Perry F. Rosenwax, MD, PhD2

1Division of Sleep Medicine, Brigham & Women’s Hospital, Harvard Medical School, Boston, MA. 2Brain Imaging Center, McLean Hospital, Belmont, MA, 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-pair, cross-sectional study conducted at two university-based hospitals.

Participants: Sixteen non-medicated individuals (8 women) with PI (mean age = 37.5 ± 8.1) and 16 (7 women) well-screened normal sleepers (mean age = 38.5 ± 4.5).

Methods and Measurements: PI was established with structured 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/magnetic resonance spectroscopy scanner.

Results: Average brain GABA levels were nearly 30% lower in patients with PI (1.18 ± 0.28) compared to controls (2.57 ± 0.9). GABA levels were negatively correlated with wake after sleep onset (WASO) in two independent PSQIs (r = -0.71, p = 0.0025 and -0.76, 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 sleepers. 1H-MRS is a valuable tool to assess GABA in vivo, and may provide a means to further light on the neurobiology of insomnia.

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


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, IMPAIRED QUALITY OF LIFE, AND CONSEQUENTLY INCREASED RISK OF INCIDENTAL MOOD DISORDERS. IN THE ABSENCE OF AN ADEQUATE UNDERSTANDING OF ITS PATHOPHYSIOLOGY, INSOMNIA IS DIVIDED INTO PRIMARY AND SECONDARY FORMS. THE LATTER OCCURS WHEN A PSYCHIATRIC OR MEDICAL DISORDER IS PRESENT. A LARGE PROPORTION OF THOSE WITH INSOMNIA ARE CONSIDERED TO HAVE PRIMARY INSOMNIA (PI).

These distinct lines of evidence point to a potential significant role of GABA in the etiology and pathogenesis of PI. 1) benzodiazepine receptor agonists (BzRAs), which act in the treatment of insomnia, increase activity at GABA receptors, the most prevalent inhibitory neurotransmitter in the CNS; 2) physiologically, neuroimaging, and cognitive methods demonstrate hyper arousal in PI, which may relate to an imbalance of excitatory and inhibitory CNS influences, in which GABA may potentially play a role; and 3) glutamate in the ventromedial preoptic nucleus (VLPO), which controls GABA, promotes sleep in lower animals through suppression of CNS arousal systems in the tuberomamillary nucleus (TMN) and the brainstem monoaminergic systems.

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). 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-to-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 (25-53 years) subjects were recruited from advertisements for a study of glucose metabolism and neuroimaging in DSM-IV defined PI (N = 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 resultant daytime distress or dysfunction. Specifically, they had to report a total sleep time < 6.5 hours and a sleep onset latency > 30 minutes or b) wake after sleep onset > 45 minutes or c) total wake time during the sleep period (sleep latency + wake after
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?