Neuropsychol Rev (2011) 21:22–40
DOI 10.1007/s11065-011-9160-3

REVIEW

Insomnia: Neurophysiological and Neuropsychological Approaches

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Received: 4 November 2010 / Accepted: 6 January 2011 / Published online: 20 January 2011

Abstract Insomnia is a symptom, a syndrome and a comorbid disorder. Its diagnosis relies on subjective reports from the afflicted individual and is defined as difficulties in initiating sleep, maintaining sleep, waking up too early or non-restorative sleep. However, insomnia and especially, primary insomnia, has received much attention in insomnia research with the use of objective measures. Insomnia, its peculiarities, most frequent subtypes and two most prominent models will first be briefly introduced. Then, insomnia will be reviewed according to results obtained with the use of neurophysiological measures as basic/traditional as polysomnography to more sophisticated ones such as power spectral analysis, neuroimaging, cyclic alternating patterns and event-related potentials. In addition, a review of the discrepancies between subjective and objective reports of cognitive alterations through neuropsychological testing is offered. The need to combine measures is then highlighted in conclusion.

Keywords Insomnia · Subtypes · PSG · Neurophysiological measures

Acronyms

APA	American Psychiatric Association
ARAS	Ascending Reticular Activating System
BZD (BZDs)	Benzodiazepine (Benzodiazepines)
CAP	Cyclic Alternating Pattern
CBT-I	Cognitive-Behavioral Therapy for Insomnia
CNS	Central Nervous System
EEG	Electroencephalogram
EKG	Electrocardiogram
EMG	Electromyogram
EOG	Electrooculogram
ERPs	Event-Related Potentials
FFT	Fast Fourier Transforms
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-aminobutyric acid
LORETA	Low Resolution Electromagnetic Tomography Analysis
N100 (N1)	Negative wave peaking at about 100 ms after stimulus onset
N350	Negative wave peaking at about 350 ms after stimulus onset
NCAP	Non-Cyclic Alternating Pattern
NREM	Non Rapid Eye Movement
P50	Positive wave peaking at about 50 ms after stimulus onset
P200 (P2)	Positive wave peaking at about 200 ms after stimulus onset
P300 (P3)	Positive wave peaking at about 300 ms after stimulus onset
PET	Positron Emission Tomography
PSA	Power Spectral Analysis
PSG	Polysomnography
REM	Rapid Eye Movement
SPECT	Single-Photon-EmissionComputed Tomography
SWA	Slow Wave Activity
SWS	Slow Wave Sleep
TMS	Transcranial Magnetic Stimulation

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Introduction

Insomnia is among the most common health complaints in medical practice and the most prevalent of all sleep disorders. Approximately 30% of the general population experiences some insomnia symptoms occasionally and, 10% suffer from chronic and persistent insomnia (Morin et al. 2006; Ohayon 2002). Frequently reported consequences related to insomnia include fatigue, sleepiness, mood disruption (Zammit 1988), impaired attention, and memory deficits (Hauri 1997). It has been observed that often, it is not the sleep difficulties per se that will be an incentive to seek medical help or treatment, but the daily consequences associated with the sleep difficulties (Morin 1993). Sleep aids, increased medical visits, and absenteeism from work imply important costs for the patient as well as society (Hillman et al. 2006; St-Jean and Bastien 2008a). Insomnia is multi-dimensional and multifaceted, yet its evaluation and diagnosis are based primarily on clinical history (Sateia et al. 2000). This review, in addition of stating some peculiarities of the disorder, will provide an overview of research devoted at circumscribing the objective deficits in insomnia sufferers while exploring the most recent research avenues offered by neurophysiological and neuropsychological approaches.

Definition

Insomnia is defined as a complaint of prolonged sleep latency (labeled "sleep-onset insomnia"), difficulties in maintaining sleep (labeled "sleep maintenance insomnia"), waking up too early in the morning (labeled "terminal insomnia"), a mix of different sleep complaints (labeled "mixed insomnia") and/or the experience of non-restorative sleep. In addition, the DSM-IV-TR (APA 2000) specifies that to be considered a disorder, "primary" insomnia or its perceived consequences cause clinically marked distress or significant impairment of occupational or social functioning. Furthermore, it is not caused by a mental or physical disorder, a primary sleep disorder, or the effects of substance abuse or a medication. Although insomnia can be acute (less than 1 month), the current definition of primary insomnia specifies that it must be present at least three times a week, for at least 1 month (thus "chronic"). Increasingly, the epidemiological literature on insomnia classifies individuals in two categories: "syndrome" and "symptom". To be included in the syndrome category, an individual must meet the definition for insomnia disorder as specified by the DSM-IV-TR. On the other hand, an individual presenting one or more symptoms without corresponding to the full spectrum of criteria of the DSM-IV-TR (for example, having a sleep difficulty only once a week or not presenting any marked distress related to his/her sleep difficulties), would be classified in the symptom category.

Peculiarities of the Disorder

Insomnia can be a problem from childhood through old age. It can stand alone as a disorder (primary), can be comorbid with another active sleep or mental disorder or be present as a symptom of another disorder. In this regard, insomnia is by far the most frequent sleep complaint amongst psychological disorders. While the essential clinical features of insomnia are similar for the symptom and the syndrome, in *comorbid insomnia*, the sleep disturbance evolves in the context of another disorder. Comorbid insomnia (National Institutes of Health 2005) replaces "secondary insomnia" as the direction of causality is not always easy to identify when insomnia is present in the context of other conditions. Comorbid insomnia can be caused by other conditions, can be completely independent of them or can also cause the disorders with which it coexists. Disorders may be psychiatric (depression and anxiety), medical (typically involving pain), circadian (phase-delay syndrome), or other sleep disorders (periodic limb movements, sleep-related breathing disorders). Like many other sleep disorders, insomnia comprises a spectrum of complaints reflecting dissatisfaction with the quality, duration, or efficiency of sleep. Unlike many other sleep disorders that are first noticed by others and require objective polysomnographic laboratory validation (for example, apnea, REM sleep behavior disorder, nocturnal myoclonous), insomnia is first reported by the individual and does not require an objective confirmation. Furthermore, the severity of the complaint is not classified into categories such as light, medium or severe such is the case for obstructive sleep apnea syndrome, but is rather distributed along a severity continuum.

Subtypes of Insomnia

The ICSD (ICSD-2, 2005) distinguishes among 11 different subtypes of insomnia. However, three of them are the most frequent: psychophysiological insomnia, sleep-state misperception (or paradoxical insomnia), and idiopathic insomnia. In some cases, complaints of sleep difficulties are objectively observable, in other cases, they are not. In other words, patient may either complain of sleep difficulties while objective polysomnographic recordings appear normal, or there may be some form of constant and important gap between objective and subjective measures of sleep (Edinger et al. 2004). Depending on the diagnostic criteria used, as much as 50% of individuals suffering from insomnia could be poor estimators and, consequently, classified as suffering from *paradoxical insomnia* (Edinger and Krystal 2003; St-Jean and Bastien 2009). While paradoxical insomniacs and good sleepers seem to be equivalent on measures of sleep macroarchitecture (for

example the observed percentage of different sleep stages), there may be subtle and finer differences in the microarchitecture characterizing both groups (Krystal et al. 2002). Among insomniacs estimating their sleep quite accurately, and presenting "real" sleep-onset or sleep maintenance difficulties are patients suffering from *psychophysiological insomnia*. These individuals are assumed to be conditioned by sleep-related stimuli in the environment (e.g., bedroom) or bedtime routine, which are then associated in the sufferer's mind with the anxiety, fear, or frustration of having trouble getting to sleep (Hauri and Fisher 1986; Harvey 2002; Espie 2002). Consequently, the level of arousal is increased, preventing a good night sleep. A third form of primary insomnia, less common but still acknowledged, is *idiopathic* or *childhood-onset insomnia*. In this case, insomnia is reported as starting in early childhood, typically before the age of 10. A higher rate of difficult and premature deliveries is found in idiopathic insomnia compared to the general population (Regestein and Reich 1983; Hauri and Olmstead 1980). Despite evidence that their sleep is often more disturbed than in psychophysiological insomnia, individuals with idiopathic insomnia tend to show less emotional distress, perhaps due to resignation or to coping mechanisms they have developed over their lifetime. Finally, different subtypes of insomnia are not all mutually exclusive. An individual can show objective sleep-onset, sleep-maintenance or mixed objective sleep difficulties once his or her sleep has been recorded in the sleep laboratory but also present important discrepancies between his or her reports and laboratory sleep observations. As such, an individual might be complaining of mixed sleep difficulties over a long period of time, without showing any signs of depression or anxiety and at the same time, be subtyped as having paradoxical insomnia.

Daily Consequences and Neuropsychological Assessment

In clinical practice, individuals suffering from insomnia often report fatigue as well as attention/concentration and memory impairments (Zammit 1988). These impairments are attributed to the sleep difficulties, create great concerns and are often the reason that will prompt an individual to seek treatment (Morin 1993). Deterioration in occupational, social and cognitive functioning is a diagnostic criterion for chronic insomnia (APA 1994, 2000).

Ancillary Measures

A number of studies have confirmed that insomniacs compared to good sleepers, score higher on questionnaires measuring fatigue and depressive/anxious symptoms (Lichstein et al. 2001; Moul et al. 2002) as well as on quality of life indexes (Hatoum et al. 1998; Zammit et al. 1999). Some epidemiological studies also report that insomniacs complain more often than good sleepers of concentration and memory deficits and of mistakes related to work demands (Léger et al. 2001; Roth and Ancoli-Israel 1999). Individuals suffering from insomnia also score higher than self-defined good sleepers on the Cognitive Failures Questionnaire (Broadbent et al. 1982).

Neuropsychological Testing

Some studies have observed that in insomniacs, compared to good sleepers, deficits were present in tasks measuring equilibrium, attention, reaction time (Hauri 1997) and access to information stored in semantic memory (Mendelson et al. 1984). However, no between groups differences are detected on psychomotor measures (Broman et al. 1992; Mendelson et al. 1984), episodic memory (Mendelson et al. 1984), divided attention (Broman et al. 1992), verbal learning and face and word recognition (Broman et al. 1992). On the other hand, contrary to what Hauri (1997) reported, Broman and colleagues (1992) had not previously observed any deficits in reaction time in insomniacs.

While many studies do report at least one impairment in insomniacs relative to good sleepers (for example: Altena et al. 2008a; Bonnet and Arand 1995; Edinger et al. 2008; Hauri 1997; Mendelson et al. 1984; Randazzo et al. 2000; Schmutte et al. 2007; Schneider-Helmert 1987; Schneider et al. 2004; Sugerman et al. 1985; Varkevisser and Kerkhof 2005; Vignola et al. 2000), other studies do not observe any difference whatsoever between the two groups of sleepers in similar studied domains (Broman et al. 1992; Dorsey and Bootzin 1997; Haimov et al. 2008; Orff et al. 2007).

Neuropsychological studies aimed at evaluating vigilance (mainly attention and motor speed) and sleepiness often yield ambiguous reports. While some studies have observed similar vigilance levels between insomniacs and good sleepers (Hauri 1997; Sugerman et al. 1985; Mendelson et al. 1984; Stepanski et al. 1988) others find better vigilance in insomniacs than good sleepers (Gu et al. 2005; Seidel et al. 1984). Our own group has also recently observed that insomniacs reported more sleepiness at pre-test, before a cognitive task (event-related potentials, ERPs), than good sleepers did. The between groups difference disappeared at post-testing (after the ERPs tasks). Thus, once insomniacs are engaged in cognitive tasks their sleepiness level becomes similar to those of good sleepers (Ropars et al. 2010). According to the cortical activation theory (see below, neurocognitive model, Perlis et al. 1997), Bonnet and Arand (1997) suggested that enhanced vigilance levels in insomniacs would result from greater cortical activation, this one

already interfering with difficulties in initiating or maintaining sleep. A compensation phenomenon could also explain that insomniacs' expectations towards their performance increase when they perceived that have not slept well (Broman et al. 1992; Schneider-Helmert 1987). As such, insomniacs are more likely to report having to provide more effort to perform and continue to perform following a bad night's sleep than good sleepers (Broman et al. 1992). It also seems that performance in insomniacs, compared to good sleepers, varies during the day being lower late at night and early in the morning (Varkevisser and Kerkhof 2005).

A meta-analysis is often indicated when ambiguous results are reported. To date, four meta-analyses have been conducted to better understand the impairments or extent of cognitive deficits observed in insomnia (Riedel and Lichstein 2000; Fulda and Schulz 2001; Shekleton et al. 2010; Fortier-Brochu et al. 2008).

Riedel and Lichstein (2000) observed that only 24% of 54 compared studies revealed cognitive deficits and similar conclusions were reached by Fulda and Schultz a year later (2001). Fortier-Brochu and colleagues (2008) observed that generally deficits in insomniacs were more common in sustained attention and vigilance, episodic and working memory, verbal fluidity and problem solving abilities. Finally, Shekleton et al. (2010) compiled studies comparing insomniacs and good sleepers on measures of attention (selective, sustained and alternate), psychomotor speed, working memory, learning and executive functioning. Again, ambiguous and sometimes contradictory results were observed between studies included in this meta-analysis. Nonetheless, these authors pointed out that individuals suffering from insomnia, compared to good sleepers, appear to present more deficits in tasks involving complex processes in attention (alternate and sustained) as well as tasks involving working memory.

Relating subjective/objective sleep parameters to neuropsychological testing scores, a study done in our own lab suggests that certain objective sleep parameters are associated with different aspects of cognitive performance (Bastien et al. 2003a). In fact, in older insomniacs and good sleepers, a good night of sleep is usually associated with a better daily cognitive performance. In addition, in both groups of sleepers, perceived sleep quality is more important than subjective sleep duration in terms of its impact on next day performance.

Short- and long-term memory consolidation are also part of the neurocognitive model and seemingly affected by hyperarousal. Since sleep has been associated with the consolidation of memory (Stickgold 2005), both declarative and procedural memory consolidation have been investigated in insomniacs and good sleepers. Nissen et al. (2006) reported impairments in procedural memory in insomniacs compared to good sleepers, and Backhaus et al. (2006) observed impairments in declarative memory in insomniacs compared to good sleepers. Although these results are interesting and appear to support the neurocognitive model, more research in this area needs to be conducted to assess how these findings might parallel reported daily consequences in insomnia.

Altogether, neuropsychological studies conducted so far suggest that only subtle cognitive deficits are observed in insomniacs, despite their subjective reports of daily cognitive alterations. It is possible that neuropsychological testing used so far is not appropriate to detect objective deficits (ecological testing or testing reflecting more adequately tasks encountered each and every day might be more appropriate and informative) or on the other hand, subtle deficits are enough to interfere with daily activities in insomniacs. Studies using more precise measures of active cognitive processes (such as ERPs) or combining evaluation measures (for example, fMRI and cognitive evoked potentials) might be the next step in trying to shed some light on cognitive deficits in insomniacs. In addition, as mentioned earlier, the quality of the preceding night of the evaluation needs to be accounted for since it appears to bare important weight, albeit be only for the perception of performance.

Theoretical Models

Many theoretical models of insomnia have been developed. The two most influential are the "neurocognitive" (Perlis et al. 1997) and "psychobiological" (Espie 2002) models. Both of these models are currently being tested using objective laboratory measures as a means to provide empirical validation. The different sections on power spectral analysis (PSA), neuroimaging and event-related potentials (ERPs) of this paper will expose different experimental designs that have been used to validate these models.

The Neurocognitive Model

Many predisposing (Spielman and Glovinski 1991), precipitating (Bastien et al. 2004), and maintaining factors (Spielman and Glovinski 1991) have been suggested as being linked to the appearance or perpetuation of insomnia. Hyperarousal has been suggested as being a core feature in insomnia. This hypothesis posits that insomniacs are overly aroused (thus "hyperaroused") at the somatic and cognitive level compared to good sleepers; in turn, this state of hyperarousal would interfere with sleep initiation and maintenance and would also interfere with daily activities (Bonnet and Arand 1997; Harvey 2002). The neurocognitive model of insomnia (Perlis et al. 1997; see Fig. 1 adapted from M. Perlis et al., Principles and Practice in

Sleep Medicine, 2010) proposes that insomniacs develop conditioned cortical arousal from the association of sleep related stimuli and encountered sleep difficulties. This conditioned hyperarousal may lead to "enhanced sensory and information processing" around sleep onset, as well as in sleep—wake transitions throughout the night. In addition, other cognitive alterations such as short- and long-term memory formation would also be jeopardized. Furthermore, hyperarousal can also be translated in the amount, or degree of discrepancies, between subjective and objective ratings of sleep (Perlis et al. 1997).

So far, many studies have provided empirical validation for the neurocognitive model, mainly through the use of Power Spectral Analysis (PSA) showing elevated beta power (Freedman 1986; Merica and Gaillard 1992; Jacobs et al. 1993; Lamarche and Ogilvie 1997; Merica et al. 1998; Perlis et al. 2001; Krystal et al. 2002; Buysse et al. 2008) or neuroimaging techniques (Nofzinger et al. 1999). Both PSA and neuroimaging studies are described later. For a more comprehensive review on hyperarousal, its interaction with the sleep-wake regulation system and contribution to the pathophysiology of insomnia, see Riemann et al. 2009.

The Psychobiological Model

The psychobiological model, put forward by Espie (2002), suggests that high levels of cortical arousal in insomnia, as hypothesized in the neurocognitive model, may not be sufficient to produce or maintain sleep difficulties. In this theory, "normal sleep processes" are deregulated and the automaticity of normal unattended sleep initiation is breached. In other words, it would be an inability to *de-arouse* or disengage from active wake processes that interferes with the normal initiation of sleep processes in insomnia. 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 insomniacs attempt to fall asleep or return to sleep during the night. Some studies have provided empirical evidence for this theory (Bastien et al. 2008a, b; Smith et al. 2002).

Although the literature so far appears to provide much empirical support for the "hyperarousal" put forward by the neurocognitive model of insomnia, the inability to "de-arouse" proposed by the psychobiological model is gaining interesting intuitive and scientific support from ongoing insomnia research.

General Insomnia Measures

Subjective Measures: The Basis of All

Although essential to make the diagnosis, a detailed clinical history/assessment of the patient's subjective complaint will

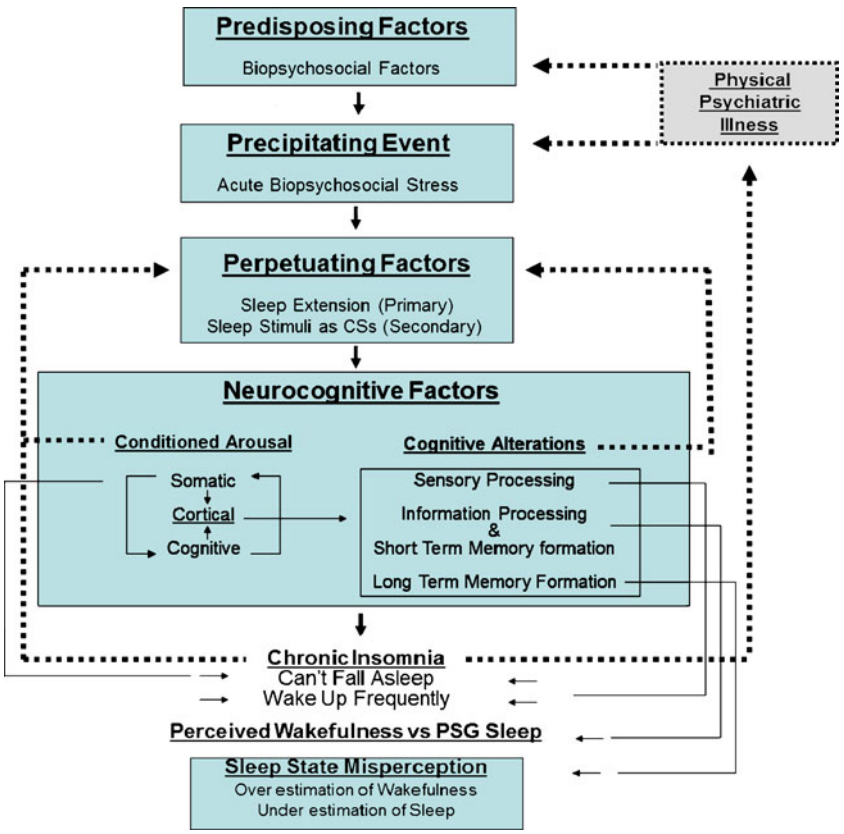

Fig. 1 Neurocognitive Model of Insomnia (Model is reproduced with the permission of Dr. Michael L. Perlis and adapted from Perlis et al. (2011). In Principles and Practice in Sleep Medicine, Kryger, Roth and Dement (Eds), 2011). After insomnia has become chronic (predisposing and precipitating factors have usually been identified), this model suggests that neurocognitive factors such as conditioned arousal and neurocognitive alterations interferes with sleep initiation and/or sleep maintenance. Neurocognitive factors (somatic, cortical and cognitive) interplay one with the other. "Cortical conditioned arousal" can be expressed through enhanced sensory and information processing as well as through enhanced short-term and long-term memory formation. These ones can be measured through experimental protocols (for example, event-related potentials for information processing)

greatly benefit or even depend on complementary data from more systematic sources such as subjective, neurophysiological and neuropsychological assessments. Sleep diary monitoring is an irreplaceable tool to document the perceived severity of insomnia. A sleep diary commonly requires self-recording of bedtime and arising time, along with morning estimates of sleep-onset latency, number and duration of awakenings, total sleep time, and several indices of sleep quality for the previous night. Even though they do not reflect absolute values obtained from polysomnography (see below), daily morning estimates of sleep parameters such as sleep-onset latency or wake after sleep onset yield a reliable and valid index of insomnia (Coates et al. 1982). By tracking sleep over several consecutive nights, a sleep diary is more likely to capture the night-to-night variability that often characterizes the sleep of chronic insomnia (Vallières et al. 2005) compared to one or two nights of polysomnography. Based on the diary measures, sleep-onset insomnia is typically defined by a latency to sleep onset greater than 30 min, and sleep-maintenance insomnia is defined by time awake after sleep onset greater than 30 min. A sleep efficiency (total sleep time divided by time in bed) lower than 85% also characterizes insomnia. On the other hand, early morning awakening can be described as a complaint of waking up earlier (more than 30 min) than desired, with an inability to go back to sleep, and before total sleep time reaches 6.5 h. These criteria, while seemingly arbitrary, are useful to operationalize the definition of insomnia.

The Gold Standard for Sleep: Polysomnography

A standard polysomnographic (PSG) montage provides comprehensive data on sleep continuity (sleep latency, time awake after sleep onset, sleep time and derived sleep efficiency) and sleep architecture (% of time spent in different stages of sleep such as non-rapid eye movement (NREM) stages 1, 2, 3 and 4 and rapid eye movement (REM) sleep, stage shifts, number and duration of cycles, and awakenings). Standard montages for sleep include horizontal and vertical eye movements recordings (electrooculogram, EOG), four electroencephalographic leads (EEG; C3, C4, O1, O2) and submental muscle tone recordings (electromyogram, EMG). These three basic recordings (EOG, EEG and EMG) are used to score sleep recordings (thus achieve sleep staging). Additional measures (e.g. airflow, respiratory effort, oxygen saturation, and anterior tibialis—leg muscle—EMG) are increasingly used by laboratories in order to detect other sleep disorders such as sleep apnea or periodic limb movements. In healthy adults, stage 1 occupies about 5% of the total night of sleep and stage 2 about 50%, stages 3–4 (combined) and REM sleep take up respectively about 15%–20% and 25%. Even though EEG leads are fixed to the scalp and then amplified and read through computerized systems, this measure of cerebral activity still remains limited. Its temporal resolution is low and it does not permit the identification of peculiar brain structures involved in normal or disturbed sleep.

On a day to day basis, PSG is not indicated or practical for the routine clinical evaluation of insomnia (Reite et al. 1995). Still, it is most useful to validate a subjective sleep complaint as in the case of psychophysiological insomnia and to rule out the presence of other sleep disorders that might contribute to the insomnia complaint (e.g., periodic leg movement). PSG is becoming a standard practice in insomnia research and is essential in mechanism/evaluation studies as well as in treatment efficacy studies (Buysse et al. 2006). Insomnia protocols are typically conducted on two or three consecutive nights of PSG recordings for pre and post-treatment comparisons. Another important limitation of PSG is that it does not provide a valid sample of a patient's typical sleep at home. Indeed, the sleep of otherwise good sleepers is more disrupted during their first night of recording in the sleep laboratory (i.e., first night effect: worst sleep efficiency on the first night compared to subsequent ones), whereas the sleep of insomniacs may actually improve in the laboratory (i.e., reverse first-night-effect: better sleep efficiency on the first night than on subsequent ones) (Pennestri et al. 2003). Still, PSG is particularly helpful when subtypes of insomnia are under study and especially in the case of paradoxical insomnia. Our own research group has suggested that this subtype is best identified after large subjective-objective discrepancies have been observed in at least two out of four consecutive recording nights in the laboratory (Bastien et al. 2008a). In any case, modest PSG differences are usually observed between insomniacs and good sleepers. "Objective" measures of insomniacs reveal they tend to spend more time in stage 1, less time in stages 3–4, and display more frequent stage shifts through the night (Coates et al. 1982; Reynolds et al. 1984; Hauri and Fisher 1986).

Differences may also be apparent in phasic EEG events during sleep such as K-complexes and sleep spindles. K-complexes are single occurrences of high amplitude low frequency waveforms that occur spontaneously in stage 2 and slow wave sleep and can also be evoked by external stimuli (Colrain 2005; Oswald et al. 1960). Sleep spindles are half second bursts of synchronized 12–15 cycles per second activity (De Gennaro and Ferrara 2003).

Both K-complexes and sleep spindles are thought to reflect sleep protective mechanisms (De Gennaro and Ferrara 2003; Jankel and Niedermeyer 1985; Hess 1965; Walter 1953) and both are used to mark the onset of stage 2 sleep (Rechtschaffen and Kales 1968). One insomnia hypothesis might be that sleep protective mechanisms are deficient or inefficient in this disorder. To test this

hypothesis, some researchers have systematically studied the behaviors of these phasic events in insomnia sufferers. While Wauquier et al. (1995) observed a lower occurrence of spontaneous K-complexes in sleep disordered individuals compared to controls, our group has shown that the occurrence and density of both spontaneous K-complexes and sleep spindles were similar in psychophysiological insomniacs and good sleepers (Bastien et al. 2009a, b). Altogether, results from phasic event studies generally suggest that sleep protection mechanisms appear intact in psychophysiological insomnia.

In line with the perception of sleep which is often erroneous in insomnia, Coates et al. (1983) reported that a greater percentage of insomniacs claimed to be awake after the appearance of the 1st spindle while a greater percentage of good sleepers reported being drowsy at that time. On the other hand, the best concordance between subjective reports and objective measures of sleep onset latency is obtained when sleep onset is defined as the first epoch of stage 2 and followed by 15 min of uninterrupted sleep (Hauri and Olmstead 1983). Some studies have compared arousal thresholds in insomniacs and controls, usually by presenting tones of increasing intensity or frequency (Mendelson et al. 1986; Haynes et al. 1985). Results suggest that arousal thresholds are similar in insomniacs and good sleepers and thus insomnia cannot be explained by differences in arousal threshold.

Finer Measures of the EEG

Power Spectral Analysis (PSA)

EEG brain waves have different amplitudes (measured in μV) and frequencies (measured in Hz). Usually, the slower is a brainwave, the higher its amplitude. PSA is performed by computing Fast Fourier Transforms (FFT) revealing the frequency and amplitude of the sine waves constituents of an analyzed portion of the EEG. Results are combined by averaging the data in different frequency bands usually defined as: slow waves (0–1 Hz), delta (1–4 Hz), theta (4–7 Hz), alpha (7–11 Hz), sigma (11–14 Hz), beta1 (14–20 Hz), beta2 (20–35 Hz) and gamma (35–60 Hz). The results of the FFT are presented as EEG power (μV^2), which corresponds to the square of the amplitude in each of the specified frequency bands (see Fig. 2 for a Spectral Graph example). Data may be presented as such (absolute power) or as the proportion of the power in a frequency band relative to the sum of the power in all frequency bands (relative power). Usually, elevated powers in fast frequency bands (e.g. beta bands) reflect increased activity (increased cortical activation) whereas an increase in a slower band (e.g. slow waves and delta) presupposes less activity (decreased cortical activation).

The hypothesis of a conditioned aroused state in insomnia has thus been the impetus for quantitative study using PSA at the sleep onset period, during the night as well as during wakefulness. Freedman (1986) first compared sleep-onset insomniacs to good sleepers from lights out to the end of the first sleep cycle. Insomniacs had significantly more beta activity and less alpha activity than normal sleepers. Merica and Gaillard (1992) and Merica et al. (1998) also observed more beta and less delta activity at sleep onset and as sleep is initiated in insomniacs compared to controls. In another study, Lamarche and Ogilvie (1997) observed higher relative beta activity during wakefulness in psychophysiological insomniacs compared to controls. During sleep, similar observations were also made. Freedman (1986) has also observed more beta activity in sleep-onset insomniacs than controls during stage 1 and REM sleep although between groups differences disappeared during stages 2, 3, or 4. Looking at the first four sleep cycles, Merica et al. (1998) found that insomniacs showed increased beta activity compared to good sleepers in both REM and NREM sleep. In REM sleep, insomniacs also presented lower powers in the delta and theta bands.

When insomniacs are compared with individuals suffering from comorbid insomnia and depression and good sleepers, insomniacs show elevated powers in beta (both beta1 and beta2) as well as in the gamma range (Nofzinger et al. 1999; Perlis et al. 2001) (See Fig. 3). As such, increased in beta activity was observed in insomniacs compared to good sleeper controls. Recently, it was also reported that in addition to an increase in beta power, women displayed more low frequency activity (delta/theta) than men, whether experiencing insomnia or being good sleepers (Buysse et al. 2008). Altogether, these results suggest higher cortical arousal, especially in the beta band

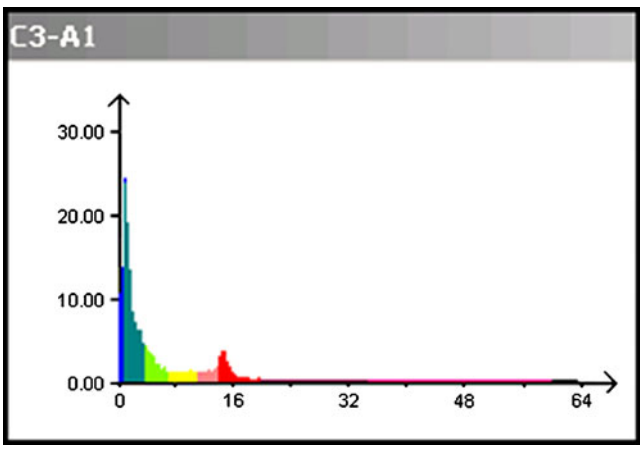

Fig. 2 Spectral graph. The spectral graph represents the result of PSA. EEG has been recorded at C3 (A1 being the reference) and PSA was performed on selected epochs of stage 2 sleep. Frequencies (Hz) are presented on the x-axis and power (μV^2) is found on the y-axis

in insomniacs than in controls, at sleep-onset, during sleep as well as during wake, strongly supporting the neurocognitive model of insomnia, with hyperarousal reflected through increased beta activity.

Regarding the different subtypes of insomnia, a report by Krystal et al. (2002) suggested that paradoxical insomniacs appeared to display greater high frequency activity than either psychophysiological insomnia sufferers or good sleepers. In a preliminary report from our own research team in Quebec (St-Jean and Bastien 2008b), using different sub typing criteria than Krystal et al. (2002), no significant differences in absolute power of the different EEG bands was observed between psychophysiological and paradoxical insomniacs. Recently, while accounting for age and gender, Ouellet et al. (2010) observed that paradoxical insomniacs displayed greater powers in lower frequency bands than those with psychophysiological insomnia. Results from these studies are difficult to reconcile, possibly because criteria for subtypes are not yet well defined, and vary between studies. On the other hand, it is also possible that PSA does not provide the information that could be related to the severity of sleep complaints. In that regard, it is possible that an individuals' perceived sleep severity is only partially explained by his or her EEG activity. As such, when subjective-objective discrepancies are too important (or at the far end of the severity continuum), they may not be reflected through elevated EEG activities. Furthermore, it is also possible that averaging multiple nights together instead of targeting nights during which "bad sleep" is reported, obscures differences between groups.

Using PSA to test the hypothesis that sleep mechanisms might be deficient in insomniacs compared to the ones of good sleepers, our group (Forget et al. 2007) has combined PSA with spontaneous and evoked K-complexes to determine if these events served the same sleep protective role in

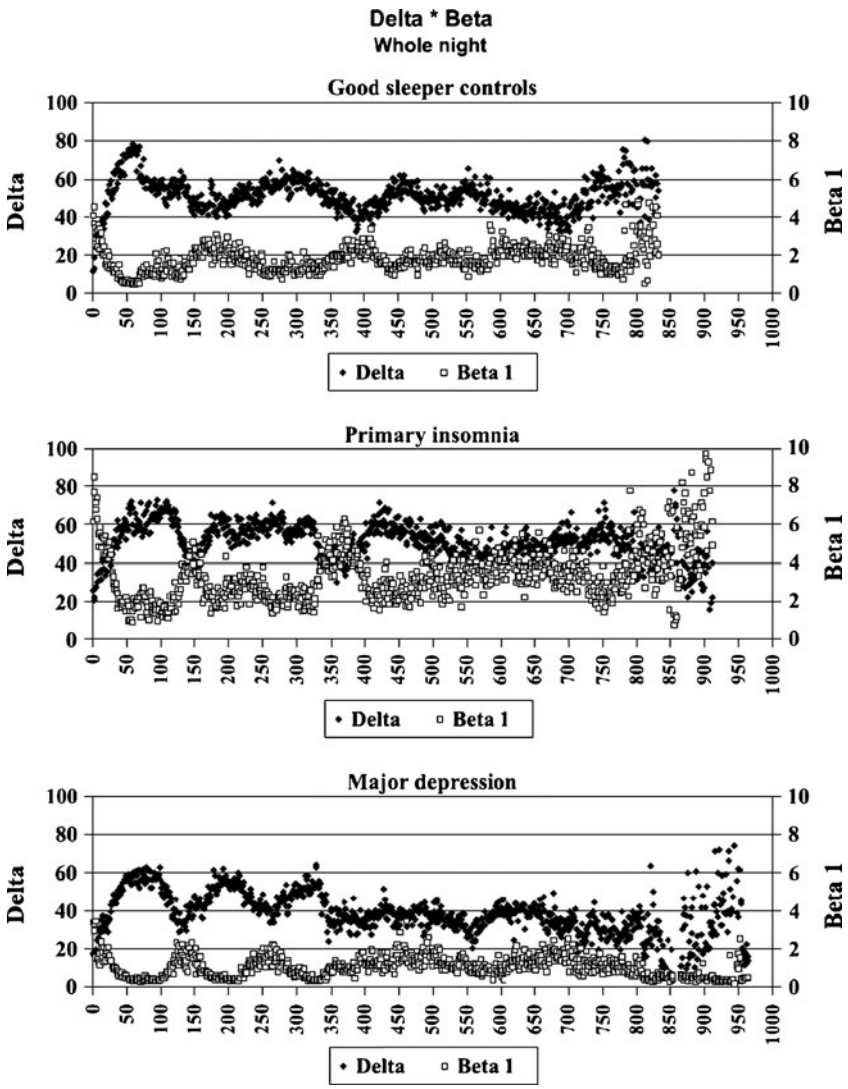

Fig. 3 (from Perlis et al. 2001). Delta and beta relative power plotted as a function of elapsed time (30 s epochs) from sleep onset to lights on. The data from the good sleepers shows the inverse cyclic nature of the relationship between delta and beta activity. More beta activity is seen in the insomnia group than in either the good sleepers of depressed patients

insomniacs and good sleepers. PSA was measured before and after the presence or absence of spontaneous or evoked K-complexes in early and late stages 2 of sleep. Results showed significant similar changes following evoked and spontaneous K-complexes (increased activity in the delta frequency band and decreased activity in theta, sigma, and beta frequency bands) for both groups of sleepers, while there were no such marked changes in EEG activity when K-complexes were not evoked by stimuli. These results suggest that both spontaneous and evoked K-Complexes promote deeper sleep, further supporting a sleep protection role of these events and that this role is unaffected in insomnia.

Cyclic Alternating Pattern (CAP)

Most of the arousal-related phasic events (spontaneous or evoked during NREM sleep) follow a peculiar time organization described as cyclic alternating pattern (CAP) (Terzano et al. 1985). CAP displays a 20–40 s cyclic rhythm and is characterized by periods of cerebral activation (phase A) followed by periods of deactivation (phase B; see Fig. 4 for an example). Phase A allows a hierarchic classification of different subtypes: A1, A2 and A3 (Ferri et al. 2005a, b; Terzano and Parrino 2000). While subtype A1 appears to be linked to the synchronization of the EEG during sleep (Ferri et al. 2005a, b), subtypes A2 and A3 appear to be linked to the EEG desynchronizing processes (Ferri et al. 2005a, b; Terzano and Parrino 2000). When the interval between two consecutive A phases exceeds 60 s, the CAP sequence ends and sleep enters into a non-CAP (NCAP) mode. While CAP sequences correspond to segments of unstable sleep, NCAP sequences are associated with stable sleep (Terzano et al. 2000, 2005).

Previous studies have shown that the A phase (activation phase) of the CAP was longer in insomniacs than in good sleepers while the B phase (deactivation phase) was shorter (Halasz et al. 2004; Parrino et al. 2004). Furthermore, CAP rate (defined as the percentage ratio of total CAP time to total NREM sleep time) was greater in insomniacs than in good sleepers (Halasz et al. 2004). Phase B occupied about 65% of the CAP sequence in good sleepers while only 50% in insomniacs. Higher CAP rates also correlated with poorer subjective sleep quality (Terzano et al. 1995, 2003). Recently, Parrino et al. (2009) compared 20 paradoxical insomniacs and 20 good sleepers on PSG and CAP parameters. Total CAP rate (58.1% vs. 35.5%) was significantly higher in paradoxical insomniacs than in good sleepers. Paradoxical insomniacs also showed significantly higher amounts of CAP rate in stages 1 (62.7% vs. 37.5%) and 2 (53.3% vs. 33.1%), but not in slow wave sleep (SWS) compared to good sleepers. In addition, A2 subtypes were significantly more frequent in paradoxical insomniacs than in controls (31% vs. 24%). The results from these studies tend again to suggest greater arousal (or "hyperactivation") in the EEG of insomniacs than in the EEG of good sleepers.

Event-related Potentials (ERPs)

An external physical stimulus or internal psychological event elicits small amplitude changes in the EEG, therefore providing a means to "probe" the extent of information processing within the nervous system during wake and

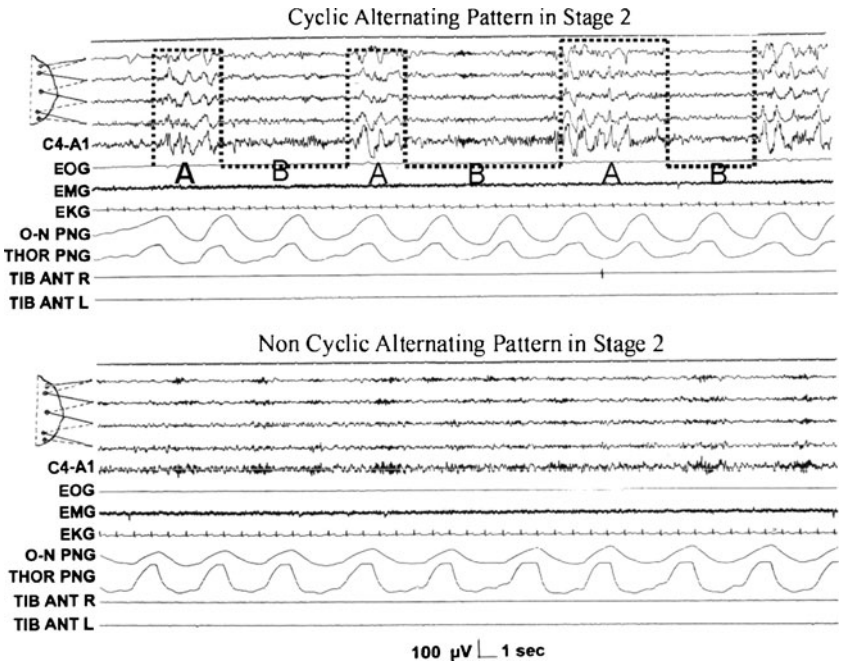

Fig. 4 Cyclic Alternating Pattern (CAP). Reproduced with the permission of M.G. Terzano. The top portion of the figure shows the Cyclic Alternating Pattern in Stage 2 sleep, with the two different phases A (EEG activation) and B (EEG deactivation). Phase A and B composes a cycle and 60 s equals to a sequence. The bottom portion of the figure display a Non Cyclic Alternating Pattern (NCAP) period of sleep, corresponding to sleep stability. The recordings are shown from frontal, central and occipital leads. In addition, the figure displays EOG and EMG, EKG (heart rate), abdominal (O-N PNG) and thoracic (THOR) respiratory efforts as well as both right and left tibialis (respectively TIB ANT R and TIB ANT L)

sleep. Event-related potentials (ERPs) have a high temporal resolution (about one tenth of a millisecond) and are thus a useful tool to provide a precise timely measure of aspects of information processing. ERP components are classified according to their latencies: early components(<80 ms approximately) reflect sensory processing, those around 100 ms are sensitive to arousal and attention, and later components usually reflect higher order central nervous system processing related to cognitive functions such as attention, vigilance, memory and inhibition of information processing in wake and sleep (Colrain and Campbell 2007). The valence and latency of peaks are used to label the different components: "N" refers to a Negative wave and "P" to a Positive wave. Thus, for example, "N100" would refer to a negative wave appearing 100 ms after stimulus onset (note that most ERPs are usually termed as N1, P2, P3 even though their respective latency is 100, 200 and 300 ms).

Although reduced relative to wakefulness, information processing still remains present during sleep. Usually, as an individual falls asleep, attention/vigilance processes decrease (thus N1 amplitude is lower from wake to sleep) and the inhibition of external stimuli becomes important to promote sleep (thus the amplitude of P2 is greater and N350 appears at sleep onset as a sign of an individual falling asleep). Because it is impossible for subjects to respond verbally or behaviorally to a stimulus while they are sleeping, the study of information processing during sleep is limited. According to Colrain and Campbell (2007), ERPs can be very useful in the assessment of daytime consequences following sleep disruption and the determination of the central nervous system function during sleep. As mentioned earlier, EEG studies have suggested that central nervous system hyperarousal is associated with insomnia. ERPs thus offer a means for direct evaluation of cortical activation to an experimental stimulus during wake and sleep. The oddball paradigm (a train of auditory stimuli containing a frequent standard tone and a deviant tone which occurs rarely) is usually used to measure cortical excitability. Participants can be instructed to pay attention to the auditory stimulation (target stimuli generating a "P3") or they can be asked to simply ignore or not to pay attention to the stimulation (recordings of N1 and P2 during wake and N1, P2 and N350 during sleep-onset and sleep).

For ERPs, general hypotheses linked to the neurocognitive model and hyperarousal theory of insomnia might be as follows, since these individuals should show signs of enhanced sensory and information processing during wake and sleep: 1) if sensory impairments are present in insomniacs compared to good sleepers, P50 (reflecting primary auditory cortex activation) amplitude should be lower; 2) if insomniacs show signs of hyperarousal (enhanced information/cognitive processing), they should display a larger N1 and a smaller P2 to standard and deviant stimuli as well as larger P3 to target stimuli relative to good sleepers; 3) if insomniacs have difficulties inhibiting cortical arousal, a smaller N350 will be observed at sleep onset in these individuals relative to good sleepers.

In 1993, Hull conducted a study using an oddball paradigm during wakefulness and sleep onset. Results showed that N350 was smaller in poor sleepers than in normal controls during the initial part of stage 2 sleep. Greater P300 amplitude immediately before sleep onset and shorter response latency in insomniacs relative to good sleepers during wakefulness was also observed in this study, suggesting a hyperarousal state in poor sleepers. That same year, Regestein and his colleagues (1993) reported a significantly larger P1-N1 in insomniacs compared to good sleepers during wakefulness. Loewy and Bootzin (1998) and Loewy et al. (1999) also recorded a larger N1 and a smaller P2 in insomniacs relative to good sleepers during wakefulness. Bastien et al. (2008b) compared primary chronic psychophysiological insomniacs and good sleepers on N1, P2 and N350 components in a multi-assessment protocol. They reported hyperarousal upon awakening in the morning (greater N1 amplitude) in psychophysiological insomniacs compared to good sleepers. In addition, these authors recorded a smaller N350 in insomniacs than in good sleepers at sleep-onset, just as Hull had reported in 1993. Altogether, these studies showed that insomniacs are more vigilant (or "aroused") during wakefulness than good sleepers controls (See Fig. 5). However, studies conducted at sleep-onset also tended to show that inhibition deficits are present in insomniacs. Finally, while comparing different subtypes of insomnia, Bastien (2008) observed that paradoxical insomniacs, compared with psychophysiological insomniacs and good sleepers, presented larger N1 and P2 as well as lower N350 in the evening as well as during sleep-onset. Bastien et al. (2008b) thus suggested that both processes, cortical arousal and inhibition deficits, are underlying neurophysiological mechanisms of chronic insomnia.

Does hyperarousal persists during sleep? First, Yang and Lo (2007) reported that insomniacs show larger N1 and smaller P2 to rare tones as well as smaller N350 to standard tones than controls during the first 5 min of continuous stage 2 sleep. However, Turcotte et al. (2009) observed that during the different stages of sleep, and contrary to what Yang and Lo (2007) had reported, insomniacs and good sleepers did not differ on measures of N1 and P2 during the night. Thus the issue of hyperarousal during the night, as measured with ERPs, requires more investigations as contradictory results are reported to this point.

So far, studies using ERPs have mainly concentrated their efforts at providing empirical support for enhanced

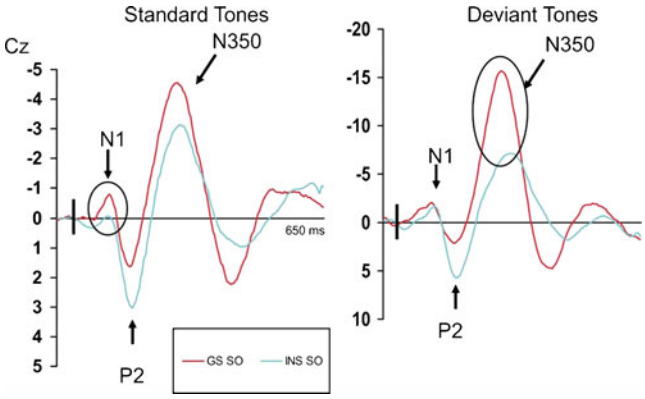

Fig. 5 (from Bastien et al. 2008b). ERPs for good sleepers (GS) and psychophysiological insomnia sufferers (INS) at sleep onset (SO). Between groups significant differences are illustrated with the black circles. N1 to the standard tones and N350 to the deviant tones are smaller for insomniacs than good sleepers

cognitive information processing. An innovative study lead by Cote's group (Milner et al. 2009), however, explored whether sensory information processing was deficient in poor sleepers compared to normal sleepers. On a single night, paired-click stimuli were delivered to groups of sleepers at pre-sleep (wake), REM and stage 2 sleep. P50 amplitude to stimuli provided an index of sensory gating, as the P50 amplitude observed to the second stimulus in each pair is typically "gated" with substantially reduced amplitude relative to that seen to the first stimulus. Lower P50 amplitudes were observed in poor sleepers compared with good sleepers during wake, similar amplitudes in REM while no P50 was present in stage 2. Thus gating was impaired in poor sleepers during wake, was similar in the two groups in REM sleep and absent in stage 2 in both groups. Milner et al. (2009) thus provide very interesting empirical data, however they remain somewhat ambiguous. These authors interpreted the data as supporting the hypothesis that poor sleepers experience enhanced sensory processing (i.e., hyperarousal) since insomniacs appeared to present deficits at "gating" the stimulation. However, since gating was less efficient in insomniacs relative to good sleepers, a failure in inhibitory mechanisms could also explain the results of their study.

Because variability in sleep quality is challenging in insomnia, it is possible that information processing varies according to the quality of the night (preceding or following ERPs recordings). Some studies have thus tried to associate sleep quality in insomnia (subjective, measured with a diary and/or objective, measured with PSG) to daytime measures of ERPs. Devoto and colleagues (2003) compared insomniacs and good sleepers after a subjective "good night" and after a subjective "bad night". They observed that P3 amplitude was lower after a good night in insomniacs compared to good sleepers. On the other hand, after a bad night, P3 amplitude was significantly higher among insomniacs than among good sleepers. In a similar design but this time using actigraphy for measuring sleep, the same group of researchers (Devoto et al. 2005) observed larger P3 in insomniacs on the worst night of sleep compared to good sleepers. Both sets of results thus appeared to support the neurocognitive theory of hyperarousal. Sforza and Haba-Rubio (2006) examined the relationship between evening-morning changes in ERPs amplitudes (N1, P2 or P3) and general PSG measures in insomniacs and controls. ERPs in the two groups were similar in the evening; however, N1 amplitude was smaller in the morning relative to the pre-sleep N1 and was significantly negatively correlated with the amount of stage 1 sleep, the number of stage changes and the number of awakenings during the night in the insomniacs. No such relations were observed for good sleepers. Turcotte and Bastien (2009) investigated the relationship between objective sleep parameters and the amplitudes and latencies of ERPs components in a multi-assessment protocol. These authors found that as the amplitude of N1 and P2 increased before going to sleep among insomniacs, the sleep quality of the following night decreased. In addition, the sleep quality of the previous night also appeared to be linked to the ERPs' amplitudes recorded on the following morning. Turcotte and Bastien (2009) concluded that the existing hyperarousal and inhibition deficits in insomniacs are directly associated with a poorer sleep quality. Considering these results, it is most probable that daily consequences of insomnia such as reported memory and attention deficits also vary with the quality of the night preceding the evaluation. Thus, it would be advisable to document the quality of the preceding night whichever cognitive evaluation is to be taken place in the morning.

Together, these studies suggest the presence of heightened cortical/cognitive arousal levels in insomnia, as was hypothesized at the beginning of this section. This increased arousal appears to be present both while insomniacs are awake as well as during sleep. However, the recordings of some ERPs (N350 and P50) suggest that inhibitory deficits appear also present in insomnia. It is thus possible that both mechanisms are at play and depending on task and demands from a cognitive point of view, results differ. Moreover, since limited data are available under conditions requiring both a motor and cognitive response, that ERPs protocols have not yet specifically targeted inhibition in a cognitive task, and because sleep quality (albeit be subjective or objective) is not always documented, the issue of hyperarousal and/or inhibition deficits in insomnia remains one of debate. Nonetheless, the utility of ERPs as a useful tool to investigate cognitive functions or information processing during wake and/or sleep in insomniacs is undisputable. In this regard, contrary to PSA

and although unlike imaging they do not identify the active brain structures at one moment in time, ERPs provide a direct measure and precise timing of cortical arousal and dynamic neural mechanisms.

Neuroimaging

Neuroimaging is relatively new in insomnia research. Although many methodological endpoints still need to be addressed (e.g. small sample sizes, small window of analysis, sleeping in the machine, etc.), neuroimaging studies have enhanced our understanding of the underlying neurophysiology of this disorder. Detailed information on studied samples, methods and recordings of the work cited on neuroimaging is depicted in Table 1.

Single-photon-emission computed tomography (SPECT) is a method allowing the visualization of cerebral metabolism by analyzing the signal emitted by a short-lived radio-active tracer injected intravenously before scanning. Using SPECT, Smith and collaborators (2002), observed that insomniacs, relative to self-defined good sleepers, showed a decrease in cerebral blood flow in the medial frontal, occipital and parietal cortices, with a profound deactivation in the basal ganglia, suggesting that patients with primary insomnia were hypometabolic rather than hypermetabolic in a 2 min window of perfusion during the first NREM sleep period when compared to good sleepers. These results thus appeared to contradict the hyperarousal theory. It is however possible that insomniacs are more aroused over the totality of NREM sleep. While this study proves the feasibility of a neuroimaging technique in combination with traditional PSG, the results remain difficult to interpret in light of methodological restrictions (small sample size and limited time window for analyses).

Positron emission tomography (PET) is a more accurate measure of whole brain activity than SPECT. It can be used during wakefulness as well as during sleep and involves the injection (usually into blood circulation) of a short-lived radioactive tracer isotope which decays by emitting a positron, chemically incorporated into a metabolically active molecule. Using PET, Nofzinger et al. (2004) showed an increased global cerebral glucose metabolism in insomniacs compared with good sleeper controls during NREM sleep (See Fig. 6). In addition, a smaller decrease in cerebral activity from wakefulness to NREM sleep states in the ascending reticular activating system (ARAS), the hypothalamus, thalamus, insular cortex, the amygdala, the hippocampus, the anterior cingulate and medial prefrontal cortices was observed in insomniacs compared with good sleepers. During wakefulness, insomniacs showed relative hypometabolism in bilateral prefrontal, left hemispheric superior temporal, parietal and occipital cortices, the thalamus, hypothalamus and brainstem reticular formation compared to good sleepers, the sleep of insomniacs being thus associated with increased brain metabolism. This relative hypometabolism in similar brain structures had previously been reported in healthy good sleepers following sleep deprivation (Thomas et al. 2000). These findings might thus suggest that insomniacs are chronically sleep-deprived and their sleep is associated with increased brain metabolism. The 'inability' to fall asleep may thus be expressed by arousal mechanisms failing to be less active.

Recently, Altena et al. (2008a, b) replicated the prefrontal hypoactivation during wakefulness in insomniacs using functional magnetic resonance imaging (fMRI) during a test performance of a category and a letter fluency task. The fMRI measures the haemodynamic response related to neural activity in the brain. Altena and colleagues (2008a, b) observed less activation in insomniacs than in controls in the left medial prefrontal cortex and left inferior frontal gyrus while individuals were performing both tasks.

Szelenberger and Niemcewicz (2001) used low resolution electromagnetic tomography analysis (LORETA) of multi-channel EEG (a non-invasive method that allows the mapping of current density measures according to a standard brain atlas, in order to localize electrical activity in the brain). They found that insomniacs showed less current density in cerebral regions involved in affect and cognitive performance (i.e., orbitofrontal, medial prefrontal and anterior cingulated cortices) relative to normal controls during wake.

In summary, these studies reveal both a hypermetabolism in certain brain regions indicating an increase in arousal or a difficulty in inhibiting arousal and a hypometabolism in specific areas that have been related to sleep deprivation. Moreover, these findings also highlight the presence of interacting neural networks including a general arousal system (ascending reticular formation and hypothalamus), an emotion regulating system (hippocampus, amygdala and anterior cingulate cortex), and a cognitive system (prefrontal cortex) in the neurobiology of insomnia. Neuroimaging studies performed on larger and heterogeneous samples of insomniacs could help classify the different subtypes (psychophysiological or paradoxical) and shed some light on possible shared neurobiological bases of different clinical representations of the disorder (stand-alone syndrome or comorbid with another psychopathology).

Treatment

Pharmacotherapy

Pharmacotherapy, using benzodiazepines (BZDs) and non-benzodiazepine hypnotic agents (like Zolpidem), is the most

Table 1 Neuroimaging studies

Authors	Objective	Participants	Methods	Sleep stages	Results	Interpretation
Studies comparing insomnia sufferers to controls						
Smith et al. 2002	Provide preliminary data on regional cerebral activity in INS vs GS.	−5 INS (W) Mage 37.8 (12.1) years −4 GS (W) Mage 34.5 (11.9)	3 PSG nights Night 1 = adaptation Night 2 = evaluation Night 3 = PSG + SPECT scan	1st NREM sleep cycle	INS showed a pattern of decreased rCBF over all regions. Compared to GS, the largest and significant reductions in INS are localized in the basal ganglia, the medial frontal cortex, the occipital cortex and the parietal cortex.	Contradicts the hyperarousal theory of insomnia. Insomnia might be associated with abnormal CNS activity during NREM sleep.
Nofzinger et al. 2004	Investigate the neurobiological basis of poor sleep and daytime fatigue in insomnia	−7 INS (4W, 3M) Mage 34.2 (8.9) years. −20 GS (13W, 7M) Mage 32.6 (8.4) years.	3 PSG nights Night 1 = adaptation Night 2 = evaluation + PET scan during the morning Night 3 = PSG + PET scan	Wake and NREM sleep.	INS showed increased global cerebral glucose metabolism compared with GS during both waking and NREM sleep, a smaller decrease in relative metabolism from wakefulness to NREM sleep and reduced relative metabolism in the prefrontal cortex while awake.	Insomnia is associated with greater brain metabolism. Daytime fatigue may reflect decreased activity in the prefrontal cortex resulting from inefficient sleep.
Studies implying treatment for insomnia						
Smith et al. 2005	Evaluate whether behaviour therapy might be associated with normalization in brain function.	−4 INS (W) Mage 34.5 (12) years.	SPECT scan during NREM sleep before and after behavior therapy.	NREM sleep	INS showed a significant increase in cerebral blood flow in the basal ganglia after treatment.	In INS, sleep therapy may be associated with a reversal in cerebral deactivation. (See Smith et al. 2002)
Altena et al. 2008a, b	Investigate functional brain activation in INS and modifications after a mutli-modal sleep therapy.	−21 INS (17W, 4M), Mage 61 (6.2) years. 12 GS (9W: 3M) Mage 60 (8.2) years.	fMRI scanning during the performance testing Sleep therapy for 6 weeks		INS showed less activation than controls in certain regions during the performance of both tasks. After treatment, the activation was restored in both tasks.	Insomnia interferes in a reversible way with activation of the prefrontal cortex during daytime performance.

INS Insomnia sufferers; *GS* Good sleepers, *W* Women, *M* Men; *Mage* Mean age; SD in parentheses, *PSG* Polysomnography, *PET* Positron Emission Tomography, *SPECT* Single-photon-emission computed tomography, *fMRI* Functional magnetic resonance imaging, *NREM* non rapid eye movement

common treatment for insomnia (Hohagen et al. 1994; Morin and Wooten 1996; Kupfer and Reynolds 1997). These psychotropic drugs bind with gamma-amino butyric acid (GABA) receptors, thus increasing CNS inhibitory effects. Although short-term use of hypnotic medications (less than 4 weeks) may be useful and indicated for acute insomnia, (NIH 1991), there is still little information on long-term efficacy. On a short-term basis, pharmacotherapy can be helpful at decreasing sleep onset and sleep maintenance difficulties as well as improving sleep continuity. On the other hand, these compounds, especially BZDs, are associated with potential adverse effects (e.g., memory impairments) and altered sleep structure (e.g., reduces stages 3 and 4). In addition, the efficacy of long-term use is questioned and it has been documented that long-term use causes tolerance and physical dependence in addition to a withdrawal syndrome upon cessation of use (Lader 2008; Lader et al. 2009).

Bastien et al. (2003) performed PSA on the EEG of three groups of older adults: medication free or long-term benzodiazepine users insomniacs and good sleepers. Benzodiazepines did not mask the effect of insomnia and less delta, less theta and more beta1 activity were observed in the different stages of sleep. Some increases in power in the delta activity band have also been reported in insomniacs and women subjectively complaining of insomnia with the use of Zolpidem, a short-acting non benzodiazepine hypnotic (Monti et al. 2000; Declerck et al. 1992). However, results were not significantly related to objective and subjective sleep improvements.

Unfortunately, many insomniacs use medications to alleviate their sleep difficulties (Holbrook et al. 2000). Knowing that usage of BZDs produce adverse effects and its long-term use dependence, and because the adverse long-term effects of non-benzodiazepines agents are still not well known, more research is needed in this area. In addition, since the GABAergic system is the most important inhibitory mechanism in the central nervous system (CNS) (Gottesmann 2002), and that it has recently been shown that a global reduction in GABA neurotransmitters is present in insomniacs compared to good sleepers (Winkelmann et al. 2008), one can again question if insomniacs do not suffer from a cortical/cerebral unbalance in inhibition and excitation mechanisms.

Non-pharmacological Treatments

Cognitive-Behavioral Treatment for insomnia (CBT-I) has been recognized as an effective non-pharmacological treatment for insomnia (Morin 2004). In most studies, CBT-I includes *behavioral* components (stimulus control and sleep restriction), *cognitive therapy*, and *sleep hygiene*. Other components may be added to treatment: relaxation (Lichstein 2000), biofeedback (Bootzin and Rider 1997), bright light exposure (Lack and Wright 2007), body temperature manipulations (Van Someren 2006) and physical activity (Martin et al. 2007). Altogether, non-pharmacological treatments for insomnia have shown short and long-term sustainable gains such as decreased sleep onset latency and wake after sleep-onset, increased total sleep time and sleep efficiency.

The *stimulus control* instructions (Bootzin et al. 1991) are aimed at re associating the bed, bedroom, and bedtime stimuli with sleep rather than with the frustration and anxiety associated with sleeplessness. The *sleep restriction* procedure (Spielman et al. 1987) consists of limiting the time spent in bed to the actual time spent sleeping. The rationale is that individuals with insomnia often spend excessive amounts of time in bed in a misguided attempt to get more sleep. Participants are instructed to determine

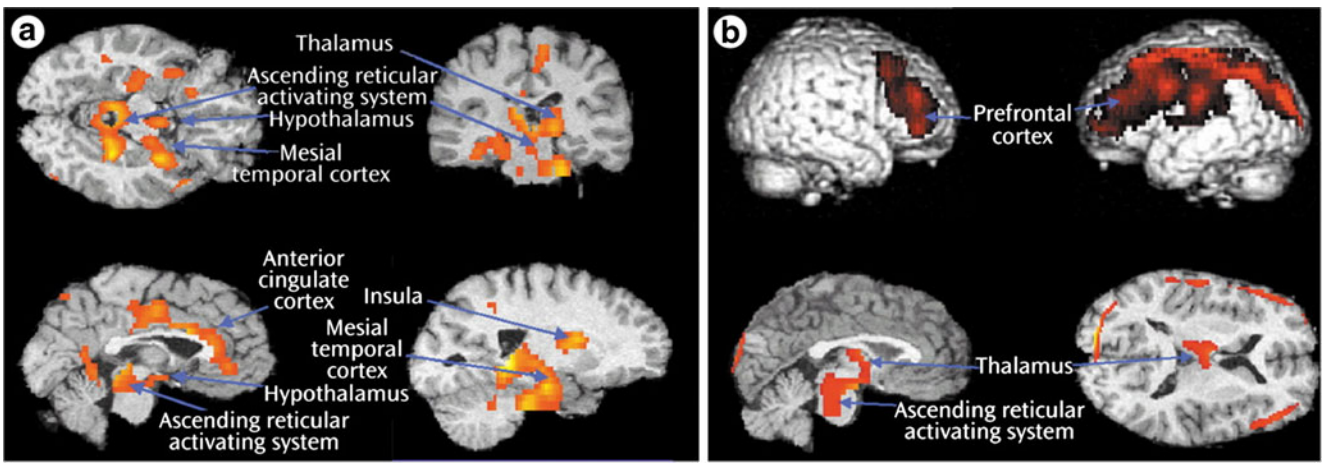

Fig. 6 (from Nofzinger et al. 2004). Brain structures that did not show decreased metabolic rate from waking to sleep states in patients with insomnia (**a**) and brain structures where relative metabolism while awake was higher in healthy subjects than in patients with insomnia (**b**) [a] Differences in all regions shown reached statistical significance at the $p<0.05$, corrected, level

their allowable time in bed according to their total subjective sleep time. *Cognitive therapy* of insomnia consists of identifying, challenging, and altering a set of dysfunctional beliefs and attitudes about sleep (Morin 1993). The objective of cognitive therapy is to break the vicious circle of insomnia, dysfunctional thoughts, and emotional distress that lead to further sleep disturbance. *Sleep-hygiene education* consists of teaching individuals about the impact of certain lifestyle habits (e.g., diet, drug use, and exercise) and the influence of some environmental factors (e.g., light, noise, and temperature) on sleep (Hauri 1991).

Non-pharmacological treatments for insomnia appear to have a positive impact on EEG frequency. For example, Jacobs et al. (1993), using a multifactor behavioral intervention for insomnia, observed a significant decrease in beta activity in insomniacs at post-treatment compared to pre-treatment. The intervention thus appeared to have reduced pre-sleep CNS arousal. Later, with CBT-I, Cervena et al. (2004) observed EEG changes at post-treatment. Some of these changes were in NREM sleep, during which slow wave activity (SWA) powers increased and beta decreased. These results led the authors to suggest that CBT-I might decrease CNS hyperarousal during sleep and reinforce the cortical synchronization and sleep pressure to maintain sleep longer.

Smith et al. (2005) examined the effects of behavior therapy on cerebral blood flow (SPECT) during NREM sleep. When comparing SPECT measures of insomniacs post- to pre-treatment, a significant increase in cerebral blood flow occurred in the basal ganglia. Using fMRI, Altena and colleagues (2008a, b) observed that after CBT-I the activation of the different brain regions was restored in insomniacs. Therefore, it was suggested that insomnia interferes in a reversible way with activation of the prefrontal cortex during daytime performance. Recently, Van der Werf and colleagues (2010) used transcranial magnetic stimulation ("TMS") to compare the degree of intracortical excitability in insomniacs and good sleepers. These authors delivered short-lived pulses of a strong magnetic field over the scalp of 16 insomniacs who were assigned either to CBT-I (plus bright light exposure, body temperature manipulations, and structured physical activity; for details see Altena et al. 2008a, b) or a waitlist control group. Pre and post-treatment results showed that even if subjective sleep latency decreased and sleep efficiency increased, an increased absolute excitability remained after treatment in insomniacs. The authors suggested that this increased intracortical excitability might be a sustainable trait in insomniacs.

It thus appears that non pharmacological treatment of insomnia can decrease 'hyperarousal' as observed with findings measuring the combination of PSA or neuroimaging with subjective sleep measures (pre- and post-treatment comparisons). This combination might afterward be helpful at disentangling the different subtypes of insomnia. Furthermore, measuring brain activity levels through EEG or neuroimaging after treatment targeting behavior or both behavior and cognitive processes (CBT-I) not only reflect therapeutic gains but validate the usefulness and genuine benefits of these treatments. In addition, on a more theoretical note, the comparison of pre and post EEG measures enhances our understanding of other active neurophysiological processes in insomnia, and one can question if CBT-I for example, unlike long-term use of BZDs, does not re-establish (at least partly) arousal levels in insomniacs.

Conclusion

Whether true insomnia is purely subjective in nature or requires presentation of objectively measured sleep difficulties is a matter of genuine debate. Insomnia, by definition, is at least primarily a subjective disorder, as it is the subjective report of the individual that will lead to the diagnosis of insomnia per se. Diagnostic criteria from the American Psychiatric Association (APA) are currently being updated and will most likely change not only our research approach to insomnia but also the whole language of it (for more information on the next set of criteria, readers are invited to visit the APA web page at http://www.dsm5.org/Pages/Default.aspx). For example, the proposed new criteria now specify that to be chronic, sleep difficulties must now last of at least 3 months.

Protocols that incorporate both subjective and objective ratings of sleep quality and cognitive processing are gaining in importance and might be more informative than any single measure used alone, albeit be PSG or more refined EEG measures. For example, by combining PSG and subjective sleep ratings with fMRI or ERPs, we can not only more thoroughly explore subjective and objective discrepancies, we can also provide invaluable information on the neurophysiological bases of the disorder. Although it appears that "hyperarousal" as has been put forward in the neurocognitive model of insomnia can be measured through EEG (e.g. PSA), the interplay between arousal and de-arousal (i.e., inhibitory) mechanisms cannot be ignored any longer. For example, ERPs studies, both measuring sensory and information processing, have shown that gating deficits and an inability to initiate normal sleep processes are indeed present in individuals with insomnia compared to good sleepers. Individuals with insomnia might thus be as afflicted with inadequate "dis-inhibition" mechanisms (expressed in an inability to disengage) in cognitive sensory and emotional processes as these individuals are inappro-

priately aroused by these same processes. Thus on a strictly theoretical aspect, our understanding of "arousal" and "de-arousal" processes at play in insomnia is still limited, but recent findings in neuroimaging, combined or not with non-pharmacological treatment, are promising and may lead to uncovering other aspects of this multidimensional disorder.

In everyday life, and general clinical practice, objective reports (from PSG to neuroimaging) are not available, nor practical. However, one must never forget that there are daily consequences to insomnia and increasingly, insomnia is recognized as a 24 h problem, even with a waxing and waning intensity/severity in sleep difficulties during defined periods of time. As such, not only are sleep difficulties important to consider, the consequences linked to these sleep difficulties must be thoroughly explored and documented. The current review has focused on the state of research on neurophysiological and neuropsychological measures while suggesting that combining measures might be the best avenue offering a more genuine picture of insomnia. In addition, promoting and increasing the use of treatments known to be well effective for insomnia, such as CBT-I, will alleviate greatly the personal burden of this disorder for individuals with insomnia while also decreasing the economic cost for our society.

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