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# Melatonin, Sleep and Insomnia

Endocrinology Research and Clinical Developments

Yolanda E. Soriento  
Editor

NOVA

# Melatonin, Sleep and Insomnia

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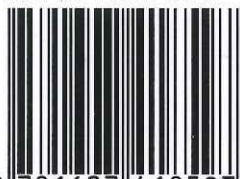
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### Chapter III

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## Non-Pharmacological Alternatives for the Treatment of Insomnia – Instrumental EEG Conditioning, a New Alternative?

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### 1. Abstract

There is already profound knowledge about the evidence that cognitive behavioral therapy (CBT) is effective for the treatment of insomnia (Benca, 2005; Morin et al., 1999; Morin, 2004; Morin et al., 2006). However, the characterization of non-pharmacological treatment effects like CBT on specific sleep parameters (e.g., sleep spindles, sleep architecture, electroencephalographic (EEG) power densities during sleep after CBT) are scarce (Cervena et al., 2004). In our approach we investigated if instrumental conditioning of 12-15Hz EEG oscillations would enhance sleep quality as well as declarative memory performance in healthy subjects. Additionally preliminary data indicating instrumental conditioning of 12-15Hz EEG oscillations as a promising treatment of insomnia will be presented. EEG recordings over the sensorimotor cortex show a very distinctive oscillatory pattern in a frequency range between 12-15Hz termed sensorimotor rhythm (SMR). SMR appears to be dominant during quiet but alert wakefulness, desynchronizes by the execution of movements and synchronizes by the inhibition of motor behavior. This frequency range is also known to be high during light

non-rapid eye movement (NREM) sleep, and represents the sleep spindle peak frequency. In the early 70ies Sterman, Howe, and MacDonald (1970) could demonstrate in cats that instrumental conditioning of SMR during wakefulness can influence subsequent sleep. Hauri (1981) was then the first to apply effectively a combination of biofeedback and neurofeedback to humans suffering from psychophysiological insomnia. Results revealed that the patients benefited from the instrumental conditioning protocols. As research surprisingly stopped at that point, we intended to clarify the effects of instrumental SMR conditioning (ISC) on sleep quality as well as on declarative memory performance with today's technologies and by using a well controlled design which included a control group receiving the same amount of attention and training. Our results confirmed that within 10 sessions of ISC it is possible to increase 12-15Hz activity significantly. Interestingly, the increased SMR activity (i) was also expressed during subsequent sleep by eliciting positive changes in various sleep parameters like sleep spindle number or sleep onset latency and (ii) was associated with the enhancement of declarative learning. In addition to these fascinating results, preliminary data from our laboratory point to the possibility that people suffering from primary insomnia could likewise benefit from this conditioning protocol as indicated by improved measures of subjective and objective sleep quality.

## 2. Introduction

Insomnia is characterized by difficulty in initiating sleep, maintaining sleep, and/or nonrestorative sleep that causes clinically significant distress or impairment in social, occupational or other important areas of functioning (Littner et al., 2003). From a psychological perspective insomnia patients typically complain of being unable to stop their reverberating thoughts and "rest their mind" which prevents them from sleeping. Insomnia is associated with decreased quality of life, absenteeism, increased work and car accidents, as well as increased general health care utilization. Insomnia may arise directly from sleep/wake regulatory dysfunction or indirectly from comorbid behavioral, psychiatric, neurological or medical conditions. Finding the underlying cause of insomnia is crucial for curing an individual's symptom. In summary, insomnia is a prevalent and clinically important problem. In fact it is the most commonly reported sleep problem in industrialized nations worldwide (Sateia, Doghramji, Hauri, & Morin, 2000). Epidemiological research shows that the prevalence of insomnia lies somewhere between 10 and 35% in the general adult population (Angst, Vollrath, Koch, & Doblelmikola, 1989; Benca, 2005; Gallup-Organization, 1995; Johnson, Roth, Schultz, & Breslau, 2006; Morin, LeBlanc, Daley, Gregoire, & Merette, 2006; Ohayon, 2002). Unfortunately, the recognition of the problem of insomnia is widely underestimated and often remains unrecognized and untreated. According to a 1995 survey (Gallup-Organization, 1995) almost 70% of patients with chronic insomnia never discussed their sleep problem with their physicians. Psychiatric conditions (above all anxiety and depressive disorders) are highly prevalent among insomnia sufferers suggesting that such conditions may play an important role in the etiology and perpetuation of insomnia symptoms. In addition to the high rates of past or present psychopathology insomnia patients also have an increased risk of the development of further psychiatric illnesses (Weissman, Greenwald, Nino-Murcia, & Dement, 1997). However, it is still discussed whether insomnia is rather an early symptom than a cause of psychiatric conditions like depression or anxiety



disorders (Buysse, 2004; Holbrook, Crowther, Lotter, Cheng, & King, 2000; Morawetz, 2003). Yet, it is well documented that insomnia gives rise to emotional distress and thus might itself be involved in the preservation, recurrence or even development of depression and anxiety disorders (Buysse, 2004; Morawetz, 2003). Empirical data demonstrates that insomnia is most often a chronic condition (defined as an inability to consistently sleep well for a period of at least one month). Retrospective studies of severely afflicted insomnia patients revealed that about 80% of the individuals had the problem for more than one year, with about 40% even reporting more than five years duration (Gallup-Organization, 1995). The consequences of chronic insomnia are severe. The most common adverse effects of sleep disturbances include fatigue/lethargy, mood disturbances, cognitive and motor impairments, social discomfort and non-specific physical complaints which often lead to seriously decreased quality of life, psychosocial discomfort, and economic repercussions including decreased work productivity (Gallup-Organization, 1995; Morin, 1993; Stepanski et al., 1989). Research indicates that already moderate levels of fatigue produce performance equivalents often greater than those observed at levels of alcohol intoxication deemed unacceptable when driving, working and/or operating dangerous equipment (Lamond & Dawson, 1999). It is thus not surprising that occupational and vehicular accidents secondary to poor sleep quality are consistently reported. Even more daunting is data suggesting that decreased sleep time (Kripke et al., 2002) and use of sleeping pills are associated with increased mortality (Kripke et al., 1998). According to a recent report by Kripke (2008) new hypnotics may increase cancer risk - especially the risk of skin cancer.

### 3. Diagnosis and Classification of Insomnia

Depending on the chosen classification system insomnia patients are categorized somewhat differently. The "International classification of sleep disorders" (ICSD-2; American Academy of Sleep Medicine, 2005) differentiates several subtypes of primary insomnia (e.g., psychophysiological, idiopathic, paradoxical, sleep state misperception).

The more general classification systems "International classification of diseases-10<sup>th</sup> revision" (ICD-10; World Health Organization, 2005) and "Diagnostic and statistical manual of mental disorders-text revision, 4<sup>th</sup> edition" (DSM-IV-TR; American Psychiatric Association, 2000) classify "nonorganic insomnia" (F51.0) and "primary insomnia" (307.42), respectively.

Since 2005 there are refined research diagnostic criteria for insomnia available which were developed by an American Academy of Sleep Medicine Work Group (Edinger et al., 2004) regarded as a starting point for improving insomnia research. As they provide the most homogeneous patient population, and satisfy traditional and cultural variations for the concept of a "primary insomnia" it is recommended to identify study participants (as well as normal sleepers) by those criteria. *Table 1* exemplarily lists research diagnostic criteria for insomnia disorder and primary insomnia, respectively. Additionally Edinger et al. (2004) provide research diagnostic criteria for the following Insomnia subtypes: insomnia due to a mental disorder, psychophysiological insomnia, paradoxical insomnia, idiopathic insomnia, insomnia related to periodic limb movement disorder, insomnia related to sleep apnea, insomnia due to

medical condition, insomnia due to drug or substance. Furthermore, they offer universal criteria to identify normal sleepers for insomnia research.

**Table 1. Research Diagnostic Criteria (modified from Edinger et al., 2004).**

Research Diagnostic Criteria for Insomnia Disorder	Research Diagnostic Criteria for Primary Insomnia
<p>A. The individual reports one or more of the following sleep related complaints:</p> <ol style="list-style-type: none"> <li>1. difficulty initiating sleep,</li> <li>2. difficulty maintaining sleep,</li> <li>3. waking up too early, or</li> <li>4. sleep that is chronically nonrestorative or poor in quality.</li> </ol> <p>B. The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.</p> <p>C. At least one of the following forms of daytime impairment related to the nighttime sleep difficulty is reported by the individual:</p> <ol style="list-style-type: none"> <li>1. fatigue/malaise;</li> <li>2. attention, concentration, or memory impairment;</li> <li>3. social/vocational dysfunction or poor school performance;</li> <li>4. mood disturbance/irritability;</li> <li>5. daytime sleepiness;</li> <li>6. motivation/energy/initiative reduction;</li> <li>7. proneness for errors/accidents at work or while driving;</li> <li>8. tension headaches, and/or Gastrointestinal symptoms in response to sleep loss; and</li> <li>9. concerns or worries about sleep.</li> </ol>	<p>A. The individual meets the criteria for insomnia disorder.</p> <p>B. The insomnia noted in A has been present for at least one month.</p> <p>C. One of the following two conditions applies:</p> <ol style="list-style-type: none"> <li>1. There is no current or past mental or psychiatric disorder.</li> <li>2. There is a current or past mental or psychiatric disorder, but the temporal course of the insomnia shows some independence from the temporal course of the mental or psychiatric condition.</li> </ol> <p>D. One of the following two conditions applies:</p> <ol style="list-style-type: none"> <li>1. There is no current or past sleep-disruptive medical condition.</li> <li>2. There is a current or past sleep-disruptive medical condition, but the temporal course of the insomnia shows some independence from the temporal course of the medical condition.</li> </ol> <p>E. The insomnia cannot be attributed exclusively to another primary sleep disorder (e.g., sleep apnoea, narcolepsy, or parasomnia) or to an unusual sleep/wake schedule or circadian rhythm disorder.</p> <p>F. The insomnia cannot be attributed to a pattern of substance abuse or to use or withdrawal of psychoactive medications.</p>



## 4. Pathophysiology of Primary Insomnia

Polysomnographic (PSG) sleep recordings of patients with insomnia show abnormalities such as prolonged sleep latency or frequent awakenings, more stage 1 and less slow wave sleep (e.g., Merica, Blois, & Gaillard, 1998; Reite, Buysse, Reynolds, & Mendelson, 1995). Krystal et al. (2001) found diminished delta and greater alpha, sigma, and beta EEG spectral power in NREM sleep, which may be an objective physiologic correlate of subjective sleep complaints. Furthermore, Parrino et al. (2004) investigated the role of sleep microstructures for insomnia and reported a more unstable sleep represented by a higher rate of cyclic alternating patterns (CAP). These activation patterns appear in NREM sleep and tend to recur in repetitive clusters with a periodicity of 20–40 s. CAPs are markers of arousal instability, composed of a phase A (activation pattern) and a phase B (interval between two consecutive A phases). CAP is the EEG translation of unstable sleep and accompanies the dynamic events of the sleep process (e.g., falling asleep, stage shifts, intrasleep awakenings).

Based on rich experimental evidence from Perlis and colleagues (Perlis, Giles, Mendelson, Bootzin, & Wyatt, 1997; Perlis, Mercia, Smith, & Giles, 2001; Perlis, Kehr, Smith, Andrews, Orff, & Giles, 2001; Perlis, Smith, Andrews, Orff, & Giles, 2001) fast brain oscillations including beta and gamma activity are elevated at sleep onset and during shallow NREM sleep stages in insomnia patients. The authors interpreted these results in terms of increased cognitive arousal at sleep onset and relate the uncommon high frequency activity to the common misperception of insomnia patients of not being subjectively asleep while objective EEG parameters indicate otherwise. The “Neurocognitive Model of Insomnia” (Perlis et al., 1997) proposes that the increase in central nervous system (CNS) tone results in increased and persistent sensory and cognitive processing where under normal circumstances (like sleep) such processes would be vastly attenuated or inhibited. According to the model the increased sensory processing and perception thus accounts for difficulties in sleep initiation and sleep maintenance. Our proposed ISC intervention builds upon these findings. Specifically, we assume that high frequency beta and gamma activity – usually elevated in insomnia patients – will be strongly diminished at sleep onset and during (early) NREM sleep after successful ISC (Hoedlmoser et al., 2008). The introduction of the neurocognitive model with its focus on cortical or CNS arousal, has renewed the interest in the neurophysiological characteristics of insomnia and as such, the use of a method like ISC directly targeting the altered brain activity has also been put forward by others (cf. Cortoos, Verstraeten, & Cluydts, 2006 for a current review) as a promising treatment modality deserving attention.

## 5. Treatment

According to the National Institutes of Health (NIH) “state-of-the science statement on chronic insomnia in adults” (2005) there is still a paucity of large randomized trials for any of the widely used insomnia treatments that include pharmacotherapy, CBT, over the counter products (OTCs), and herbal remedies. The NIH states that the most common treatments for chronic insomnia are OTCs, alcohol, and prescription of medications although CBT has been proven to be as effective as sedative-hypnotic pharmacotherapy. Furthermore, there is no

evidence that OTCs, melatonin, or herbal remedies are more effective than a placebo. According to the NIH there is convincing evidence that the beneficial effects of CBT, in contrast to many of those produced by medications, last well beyond the termination of treatment. However, because few health professionals are experts in the use of psychotherapeutic interventions like CBT, it is still not a very widespread treatment. This is even more true for ISC which is methodologically complex and which has not been rigorously tested for efficacy in insomnia disorders.

## 5.1 Pharmacological Treatment

A variety of drugs are available to treat insomnia. The following classes of drugs and individual agents are most commonly used: benzodiazepines and nonbenzodiazepines acting at benzodiazepine receptors, sedating antidepressants, antihistamines and antipsychotics (Walsh, Roehrs, & Roth, 2005). There are two pharmacological classes of hypnotics being approved by the United States Food and Drug Administration (FDA): benzodiazepine-receptor agonists (BRA; including the traditional benzodiazepines like flurazepam, temazepam as well as the non-benzodiazepine receptor agonists like zolpidem, eszopiclone, zaleplon) and melatonin-receptor agonists (e.g., ramelteon). BRA are occupying benzodiazepine receptors on the gamma-aminobutyric acid (GABA), type A, receptor complex, resulting in the opening of chloride ion channels and facilitation of GABA inhibition. All BRA hypnotics reduce sleep latency, most of them increase total sleep time, although decreasing the duration of SWS (Walsh, Roehrs, & Roth, 2005). However, even highly effective at reducing sleep latency, BRA are associated with varying degrees of residual daytime sedation, abuse liability, and toxicity (Griffiths & Johnson, 2005). Ramelteon is the first FDA-approved melatonin receptor (MT1, MT2) agonist. In patients with chronic insomnia, ramelteon reduces latency to persistent sleep and increases total sleep time.

Although prescription of hypnotics is still the most widely used treatment for insomnia, it is sometimes inadvisable or contradicted. Some patients for example simply do not want to use hypnotics for various reasons (Morin, Gaulier, Barry, & Kowatch, 1992). For others hypnotic drugs do not alleviate their insomnia at all or gradually lose their efficacy after some initial relief. Furthermore, hypnotic medication may be contraindicated by the use of other medications, existing medical conditions, a patient's high risk to substance abuse or addiction and age (above all pediatric or geriatric patients). Adverse events that are associated with sedative use, such as ataxia, falls, or memory impairment are known to be particularly problematic for older people. However, there are additional variables (e.g., gender) that have to be considered when prescribing hypnotics (Toner et al., 1999).

According to the NIH sedative-hypnotics have only been proven to be effective in the short-term management of insomnia (studies usually averaging 7 days) with adverse effects of these medications including daytime sleepiness, dizziness, cognitive impairment, motor incoordination, dependence, and rebound insomnia. However, it has to be mentioned that there are now three hypnotics approved by the FDA for indefinite use (eszopiclone, ramelteon, and zolpidem CR). Yet, empirical evidence suggests that daytime functioning of



the suffering patients is often unchanged. That is, medication might sometimes only alter the perception of sleep (Perlis et al., 1997) but does not normalize sleep architecture. Therefore we believe that it is highly needed to assess new non-pharmacological alternatives directly aiming to produce more “sleep-like” EEG patterns (e.g., by ISC treatment) and evaluate their effects on daytime variables such as subjective quality of life, attention and memory performance. For review and further discussion on the topic please refer to Perlis and colleagues (2003).

## 5.2 Non-Pharmacological Treatment of Insomnia

Reports from patients with insomnia suggest that the disorder often starts as a stress-related phenomenon (Hauri & Fisher, 1986) with the individual emotional and behavioral response to the condition playing an important role in the final outcome of the situation. We believe that these maladaptive cognitive, behavioral and emotional responses - precipitating and perpetuating insomnia - may be well dealt with non-pharmacological treatments (i.e., CBT and ISC). Indeed, there is already promising evidence that non-pharmacological methods besides hypnotics can be (i) efficient in treating insomnia symptoms (Morin et al., 2006; Morin, Colecchi, Stone, Sood, & Brink, 1999; Perlis et al., 2003) i.e., improving objective sleep measures such as sleep onset latency, wake after sleep onset, or total sleep time and can also (ii) lead to *subjective* improvement of patient complaints, with higher measurable quality of life after treatment.

## 5.3 Cognitive Behavioral Therapy (CBT)

There is growing evidence that Cognitive Behavioral Therapy for Insomnia (CBT-I) is as effective as sedative hypnotics during acute treatment (4-8 weeks) and more effective even considering the long term efficacy. According to Morin (1999) between 70-80% of insomnia patients benefit from treatment, 50% achieve clinically meaningful outcomes and about one third become good sleepers. Until now there is little knowledge about effects of CBT-I on objective data like sleep architecture and sleep EEG power densities. Cervena et al. (2004) could show that after 8-weeks of CBT-I both subjective and objective sleep quality was improved: stages 2, REM sleep and SWS durations were significantly increased; slow wave activity (SWA) was increased and SWA decay shortened, beta and sigma activity during NREM sleep were reduced. Thereby they provided the first evidence that CBT-I may have a positive effect on CNS hyperarousal by decreasing high EEG frequencies and enhance sleep pressure and improve homeostatic sleep regulation by increasing SWA during NREM sleep.

There are 3 main components of cognitive-behavioral management for insomnia complaints: behavioral, cognitive and educational modules (Morin, 2004). Interventions like “Sleep Hygiene Education”, “Relaxation Training”, “Stimulus Control”, “Sleep Restriction” and “Cognitive Therapy” can be administered effectively in a group or individual therapy setting. When applied correctly CBT-I has the potential to alleviate insomnia and to help

patients understanding and eliminating probable causes for their condition. *Table 2* gives an overview about current cognitive-behavioral treatment practices for primary insomnia.

**Table 2. Cognitive-Behavioral Interventions for Insomnia (CBT-I).**

CBT-I INTERVENTION	DESCRIPTION
Sleep Hygiene Education	Education about sleep practices, habits and environmental factors that may affect sleep
Relaxation Training	Inhibition of autonomic activity and physiological arousal; facilitation of mental de-arousal
Stimulus Control	Sleep stimuli (e.g., bedroom, bed) have to become re-associated with sleep; temporal adjustment to a consistent sleep pattern
Sleep Restriction	Reduction of time in bed to approximate time spent in bed to the length of actual sleep time
Cognitive Therapy	A psychotherapeutic method to identify and change dysfunctional cognitions about sleep and insomnia

Sleep hygiene education and relaxation training are often used as starting point in CBT-I. Sleep hygiene education refers to general guidelines about health practices and environmental factors that may affect sleep. The main external factors known to have an effect on sleep are: caffeine (“Avoid caffeine and all stimulants after dinner”), nicotine (“Avoid smoking near bedtime and upon night wakings”), alcohol (“Do not drink alcohol in the late evening”), exercise (“Do not exercise too close to bedtime; regular exercise in the late afternoon or early evening may deepen sleep”) as well as noise, light and room temperature (“Minimize noise light, and excessive temperatures”). Relaxation training is the most commonly used non-pharmacological therapy for insomnia. Thereby “standard progressive muscle relaxation” has been the most widely investigated relaxation technique for insomnia. Relaxation techniques require disciplined, daily training and practice. Relaxation-based treatments may inhibit two types of arousal that interfere with sleep: autonomic and cognitive. According to Morin et al. (1999, 2006) progressive muscle relaxation meets the American Psychological Association (APA) criteria for empirically-supported psychological treatments for insomnia, whereas there is no evidence that sleep hygiene education has a detrimental effect on outcome. However, sleep hygiene education is a necessary treatment component and should be incorporated into the overall intervention.

Another step within CBT-I is “Sleep Scheduling” which comprises the interventions stimulus control and sleep restriction. According to Bootzin (1991) insomnia is the product of maladaptive sleep habits. Typical sleep stimuli do not cause drowsiness and sleep, but instead are associated with wakefulness. Morin (2004) recommends 5 simple instructions that can help patients to re-associate sleep stimuli with the proper behavior: i) Go to bed only when sleepy, ii) Use the bed or bedroom only for sleeping (sexual activity is the only exception to this rule), iii) Get out of bed when unable to sleep after 15 minutes spent in bed, iv) Arise at the same time every morning, and v) avoid daytime naps. On the other hand sleep restriction can be used parallel, to compress sleep toward greater continuity, reduced wakefulness in bed



and increased sleep efficiency. This intervention was induced by Spielmann (1987) who encouraged his patients to limit the amount of time spent in bed to the amount of time spent sleeping. Thereby a mild state of sleep deprivation is induced and leads to a faster sleep onset as well as greater sleep continuity and quality. Both treatments stimulus control and sleep restriction meet the APA criteria for empirically-supported psychological treatments for insomnia (Morin et al., 2006).

Finally CBT-I seeks to identify and to change dysfunctional cognitions (faulty or distorted beliefs, expectations, appraisals or attributions) in insomnia. Cognitive therapy targets these cognitions and attempts to alter them. According to Morin (2004) these cognitions are the dangerous insomnia-bolstering concomitant of the maladaptive behaviors that perpetuate insomnia. Patients have to learn to re-evaluate the accuracy of their thinking and to re-interpret events and situations they experience in a more realistic and rational way (Morin & Espie, 2003). The main targets of cognitive therapy are: i) unrealistic expectations about sleep needs and daytime functioning, ii) misconceptions and false attributions about the causes of insomnia, iii) distorted perceptions of its consequences and iv) faulty beliefs about sleep-promoting practices. In general cognitive therapy should guide patients to view insomnia and its consequences from a more realistic and rational perspective. Corresponding to APA criteria (Morin et al., 2006) cognitive therapy meets criteria for empirically-supported psychological treatments. Additionally there is evidence that paradoxical intention – an individual cognitive restructuring technique to alleviate performance anxiety – meets the APA criteria for empirically-supported psychological treatments for insomnia (Morin et al., 1999; 2006).

## 5.4 Biofeedback

Biofeedback is a technique in which people learn how to self-control certain internal bodily processes that normally occur involuntarily, such as heart rate, blood pressure, muscle tension, skin temperature and brain activity. To provide biofeedback special computer hardware is required. Biofeedback instruments are supposed to i) monitor a physiological process of interest, ii) measure what is monitored and finally iii) present what is measured as meaningful information by translating the raw signal e.g., into a tone that varies in pitch, a visual meter that varies in brightness, or a computer screen that varies the lines moving across a grid. The patients have to find mental strategies to self-control the parameter of interest. Through trial and error participants learn to identify and control their mental activities that will bring about the desired physical changes. The three most commonly used forms of biofeedback are i) electromyography (EMG; muscle tension) biofeedback, ii) thermal biofeedback (skin temperature) and iii) EEG biofeedback (neurofeedback; brain activity). Concerning biofeedback as treatment for sleep disorders there are two types of biofeedback that have been effectively used: EMG and EEG biofeedback. According to the “Practice Parameters for the Psychological and Behavioral Treatment of Insomnia” by Chesson et al. (1999) and Morgenthaler et al. (2006) biofeedback is an effective and recommended therapy in the treatment of chronic insomnia. It has been rated as probably efficacious indicating that multiple observational studies, clinical studies, wait list controlled studies, and within subject

and intrasubject replication studies demonstrated efficacy. However, after receiving considerable attention in the 1970s and 1980s (cf. *Table 3*) there has been a big gap until today – only one study of biofeedback treatment for insomnia has been published in the last 20 years (Sanavio et al., 1990). This lack of research interest may be related to the fact that biofeedback requires more time than comparable forms of relaxations therapies with only little appreciable advantage.

Additionally commercial hardware for detecting and managing psychophysiological parameters are needed and the biofeedback operator should understand the fundamental principles and methods for detecting and measuring physiological processes in depth. Despite this lack of research, biofeedback seems to be an efficacious treatment for insomnia. It is also to note that after the intense and promising research in the 1970s many people in the field applied the method rapidly to a variety of clinical disorders (e.g., migraine headache, anxiety disorders, epilepsy, tinnitus, attention deficit (hyperactivity) disorder, chronic pain) thereby skipping the much needed basic research documenting biofeedback efficacy convincingly. Therefore our starting point was to vigorously and objectively test the EEG biofeedback (or neurofeedback) methodology by conducting a highly controlled study using sensorimotor (12-15Hz, SMR) "instrumental conditioning" with the aim to influence brain patterns during waking as well as sleep (cf. chapter 5.5.1).

**Table 3. Overview of literature concerning Biofeedback and Insomnia**

Reference	Subjects	Feedback protocol	Number and duration of sessions	Results
Coursey et al. (1980)	22 subjects suffering sleep onset insomnia	EMG frontalis biofeedback; relaxation therapy (autogenic training); "Electrosleep Therapy"; PSG	<b>12</b> (2 a week); 35-45min 1 month follow up	EMG biofeedback and relaxation therapy compared to "Electrosleep Therapy": ↓ sleep onset latency; ↑ sleep efficiency
Engel-Sittenfeld et al. (1980)	35 subjects suffering chronic insomnia	EMG frontalis biofeedback and EEG theta NFT; relaxation therapy (autogenic training); client-centred psychotherapy	<b>19</b> (2 a week); 1,5 hours 6 months follow up	↓ hypnotic medication
Freedman & Papsdorf (1976)	18 subjects suffering sleep onset insomnia	EMG frontalis biofeedback; relaxation therapy (progressive relaxation); control group: placebo ("relaxation" exercises); PSG	<b>6</b> (3 a week); 30 min 2 months follow up	EMG biofeedback and relaxation therapy: ↓ sleep onset latency
Hauri (1981)	48 subjects suffering primary Insomnia	4 modalities: (i) EMG frontalis, (ii) EMG-theta, (iii) SMR (12-14Hz) and (iv) no treatment; sleep logs, sleep recordings; PSG	<b>15 - 62</b> (2-4 a week); 1 hour 9 months follow up	amount of SMR-feedback-learning correlated significantly with sleep improvement
Hauri et al. (1982)	16 subjects suffering	2 groups: (i) frontalis EMG and theta, (ii)	<b>32</b> (2-3 a week);	objective sleep recordings revealed that tense and anxious

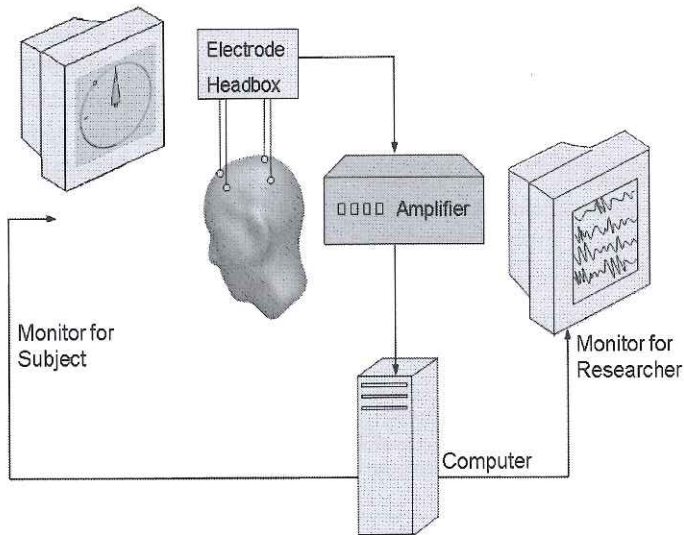


	primary Insomnia	frontalis EMG and SMR (12-14Hz); T7/T8, C3/C4; visual NFT; sleep logs; sleep recordings; PSG	1 hour 6 x EMG 26 x theta/SMR 9 months follow up	insomniacs benefited only from theta-NFT, while those who were relaxed only benefited from SMR- NFT; according to sleep logs both NFT groups seems to be effective
Hughes & Hughes (1978)	36 subjects suffering chronic insomnia	EMG biofeedback; relaxation therapy; stimulus control; control group: pseudo- biofeedback	1-5 1 hour 6 months follow up	↓ sleep onset latency for patients of all four groups (no sign. group differences)
Nicassio et al. (1982)	40 subjects suffering sleep onset insomnia	EMG frontalis biofeedback; relaxation therapy (progressive relaxation); control group: pseudo- biofeedback; no treatment	5 1 hour; 6 months follow up	relaxation therapy and EMG biofeedback: ↓ sleep onset latency
Sanavio (1988)	24 subjects suffering psychophysiol ogical insomnia	EMG frontalis biofeedback; cognitive behavioral therapy (CBT)	6 (3 a week); 1 hour 3 and 12 months follow up	EMG biofeedback and CBT: ↓ sleep onset latency; CBT: ↓ reverberating thoughts; EMG-biofeedback: ↑ relaxation before falling asleep
Sanavio et al. (1990)	40 subjects suffering sleep onset insomnia	EMG biofeedback; CBT; stimulus control + relaxation therapy (progressive relaxation); control group: waitlist	6 (3 a week); 1 hour 36 months follow up	EMG biofeedback; CBT; stimulus control + relaxation therapy: ↓ sleep onset latency, ↓ WASO; effects remain stable after 1 and 3 years follow up
VanderPlate & Eno (1983)	36 subjects suffering sleep onset insomnia	EMG biofeedback; pseudo-biofeedback; self-monitoring; control group: waitlist	3 1 hour 2 months follow up	EMG biofeedback and pseudo- biofeedback: ↓ sleep onset latency

Abbreviations: ↑ = increase; ↓ = decrease; WASO = wake after sleep onset; CBT = cognitive behavioral therapy; PSG = polysomnography; EMG = electromyography; NFT = neurofeedback-training; SMR = sensorimotor rhythm; EEG = electroencephalography

## 5.5 Instrumental EEG Conditioning (IEC)

Instrumental conditioning of EEG parameters – often called neurofeedback or EEG biofeedback - is a very sophisticated type of biofeedback and refers to an operant conditioning paradigm (for review see Budzynski, Budzynski, Evans, & Abarbanel, 2009; Serman, 1996). Participants are instructed to learn to self regulate distinct parameters of their cortical activity (e.g., amplitude, frequency or coherence) as assessed by the means of EEG. The aim of IEC is to teach individuals what specific states of cortical arousal feel like and how to activate such states voluntarily. During IEC - as depicted in *Figure 1* - EEG is recorded and the relevant components are extracted and “fed back” to the individual using an online feedback loop (audio, visual or combined audio-visual). The individual’s task may then be to increase/decrease the respective cortical parameter. When the correct EEG-pattern is produced, the subject receives a positive response or reward by the computer.



**Figure 1.** Equipment requested for IEC. Scalp electrodes capture brain oscillations and transmit them to the amplifier. After amplification signals are transmitted to the computer where online calculations (e.g., Fast Fourier Transformation) are performed. Pre-processed data are presented to the subjects either visually (e.g., compass-needle) and/or acoustically (e.g., varying tone pitches). During IEC subjects permanently get real-time feedback of the parameters (e.g., SMR band power) intended to be changed (e.g., by relaxing). Additionally the researcher can supervise the session by a separate monitor.

It is proposed that IEC is not successful below 10 training sessions (Egner & Gruzelier, 2003) and there is a very high variability (from 1 up to 50) in the number of sessions used for training throughout literature (cf. *Table 4*). After an initially enormous research interest in the 60ies and 70ies and a dramatic decrease thereafter a kind of “Neurofeedback Renaissance” seems to take place. Today IEC is mainly used as a therapeutic tool to treat different types of disorders like epilepsy (Lantz & Sterman, 1988; Kotchoubey, Strehl, Holzapfel, Blankenhorn, Fröscher, & Birbaumer, 1999; Sterman & Lantz, 2001; Strehl et al., 2006; for review see Sterman & Egner, 2006; Tan et al., 2009) or attention-deficit hyperactivity disorder (ADHD; Beauregard & Lévesque, 2006; Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Gevensleben et al., 2009; Kaiser & Othmer, 2000; Leins et al., 2007; Lubar, Swartwood, Swartwood, & O'Donnell, 1995; Lubar, Swartwood, Swartwood, & Timmermann, 1995; Strehl, Leins, Goth, Klinger, Hinterberger, & Birbaumer, 2006; for review see Arns, de Ridder, Strehl, Breteler, & Coenen, 2009; Heinrich et al., 2007; Monastra, 2005). Within the treatment of other clinical disorders such as depression (Rosenfeld, Baehr, Baehr, Gotlib, & Ranganath, 1996; for review see Hammond, 2005), tinnitus (Gosepath, Nafe, Ziegler, & Mann, 2001; for review see Dohrmann et al., 2007), anxiety (Hardt & Kamiya, 1977) and substance abuse (Moore, Trudeau, Thuras, Rubin, Stockley, & Dimond, 2000; for review see Peniston & Kulkosky, 1999; Sokhadze et al., 2008) IEC has also been reported to be a useful



instrument. Furthermore, the exciting progress since the pioneering work of Nicolelis (for review see Nicolelis, 2003) in the field of brain-computer or brain-machine interface enabling “locked-in” and partly paralysed patients to communicate or to produce movements, respectively, by voluntarily controlling neuronal activity (Birbaumer et al., 1999; Hinterberger et al., 2004; Pfurtscheller, Müller, Pfurtscheller, Gerner, & Rupp, 2003; for review see Birbaumer & Cohen, 2007; Birbaumer, Ramos Murguialday, Weber, & Montoya, 2009) benefits from this specific method.

Of high interest for our approach are the early findings by Sterman et al. (1970) who could show that facilitation of sensorimotor rhythm (SMR) by IEC during wakefulness in cats (i) selectively enhances spindle activity during sleep and (ii) produces longer epochs of undisturbed sleep. EEG recordings over the sensorimotor cortex show a very distinctive oscillatory pattern in a frequency range between 12-15Hz termed SMR (Sterman & Wyrwicka, 1967; Chase & Harper, 1971; Howe & Sterman, 1972). These brain activities are also known as “rolandic mu rhythms” or “wicket rhythms” (Gastaut, 1952; Niedermeyer, 2005). SMR appears to be dominant during quiet but alert wakefulness (Roth, Sterman, & Clemente, 1967) and desynchronizes during planning, execution and also imagination of hand, finger, foot and tongue movements (Neuper, Wörtz, & Pfurtscheller, 2006; Pfurtscheller, Brunner, & Schlögl, 2006). Active inhibition of motor behavior on the other hand results in SMR synchronization (Howe & Sterman, 1972). Furthermore this frequency range is known to be abundant during light NREM sleep, and is representing the classical sleep spindle band. First spindles emerge at sleep onset, have a waxing-and-waning appearance and are known to be generated in thalamocortical circuits (Steriade, 1999). Sterman and colleagues postulated that instrumental SMR conditioning can transfer into sleep, inducing a facilitation of spindle burst sleep and decreased sleep fragmentation (i.e., reduced waking and movements during NREM sleep) in normal adult cats. By instrumental conditioning the occurrence of SMR and the related suppression of movement could be induced in cats (Wyrwicka & Sterman, 1968). EEG was recorded from lateral pericruciate cortex (on both sides) and posterior cortical sites in eight cats. The animals were placed in a recording chamber equipped with an automatic feeding device. After adaptation to this chamber, three independent recordings of sleep were obtained as baseline. At least two sleep cycles (quiet sleep being interrupted eventually by periods of active sleep or spontaneous shifts back to the waking or hypnagogic state). Subsequently the eight cats were split in two groups of four each and both groups were trained to produce specific patterns of EEG activity recorded over sensorimotor cortex (either SMR or low voltage [ $<20\mu\text{V}$ ], fast [18-30Hz] activity [LVF]) during daily sessions to receive food. One training session consisted of 60 reinforcements by food for producing the desired activity. In the SMR-condition a signal containing at least 0.5sec 12-14Hz activity at a voltage 100% above background level produced a reward. Most animals received maximum performance after 2-4 weeks of daily training. In a first test session cats were allowed to obtain unlimited reinforcement and remained in the chamber until several complete sleep cycles were recorded. In a second run training (SMR, LVF) was reversed for the two groups. A final sleep recording 1 month after the end of the second training block served as a follow-up. Results show that instrumental conditioning of SMR activity in the waking cat produce significant changes in spindle-burst activity (number and duration of spindle bursts) and sleep duration. An increase in spindle-

burst activity during sleep following SMR was observed in both groups whereas spindle-burst activity in the follow-up 1 month later was enhanced only in the group receiving SMR-training in the second run, but was not sustained in the second group where intervening LVF conditioning was given. Additionally the mean duration of quiet-sleep epochs was significantly increased immediately after SMR conditioning, but not in the follow-up, supporting the findings by Roth et al. (1967) that phasic motor behavior suppression is related to SMR activity.

Moreover at those early times, 12-14Hz IEC has already been effectively used in treating patients suffering from psychophysiologic insomnia (Hauri, 1981; Hauri, Percy, Hellekson, Hartmann, & Russ, 1982). In Hauri et al. (1982) sixteen subjects suffering from psychophysiologic insomnia were randomly assigned to either an EMG / theta-feedback or EMG/SMR-feedback treatment group. At first subjects were evaluated for 3 nights in a sleep laboratory, including different psychological questionnaires, sleep logs and a psychiatric interview. Patients who satisfied criteria for psychophysiological insomnia defined by chronic, serious and relentless sleeping problems for at least 2 years; insomnia has been shown for at least 8 of the 14 nights reported by home sleep logs; >30min sleep latency or <85% sleep efficiency during the second and third laboratory night; no medical insomnia or serious psychiatric disorders) first received 6 frontalis EMG sessions to learn how to sit comfortably in an easy chair for at least half an hour and can relax at least to the degree that EMG artefacts on the EEG channel become rare. Once adequately relaxed, patients started with either Theta or SMR training sessions. All of them received 26 sessions of Theta or SMR training within 13 weeks. According to evaluations by home sleep logs both treatment-groups could benefit from IEC, whereas objective evaluations at the sleep laboratory revealed that tense and anxious insomniacs benefited only from theta but not from SMR training, while those who were relaxed but still could not sleep benefited only from SMR- but not from theta training. Therefore Hauri et al. (1982) could show that appropriate IEC has a long-lasting effect on insomnia, although patients have to be carefully selected, as the same type of IEC did not appear effective for all insomniacs.

A further approach of IEC patterns during wakefulness reaching translation into sleep EEG was presented by Amzica, Neckelmann and Steriade (1997). Cats were trained to generate fast (20-50Hz) oscillation bursts within the motor cortex (area 4) as well as the visual cortex (area 17). The training of each animal consisted of seven sessions of motor cortex conditioning, three sessions of extinction and seven sessions of visual motor cortex conditioning. Extinction sessions were used to abolish the local increase in generation of fast oscillation bursts and to reset the thalamocortical synchrony of fast oscillations to control values. During the training sessions every 10sec a light flash was delivered into the visual field of the cat (conditioned stimulus) – at least 200 stimuli per session. If there was a qualifying burst (conditioned response) produced within the next 2sec, the animal was rewarded by a jet of water 100ms later. The experimental paradigm was successful in conditioning an increase in generation of fast oscillation bursts within both locations. Furthermore, the increased burst-generation was associated with an enhanced synchrony of fast oscillations at different levels of the thalamocortical network. Most interestingly for the present investigation, the increased thalamocortical synchrony acquired during the conditioning sessions was also expressed during subsequent quiet waking, NREM sleep and



REM sleep, indicating that the facilitation of the desired oscillation bursts through instrumental conditioning during wakefulness selectively enhances similar patterns during subsequent sleep (for details see Amzica et al., 1997).

Additionally, more recent research focused on healthy individuals providing evidence that subjects who are able to gain control over different EEG parameters might even succeed in increasing performance levels in various tasks (for review see Gruzelier, Egner, & Vernon, 2006; Vernon, 2005). Those studies have pointed out that distinct IEC-protocols can be successfully used to improve attentional processing (Egner & Gruzelier, 2001, 2003; Egner, Strawson, & Gruzelier, 2002), increase accuracy in working memory tasks (Vernon et al., 2003) or improve performance in mental rotation (Hanslmayr, Sauseng, Doppelmayr, Schabus, & Klimesch, 2005).

Taken together there is a growing body of evidence suggesting that it is feasible to learn to regulate specific brain oscillations. Thereby it becomes possible to directly counteract the maladaptive brain activity which is associated with various disorders such as epilepsy, ADHD or sleep disorders. Unfortunately, much of the previous research concerning IEC has suffered from a lack of standardized measures of target symptoms, neglected the assessment of EEG changes and control groups or was conducted with insufficient sample sizes. Additional, well-controlled investigations are thus recommended before IEC can be considered a reliable non-pharmacological treatment for several disorders such as epilepsy, ADHD or even insomnia.

To provide an insight into the vast amount of studies concerning the issue "Instrumental EEG conditioning" an overview of the current IEC literature is presented in *Table 4*.

**Table 4. Overview of current IEC literature**

Reference	Subjects	Feedback protocol	Number and duration of sessions	Results
Berner et al. (2006)	11 healthy subjects	↑ 11.6-16Hz (sigma); Cz; sleep spindle activity + overnight memory performance change; neurofeedback-training (NFT) vs. pseudo-neurofeedback-training (PFT); visual NFT	1 4 x 10 consecutive min	↑ sigma power during subsequent sleep-stage 2-4 (NREM)
Birbaumer (1999)	2 "locked-in" patients	negative/positive slow cortical potentials (SCP); Cz; brain-interface; spelling device; imagery strategy	288 / 327 6-12 per day 5-10 min	both patients were better producing positive SCP; subjects were able to communicate by that kind of spelling device
Beauregard & Lévesque (2006)	20 children (8-12 years) diagnosed with attention-deficit hyperactivity disorder (ADHD)	experimental group (EXP): ↑ beta (15-18Hz) and sensorimotor rhythm (SMR; 12-15Hz), theta (4-7Hz); control group (CON): no NFT; digit span, integrated visual and auditory continuous performance test (IVA), Conner's parent rating scale-revised (CPRS-R); experiment 1: counting stroop task, experiment 2: go/no-go task during functional magnetic resonance imaging (fMRI; pre and post training)	40 (3 per week) 13,5 weeks 60 min	EXP: ↑ scores on digit span and IVA; ↓ CPRS-R scores; ↑ scores on accuracy (stroop-task, go/no-go task); fMRI-data indicate that NFT has the capacity to functionally normalize brain systems mediating selective attention and response inhibition in ADHD children

**Table 4. Overview of current IEC literature. (Continued)**

Reference	Subjects	Feedback protocol	Number and duration of sessions	Results
Egner & Gruzelier (2001)	22 healthy subjects	↑ beta 1 (15-18Hz) and ↑ SMR (12-15Hz), without concurrent rises of theta (4-7Hz) or high beta (22-30Hz); attention task; C3/C4; audio-visual NFT; oddball task; test of variables of attention (T.O.V.A.)	<b>10</b> (2 per week) 30 min	↑ task performance and ↑ P300 after NFT; correlation between NFT learning rates and measure changes
Egner et al. (2002)	18 healthy subjects	↑ theta/alpha ratio; ↑ theta (5-8Hz), ↓ alpha (8-11Hz); NFT vs. PFT; Pz; audio-visual NFT	<b>5</b> (2-3 a week) 15 min	subjects receiving NFT could significantly increase theta/alpha ratio
Egner & Gruzelier (2003)	25 healthy subjects	↑ beta1 (15-18Hz) or SMR (12-15Hz); Cz; PFT; T.O.V.A.; auditory oddball paradigm; audio-visual NFT	<b>10</b> (once a week) 15 min	↑ SMR activity is associated with ↑ attention whereas ↑ beta activity with ↑ arousal
Fuchs et al. (2003)	34 children (8-12 years) diagnosed with ADHD	NFT-group (22) vs. pharmacotherapy-group (12); reward bands: SMR (12-15Hz) / beta (15-18Hz); inhibition bands: theta (4-7Hz) / beta2 (22-30Hz); C4 / C3; audio-visual NFT; T.O.V.A.; attention endurance test (d2); Conner's behavior rating scale (CBRS) for teachers and parents	<b>36</b> (3 a week) 30-60 min	NFT as well as pharmacotherapy leads to comparable results: improvements in all subscales of T.O.V.A.; ↑ speed + accuracy (d2); ↓ ratings in CBRS
Gevensleben et al. (2009)	102 children (8-12 years) diagnosed with ADHD	EXP: combined training: SCP and theta/beta; CON: computerised attention skills training; behavioral rating scales (parents, teachers)	<b>36</b> (2-3 a week) 3-4 double-sessions / week (à 2 x 50min)	only experimental group: ↑ parent and teacher ratings
Gosepath et al. (2001)	40 subjects suffering tinnitus; 15 controls	↑ alpha, ↓ beta; P4; electromyography (EMG); audio-visual NFT; tinnitus questionnaire	<b>15</b> (2-3 a week) 5 x 5min 6 months follow up	significant reduction of the score in the tinnitus questionnaire; 24 subjects could ↑ alpha, 16 subjects ↓ beta; controls: no changes in EEG activity
Hanslmayr et al. (2005)	18 healthy subjects	↑ upper alpha, ↓ theta frequency (individually adjusted frequency bands); F3, Fz, F4, P3, Pz, P4; mental rotation task; visual NFT	<b>1</b> 2 x 4 x 5 consecutive min	subjects that could ↑ upper alpha activity could improve cognitive performance
Hardt & Kamiya	16 male subjects	anxiety-therapy; ↑↓ alpha (8-13Hz) ;	<b>7</b> 32 min	↑ alpha reduces state anxiety, ↓ alpha increased state anxiety in



(1977)		Oz, O1, C3; audio NFT; eyes closed; Minnesota multiphasic personality inventory (MMPI); mood scales; high vs. low anxiety group		high anxiety group; low anxiety group was superior at ↑↓ alpha
Hinterberger et al. (2004)	54 healthy subjects	↑↓ SCP; Cz; 3 NFT-modalities: (i) visual, (ii) auditory and (iii) combined; thought translation device (TTD); "locked-in syndrome"	3 500 trials per session 250 ↑ SCP, 250 SCP↓	Auditory as well as combined visual-auditory feedback is feasible to self-regulate SCPs; combined NFT showed the smallest learning effect
Hoedlmoser et al. (2008)	27 healthy subjects	↑ SMR (12-15Hz) or randomized IEC protocol (randomized 3Hz frequency bins between 7-20Hz (except 12-15Hz) was used as relevant conditioning parameter	10 8 x 3 min	only EXP (SMR-conditioning): ↑ declarative learning, ↑ spindle number, ↓ sleep onset latency
Kaiser & Othmer (2000)	1089 subjects with attentional complaints	↑ SMR (12-18Hz) or beta (15-18Hz), ↓ theta (4-7Hz) and beta2 (22-30Hz); C3/C4; audio-visual NFT; T.O.V.A.	20 – 40 30 min	↑ attentiveness, impulse control and response variability; subjects performing 40 sessions showed better results than those performing 20
Kotchoubey et al. (1999)	27 subjects suffering focal epilepsy	SCP; Cz; visual NFT; transfer trials; seizure rate	35 (2 a day) 140 trials per session 20 sessions – 8 weeks break – 15 sessions	patients who produced larger negative SCP during the first 20 sessions showed no decrease in seizure frequency
Lantz & Sterman (1988)	24 subjects suffering epilepsy	↑ SMR (11-15Hz), ↓ delta (0-5Hz) and beta (20-25Hz); C1, C5; audio-visual NFT; Dodrill's Neuropsychological Battery for Epilepsy	18 (3 a week) 30 min	reduced seizures; ↑ memory performance
Leins et al. 2007	38 children (8-13 years) diagnosed with ADHD	1 <sup>st</sup> group: SCP, Cz; 2 <sup>nd</sup> group: ↓ theta (4-8Hz), ↑ beta (12-20Hz), FC3, FC4; parental + teachers ratings, IQ (full scale, verbal, performance); test of attention	30 60 min (4 x 38 trials) 6 months follow up	both groups: intentional regulation of cortical activity; ↑ attention and IQ; parents and teachers reported ↑ behavior ratings and ↑ cognitive performance; effects remain stable six month after treatment
Lubar, Swartwood, Swartwood, & Timmermann (1995)	19 subjects (8-19 years) diagnosed with ADHD	↓ theta (4-8Hz), ↑ beta (16-20Hz); CPz, FCz; audio-visual NFT; T.O.V.A.	40 (5 a week) 60 min	successful NFT (N=12) resulted in ↑ T.O.V.A.-performance

**Table 4. Overview of current IEC literature. (Continued)**

Lubar, Swartwood, Swartwood, & O'Donnell (1995)	17 children (8-15 years) diagnosed with ADHD	↑ beta (16-20Hz), ↓ theta (4-8Hz); CPz, FCz; audio-visual NFT; T.O.V.A., continuous performance task, behavior rating scale	30 – 45	success in NFT can be monitored by changes in the overall EEG; NFT-responders (N=12) showed stronger improvement on T.O.V.A. than NFT-non-responders (N=7)
Moore et al. (2000)	35 male subjects suffering substance abuse	3 conditions: (i) ↑ alpha (8-12Hz), (ii) ↑ theta (4-8Hz), ↓ alpha and (iii) EMG (25-32Hz); O2; theta/alpha ratio, theta/alpha crossover; audio NFT; eyes closed; imagery content (imagery occurring during feedback measured by questionnaire)	~20 40 min	all 3 conditions were associated with similar amounts of average theta/alpha ratio and percentage of theta/alpha crossover; self-reported production of imagery is not related to any EEG/EMG correlate
Pfurtscheller, Müller et al. (2003)	1 tetraplegic patient	↑ beta (16-18 Hz); two electrode pairs located over the right hand foot representation areas (2.5cm anterior and posterior to position C3/C4 or Cz, respectively); functional electrical stimulation (FES); imagination of foot movement; brain-computer interface (BCI) for hand grasp restoration;	62 2-4 sessions a day 60 min ~5 months	by producing beta bursts and using BCI a FES device could be controlled; the patient was able to grasp a cylinder with the paralyzed hand
Rosenfeld et al. (1996)	5 subjects suffering depression	↑ alpha (8-13Hz); F3-Cz, F4-Cz; auditory NFT; alpha asymmetry training; eyes closed; mood scale prior and after each session	8 - 19 30 min	significant correlation between alpha asymmetry score and affect change score
Sterman et al. (1970)	8 cats	↑ SMR (12-14Hz) vs. low voltage fast activity (LVF); lateral pericruciate and posterior cortical sites; food reward; sleep recordings	14 - 28 daily 2 - 4 weeks 1 month follow up	↑ spindle activity and epochs of undisturbed sleep
Sterman & Lantz (2001)	20 epileptics unilateral temporal lobe lesion	↑ SMR (11-15Hz), ↓ delta (0-5Hz) and beta (20-25Hz); C1, C5; audio-visual NFT; Dodrill's Neuropsychological Battery for Epilepsy	18 (3 a week) 30 min	successful NFT leads to improvement on memory tasks specific to the hemisphere contralateral to the lesion
Strehl, Leins et al. (2006)	5 subjects suffering Epilepsy	EEG & fMRI; negative/positive SCP; Cz; visual NFT; hemodynamic changes (blood oxygen level-dependent [BOLD] - response) during producing positive SCP	35 à 145 trials 6 months follow up;	2 successful "regulators"; during positive SCP BOLD response indicated deactivation around the recording electrode Cz, frontal lobe and thalamus
Strehl, Trevorrow et al.	23 children (8-13 years) diagnosed	↑↓ SCP; Cz; audio-visual NFT; parent ratings; IQ and	30 (3 phases à 10 sessions)	children learned to self regulate negative SCP; significant improvement in



(2006)	with ADHD	attention; behavior ratings for teachers and parents	6 months follow up	behavior, attention and IQ; all changes proved to be stable at the follow up
Vernon et al. (2003)	30 healthy Subjects	↑ theta (4-7Hz) while ↓ delta (0-4Hz) and alpha (8-12Hz) or ↑ SMR (12-15Hz) while ↓ theta and beta (18-22Hz); Cz; audio-visual NFT; continuous performance task (attention, CPT); conceptual span task (working memory, CST)	8 (2 a week) 5 x 3 min	SMR-NFT increased SMR-activity and CPT- and CST-performance; theta-NFT failed to exhibit any changes

**Abbreviations:** ↑ = increase; ↓ = decrease; min = minutes; Hz = hertz; NREM = non rapid eye movement sleep; NFT = neurofeedback-training; PFT = pseudo-neurofeedback-training; SCP = slow cortical potentials; EXP = experimental group; SMR = sensorimotor rhythm; CON = control group; IVA = integrated visual and auditory continuous performance test; CPRS-R = Conner's parent rating scale – revised; fMRI = functional magnetic resonance imaging; ADHD = attention- deficit hyperactivity disorder; T.O.V.A. = test of variables of attention; CBRS = Conner's behavior rating scale; EMG = electromyography; EEG = electroencephalography; MMPI = Minnesota multiphasic personality inventory; TTD = thought translation device; FES = functional electrical stimulation; BCI = brain computer interface; LVF = low voltage fast activity; BOLD = blood oxygen level dependent; IQ = intelligence quotient; CPT = continuous performance task; CST = conceptual span task.

### 5.5.1 Instrumental SMR Conditioning (ISC) and its Impact on Sleep Quality and Declarative Learning

Recently we applied the earlier described IEC method to investigate the effect of instrumental 12-15Hz (SMR) conditioning (experimental group) as compared to randomized IEC (control group) on sleep as well as declarative memory performance (Berner, Schabus, Wienerroither, & Klimesch, 2006; Hoedlmoser et al., 2008).

In a pilot study done in our laboratory (Berner et al., 2006) we investigated whether (i) ISC can have direct influence on sleep spindles produced during the night and whether (ii) a subtle change in this activity could even have an impact on successful memory encoding or overnight memory consolidation. These questions were hypothesized according to earlier findings where we indicated a significant positive correlation between overnight change in the number of recalled words in a declarative word-pair association task and spindle activity change from a control to experimental night (Schabus et al., 2004). Although sleep spindle activity remained unchanged after ISC in this first study, we found enhanced “spindle frequency” band power during sleep, indicating that ISC effects become most easily evident in the actual trained frequency bands rather than in associated phasic spindle “events”. The caveat of this pilot study, however, was the amount of ISC-sessions: the ISC-protocol consisted only of four 10min long blocks, thus, was not comparable to the much more intense ISC-protocols used in previous studies.

Inspired by this preliminary pilot study we continued our investigations by a more extensive approach. Twenty-seven healthy subjects (13 male, 14 female; mean age = 23.63 years, SD=2.69) were randomly assigned (parallel group design) to either (i) a SMR-conditioning protocol (experimental group; N=16) or to (ii) a randomized IEC protocol

(control group; N=11). As depicted in *Figure 2* all of them attended the laboratory on 13 occasions.

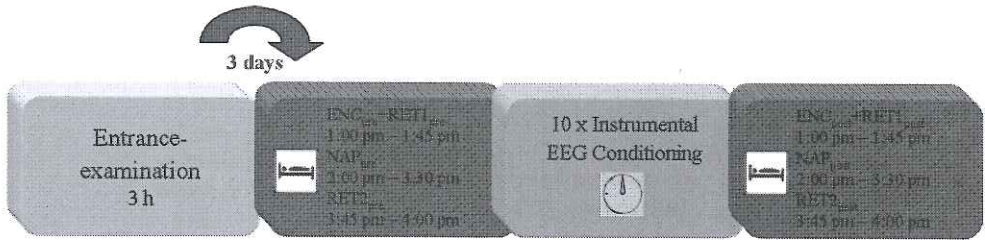


Figure 2. Study design. Subjects had to attend the laboratory 13 times. The first visit – 3 days prior to pretreatment – served as entrance examination. Pretreatment included a declarative memory task (encoding [ENCpre], retrieval before nap [RET1pre], retrieval after nap [RET2pre]) as well as a 90min nap (NAPpre) and was followed by 10 IEC sessions on 10 consecutive days (except weekends). Posttreatment (same procedure like pretreatment: ENCpost, RET1post, NAPpost and RET2post) - one day after the last conditioning session - completed the study protocol. Figure reprinted with permission from Hoedlmoser et al. (2008).

First subjects had to pass an entrance examination consisting of several parts: clinical evaluation of sleep quality [Pittsburgh Sleep Quality Index (PSQI); Buysse, Reynolds, Monks, Berman, & Kupfer, 1988]; anxiety (self-rated anxiety scale; Zung, 1971); depression (self-rated depression scale; Zung, 1965); memory („Wechsler Memory Scale – revised“; Härting, Markowitsch, Neufeld, Calabrese, & Deisinger, 2000) and intelligence (Advanced Progressive Matrices; Raven, Raven, & Court, 1998). Throughout the study participants had to complete a sleep diary every day in the evening and in the morning (Self-rating scale for Sleep and Awakening quality; Saletu, Wessely, Grünberger, & Schultes, 1987) to control their sleep-wake-cycle and to prevent sleep deprivation prior to laboratory examination. During the nap-session before (NAPpre) and after (NAPpost) ISC subjects performed a declarative word-pair association task (Plihal & Born, 1997). Subjects had to learn a first list of 80 word-pairs during NAPpre, and a second one during NAPpost. Polygraphic sleep recordings using Synamps EEG amplifiers (NeuroScan Inc.) started at 2:00 pm and ended at 3:30 pm. Fifteen gold-plated silver electrodes were attached according to the international 10/20 system. In addition, four electrooculogram (EOG) channels, one submental EMG channel, one electrocardiogram channel (ECG) and one respiratory channel (chest wall movements) were recorded. Between pre- and post-treatment the subjects were trained to enhance their band amplitude within specific frequency bins during 10 IEC sessions on 10 consecutive days (except weekends) using visual online feedback. Each session was conducted in a standardized procedure and lasted for about 1 hour (including electrode adjustment). Immediately before and after instrumental conditioning subjects were instructed to relax during a 2min eyes-closed resting condition followed by a 2min eyes open resting condition. EEG was recorded from C3 with reference on the right earlobe and ground electrode placed on the left earlobe. For offline artefact rejection a bipolar vertical EOG channel was recorded. The ongoing EEG at site C3 was band-pass filtered to continuously extract amplitude values within the frequency of interest. Band amplitude of interest was calculated online and used as relevant conditioning parameter. The instrumental conditioning



design was performed as depicted in *Figure 3*. One trial consisted of a 3sec baseline followed by a continuous feedback interval lasting until the EEG signal exceeded the predefined reward threshold measured during the baseline for more than 250ms. Any time the subject was able to produce the requested EEG rhythm, the compass needle moved to the left. The aim was to move the needle as far to the left as possible reaching the previously fixed threshold represented by a green dot. In case of exceeding the amplitude threshold for at least 250ms, subjects got an audiovisual reward (appearance of a sun for 2sec accompanied by a 200ms lasting sound of 800Hz).

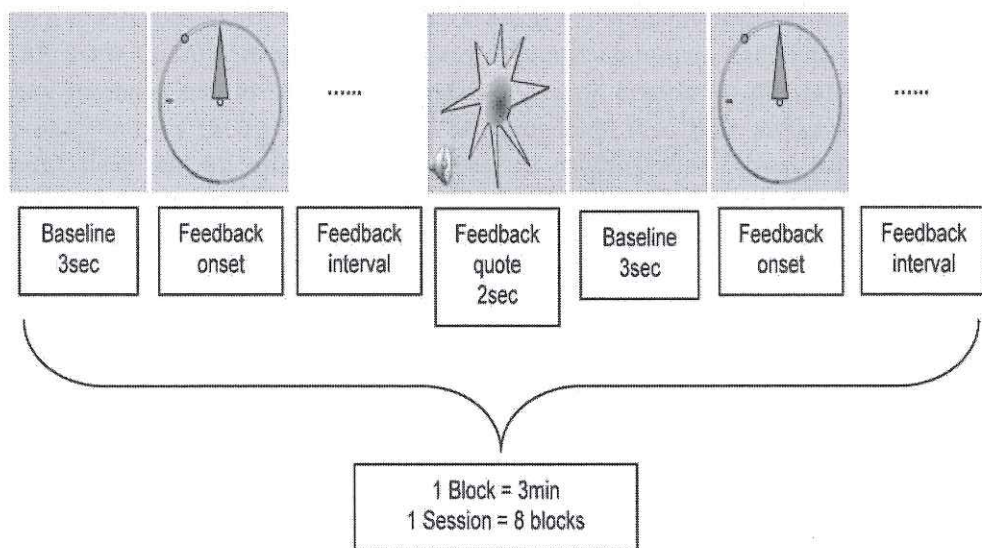


Figure 3. Schematic representation of one block within an IEC session. A 3sec lasting “Baseline” before visual feedback onset was used to calculate the mean amplitude within the frequency of interest which served as reference during “Feedback interval”. An audiovisual “Feedback quote” was triggered by an EEG signal containing at least 250ms of the frequency of interest at an amplitude exceeding a certain reward threshold measured during the 3sec baseline. Figure reprinted with permission from Hoedlmoser et al. (2008).

There were no specific instructions for the subjects as everybody was encouraged to find his or her own appropriate strategies like physiological relaxation combined with positive mental activity. To prevent rewards elicited by movements, eye, or muscle artefacts, trials with amplitudes exceeding  $200\mu\text{V}$  were abandoned by starting a new trial. Experimental and control group only differed concerning frequency adjustments. Subjects of the experimental group had to enhance the amplitude within their 12-15Hz frequency range throughout all sessions, whereas for the control group the band amplitude of randomized, each session varying 3Hz frequency bins between 7 and 20Hz (except 12-15Hz) were used as conditioning parameter. Subjects were not aware about their treatment until the study was over.

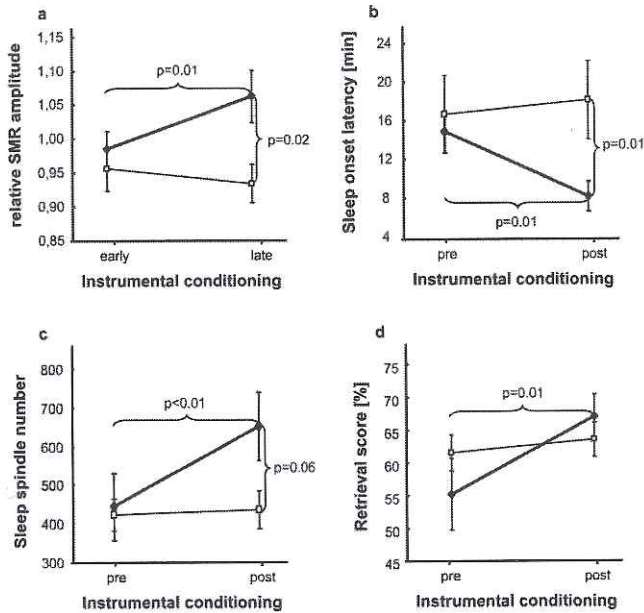


Figure 4. Main effects of ISC compared to randomized IEC on sleep and learning. 2-way ANOVAs depicting differences between experimental ( $\blacklozenge$ ) and control ( $\square$ ) group. a Significant increase of relative SMR amplitude after ISC (experimental group) vs. randomized IEC (control group). b Significant reduction of sleep onset latency during NAPpost compared to NAPpre. c Significant increase of sleep spindle number from NAPpre to NAPpost. d Significant enhancement of retrieval score computed at immediate cued recall (RET1) after ISC (experimental group) compared to randomized IEC (control group). Note that only 12-15Hz conditioning (experimental group) could increase relative SMR amplitude, sleep spindle number and retrieval score as well as decrease sleep onset latency. Error bars indicate standard errors of mean. Reprinted with permission from Hoedlmoser et al. (2008).

As depicted in *Figure 4a* significant SMR amplitude changes from early to late conditioning sessions confirmed the success of our ISC paradigm. Most interestingly, these EEG changes transferred into sleep (*Figure 4b-c*) and even improved immediate memory retrieval after learning (*Figure 4d*). There were no effects on memory consolidation (i.e., “overnap” change in memory performance after ISC) indicating a more unspecific effect of ISC. Heightened attention or relaxation levels after ISC are supposed to cause the improvement in word-pair recall. Our results therefore demonstrate to our best knowledge for the first time successful ISC in a healthy human population (cf. *Figure 4a*) leading to enhancement of sleep spindles (cf. *Figure 4c*) and thereby indicating that specific neural mechanism trained during wakefulness can be translated into sleep. There was no change in the duration of stage 2 sleep and therefore it can be ruled out that the spindle increase is caused by an increase of stage 2 sleep. Furthermore, sleep onset latency (cf. *Figure 4b*) was significantly shortened after ISC compared to a randomized IEC paradigm. Therefore our results additionally support Hauri’s approach (1981, 1982) to use ISC as an alternative treatment for primary insomnia. Note that here we used a much more rigorous control group



than usually adopted. Subjects of the control group underwent exactly the same study protocol with only the type of IEC being altered.

## 6. Prospects: ISC as Treatment for Primary Insomnia?

Given our recent findings (Hoedlmoser et al., 2008) we further aimed at changing sleep quality in humans suffering from primary insomnia by using ISC.

In a preliminary study we recruited 12 subjects (11 women) aged between 19 and 48 ( $M = 29.33$ ;  $SD = 10.56$ ) with clinical symptoms of primary insomnia. Individuals suffering from primary insomnia had to meet the following inclusion criteria: a) difficulty initiating [i.e., sleep-onset latency (SOL),  $>30\text{min}$ ] and/or maintaining (i.e., time awake after sleep onset  $>30\text{min}$ ) sleep and b) insomnia or its perceived consequences caused marked distress or significant impairment of occupational or social functioning. Several questionnaires [PSQI, Buysse et al., 1989; Becks Depression Inventory (BDI-II), Beck et al., 1996; Becks Anxiety Inventory (BAI), Margraf & Ehlers, 2007)] as well as a semi structured clinical interview for sleep disorders ("Strukturiertes Interview für Schlafstörungen nach DSM-III-R" (SIS-D), Schramm et al., 1993) were used to evaluate subjects compatibility (primary insomnia without comorbidities).

A counterbalanced within subjects design was used. Subjects had to attend the sleep laboratory 19 times over the course of 3 to 6 weeks (4 nights, 10 x ISC, 5 x randomized IEC; cf. *Figure 5*). Participants were instructed to arrive at the sleep laboratory at 7:30 pm each night. Polysomnographic recordings (PSG) started between 11:00 and midnight and were terminated after eight hours time in bed (TIB). The first PSG night served as screening and adaptation night. During experimental nights (1 x pre-treatment, 2 x posttreatment) a standard PSG montage with 21 gold plated silver electrodes was applied.

Concerning ISC we used the same method like in our previous study (Hoedlmoser, 2008) however, this time a within subjects design was implemented. Subjects were randomly assigned to either a protocol starting with ISC followed by randomized IEC or to a protocol starting with randomized IEC followed by ISC. Therefore every subject received both treatments – ISC and randomized IEC (cf. *Figure 5*).

Preliminary results confirmed the increase of 12-15Hz activity over the course of the ten ISC training sessions ( $p=0.027$ ) but not over the course of the randomized IEC training sessions. Interestingly, the increased SMR activity was associated with the enhancement of subjective sleep quality measured by the PSQI ( $p=0.001$ ). Furthermore sleep onset latency was tendentially reduced after ISC ( $p=0.056$ ) but not after randomized IEC. However, there were no significant changes concerning sleep spindle activity like we could show in our previous study (Hoedlmoser et al., 2008).

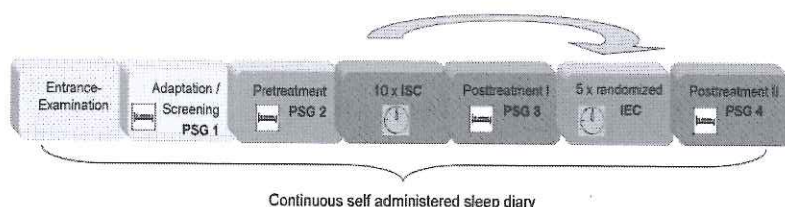


Figure 5. Study design. Subjects suffering from primary insomnia take part in a first adaptation/screening night (PSG1) followed by an experimental pre-treatment night (PSG 2). Pre-treatment night was either followed by 10 ISC sessions or by 5 randomized IEC sessions. Note that the order of treatments (ISC or randomized IEC) was counterbalanced. Post-treatment nights (PSG3, PSG4) were each conducted one day after the last conditioning session of ISC or randomized IEC, respectively.

Therefore our current preliminary data indicate that people suffering from primary insomnia experience subjective benefits from ISC before objectively verifiable. Further research is highly needed in order to reveal whether more intense ISC – or other forms of biofeedback or neurofeedback are able to consistently improve also objective sleep parameters such as wake after sleep onset or total sleep time.

Taken together our recent work confirms that instrumental conditioning of SMR has positive impact on sleep quality as well as on declarative learning in healthy participants (Hoedlmoser et al., 2008). Whether a similar instrumental conditioning protocol is also effective in the treatment of sleep disorders such as primary insomnia has yet to be revealed by well-controlled empirical studies.

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