Hyperarousal and insomnia

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Primary or psychophysiological insomnia has alternatively been viewed as either a predominantly psychological problem or as a predominantly physiological problem. Several early studies of patients were not able to document physiological differences, but more recent studies have found that many patients with primary insomnia take longer than control subjects to fall asleep on daytime nap tests despite feeling fatigued and they have elevated metabolic rate throughout both night and day. Other recent studies have found that increasing physiological arousal level for a week in normal sleepers produced the major secondary symptoms reported by insomniacs. In contrast, producing the disturbed sleep of insomniacs in a group of normal sleepers did not produce the typical pattern of secondary symptoms. Taken together, evidence is presented which supports the contention that primary insomniacs suffer from a disorder of hyperarousal and that the elevated arousal produces the poor sleep and other symptoms reported by patients. It is therefore suggested that new treatment strategies directed at reduction of arousal level be considered in these patients.

Key words: Sleep, sleep disorders, insomnia, hyperarousal, psychophysiological insomnia, primary insomnia, sleep disturbance

Introduction

Of the problems faced in Sleep Medicine, chronic primary insomnia remains as one of the most difficult treatment situations. Expanded polygraphic recordings have yielded much information concerning respiratory and muscle pathology during sleep. However, treatment options for primary insomnia have remained focused on behavioral therapy for many years, at least in part because it has not been possible to identify a clear physiological disease entity. This paper will provide a theoretical background and review selected recent insomnia research that supports the hypothesis that patients with primary insomnia suffer from a primary physiological disorder of hyperarousal that can be consistently measured and treated.

Since patients with primary insomnia typically have (1) a symptom complex which includes tension, anxiety, fatigue, and irritability [1]; (2) characteristic MMPI elevations [2]; and (3) an insomnia onset following a significant life-stress event [3], many...
hypothesize that insomnia is the product of internalization of psychological factors that produce a state of emotional arousal.

Other thoughts concerning the development of insomnia have held that emotional arousal or other events result in physiological activation that leads to insomnia [4] or even that insomnia develops entirely from physiological activation, as in phase shift insomnia. In a classic study, Monroe [5] found significantly increased physiological activation (increased rectal temperature, heart rate, basal skin resistance, and phasic vasoconstrictions) 30 min before and during sleep in insomniacs as compared to normal sleepers. Careful studies of sleep-onset insomniacs [6, 7] have shown that before sleep onset, patients with sleep-onset insomnia had increased frontalis and mentalis EMG, increased heart rate, increased finger temperature, and more beta and less alpha frequencies in their EEG. At sleep onset, the physiological parameters normalized except for the EEG changes, which were seen during stage 1 sleep and again during REM. Significantly elevated body temperature has been reported in some studies of poor sleepers [5, 8] but not in other studies [9, 10]. Poor sleepers have increased secretion of corticosteroids [8, 10, 11] and adrenaline [8, 11] compared with good sleepers in most studies. More recent studies have begun to show that physiological differences in insomniacs can be found throughout the day as well as at night. Several studies have shown that insomniacs both display poor sleep at night and take longer than normal to fall asleep during the day in multiple sleep latency test (MSLT) evaluations [12-15]. Another recent study has shown that primary insomniacs have an elevated metabolic rate throughout the night and day as compared to controls [12].

Because insomnia patients typically display both mood alteration and evidence of physiological arousal, differentiation of the cognitive and physiological hypotheses has been difficult. Production of consistent and long-lasting mood changes in normal individuals to test the effect of mood change on sleep is difficult. However, it was possible to produce a state of chronic physiological activation and to follow these activated normals for the development of symptoms of insomnia [16].

In that study [16], caffeine 400 mg TID was given to normal young adult sleepers for a week as a means of increasing physiological arousal and standard insomnia outcome variables were measured. As expected, the chronic use of caffeine increased arousal level, as measured by whole body metabolic rate, and sleep efficiency declined.
Table 2  The relationship between short and long sleep requirements and low and high basal arousal levels

<table>
<thead>
<tr>
<th>Sleep requirement</th>
<th>Basal arousal level</th>
<th>High</th>
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<tbody>
<tr>
<td>Short</td>
<td>Sleepiness without objective findings</td>
<td>Insomnia</td>
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<tr>
<td>Long</td>
<td>Idiopathic hypersomnolence</td>
<td>Sleep State Misperception</td>
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significantly. During the initial days of caffeine use, Ss had elevated MSLT scores (i.e. took longer to fall asleep) and reported increased subjective vigor (see Table 1 for a summary of results). However, by the end of the week of caffeine use, significantly increased daytime fatigue was reported despite MSLT scores that still remained significantly elevated as compared to baseline. In addition, anxiety, as measured by the anxiety scale of the MMPI (Pt), moved significantly toward psychopathology. The finding from this study that chronically elevated levels of physiological arousal would paradoxically lead to reports of increased fatigue even while objective sleepiness was decreased was a strong indication that physiological activation by itself could be responsible for the same paradoxical reports in patients with insomnia. The increase on the anxiety scale of the MMPI, a non-transparent trait measure of personality, offered additional compelling evidence that cognitive and personality components frequently seen in patients with insomnia could be significantly influenced by a chronically increased level of CNS arousal.

A theoretical construct to understand hyperarousal

These physiological findings led us to speculate that there is more involved in our expression of sleep than simply how long we have been awake. The ability to fall asleep may be determined not only by how long we have been awake (the sleep system) but also by the level of physiological arousal (arousal system). In other words each individual has his own sleep requirement determined by his sleep system and each individual has a basal level of arousal determined by his arousal system. Sleep deprivation will eventually override the arousal system, but the arousal system can also mask the sleep system. By thinking of these systems as relatively independent, one can dichotomize their effects as presented in Table 2. There are four possible combinations of extremes that could lead to pathology: individuals with abnormally low or high levels of basal arousal and individuals with abnormally low or high sleep requirements. For example, a patient with a low level of basal arousal would have a circadian physiological arousal rhythm that was normal in phase and amplitude but which was simply set a little lower at all points in time. An individual with a low arousal level might report a low energy level, might appear calm or stoic, and might fall asleep easily even after having a normal night of sleep. If a patient with a low arousal level also had a long sleep requirement, he would probably be sleepy secondary to not being able to meet his long sleep requirement and, coupled with low arousal, would probably always fall asleep easily. As such he could easily be classified as having idiopathic hypersomnolence (780.54–7). In contrast, if this patient instead had a short sleep requirement, he would not fall asleep as quickly (not sleep deprived)
but might report decreased energy and alertness. As such, he could be classified as complaining of sleepiness without objective findings (780.52–9) based on an MSLT. Individuals with a low level of basal arousal would always be prone to fall asleep quickly if their normal sleep quota were not filled.

Patients with a high level of basal arousal would be identified by an elevated circadian metabolic curve. Patients with a high level of basal arousal would be predisposed to present with some difficulty falling asleep and remaining asleep. An individual with a high arousal level and a short sleep requirement would likely complain of not being able to sleep long or well (short sleep requirement), and would report difficulty relaxing and daytime fatigue secondary to hyperarousal (as in our chronic caffeine administration study [16]). These sleep and arousal complaints would lead to a diagnosis as an objective idiopathic insomniac (780.52–7) or psychophysiological insomniac (307.42–0) because this patient would not be able to maintain sleep for 8 hours (sleep satiation). In contrast, a patient with a high basal arousal level and a long sleep requirement would have a normal night of EEG sleep, while the hyperarousal would cause him to feel fatigued and to believe his sleep was insufficient. He would be diagnosed as having “sleep state misperception (307.49–1)”.

If he had a large enough sleep requirement, such a patient might even have decreased sleep latencies during the day [17] while complaining of unsubstantiated poor sleep at night. In general, individuals with a high level of basal arousal would find it somewhat difficult to initiate sleep and might suffer from inability to maintain sleep as their core sleep requirement neared fulfillment.

Situational factors such as sleep or sleep deprivation, drugs, circadian time, and activity clearly cause phasic modification of arousal around the basal arousal level. For example, if a patient with a high basal arousal level drinks three cups of coffee, that patient would have a further increase in arousal and would have significant difficulty initiating sleep. A person with a low arousal level given three cups of coffee might be able to fall asleep at night without difficulty, because the caffeine only increased his arousal level to “normal”. A high level of basal arousal would make sleep more difficult to initiate and maintain but would not decrease the sleep requirement. In an extremely aroused individual, sleep deprivation would eventually overcome the arousal system so that sleep would occur, but as sleep was recovered, the impact of hyperarousal might become increasingly pronounced again. Therefore, when insomniacs are totally deprived of sleep, their recovery sleep is improved [18, 19]. However, their insomniac sleep pattern returns when the phasic influence of the sleep deprivation passes [18].

In terms of treatment, this conceptualization implies that: (1) individuals complaining of sleepiness but without objective findings may have a physiological disorder of low arousal indexed by metabolic rate or heart rate or other physiological index and could be effectively treated with stimulants that could increase arousal above their basal arousal level; (2) individuals with idiopathic hypersomnia, who have an increased sleep requirement and low arousal level, could not be treated effectively with stimulants alone. Stimulants would have a transitory effect on arousal level but would have only limited effectiveness in overcoming the need for more sleep. These patients could be treated more effectively by a combination of increased sleep length and stimulants; (3) insomniacs could be treated by chronically decreasing their hyperarousal; (4) subjective insomniacs could be treated by increasing their sleep length and decreasing their hyperarousal. However, effective treatments for all of these disorders would be 24-hour treatments not limited to sleep onset.
It must be noted that this discussion is not designed to explain all varieties of insomnia. Patients with insomnia secondary to medical illness or chronic pain might or might not have increased levels of basal arousal. However, many older patients do suffer from middle of the night awakenings which might be secondary to a flattening of their circadian arousal curve [18], which would leave basal arousal at a higher level during the night. Other patients undoubtedly suffer from sleep onset insomnia or early morning awakening secondary to the period length of their underlying circadian arousal curve [20]. These latter disorders of insomnia can also be placed into a comprehensive physiological context. This conceptualization allows one to understand not only psychophysiological insomniacs but also sleep state misperception insomniacs, idiopathic hypersomniacs, and patients complaining of sleepiness that cannot be objectively verified.

One body of evidence that supports the idea of a relatively stable physiological arousal level is the study of twins and inbred animal strains. Several studies have shown a genetic association for both hypersomnia [21, 22] and insomnia [23, 24]. The latter study, a large twin study, estimated that genetic differences accounted for 33–60% of the variance in various aspects of sleep quality and sleep disturbance including several discrete varieties of insomnia. Short-term environmental factors accounted for about 30% of the variance. Evidence for genetic components in sleep disturbance alone could be accounted for by the heritability of sleep requirement or sleep depth. However, other evidence supports genetic components of anxiety and depression [25, 26] as well. As such, it is equally likely that there is a genetic basis for both sleep characteristics and arousal system characteristics that might predispose some individuals to sleep disorders or to arousal disorders.

Traditional therapies for insomnia are successful, within the context of the hyperarousal theory discussed here, if they can precipitate a decrease in arousal. Benzodiazepines have direct effects on metabolic rate [27] and body temperature [28] and might be effective in improving sleep either directly, by reducing arousal, or by having both effects. “Rebound anxiety” [29] could reflect the reappearance of hyperarousal as a short-acting benzodiazepine loses effect. Relaxation therapies reduce metabolic rate by muscle relaxation. Sleep restriction therapy causes partial sleep deprivation, and increased sleep drive could balance the increased arousal level.

The ability of central nervous system arousal to mask sleep tendency leads to several implications including: (1) a probable physiological basis for idiopathic insomnia and hypersomnia; (2) the possibility that these pathologies could be indexed by a physiological measure; (3) the possibility that these disorders may not be solely related to sleep loss or sleep need; (4) that treatment of these disorders might involve long-term modification of arousal level. In practice, this differentiation means that exhorting a lethargic patient to “get more sleep” may be of little benefit if the patient has a low arousal set point. Conversely, behavioral therapy or prophylactic treatment of sleep may not be of benefit to a patient who is chronically hyperaroused. In short, in a group of people there will be a natural continuum of basal arousal levels ranging from the hypersomnolence of idiopathic hypersomnia to the hyperarousal of insomnia, and this continuum may exist independently of sleep need, which may also differ from usual sleep amount.

Level of alertness at a given time could be seen as the combination of the basal arousal level at that time plus amount of sleep pressure modified by various situational factors such as activity level, age, and drugs. As such, the impact of these variables is
Do the complaints of insomniacs reflect their poor sleep?

Throughout this discussion, it has been implied that increased physiological arousal, perhaps as an innate phenomenon, produces an environment in which an individual is prone to report insomnia. Many insomniacs, however, feel that their sleep is the central problem and that the poor sleep leads to their symptoms of fatigue and dysphoria. In our study of chronic caffeine use, for example, it is possible that the changes in mood and alertness that were produced occurred as a function of the poor sleep and not really secondary to hyperarousal. To test the role of the insomniac sleep pattern in the production of hyperarousal and the other symptoms of primary insomnia, the poor sleep found in insomniacs was produced for a week, and subjects were followed for the development of associated symptoms [30]. Primary insomniacs were identified by standard sleep criteria and the sleep parameters of those insomniacs were used in a yoke-control fashion to produce comparable sleep in a group of matched normal sleepers. It was hypothesized that if the yoked normal sleepers developed the spectrum of secondary symptoms seen in the “true” insomniacs after sleeping like the insomniacs, then those symptoms could be seen as secondary to the poor sleep. On the other hand, if the yoked normal sleepers did not develop the symptoms seen in the “true” insomniacs, then some factor other than poor sleep itself would be responsible for the secondary symptoms.

In this study, the EEG sleep characteristics of primary insomniacs were reproduced in a group of carefully matched normal sleepers for a week. Sleep patterns were matched by making experimental arousals and awakenings throughout the night in normal sleepers to match the pattern of wake time and arousals seen in the patients with insomnia. Since the EEG sleep produced in the study was similar to that found in patients reporting insomnia, changes in the outcome variables should have reflected the consequences of pure “poor” sleep. Table 1 provides a summary of typical findings in patients with insomnia and compares those findings with the results of the yoke-control study and the caffeine study. Changes secondary to the poor sleep produced in the yoke-control study were clearly different from the symptoms most frequently reported by insomniacs. Insomniacs typically have difficulty falling asleep both at night and during the MSLT [12-15]. However, both sleep latency and MSLT data from the yoke-control study supported significantly increasing ease of falling asleep as the nights of insomnia increased. Insomniacs frequently have elevated body temperature and whole body metabolic rate [5, 8, 12]. Except for an increase in nocturnal metabolic rate probably associated with the experimental sleep disturbance itself [31], the trends in the yoke-control study showed lower metabolic rate and decreased body temperature during the day. Insomniacs typically report increased stress, anxiety, or depression [1, 12]. However, in the yoke-control study, the state measures of tension and depression decreased significantly during the study. Insomniacs typically have elevated MMPI scales, but the MMPI measures were unchanged in this study. Insomniacs report increased fatigue and decreased vigour, and similar changes were found in the yoke-control study. However, these changes are also found during simple sleep deprivation. Finally, insomniacs overestimate their time spent awake during the night. Despite
increased awakenings and wake time in the yoke-control study, the normal sleepers continued to estimate their wake time during the night correctly.

The most parsimonious explanation for the results was that insomniac sleep given to normals resulted in partial sleep deprivation. The increase in the percentage of REM sleep and rebounds of REM and SWS along with decreasing MSLT values that were found during recovery are clear signs of sleep loss. Decreases in vigour and body temperature also suggest simple sleep loss. Since total sleep time in the study was reduced to 6 hours for a week, this could have resulted in partial sleep deprivation. For example, a study by Rosenthal et al. [32] has shown increased sleepiness on the MSLT after just one night of 5.6 hours of sleep.

In a similar study [33], patients with sleep maintenance insomnia were allowed only 80% of their already reduced total sleep each night for seven consecutive nights. This sleep reduction was accomplished by waking patients up at the end of each quarter of the night if they accumulated more than 80% of their baseline sleep for that quarter of the night (while holding time in bed for the entire night at the baseline level). This paradigm produced very poor sleep (total sleep of 4.2 hours on each night for the week). The literature indicates that there is a significant positive correlation between inability to fall asleep at night and inability to fall asleep on the MSLT in insomniacs [12, 13, 15]. Such a relationship makes sense if CNS arousal level masks sleepiness (i.e. the greater the CNS arousal level, the less likely sleep should occur at any time). It was hypothesized that if the daytime symptoms of insomnia were secondary to the nocturnal EEG values, it would be expected that the EEG laboratory insomnia that was produced would make the secondary symptoms worse. On the other hand, if hyperarousal caused both the poor sleep and the secondary symptoms in patients with insomnia, our EEG laboratory poor sleep would have no effect or might actually improve secondary symptoms that were related to hyperarousal.

In our study with insomniacs, reduction of total sleep time by experimental awakenings resulted in a significant decrease in their daytime MSLT values. After seven nights of 4.2 hours of sleep, MSLT values had decreased from 15.6 to 11.1 min, still within the normal range for the test despite apparent significant sleep loss. Such a result indicates that when the sleep of insomniacs is reduced secondary to simple sleep loss, they display increased sleepiness during the day in agreement with the expectancy in normals but not in insomniacs. Despite the large reduction in total sleep, the insomniacs did not become pathologically sleepy on the MSLT, and this probably indicates the degree to which their hyperarousal was successful in masking their sleep tendency. Of equal interest, these patients did not report significant decreases in their sleep quality when their wake time during the night was increased by two hours. In a similar paradigm with increased wake time of one hour, normal sleepers reported significant decreases in sleep quality. One conclusion from such data is that the reports of poor sleep quality and daytime dysphoria from insomniacs are not directly related to their EEG sleep at all but rather to their level of arousal. In the real world, degree of hyperarousal would vary from night to night. On nights with less hyperarousal, insomniacs would have improved EEG sleep and would also report a good night of sleep, but the change in arousal level could be the cause of both events. For example, Chambers and Kim [34] reported a significant negative correlation between state anxiety at bedtime and reports of feeling rested on the next day in insomniacs but neither anxiety nor reports of feeling rested were significantly correlated with sleep values.
These findings indicate that the consistent secondary symptoms reported by insomniacs arise from their hyperarousal. As can be seen from Table 1, these secondary symptoms appeared in normal sleepers who were hyperaroused [16]. However, because the production of hyperarousal using caffeine TID also produced poor sleep, that study could not determine whether hyperarousal or poor sleep produced the symptoms reported. The results of the yoke-control study and study of increased wake time in insomniacs have eliminated poor sleep per se as a major contributor to those secondary symptoms.

Other support for arousal system influences on sleep

Earlier it was hypothesized that a group of patients would exist who suffered from increased physiological arousal and who also had an increased need for sleep. It was proposed that these patients would report insomnia but would display normal EEG patterns. Sleep State Misperception insomniacs have been shown to have a stable pattern of good sleep with continued subjectively reported insomnia [35]. A recent study compared sleep and metabolic rate in Sleep State Misperception patients and in a group of matched normal sleepers [36]. In this study, the Sleep State Misperception patients, as expected, perceived their laboratory sleep as poor but had EEG parameters that did not differ statistically from matched normal controls. Sleep State Misperception insomniacs had abnormal MMPI values and were subjectively more confused, tense, depressed and angry than matched controls. These observations were similar in direction and magnitude to those seen in patients with psychophysiological insomnia. Sleep state misperception insomniacs were also found to have significantly elevated 24-hour metabolic rate compared to matched normals. The increase in metabolic rate in the Sleep state misperception patients was about 6% overall compared to their controls. In contrast, an overall increase in metabolic rate of 9% was found in patients with primary insomnia as compared to their control subjects [12]. For this reason, it is also possible that the Sleep State Misperception patients had less hyperarousal than the primary insomniacs. However, of more importance, Sleep State Misperception can be seen as a physiological as opposed to a psychological disorder and may be amenable to treatment as a disorder of hyperarousal as hypothesized.

In addition, one might predict that degree of hyperarousal should be related to degree of misperception of sleep parameters. Therefore, we decided to look at several physiological manipulations to determine if they produced changes in the perception of sleep onset. Insomniacs subjectively estimate that it takes much longer for them to fall asleep than EEG measures indicate [37]. One means of examining this phenomenon is to divide the subjective estimate of sleep latency by the EEG estimate to derive a unitless indicator of degree of estimation difference. For example, sleep deprivation or the use of benzodiazepines will decrease level of arousal and were hypothesized to decrease this subjective to objective ratio of sleep latencies. Conversely, administration of caffeine, which increases arousal level, or sleep during the daytime, when level of arousal is higher, should increase the ratio. When these several manipulations were examined in several data sets [38], the hypotheses were generally confirmed. Specifically, results from several studies indicated that the ratio of subjective to objective sleep latency decreased when subjects were given triazolam or diazepam, and the decreases tended to be dose related. Similarly, the ratio of subjective to objective sleep latency decreased during sleep deprivation, and, again, the decreases were related to
the amount of sleep lost. In two tests of increased arousal, the ratios of subjective to
objective sleep latencies increased after an initial night of caffeine consumption and
were greater during sleep periods that began midday than in sleep periods that began
later in the evening. These data supported the contention that the perception of falling
asleep was related to the level of physiological arousal at sleep onset. The consistency
of the findings over six independent studies with several differing designs presents a
persuasive argument that estimates of sleep latency are dependent upon level of
physiological arousal.

These data support the idea that subjectively reported poor sleep or insomnia is a
physiological phenomenon that can be controlled by varying level of arousal. The
point is that poor sleep, whether it be acute or chronic, is a physiological (as opposed
to a psychological) event that is amenable to physiological exploration and modification.

Typical physiological changes found in insomniacs include increased heart rate,
increased body temperature and increased whole body metabolic rate. These elements
and other reported physiological parameters suggest increased sympathetic nervous
system activity. As a result, we have recently begun to explore changes in heart rate
variability in primary insomniacs to determine if this indicator of sympathetic and
parasympathetic nervous system activity is also different in primary insomniacs as
compared to normals [39]. Preliminary data suggests that insomniacs, as expected, have
both increased sympathetic nervous system activity and decreased parasympathetic
nervous system activity throughout all stages of sleep.

These several empirical studies have shown that manipulations of arousal level can
produce or reverse symptoms of insomnia while manipulations of sleep per se cannot
and are persuasive in demonstrating that the reports of poor sleep that we associate
with insomnia are in truth secondary symptoms of elevated arousal. When placed in
context, it is clear that manipulations that significantly increase level of arousal should
produce the symptom complex of insomnia, which may or may not include changes
in EEG sleep parameters (primary vs sleep state misperception insomnia, for example).
EEG sleep parameters should be more related to underlying physiological sleep need.

At another level, it is also clear that therapeutic approaches that primarily seek to
change EEG parameters may be misguided, particularly in the case of sleep state
misperception insomniacs, who have normal EEG parameters and are therefore per-
ceived as having a psychological problem. Therapeutic approaches that have historically
been beneficial in treating insomnia have probably produced success by reducing
sympathetic nervous system activity. However, attempts at desensitization or muscle
relaxation at the point of sleep onset may have little overall impact in patients who
have a significantly elevated arousal set point 24 hours per day. Therapies designed
to treat the total disorder of insomnia need to be developed. For example, physical
training, which produces an increase in parasympathetic nervous system tone, could
be a primary behavioral treatment for primary insomnia. Evidence does exist that
physical training in the elderly [40, 41] can result in improved sleep quality and
circadian temperature rhythm. Treatment with benzodiazepines is effective in reducing
level of arousal as measured by metabolic rate and body temperature [27, 28].
However, use of short half-life medications may only treat the nocturnal symptoms
of hyperarousal but not the daytime component resulting in apparent rebound anxiety.
We have recently looked at lorazepam TID as a possible treatment option in primary
insomnia [42]. From this study it was apparent that lorazepam could help with some
of the daytime symptoms but also that the half-life of the medication was too short
to avoid shifts in mood near the end of medication activity. Nonetheless, the daytime
effects of medications used to improve sleep need to be re-examined. We need to look carefully at 20-minute sleep latencies on the MSLT to determine whether they represent a fully satiated sleep system or whether they represent sleep tendency masked hyperarousal. Finally, investigators need to consider unique medical approaches that decrease sympathetic nervous system activity or increase parasympathetic nervous system activity. Such treatments may have minimal impact on the sleep system per se but may be useful for patients suffering from “hyperarousal disorder”.

Practice Points

Insomnia is a 24-hour disorder.
Consider treatments that can reduce arousal day and night.
Patients with “normal” EEG sleep and an insomnia complaint may still benefit from treatment of their arousal level.

Research Agenda

Development of treatments to reduce sympathetic nervous system arousal.
Are 20-min latencies on MSLT pathological?
Do insomniacs benefit from daytime treatment?

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References


