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Review Article

The Advantages of Substitution of REM Sleep Stages with Waking Episodes to Perform REM Sleep Reduction

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Abstract

A number of significant reports have been devoted to REM sleep deprivation (RSD) methods and effects since REM sleep discovery in humans and animals. Different chemical or nonchemical RSD strategies are often used to understanding REM sleep functional significance or regulation. REM sleep reduction is considered as one of the way to prevent depressive symptoms associated with REM sleep abundance. However, it has been difficult to find valid nonchemical technique to perform RSD without accumulation of the need for REM sleep or its rebound after cessation of awakening manipulations. The present review is aimed to assess the validity of well-known 'classical' RSD strategy and less-known method of REM sleep substitution with waking episodes on the basis of consideration of consecutive effects. Despite that classical method is non-stressful and does not affect motivational-emotional behavior or learning/memory consolidation, sleep-wake architecture is destroyed because of increased REM sleep propensity led to developing of dissociative processes during deprivation, and quantitative/qualitative increase of REM sleep is appeared in post-deprivation period that diminishes effectiveness of classical RSD using for basic or clinical purposes. Comprehensive discussion of the results of REM sleep substitution with active waking episodes allows making conclusion about availability to perform RSD without increasing of propensity and quality of REM sleep or occurrence of selective rebound of this unique sleep stage. It is suggested that insert of waking episodes following forced awakenings from REM sleep would be effective for the prevention of endogenous depression through the correction of destroyed sleep architecture due to increased REM sleep pressure and improvement of mood as well.

Keywords: *REM Sleep Deprivation; Sleep-Wake Architecture; REM Sleep Quality*

An alternation of different states of sleep-wakefulness cycle (SWC) is developed on the basis of complex and highly organized neurophysiologic and neurochemical processes. The structure of SWC itself precisely reflects homeostatic processes, taking place in the brain [1]. There is an optimal relationship between different stages in normal SWC [2-4]. A gradual accumulation of neurohumoral factors and dynamic formation of specific inner need for one or other sleep stage promotes onset and development of every subsequent stage [1,3-9]. Since the discovery of rapid eye movement (REM) sleep [10], so-called paradoxical sleep [11], many original reports have been devoted to the understanding functional significance of this unique sleep stage. In this purpose different non-chemical instrumental techniques or chemical strategies have been elaborated for REM sleep deprivation (RSD) considering comprehensive effects of REM sleep lack. Non-chemical RSD is often used in clinical sleep research for the improvement of mood and depressive state which is characterized by REM sleep augmentation. However, prevention of REM sleep pressure during deprivation or REM sleep rebound in post-deprivation SWC has been remained an actual problem in sleep science.

This report is aimed to assess the validity of 'classical' method for RSD [12] and less-known comparatively novel method of REM sleep substitution with waking episodes [9,13,14] on the basis of consideration of quantitative and qualitative changes in the SWC architecture due to two RSD strategies.

It is well-known that classical method for RSD entails forced awakenings of experimental subjects at the onset of every REM sleep episode. This method is considered as non-stressful as the deprivation procedure is performed in the same environment where baseline SWC is registered and the subjects are already adapted to the experimental conditions; therefore stress factors are more or less limited [9,14]. However, W. Dement who carried out first RSD experiments in humans [12] as well as other researchers reported that progressively increased forced awakenings to prevent REM sleep developing make difficult or even impossible to perform REM sleep elimination for more than 2-3 nights [2,15-18].

Nonchemical strategy of short-term RSD through forced awakenings has been more frequently used in humans than animals [19-28]. Moreover, it is known that REM sleep reduction has anti-depressive effect [3,29-36]. Therefore, the evaluation of the classical method based on comprehensive assessment of its effects would be important for basic and clinical sleep research.

When we consider consequences of 72-hour REM sleep elimination in cats that was performed by the using of external stimuli or electrical stimulation of midbrain reticular formation [6,8,9,13,14], it should be noted an increase of REM sleep pressure along with prolongation of deprivation session, and accordingly forced awakening manipulations were used more and more frequently. However, acceleration of emotional tension following awakenings was not observed as high activity of brain structures, characteristic of REM sleep was passed into comparatively low level without any significant changes in the heart rate [8,37].

An assessment of the effect of REM sleep reduction by classical method on the dynamics of heart rate, excitability of brain structures, motivational processes or elaboration of conditioned alimentary reflexes allowed us to declare that REM sleep restriction carried out in not-stressful situation does not considerably affect central nervous system, motivational-emotional behavior, or learning and memory consolidation . Therefore, we cannot agree with the group of those researchers [17,38-43], who explain alterations in physiological processes by REM sleep lack. Moreover, neurophysiological analysis of the RSD, performed by method of REM sleep substitution with waking episodes [4,6,8,13,14,45-47], on the one hand and Horne's review on assessment of neurobiological significance of REM sleep [32], on the other hand, give us reason for debates. It should be also noted here, that REM sleep reduction conducted in rats by stimulation of MRF, causes neither alterations of emotional-motivational behavior of rats, nor stress [48]. As in the deprivation session an amount of slow-wave sleep (SWS) doesn't decrease either, and in recovery day SWS rebound doesn't develop, it might be supposed that in the case of classical RSD more or less selective loss of this sleep stage is occurred [4,5,44,45,47,49]. In this respect, 'classical' method for RSD seems suitable among non-chemical techniques. However, following detailed assessment of changes in cat's SWC architecture due to classical RSD it was found that regular alternation of SWC stages was disturbed because of REM sleep pressure which was gradually and progressively accelerated along the prolongation of deprivation session [9,13,14,44,49,50,51]; there were observed dissociative processes and intervention of phasic or tonic components of REM sleep (such as ponto-geniculo-occipital (PGO) waves or theta-rhythm) in SWS or even wakefulness [2,18,50,52]. This phenomenon was considered as the evidences of partial satisfaction of REM sleep need [2,53-55]. In our opinion the EEG dissociation is a result of self-awakenings from REM sleep which is elaborated like classical conditioned reflexes that make a false expression on the isolated occurrence of REM sleep features in other sleep-wake stages [9,50-52]. On the other hand, REM sleep may appear between forced restriction and self-awakening trials even before SWS onset that may be also is a reason of incorrect assessment of isolated appearance of any signs of REM sleep during EEG recordings of the wakefulness. Moreover, the cases of the REM sleep onset on the background of muscle tone in prolonged deprivation sessions we may consider as sleep abnormalities characteristic of some neurological sleep disorders such as REM sleep without atonia or narcolepsy. Unfortunately, less attention have been focused on above-described facts in the REM sleep deprivation studies performed in humans [3,19-22,24,28,32,36,55-57].

REM sleep augmentation and decrease in the latency, characteristic of endogenous depression in humans, as well as REM sleep rebound after cessation of deprivation manipulations are described on the animal model of depression [36]; such features with increasing fragmentation of sleep have been shown in other works too [58], manifesting behavioral and hormonal disorders similar to depression [59] that is considered as the consequences of strengthening of REM sleep propensity [6,8,9,13,20,28,47,49,50,56,60,61,62]. We agree with the researchers who reported that a sharp increase of forced awakenings required to restrict REM sleep in healthy subjects reflects the intensification of homeostatic drive of REM sleep [20,28,34] though they explain the 'release' of REM sleep by the decreasing of SWS intensity as well. In our opinion, the cause of the latest is REM sleep pressure due to frequent forced restriction of this sleep stage or its self-deprivation.

Comprehensive assessment of changes in sleep-wake architecture in recovery following classical RSD showed a significant decrease in waking state accompanying with REM sleep latency decreasing and selective rebound of REM sleep with strengthening its 'orchestra' manifested in the increase of the frequency of phase components of REM sleep (i.e. rapid eye movements (REMs) and PGO-waves) and heart rate [6,8,9,13,14,44,49] that confirms REM sleep increase in quantity and quality and intensification of brain mechanisms responsive for REM sleep developing.

Taking into account that endogenous depression is accompanied by the increasing tendency to REM sleep [26,27,35,57] and that in the period of deepening of depression state significant decrease of REM sleep latency, prolongation of episodes of REM sleep and increasing of frequency of grouped rapid-eye-movements are often described, the open questions remain concerning priority and effective using of classical RSD for the improvement of depressive state. Here we should mark the study [63] where attention is focused on significance of mechanisms involved in REM sleep regulation and impossibility of studying of pathophysiology of depression in the conditions of increasing of frequency of forced awakenings from REM sleep. In this respect, it is interesting, that some researchers [23-25] do not agree with the opinion of Vogel [36,55,57] about antidepressant effect of RSD. M Grözinger with his colleagues performed RSD via classical method in depressive patients [25] and noted that though symptoms of depression lessened after deprivation night, the patients' mood worsened following recovery nights what the authors explained by REM sleep rebound [23,24]. Accordingly, our presumption, that classical method is not adequate to perform RSD in the purpose of the prevention of depressive symptoms has been approved.

Having discussed the scientific literature relative to consequences of REM sleep nonchemical reduction, it is difficult to find any strategy not leading to the increase of the intensity of brain mechanisms of REM sleep in deprivation or recovery periods. REM sleep rebound, even delayed, is characteristic of almost every instrumental technique as well as chemical method. However, the strategy of substitution of REM sleep stages with active waking episode seems most adequate and valid to perform selective and complete reduction of REM sleep in SWC. Through the using of this method it has been possible to avoid increase of specific need for REM sleep, without noticeable changes in sleep-wake structure, motivational-emotional behavior, learning or memory [4,8,9,14,44,46,47,51].

The occurrence of spontaneous insert of more or less duration of waking episodes in SWC in the case of prolonged classical REM sleep deprivation following progressive increasing frequency of forced REM sleep restrictions and significant delay of further appearance of REM sleep features in cats indicate that the active wakefulness is really 'able' to satisfy the need for REM sleep [5,9,44,46,47]. Competitive relationship between waking and REM sleep is evident also in the recovery where total amount of wakefulness was decreased because of increase of REM sleep in quantity or quality, after cessation of classical RSD manipulations, in recovery.

It should be noted that REM sleep substitution with active waking episodes in cats does not lead to the dissociative processes, decrease of the REM sleep latency or increase of the pressure of this sleep stage or its selective rebound unlike classical or other non-chemical RSD deprivation strategies if restriction of every REM sleep stages is followed by the maintenance of active waking episodes equal with average duration of REM sleep episodes in cats [9,13,14,46,47] or healthy subjects where waking state was maintained for 20 minutes [51] according mean duration of REM sleep in young adults; otherwise, intensification of need for REM sleep is expectable as in the studies where after forced awakenings from REM sleep the subjects were required to stay in the waking state for 2-3 minutes [20,22] a dynamic increasing of REM sleep frequency was not prevented though this increase was not as progressive as in the case of classical RSD. Increasing of wakefulness up to 15 minutes turned out to be more effective for avoiding REM sleep pressure [64] though insignificant increase

of both - REM sleep onset in the second deprivation night and increase in REM sleep percent in the recovery night still takes place. Taking into account that usually REM sleep episode on average is 20-minutes in healthy young adults, it would be better, in our opinion, if the subjects were not allowed to fall asleep in this period of time; however, it is important to underline here, that retaining of 15-minute waking episodes following REM sleep interventions causes neither daytime sleepiness, nor worsening of attention and mood [64].

When discussing effect of RSD on sleep-wake architecture, an assessment of SWS quality in deprivation or post-deprivation periods is also required special attention. In the case of using classical method for RSD, decrease of slow-wave-activity in human's nocturnal sleep is described in a number of reports [3,20], while REM sleep substitution with active waking episodes turned out to be effective in terms of improvement of SWS quality [51]. Not less important is that that during deprivation nigh self-awakenings from REM sleep were observed at the very beginning of REM sleep episodes even before any interventions [51]. T Oniani declared a very original idea on self-deprivation phenomenon: "In this case we deal with a well-known to date phenomenon of self-deprivation, forming of habit by the principle of conditioned reflex, which develops on the grounds of lucid dreams; hence, it's obvious that human brain is able to act in a highly coordinated way and manifest complex integrative psycho-physiological processes even in the period of REM sleep, as well as in waking state". J Horne's opinion that definite portion of REM sleep is not necessary and can be replaced by wakefulness [32] properly conforms to above-mention.

The findings, that REM sleep replacement by wakefulness is not followed by decrease of REM sleep latency, intensification of theta rhythm, or increasing of frequency of PGO-waves and REMs or heart rate in post-deprivation REM sleep episodes, undoubtedly can be considered as a positive consequences indicating that this strategy does not lead to enhancement of either intensity, or quality of REM sleep in the recovery [8,9,13,14,45,46] and accordingly activation of brain mechanisms responsible for REM sleep triggering or increasing of excitability does not take place there unlike the consequences of classical RSD [8]. As noticeable changes in motivational-emotional behavior are not observed in the case of using method of REM sleep substitution with wakefulness this strategy has already deserved attention of sleep researchers [17,20,32].

As discussion on the relationship between REM sleep and memory processing is still actual in modern sleep science, it is important to mark the studies where is shown that REM sleep lack has no negative effect on the learning or memory consolidation if RSD is performed in non-stressful conditions through maintenance of waking state (8 - 10 min-in-duration) following REM sleep restriction [8,9].

An assessment of the strategy of REM sleep substitution with active waking state allows concluding that waking state prevents an accumulation of the need for REM sleep. Although open questions or debate remain, the overall evidence suggests that an insert of active waking episodes is not accompanied with increasing REM sleep propensity and does not lead to selective REM sleep rebound [8,13,46].

With respect to the evidences mentioned above, the method of replacement of REM sleep by active wakefulness could be assessed as a valid strategy for selective RSD, because it does not cause significant changes in integrative activity of the brain [9]. The model of replacement of REM sleep by active wakefulness was patented in National Intellectual Property Center of Georgia - "Sakpatenti" as a useful way for the improvement of human's mood. It is suggested that this less-known method could be advisable for basic and clinical sleep research. Moreover, the evaluation of sleep-wake stages in quantity or quality during deprivation or recovery gives us a basis to recommend the strategy of REM sleep substitution with wakefulness for using it in practical medicine to prevent symptoms of depression which are related to sleep abnormalities due to increasing of REM sleep propensity. An approbation of this method in healthy young adults [51] as well as depressive subjects (found in the limits of the ISTC Project), encourages us to make such recommendation [65,66].

Conclusion

Though a 'classical' RSD strategy is considered as non-stressful way for REM sleep reduction in humans or animals, increasing of REM sleep pressure with the deterioration of SWC architecture, developing of dissociative processes, worsening of SWS quality and abnormal onset of REM sleep during deprivation or decrease in its latency as well as REM sleep increasing in quantity or quality in post-deprivation

SWC, clearly indicating an enhancement in emotional tension or brain excitability during REM sleep, make questionable the validity of classical method. Moreover, as acceleration in REM sleep disposition along with weakening of brain mechanisms of wakefulness is characteristic of endogenous depression, it is expected an augmentation of depression with mood worsening instead of antidepressant effect.

A less-known RSD strategy – REM sleep substitution with waking state should paid an attention as it does not cause any significant changes in integrative activity of the brain and is not accompanied by accumulation of a specific need for REM sleep or its selective rebound and increasing of REM sleep quality in contrast to other non-chemical RSD techniques; an improvement of SWS quality following insert of active waking episodes is no less important. Thus, comprehensive assessment of this RSD strategy allows recommending it for basic or clinical sleep research. The substitution of REM sleep episodes with wakefulness would be effective in terms to prevent SWC abnormalities due to increased REM sleep propensity as well as to improve the mood in depressive subjects.

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