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**Fatemeh Erfani Sharifian, Farideh Bahrami, Hamed Yeganegi & Mehdi Geraily Afra**

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ORIGINAL ARTICLE

# Alteration in REM sleep and sleep spindles' characteristics by a model of immobilization stress in rat

Fatemeh Erfani Sharifian[1,2] · Farideh Bahrami[1,2] · Hamed Yeganegi[3] · Mehdi Geraily Afra[2]

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## Abstract

Investigation of sleep spindles' oscillations is increasingly considered as a major avenue of inquiry in analyzing the micro-architecture of sleep. Previous studies highlight a strong mutual interaction between sleep and stress. In the present study, we investigated the effects of multiple stresses, provoked by animal immobilization in the narrow Plexiglas boxes with additional stress by placing some stones on the floor. Male Wistar rats ($n = 14$) were subjected to 2 h of immobilization per day in a narrow, uneven and stony place for 3 consecutive days. The electroencephalogram (EEG) was recorded with stainless steel screw electrodes placed over the skull and the electromyogram (EMG) was recorded from dorsal neck muscles. The sleep stages were recorded during 2 h before and 2 h after stress exposure for 3 days. Apart from sleep stages' variations, sleep spindles' density as well as their time- and frequency-domain characteristics were investigated rigorously by a semi-automatic sleep scoring method developed in MATLAB. Results indicate that multiple stresses containing immobilization as well as physical stress attenuate rapid eye movement sleep (REM). However, the stress effect on spindles is more sophisticated in NREM stages. Although spindle density does not undergo a significant change, spindle amplitude and sigma power of EEG during spindles raised significantly. Besides, a decrease in the mean frequency of spindles depicts a dramatic multiplication in delta slow oscillations. An especially mixed immobility including psychological and physical stress which we applied could affect sleep stability through an alteration in the sleep spindles' amplitude and frequency but not the density of spindles and also through a reduction in REM sleep.


**Keywords** Immobilization stress · Sleep spindles · REM sleep · Non-REM sleep

## Introduction

According to animal studies [1, 2], the sleep spindles are usually defined as distinct electroencephalography (EEG) waves having a frequency of 7–14 Hz with almost 0.5–1 s duration and usually maximum amplitude over central brain regions. Sleep spindles are related to cross-talk between thalamic reticular and cortical pyramidal network. These thalamocortical loops control the sleep spindles [3] and the spindles' properties alter during lifespan [4].

✉ Farideh Bahrami
faridehbahrami@protonmail.com

1 Neuroscience Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

2 Department of Physiology and Medical Physics, School of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran

3 Research Department, Science Beam Co., Tehran, Iran

Recent studies have dramatically highlighted the role of sleep spindles in cognitive processes. Astori et al. discussed the role of spindle activity in neuronal development, by considering associations between increased spindle activity and neuro-developmental milestones [5]. Fogel and Smith provided a review of a compelling body of evidence that establishes a relationship between the function of sleep spindles and intellectual ability and memory consolidation [6]. Besides, many studies offer important interactions between spindles and brain dysfunction and the pathophysiology of disease [3]. As an example, it has been shown that generally aging as well as Alzheimer's disease associated with a reduction of spindles [7].

Stress is a multidimensional phenomenon that consists of the stimulus, cognitional processes and physiological response of the organism [8]. It has been associated with negative health effects and can lead to sleep disturbances. In patients with various mental or physical disorders such as depression, chronic fatigue, post-traumatic stress disorder

(PTSD), burn out syndrome, severe sleep disturbances or various forms of insomnia are observed [8, 9]. Animal studies have shown significant alterations in sleep stages and sleep architecture caused by various kinds of physiological and psychological stress [9].

Immobilization is one of the common procedures for stress induction in the rodent. In some cases, immobilization is considered as a 'psychological' stressor [10, 11]. There is a report that 2 h of immobilization in the dark phase increases the paradoxical sleep [12]. Gonzalez proposed 1 h of immobilization increases both REM and NREM sleeps, their study indicated the role of the noradrenergic system in this increment [13]. Another study reported the increase in REM and NREM sleep during the 11 h following the immobilization stress which may be due to sleep recovery [14]. It is also shown that the time of immobilization before stress has different effects on rats. Animals with 2 h immobilization had shown to expand NREM sleep, but 4 h showed no increment [15].

The long periods of immobilization were associated with decreases in REM sleep and SWS [16, 17]. According to the study of Tang et al. in 2005, restraint stress could decrease REM sleep for 2–3 h in C57BL and BALB mice that correspond to the increase in plasma corticosterone [18]. As Aaron et al. have mentioned in 2008, stress effect on sleep depends on the animal's first stress reactivity [19].

As the literature portrays, the influence of immobilization stress on different sleep stages has somewhat been investigated but the study of its influence on sleep spindles has been neglected yet.

During the past decades, a key limitation for sleep researchers has been the lack of automated systems for sleep scoring and analyzing electroencephalography (EEG) oscillations. Although visual scoring is still the gold standard but is time-consuming and is affected by subjective judgments [3].

Because of strong ties between sleep spindles and cognitive abilities, stress may affect cognitive function through influence on sleep spindles and perhaps contribute to cognitive disorders.

The present study aims to investigate, how the psychological stress (immobilization) combine with physical stress (narrow place and stony texture), influence the sleep spindles, both in terms of density as well as their amplitude and frequency characteristics, apart from effects on sleep stages.

## Methods

Fourteen male Wistar rats weighing 200–250 g and 2–3 months old were used in this study and divided into two groups, control ($n=7$) and stress-subjected group ($n=7$).

### Stress protocol

All rats were adapted with laboratory conditions for 1 week. For stress application, we used Hoheisel et al. methods with some modifications [20]. The animals were placed in a narrow Plexiglas box with 16 cm length and 7 cm inner diameter which were flooring with some stones. The rats in the stress-subjected group were immobilized at the same time of day during the light cycle for 2 h per day in 3 consecutive days.

### Electrophysiological recording of sleep

Electrophysiology recordings were performed before and after stress exposure during daylight. A total amount of 4 h were recorded from each animal (2 in the baseline, 2 post-stress). The animals were anesthetized with Ketamine (65 mg/kg) and Xylazine (15 mg/kg) and fixed on a stereotaxic apparatus. Three stainless steel screw electrodes were implanted in the skull for EEG recording and the electromyogram (EMG) was recorded from dorsal neck muscles via two Teflon-coated stainless steel wire electrodes. The EEG and EMG data were collected by the electrophysiology recording system (Ruby Mind, NY, US) in the 3000 Hz sampling rate. The signals were amplified and filtered (EEG 0.5–40 Hz, EMG 15–500 Hz).

### Semi-automatic sleep scoring

The sleep stages were extracted semi-automatically using EEG and EMG recordings. The procedure for sleep scoring is as follows. First, three distinct and typical samples from EEG and EMG that were corresponded to wake, SWS, and REM were extracted by visual inspection. Each part was at least 30 s. Then, a KNN classifier was developed in MATLAB (Math Works Inc., Natick, MA) to categorize every 5 s bin of data into the three relevant classes based on available visually extracted samples. KNN classifies each part of recorded sleep data based on the similarity of EEG and EMG of that part to the visually identified parts.

### Automatic sleep spindle detection

The methodology to automatically detect sleep spindles is similar to that of [22]. We exploited the unique temporal frequency components of spindle events. In human studies spindles are defined as transient oscillations in a particular frequency range, usually the 12–16 Hz range [21, 22]. However, in a more general sense, particularly to monitor spindle frequency alterations during the human lifetime, the broader 8–18 Hz band has been adopted as spindles' central frequency [23]. In this study, we calculated the EEG spectrogram along time and using spectrogram values, extracted the power of the extended sigma band (12–20 Hz). To identify spindle events having the power in this band, a threshold was defined and a spindle was identified as the sigma power exceeded this predetermined threshold. We utilized a 12–20 Hz frequency range to extract power as it led to the most accurate detection in our data and also fine-tuned the detection threshold value in such a way to boost conformity with visual identification of sleep spindles. We also add the criteria for spindles to last between 0.5 and 2 s. The procedure was developed as a MATLAB script.

### Statistical analysis

The paired *t* test statistical analysis was performed for comparing the different variables (total time of REM, NREM, and wake as well as sleep spindle density before and after stress exposure) in baseline and post-stress sleep, after averaging three days (the *P* values less than 0.05 were considered as significant).

For spindles, we computed amplitude in terms of root mean square (RMS), power of different frequency components within spindle (Fourier analysis), as well as the mean frequency of spindles. Mean frequency is the weighted average of the diverse frequencies (Fourier components) in the EEG wave weighted by their corresponded power. The computations were conducted in MATLAB. To compare results across the groups, a paired *t* test was carried out with 0.05 level of significance.

## Results

### Stress effects on sleep

Daily assessment of sleep stages after 2 h immobilization in the narrow, uncomfortable stony place indicated reduction trend in post-stress REM sleep which was significant in third day ($P < 0.05$) (Fig. 1a), but there were no significant changes in NREM and vigilance time (Fig. 1b, c). On the third day, an increase in REM sleep was observed before exposure to stress position which may attribute to stress induction in previous days (Fig. 1a). Adding up the value of sleep stages during 3 days showed also a small but significant reduction in REM sleep no variance was observed in NREM and wakefulness times (Fig. 1d).

### Sleep spindles' detection

A segment of EEG recording along with its spectrogram and 10–20 Hz band power is presented in Fig. 2. The first

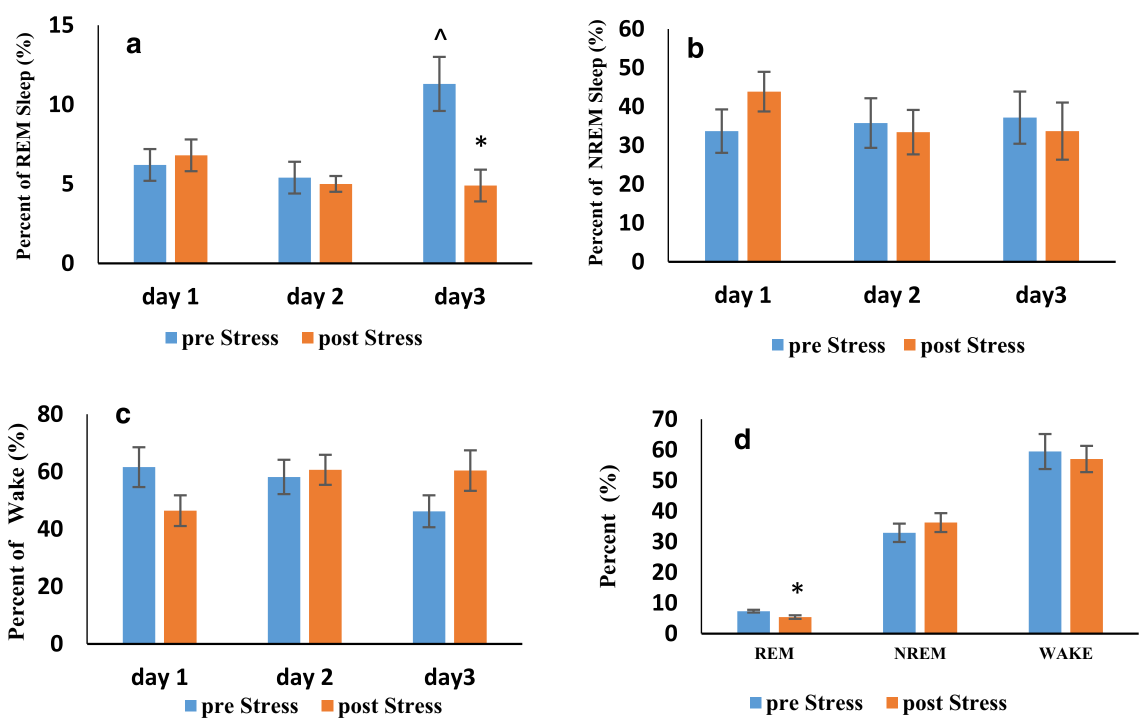


**Fig. 1** Alterations in sleep stage durations before and after exposure to immobilizing conditions. REM sleep has undergone a significant reduction in the post-stress condition in the third day (**a**), and in the sum of sleep during 3 days (**d**) $*P < 0.05$. An increase in REM sleep was showed in the third day before stress exposure in comparison with the first-day baseline (**a**) $\^{}p < 0.05$

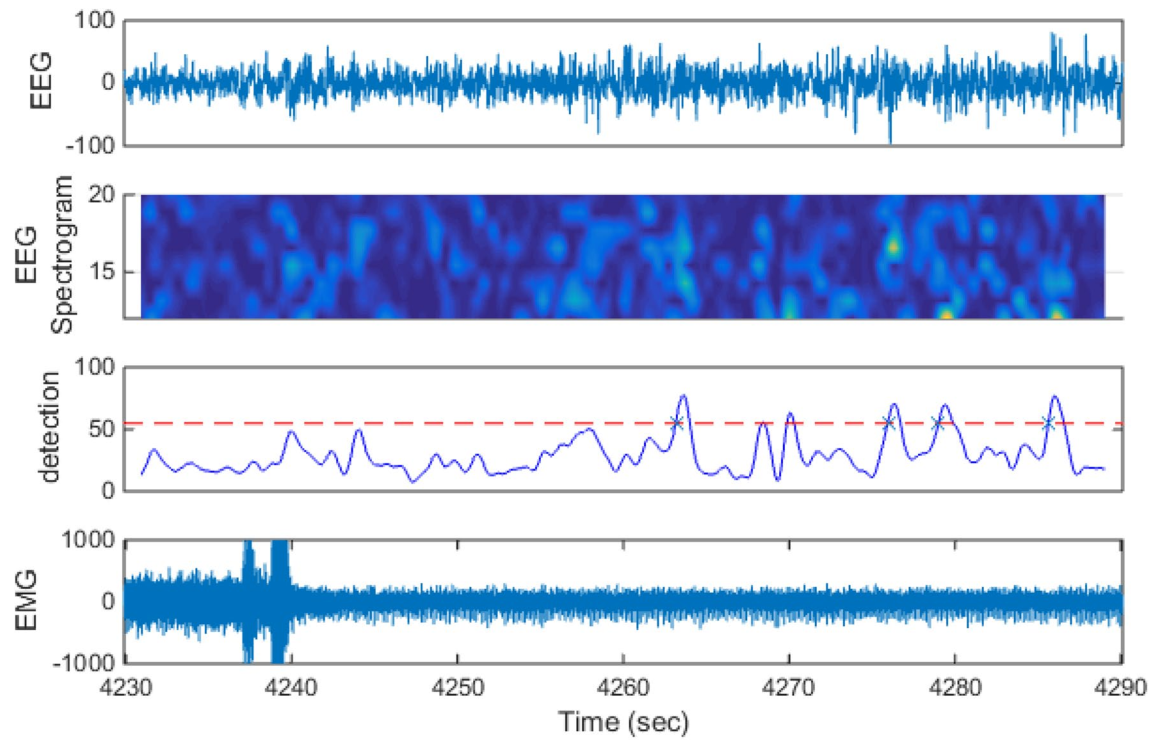


**Fig. 2** Spindle detection procedure: First row: a 1 min extract of EEG containing four spindle bursts in the last half of the data. Second row: The spectrogram shows the power of different frequency components at each time instant; hot spots (yellow ones) imply high power of sigma oscillations in the corresponded times. As it appears hot spots (high powers) are recognizable during spindles. Third row: The total power of the 10–20 Hz band (blue solid line) was calculated by integrating the spectrogram over all frequencies. Spindles are discernible straightforward by comparing the total power with a predetermined threshold value (dashed red line). Fourth row: EMG level verifies that the spindles have accrued not in stage one NREM nor paradoxical sleep

trace of the figure indicates the EEG signal which consists of bursts of spindles. The second trace shows the spectrogram in which its hot spots are in synchrony with bursts of spindle occurrence in EEG trace (the hot colors with 10–20 Hz frequency). The third trace in this figure (blue line) represented the sum of power in the 10–20 Hz frequency band and the red dash line portrays the detection threshold. In four points the occurrence of spindles was identified and they correspond with picks in-band power (third trace) and hot colors in the spectrogram (second trace). The fourth trace indicated EMG and verifies being in NREM sleep (Fig. 2).

Figure 3 illustrates the subsample of sleep spindles identified by our semi-automatic method in the part of the signal already shown in Fig. 2. This figure presents a detailed view of the time and frequency features of the spindles.

## Stress impact on sleep spindles

The percentage-based density of spindles' occurrence has been shown in Fig. 4, the data indicated that the 2 h immobilization in an arrow, stony place for 3 days could not change significantly the total number of sleep spindles. However, as we will see, it could change the amplitude and frequency of spindles as follow:

To compare amplitudes, the root mean square (RMS) of spindle waves was calculated in both groups. The mean RMS amplitude in pre- and post-stress groups was 54.3 µV and 62.7 µV, respectively. Spindles' amplitude has increased significantly after stress ($p < 0.05$).

We calculated the power of different frequency components for spindle waves, before and after stress exposure. The result is depicted in Fig. 5. As expected there is a local maximum in both groups at the frequencies of spindle range (around 16 Hz) since, by definition, spindles come by a rise of power in this band. However, the pattern differs in the two groups in two distinct frequency ranges, 2–3 Hz and 12–23 Hz. The power of these oscillatory components has increased after the stressful condition.

The difference is significant for all frequencies of 2–3 Hz and 12–23 Hz. However, the level of significance is different and the values are depicted in Fig. 5 using asterisk convention.

In total, we identified 2337 spindles in before-stress data and 2939 in the recordings after stress exposure. We calculated the relative power for two different frequency

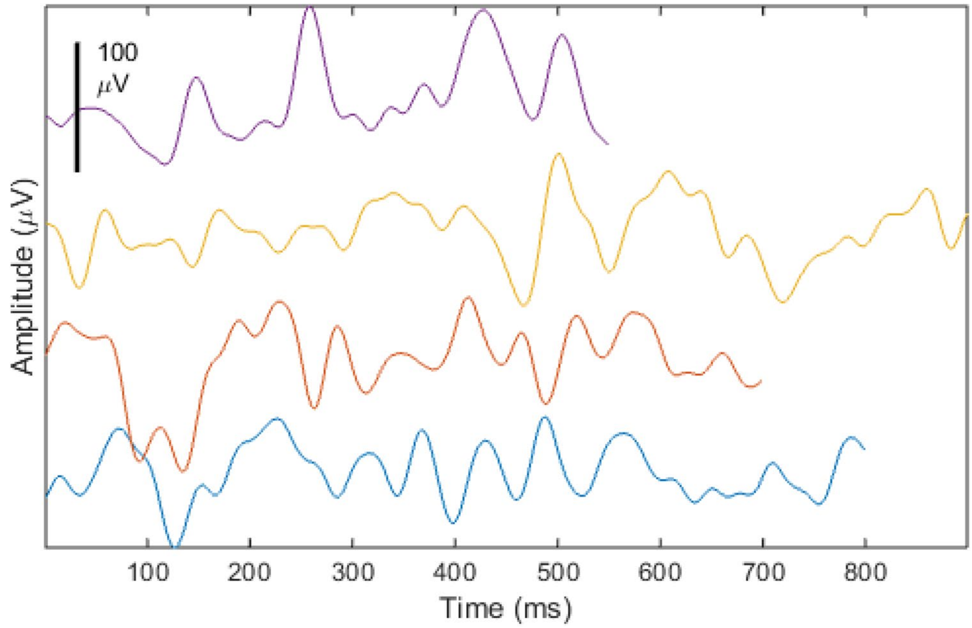


**Fig. 3** The samples of four identified spindles in the part of the signal shown already in Fig. 2 shown on an extended time scale. Spindles' duration is constrained between 0.5 and 2 s; here all of them last for less than one second

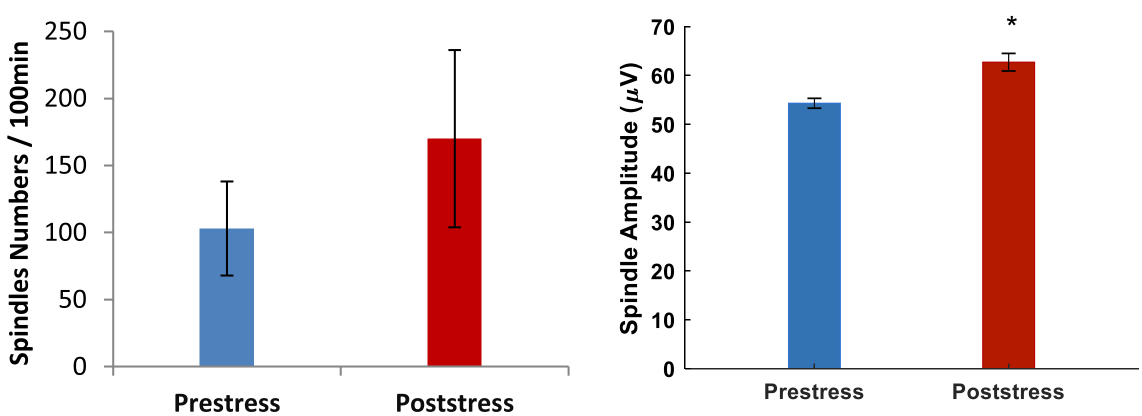


**Fig. 4** Changes in occurrence rate and amplitude of spindles before and after stress. Left: On average, immobilization stress has raised spindle density. But the growth was not significant. Right: The stress increased the amplitude of spindles significantly, as quantified by RMS of the waves. Height and error bars display mean and standard error, respectively

bands, 2–3 Hz (delta), and 12–20 Hz (beta), in spindles before and after stress exposure. To do so, the power of those specific bands is divided by the total power in the whole frequency range of 0–500 Hz. In delta band power has increased significantly from 11.98% to 15.12% ($p < 0.001$, two-sample $t$ test). Beta band power has risen, almost significantly, from 13.75% to 14.55% ($p = 0.056$, two-sample $t$ test).

Briefly speaking, stress has expanded both sigmas as well as low frequencies. This is consistent with our earlier result that the overall amplitude of the spindles has raised after exposure to stressful conditions.

## Discussion

### Sleep changes with stress

The results of this study indicated that 2 h immobilization for three consecutive days could change the REM sleep stage. Although there was a rebound in REM sleep on the third day immediately after stress exposure, it decreased significantly and the sum of the REM sleep during the 3 days also demonstrated a reduction in REM sleep.

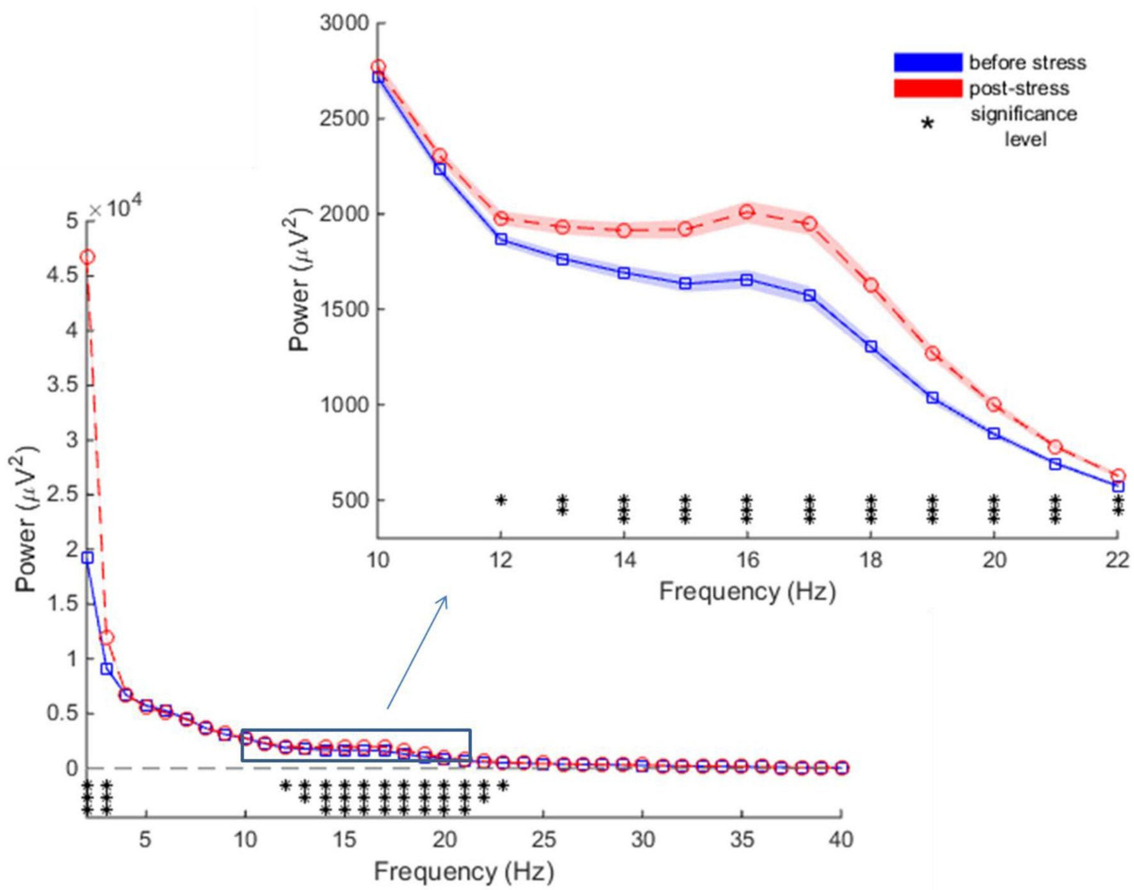


**Fig. 5** Power of different frequency components during spindle events for the two groups. After exposure to immobilization-stress conditions (red traces) the frequency component of spindles changes at two distinct ranges 12–23 Hz, essentially spindle range, and low (2–3 Hz) frequencies. The inset zooms in the spindle-range frequencies. Solid lines represent mean and the shadows indicate one-standard-error interval. A number of asterisks indicate the level of significance between groups. 1, 2, and 3 asterisks corresponds to $p$ values equal to 0.05, 0.01, 0.001 accordingly

From a biochemical point of view, several neurotransmitters in the nervous system are believed to regulate the sleep pattern: noradrenergic (NA) induce waking, release of Acetylcholine (Ach) from the pontine reticular formation induce and regulate REM sleep and serotonin (5HT) is involved in the regulation of delta sleep [24]. It is worth noticing that a number of common brain regions mediate both stress and sleep processes; the two main systems, the locus coeruleus in the brain stem and the HPA axis, are involved in the regulation of stress [25]. In the HPA axis the ACTH, in turn, increases waking by reducing REMs [19, 26], and noradrenergic neurons of locus coeruleus interact with both sleep and stress phenomena.

One of the important factors which manipulate the effect of immobilization stress on sleep is length or period of it. As mentioned in the introduction 1 or 2 h of immobilization could increase REM sleep [12, 13] but a long period of immobilization could decrease it [16, 17]. Mariansco and his co-workers reported the curve of sleep rebound against the length of immobilization stress during 2 h of immobilization, the percent of NREM sleep rebound decreased as well as REM sleep, but after 4 h, the curve inverted and the rebound was suppressed [15, 27]. These data confirm our results which 6 h immobilization during three consecutive days could decrease the REM sleep.

Furthermore, the nature of the stressor is the other important variable that has been investigated by Pácak and Palkovits in detail [28]. However many investigations depict that a mild and short restraint is not a high-stress condition for animals and stress intensity is an important factor for subsequent sleep [19]. Numerous studies report the REM or NREM sleep rebound as an adaptive response to stressful conditions [27]. Palma et al. in a comparative study provided evidence that 1 h of physical, psychological, or mixed stimuli lead to an expansion in SWS, REM, or alertness times, based on the stressor type.[29, 30]. In our study, we applied mixed of psychological stress (immobilization) and physical stress induced by stony and narrow place. This immobilization model over ally leading to a reduction of REM sleep. It seemed that REM sleep rebound occurred before the last session of stress but it suppressed with stress exposure.

### Methodology in sleep signal processing

Recently many investigations are focused on the issue of spectral analysis of EEG and sleep spindles during rhythmic neural activity of sleep which proved to be useful in sleep disorders recognition [33]; in this regard, scientists utilize several methods for sleep oscillation measurement: the gold standard method is visual scoring conducted by a sleep EEG expert and the second, and most recent one is based on automated analysis using event detector algorithms or using tracing spectral power within specified frequencies, e.g. 10–14 Hz for detection of sleep spindles. Considering the problem of time-consumption well as the conundrum of diversity in subjective judgments in visual-based scoring; a large body of investigators prefer to take advantage of computer-based automated methods [31]. On the other hand, the automated methods are affected by the algorithm and detector parameter settings such as signal duration and frequency and amplitude characteristics which have been chosen by the signal analyzer. Previous studies indicate that automated procedures that consider both amplitude and temporal features of spindles outperform the ones that are based solely on amplitude [6]. In this study, we exercised the use of an automated routine which was based on sigma power in the EEG signal. Furthermore, we considered duration criteria, as well as EMG amplitude to satisfy the condition of occurrence in SWS.

### Stress impacts on spindles

It is also noticeable that based on recent studies, although during sleep generally synaptic activity in brain declines in some areas synaptic transmission strengthens and this is essential for many physiological and psychological functions [25]. The occurrence of spindles' activity which is generated in the cross-talk between thalamus and cortex are an example of this activity or transmission during sleep [32].

The investigators argued that spindle activity contributes to neuronal development and memory consolidation, and maintenance of sleep continuity. They reported increased spindle activity/density following exposure to a pre-sleep learning task, and positive correlations between spindle parameters and post-sleep test performance [33] . The spindle damages during stress may be the causal effect of stress on learning and memory.

According to the study of Thien Thanh Dang-Vu stress, full condition induces insomnia which is predictable by lower spindle activity at the beginning of the night and this incident is affected by individual differences in the activity of spindles [34].

Although the relation between sleep spindles and cognition is well known and also some studies examine sleep spindles in different kind of sleep disorders [35], but unfortunately less is known about spindle oscillation during stress condition and in this study, we focused on sleep spindle characteristics include density, frequency, amplitude, and duration in a special model of immobilization which may be the novelty of our investigation.

In our study, the immobility stress did not induce insomnia and did not increase the total sleep time but affected the REM sleep and shrinkage in it. Although the spindle density experienced growth it was not significant. However, the power of oscillatory components of spindles below 16 Hz was damped after stressful conditioning and the spindles' amplitude has increased significantly after stress and also calculating the root mean square (RMS) of spindle waves indicate the increment in stress condition. Finally, Knoblauch et al. in their research documents that there is a reciprocal interaction between spindle frequency activity (SFA) and slow-wave activity (SWA) [35].

In conclusion, this study identifies that especially mixed immobility including psychological and physical stress which we applied could affect sleep stability through an alteration in the sleep spindles' amplitude and frequency but not the density of spindles and also through a reduction in REM sleep.

**Funding** There is no funding for the present study.

### Compliance with ethical standards

**Conflict of interest** There is no conflict of interest for the present study.

**Ethical approval** The method of this study was approved by the bioethics committee of the animal house in the Baqiyatallah University of Medical Science which is in accordance with the NIH guidelines for the care of animals.

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