REVIEW ARTICLE

Relation of sleep related events and spontaneous arousals during slow wave & REM sleep in healthy individuals

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Abstract

Background & purpose: Focussed studies about association between arousals and phasic sleep events are few. We analyzed the association between arousals and sleep events during slow wave (N3) & REM (R).

Methodology: Overnight PSG recording of 30 healthy adults were analyzed using AASM manual (2007). Occurrence of various sleep events and arousals were analyzed.

Results: There were 405 arousals, only 45 were de novo. In N3, sleep events associated with arousals included PLM-110 (88.7%); sleep spindles-48 (38.7%); desaturation-4 (3.2%); snore-13 (10.5%); and apnea-3 (2.4%). During R, sleep events associated with arousals included PLM- 203 (72.2%); rapid eye movement-99 (35.2%); snore-53 (18.9%); desaturation-2 (0.7%); and apnea-12 (4.3%). Number of arousals in N3 and R that occurred de novo, and with single and multiple events were: a) N3-de novo 9 (7.3%); single event-61 (49.2%) and multiple events-54 (43.5%); b) REM: de novo-36 (12.8%); single event-132 (47.0%) and multiple event-113 (40.2%).

Conclusions: Majority of arousals (88.9%) in normal individuals are associated with phasic sleep events. Such studies might unravel the understanding of arousals in sleep and its mechanism.

Keywords: Arousals, N3, REM, phasic sleep event

Introduction

An arousal is considered an overt phenomenon, resulting from a change in vigilance level manifesting with electroencephalographic (EEG), behavioural and autonomic changes. It is a cluster of physiological manifestations characterized by cortical activation, increase in blood pressure and muscle tone and a variable heart rate[1]. Traditionally viewed as markers of sleep disruption, arousals are now considered to be an integral part of sleep that ensures reversibility of sleep. Arousals filter the relevant incoming information so that the organism adapts and responds to external dangers and demands. Arousals also restore the cardio-respiratory failure during sleep, thus ensuring a continuous excitation drive for all vital processes[1]. This revelation has resulted from a large volume of data in the last few decades. However, there has been considerable heterogeneity in

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the approach to the phenomenology of arousals in physiological and pathological situations. Dedicated studies of arousals and their relation to various physiological events in various stages of sleep are far and few.

The aim of this study was to analyze the relationship between arousals and various phasic sleep events in slow wave (stage N3) and Rapid Eye Movement (REM, stage R) sleep in normal healthy individuals.

Methodology

This study was conducted at the sleep laboratory, Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore. Thirty healthy volunteers underwent overnight polysomnography (PSG) between April, 2010, and December, 2012. PSG was recorded using standard parameters: (i) eight-channel EEG; (ii) electro-oculogram (EOG); (iii) electromyogram (EMG) from submental and right tibialis anterior muscles; (iv) electrocardiogram (ECG); and (v) recording of respiratory events: nasal airflow, thoracic and abdominal respiratory movement, pulse oximeter, and snore monitor. The subjects were apparently normal healthy adults without any medical or neurological illnesses. There was no history of any substance abuse. None reported any sleep disturbance. All were screened using standard sleep questionnaires namely Epworth Sleepiness Score (ESS), and Pittsburg Quality of Life Index (PSQI) for any sleep disturbance.

Sleep was staged in 30-second epochs using standard criteria[2]. The following operational definitions were used: a) *Arousal:* An abrupt shift in EEG frequency including theta and alpha, and/ or frequencies higher than 16Hz, but excluding spindles. The EEG frequency shift must be at least three seconds or longer in duration, and may or may not be accompanied by EMG activity, change in heart rate or body movements. A concomitant increase in submental muscle activity for at least one second was considered mandatory for scoring an arousal in stage R.[3] B) *Arousal associated with a phasic sleep event:* An arousal occurring within an arbitrary time frame of five seconds of a phasic sleep event. The various phasic sleep events included (i) sleep spindles; (ii) eye movements; (iii) leg movements; (iv) snore; (v) apnea; and (vi) desaturation. C) *'De novo' arousals:* Arousals occurring spontaneously in the absence of any of the phasic sleep events.

Thus arousals occurring in N3 and R were scored separately. The relationship of arousals to various phasic sleep events was analyzed and arousals were categorized as follows: (i) arousals occurring 'de novo'; (ii) arousals associated with single phasic sleep event; and (iii) arousals associated with multiple phasic sleep events. Further, based on the temporal relationship with the arousals, the phasic sleep events were classified as occurring in the (i) pre-arousal period; (ii) simultaneously with an arousal; and (iii) post-arousal period. The data thus acquired was incorporated into SPSS (version 15.0) for further analysis.

Results

The cohort comprised 17 men and 13 women. The mean age was 24.0 $\pm$ 4.0 years. The mean total sleep time per subject was 6.28 $\pm$ 0.75 hours per night. The mean duration of N3 and R was 84.38 $\pm$ 28.9 minutes and 69.97 $\pm$ 18.8 minutes respectively. During this time, a total of 405 arousals were scored in stages N3 and R. The mean arousal per subject was 13.47±6.82 (median: 14; range: 4-39). Arousals were significantly more common in stage R (281, 69.3%) compared to stage N3 (124, 30.6%). Only 45 (11.1%) of the arousals occurred de novo. A statistically significant number of arousals occurred in association with phasic sleep events; 193 (47.6%) (N3: 61; R: 132) arousals were associated with only single phasic sleep event while 167 (41.2%) (N3: 54; R: 113) were associated with multiple phasic sleep events. The various phasic sleep events associated with arousals in N3 and R are depicted in table 1.

Table 1: Phasic events in sleep associated with EEG arousals in N3 and R

Parameters	N3	REM	N3 vs. REM 'p' value
'De novo'	9	36	0.0001
Event associated arousal: Single Multiple	61 54	132 113	0.910
Sleep spindle	48	-	-
Eye movement	-	99	-
Limb movement (Periodic/ Isolated)	110	203	0.0002
Desaturation	4	2	0.074
Snore	13	53	0.041
Apnea	3	12	0.569

Of these, arousals associated with leg movements and snore was significantly commoner in stage R compared to N3. Multivariate regression analysis showed that there was no significant correlation between any of the individual phasic sleep events and arousals, except for snore in stage R. The temporal relationship of arousals and phasic sleep events is depicted in Figure 1.

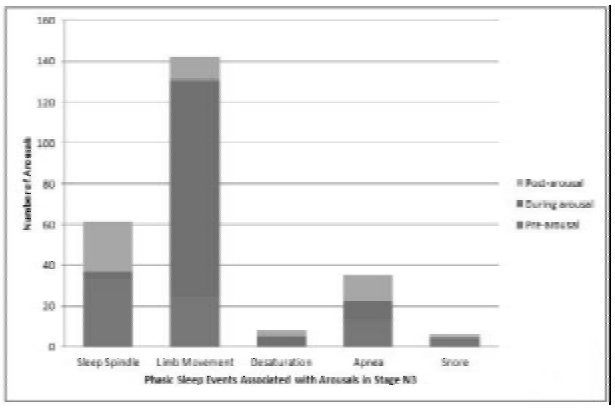

Figure 1A: Shows the temporal relationship of arousals to phasic sleep events in stage N3 of sleep. 69.7% of arousals in N3 were preceded by sleep spindles (SS), 8.4% occurred simultaneously and 50% were followed by SS. 25% of EEG arousals associated with desaturation were preceded by desaturation, 100% occurred simultaneously and 75% were followed by desaturation. In apnea associated arousals, 100% of EEG arousals were preceded by apnea, 66.7% occurred simultaneously and 100% were followed by apnea. Arousals associated with limb movements showed that 22.7% of EEG arousals were preceded by limb movements, 96.4% occurred simultaneously and in 10% limb movements occurred in the post arousal period. In arousals associated with snore, 100% of EEG arousals were preceded by snore, 15.4% occurred simultaneously and 38.5% were followed by snore.

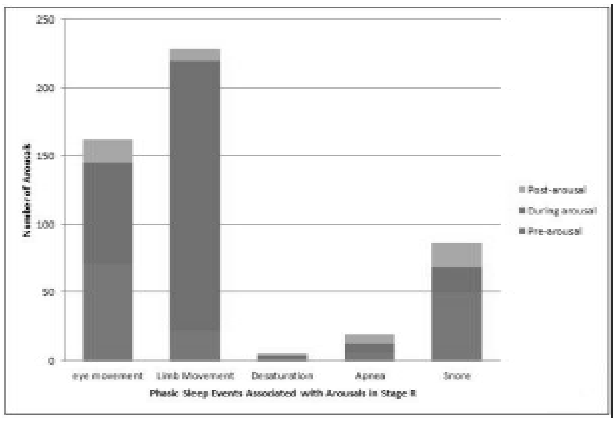

Figure 1B: Shows the temporal relationship of arousals to phasic sleep events in stage R of sleep. In arousals associated with rapid eye movement, 71.7% of EEG arousals were preceded by rapid eye movements, 74.7% occurred simultaneously and 17.2% were followed by rapid eye movements. Arousals associated with desaturation, 50% of EEG arousals were preceded by desaturation, 100% occurred simultaneously and 100% were followed by desaturation. Apnea associated arousals were preceded by apnea in 50%, while 50% occurred simultaneously and 54.5% were followed by apnea. In case of limb movement associated arousals 10.8% were preceded by PLM, 97.5% occurred simultaneously and 3.9% were followed by PLM. Arousals associated with snore, of 94.3% of EEG arousals were preceded by snore, 34% occurred simultaneously and 34% were followed by snore.

Discussion

The concept that 'arousals' are detrimental to sleep is fast changing as it is being increasingly recognized that arousals form an integral part of sleep. Different forms of arousals are recognized depending on the extent of EEG, behavioral and autonomic manifestations[1]. In the current study, cortical arousals as defined by the ASDA (1992) were studied in normal healthy adults. An attempt was also made to correlate these with the various phasic events in different sleep stages.

Arousals are influenced by endogenous and exogenous stimuli. Exogenous sensory stimuli best elicit arousals in superficial sleep stages and least in deep sleep stages[4].

An arousal response thus depends on the 'state specific reactivity', which means that an arousal response to a stimulus depends on the state in which the stimulus arrives[1]. The effect of ascending and descending slopes of sleep cycles on arousals has also been studied by various authors[5]. In the current study, arousals were significantly more common in stage R than in stage N3. We interpret this as a reflection of the effect of the state specific reactivity of the brain in different sleep stages. The deep stage of sleep N3 is less predisposed to arousal compared to stage R. A previous study of the effects of time of night on arousal response in normal healthy subjects showed that micro-arousal index is increased in stages N1 and R of sleep[6] .

Majority of arousals in the current study were non 'de novo'. Arousals were associated with one form of phasic sleep event or the other. The most common phasic sleep event associated with arousal was leg movement. Majority of the leg movements occurred concomitantly

with an arousal rather before or after an arousal. In an earlier study that evaluated the temporal relationship of leg movements with EEG arousals and awakenings in patients with Periodic Limb Movements (PLM) showed that only 30.61% of the leg movements occurred simultaneously with an arousal. Nearly half the leg movements preceded an arousal.[7] In contrast the present study found that in 97.5 % (198/ 203) and 96.4% (106/ 110) of the arousals associated with leg movements in N3 and R respectively, leg movements occurred simultaneously with arousal. In another study of 23 subjects with PLM/ Restless Leg Movements (RLS), 60% of the PLM were found to be associated with an arousal response.[8] PLM associated with arousals were more common in stages N1 and N2, while, PLM without arousal occurred more often in N3 and R. this study however did not investigate the temporal relationship of leg movements with arousals.

Studies of arousals in relation to respiratory events like apnea, snore, and desaturation have mostly been done in pathological conditions such as neuromuscular disorders.[9] The key observations are snore and apnea with or without desaturation result in increased arousals and nocturnal awakenings and lead to reduced sleep efficiency and increased daytime sleepiness. In the current study, 66/ 405 (16.3%) of the arousals in normal healthy individuals were associated with snore. Snore associated arousals were significantly more common in stage R than N3. This is not unexpected as the axial muscle tone significantly declines in stage R. None of the subjects in this cohort reported any sleep disturbance when assessed using standard, sensitive and validated sleep questionnaires.

Arousal is a concept that is shrouded with contradictions and controversies. They form an integral part of sleep and are affected by state specific reactivity in sleep and various phasic events in sleep. Previous studies have shown that 40 to 87% of the arousals are associated with K complexes.[10, 11] In a recent study, it has been shown using EEG spectral analysis that cortical changes precede and follow visually recognized EEG arousals by up to 21 seconds in normal individuals.[12] Adding to the conundrum is the fact that not all arousals are reflected as EEG changes as originally defined by the ASDA (1992). Only half the 'autonomic' arousals in Non REM and non in REM sleep have been found to be associated with EEG arousals.[13] The exact biological basis of arousals and phasic events is elusive at present. In addition, the role of arousals in maintaining the reversibility of sleep in physiological state vis a vis contributing to sleep fragmentation in pathological condition remains enigmatic. Further studies may help to unravel the understanding of arousals and their mechanisms.

The current study has few limitations namely, visual scoring of arousals is subject to intra and inter observer variability, and the phasic sleep events unassociated with arousals were not studied. Nevertheless, it was demonstrated that majority of arousals in stages N3 and R are associated with sleep related physiological events. It is likely that these events might act as endogenous stimuli for arousals. Alternately, the phasic sleep events together with the cortical EEG changes may be a manifestation of a common cerebral and/ or brainstem generator of arousals that maintain reversibility of sleep.

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