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Progressive Changes in Cortical State Before and After Spontaneous Arousals from Sleep in Elderly and Middle-aged Women

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Abstract

Arousals are often considered to be events which have an abrupt onset and offset, indicating abrupt changes in the state of the cortex. We hypothesized that cortical state, as reflected in EEG signals, exhibits progressive systematic changes before and after a spontaneous, isolated arousal and that the time courses of the spectral components of the EEG before and after an arousal would differ between healthy middle-aged and elderly subjects. We analyzed the power spectrum and Sample Entropy of the C3A2 EEG before and after isolated arousals from 20 middle-aged (47.2+/−2.0 yrs) and 20 elderly (78.4+/−3.8 yrs) women using polysomnograms from the Sleep Heart Health Study database. In middle-aged women, all EEG spectral band powers <16 Hz exhibited a significant increase relative to baseline at some time in the 21 sec before an arousal, but only low- (0.2–2.0 Hz) and high-frequency (2.0–4.0 Hz) delta increased in elderly and only during the last 7 sec pre-arousal. Post-arousal, all frequency bands below 12 Hz transiently fell below pre-arousal baseline in both age groups. Consistent with these findings, Sample Entropy decreased steadily before an arousal, increased markedly during the arousal, and remained above pre-arousal baseline levels for ~30 sec after the arousal. In middle-aged, but not in elderly, women the presence of early pre-arousal low delta power was associated with shorter arousals. We propose that this attenuation of the effect of the arousing stimulus may be related to the slow (<1 Hz) cortical state oscillation, and that prolonged alterations of cortical state due to arousals may contribute to the poor correlation between indices of arousals and indices of sleepiness or impaired cognitive function.

Keywords

cortical arousal; EEG; sleep; aging; sleep fragmentation; Sample Entropy

1. INTRODUCTION

The incidence of spontaneous cortical arousals increases significantly with age even in healthy subjects without chronic pain, restless legs syndrome, periodic limb movement disorder, or sleep disordered breathing (Mathur and Douglas, 1995; Boselli et al., 1998;

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Bonnet et al., 2007a). When normalized by total sleep time, the number of arousals occurring during light sleep (NREM stages 1 and 2) and REM, but not deep sleep (NREM stages 3 and 4), was found to be significantly higher in elderly subjects (≥ 60 yrs) than in all other groups ranging in age from 10 to 59 (Boselli et al., 1998). In a separate study of symptom-free middle-aged and elderly subjects, the arousal index was also reported to increase with age, albeit to a greater extent in men than in women (Walsleben et al., 2004). The elderly are also at increased risk for apneas and hypopneas which are often followed by arousals (Poyares et al. 2002; Thomas, 2003; Younes, 2004). The impact on sleep quality of spontaneous, brief sleep disruptions throughout the night has been difficult to determine due, in part, to the weak correlations observed between readily available measures, such as number of arousals per hour, and reports of daytime sleepiness in individual subjects (Stepanski et al., 1984; Roehrs et al., 1989; Martin et al., 1997). On the other hand, it is clear that evoking frequent arousals during the night using external stimuli such as auditory tones leads to excess daytime sleepiness and impaired cognitive function (Martin et al., 1996; Guilleminault et al., 2006).

Arousals are often considered to be events which have an abrupt onset and offset, representative of a rapid (switch-like) response to a sudden stimulus of sufficient magnitude (e. g., a discrete external stimulus such as a brief auditory tone, or the crossing of a pressure threshold during obstructed breathing). Indeed, the definition of an arousal from the American Sleep Disorders Association (ASDA), which is based on visual analysis of electroencephalograph (EEG) signals displayed at a particular time resolution, reinforces the perception of an arousal as an abrupt phenomenon. Supporting this interpretation is the abundant experimental evidence that cortical neural activity responds within tens of milliseconds to stimulation of brainstem and midbrain loci which elicit low-amplitude, high-frequency activity in the cortical EEG (Foote et al., 1980; Berridge and Foote, 1991; Whalen et al., 1994; Dringenberg and Vanderwolf, 1997; Curto et al., 2009). Visual analyses, however, may fail to detect more subtle changes in the EEG signal preceding or following the obvious changes associated with an arousal, and therefore visual criteria may underestimate the total duration of sleep disruption.

There is suggestive evidence that cortical changes may precede arousals scored using the ASDA definition. First, there is often a burst of delta activity (De Carli et al., 2004) preceding an arousal; this activity, however, may be associated with autonomic responses (Davies et al., 1993; Martin et al.,1997b; Halasz, 2004) that are only putatively related to the arousal. Second, there are progressive EEG spectral changes during apneas (Svanborg and Guilleminault, 1996) preceding an arousal. These spectral changes, however, may be associated with increasing respiratory efforts against a narrowed or obstructed airway that impede contraction of respiratory muscles and cause excessively negative intrathoracic pressures (Thomas, 2003; Younes, 2004). If systematic subtle changes in the EEG do occur before a spontaneous cortical arousal, it is not clear whether these changes are part of the arousal or whether they reflect the activation of mechanisms which have increased the likelihood of the subsequent arousal.

Although there is no direct evidence in the current literature that cortical state changes progressively before an ASDA arousal, there is somewhat stronger evidence that cortical EEG activity returns to its pre-arousal state gradually after the arousal. Evidence that gradual cortical changes may follow an arousal include the following: (i) a gradual change in processed EEG activity (called “sleep depth” by the authors) after an apnea-related or hypopnea-related arousal (Stradling et al., 1999) (although this result may be due to arousals of different length being averaged); (ii) the slow return of the EEG spectrum to baseline after a tachycardia event (Halasz, 2004; Colrain, 2005) (but it is debated whether such

events are related to true cortical arousals); (iii) the slow recovery of low-frequency EEG after a brief somatosensory stimulus (Whalen et al., 1994).

The above issues raise the question of whether the initiation and termination of an arousal are switch-like events or are a consequence of more progressive changes in neural activities which may culminate in a rapid change. The difference is consequential because the latter mechanism might be modulated by other coincident inputs, whereas the response of a switch is an all-or-none phenomenon. That is, in the progressive case the well-known, highly variable nature of an arousal may be due in part to other activities that occur during the initiation or termination of the arousal. Furthermore, whether arousals are switch-like or progressive events may be relevant to the increased rate of arousals in elderly subjects because extended transient changes in cortical state before or after an arousal may predispose the elderly to another arousal by prolonging the deviation from a normal cortical state.

In this study we hypothesized that cortical state, as reflected in EEG signals: (i) exhibits systematic changes before the onset of a spontaneous, isolated, ASDA arousal, and; (ii) does not return to its baseline state by the (visual) end of the arousal. We also hypothesized that alterations of cortical state both pre- and post-arousal in elderly subjects would be of longer duration than in middle-aged subjects, thus predisposing the elderly to additional arousals. To address these hypotheses, we analyzed the time courses of power spectrum and entropy of a central EEG signal before and after spontaneous, isolated arousals in sleeping middle-aged and elderly women.

2. METHODS

3.1. Subjects

The study was conducted on previously-existing EEG datasets from polysomnograms (PSGs) obtained from the NIH-sponsored, multi-center Sleep Heart Health Study (SHHS) (Quan et al., 1997). The overnight PSG studies were conducted in the SHHS participants homes by certified technicians (Iber et al., 2004), and were recorded using the Compumedics P-series Sleep Monitoring System. Data recorded for each participant from the PSGs included: EEGs recorded from leads C3/A2 and C4/A1, a right and a left electro-occulogram, a bipolar submental electromyogram, electrocardiogram, nasal airflow, respiratory excursions of the thorax and abdomen, and finger pulse oximetry. Sleep staging was scored by SHHS personnel at 30-sec intervals based on the Rechtschaffen and Kales criteria (1968), and apneas, hypopneas and arousals were marked on the PSGs.

The study population consisted of Caucasian women: 20 were selected from the youngest subjects and 20 were selected from the oldest women in the SHHS data base. The mean (± S. D.) age of the first group, designated the middle-aged women, was 47.2 ± 2.0 yrs (range: 42–50 yrs), and the mean age of the elderly women was 78.4 ± 3.8 yrs (range: 71–86 yrs). The body mass indices of the women studied were ≤ 30. The subjects did not have a clinically-diagnosed sleep disorder including sleep disordered breathing, restless legs syndrome, or periodic limb movement disorder. In response to questions from SHHS personnel, no subject reported being aware of leg movements during the night. The subjects did not have a history of heart disease or stroke, were not taking any medications known to interfere with sleep, and did not take frequent naps during the daytime. None of the subjects included in the study were current smokers. The median arousal index, i.e. the median value for the number of arousals per hour, was 16.35 (25^{th} percentile, 11.01; 75^{th} percentile, 24.60) for the middle-aged and 16.83 (25^{th} percentile, 7.79; 75^{th} percentile, 22.74) for the elderly women. The apnea-hypopnea index was 1.48 ± 2.48 in the middle-aged and 2.54 ± 2.54 in the elderly subjects.

3.2. Signal Analysis

Cerebral montage C3/A2 was used for the EEG analyses. EEG signals were filtered between 0.48 and 30.0 Hz and digitized at a sampling frequency of 125 Hz. Each EEG signal to be analyzed was first upsampled to 250 Hz, then lowpass filtered at 25 Hz using a 21-point, FIR filter based on a Hamming window. Finally, the signal was downsampled to 50 Hz. (See Appendix for details)

Spectral power of the EEG signal was calculated in frequency bands, defined as low frequency delta (0.2–2.0 Hz), high frequency delta (2.0–4.0 Hz), theta (4–8 Hz), alpha (8–12 Hz), sigma (12–16 Hz), and beta (16–23 Hz) bands. To separate the EEG signal into these frequency bands, the filtered and downsampled EEG signal was passed through 6 bandpass filters in parallel. (See Appendix) Each filter selected one of the frequency bands specified above. The EEG signal was passed through the filters forwards and backwards to eliminate phase distortions. The mean level was removed from each filter output, and the mean absolute value of each output was calculated over a sliding window (i.e., a moving average) of 2-sec duration (4-sec duration for the low delta signal) which advanced through the data in steps of 0.02 sec. This signal was squared to estimate power. Each mean square value, which is an estimate of the variance or total power of the signal in the analysis window, was plotted at the time of the middle of the time window. It should be noted that this measure represents absolute power in each band and is not normalized by total power of the EEG signal.

All Stage 2, Stage 3 and REM arousals identified by the SHHS scorers, who used ASDA criteria to score arousals (The Atlas Task Force, 1992), were evaluated to assess suitability for further analysis. To avoid the potential influence of another arousal, hypopnea, or apnea on changes in Sample Entropy or spectral power of the EEG, we excluded arousals that started ≤ 30 sec after, or ended ≤ 30 sec before, any of these events as well as excluding those arousals containing movement artifacts. Where indicated in the text, arousals were excluded if they occurred within 30 sec of a change in sleep stage. Because of these exclusions, we analyzed a small fraction of total arousals in each subject: for middle-aged subjects, we analyzed 6.75% +/− 4.65% of the total arousals; for the elderly the corresponding number was 9.5% +/− 6.1%

3.3. Identification of the Beginning and End of SHHS-Scored Arousals

To date, no automated approach to the identification of onset and termination of arousals during sleep has emerged that is widely accepted. To address this issue, we developed an algorithm to determine both the precise time at which alpha + beta + theta power increased at least 2-fold relative to the background activity determined over the preceding 30 sec and how long the sum of the powers remained elevated. Our intention was not to identify arousals *de novo* but rather to determine, with greater precision and consistency than is possible by human scorers, the beginnings and ends of arousals that had been previously identified by the SHHS scorers. The details of our method are given in the Appendix. It should be noted that our approach often detects an increase of alpha, beta, or theta power before the eye can do so in a polysomnogram when there are low-frequency components also present.

3.4. Calculation of Sample Entropy

Sample Entropy, a measure of the temporal regularity of the EEG signal, was calculated as previously described (Bruce et al., 2009) using the approach of Richman and Moorman (2000). Our calculation used an embedding dimension of 2 and a neighborhood size equal to 20% of the standard deviation of the data. The original data records were segmented into nonoverlapping records (each of which was 6 sec in length), five before and five after each

arousal, and Sample Entropy was calculated for each 6-sec record. The 6-sec interval that immediately preceded each arousal was excluded from the analysis of Sample Entropy to avoid the delta burst that often precedes Stage 2 and Stage 3 arousals (De Carli et al., 2004).

3.5. Statistical Analyses

For both the middle-aged and the elderly women, the significance of the trend in subject mean Sample Entropy values both before and after the arousals was assessed by a linear regression analysis (SYSTAT 9 Statistics I, SPSS Inc., Chicago, IL). Trends were considered significant for p values < 0.05. To determine whether Sample Entropy values increased after arousals, a one-sample t-test with Bonferroni s correction for multiple comparisons was used to test the hypothesis that the ratio of subject mean values for Sample Entropy pre-arousal divided by Sample Entropy post-arousal was greater than one.

EEG spectral power in each of the six bands identified above was first averaged in nonoverlapping 3-sec windows for the periods 36 sec immediately before, and 36 sec immediately after, each arousal. On the basis of visual inspection of the power in each frequency band, mean power in the interval 36 – 21 sec before the arousals was designated as the baseline. The spectral power in each frequency band was then normalized to the average baseline power, and the normalized power measure was averaged over three 7-sec intervals immediately before arousals (21 – 14 sec, 14 – 7 sec, and 7 – 0 sec) and immediately after arousals (0 – 7 sec, 7 – 14 sec, and 14 – 21 sec).

To determine whether spectral power in any of the frequency bands differed significantly from the designated baseline level, a value of 1.0 was first subtracted from the normalized mean power in the 7-sec intervals (three before and three after arousals). These power values were then analyzed by a MIXED LINEAR PROCESS MODEL using SAS 9.2 software (SAS Institute Inc., Cary, NC) to identify changes in power spectra due to arousals (AR) with STATE (2 levels: PRE-AR vs. POST-AR) and TIME nested within state (3 levels: 21 – 14 sec; 14 - 7 sec; 7 – 0 sec from AR) as fixed effects. Because the number of arousals was different for each subject, the index for each arousal, AR_ID, was nested within the subject, SUBJ_ID. Random effects corresponding to the variance components of SUBJ_ID, AR_ID, SUBJ_ID*TIME(STATE), and AR_ID(SUBJ_ID)*STATE were also included in the model. The degrees of freedom of the model were calculated using the Satterthwaite Approximation. The power measure of each spectral band (low frequency delta, high frequency delta, theta, alpha, and sigma) was analyzed separately for the middle-aged and for the elderly groups to identify significant pre- and post arousal changes in the EEG power spectra before vs. after arousals in each of these age groups. Beta power was not included in this analysis because it was very similar in the two age groups. To correct for multiple tests (five spectral bands and two age groups), a manual correction to the estimated P values was applied. Values were considered to differ significantly when P was < 0.01.

The possibility of a relation between low frequency delta power and the duration of the subsequent arousal was tested by analyzing the normalized pre-arousal low delta power values in middle-aged women. A MIXED LINEAR PROCESS model was again used to compare changes in low delta power in each of the three 7-sec pre-arousal intervals for SHORT ($\geq$3 sec and $<$ 8 sec) vs. LONG ($\geq$ 8 and $\leq$ 15 sec) arousals. Because the number of arousals from each subject was not the same and because the classification of arousals by duration caused further imbalance in the data, mean spectral power per subject was used as the response, thus eliminating random effects related to AR_ID in the mixed model. One subject who had no long arousals was identified as an outlier and eliminated. The Linear Mixed Model was fit to this data with fixed effects of DURATION, TIME and DURATION * TIME interaction. A significant DURATION*TIME effect implied that the time course of the low delta power measure in the pre-arousal state differed significantly between short and

long arousals. A post hoc pair-wise comparison of the least squares means was carried out to determine at which 7 sec. interval the power measure varied significantly due to the duration effect.

3. RESULTS

4.1. Identification of the Beginning and End of Stage 2, Stage 3 and REM Arousals

A total of 153 arousals from the group of 20 middle-aged women (116 in Stage 2, 17 in Stage 3, and 20 in REM) and 159 arousals from the group of 20 elderly women (122 in Stage 2, 26 in Stage 3, and 11 in REM) met the criteria for inclusion in the study as described in Methods.

More than half of all arousals selected from each of the age groups were found by our algorithm to begin within ± 2.0 sec of the time of onset indicated by the SHHS scorers (58% of Stage 2 + Stage 3 arousals and 70% of REM arousals in the middle-aged subjects and 66% of Stage 2 + Stage 3 arousals and 54% of REM arousals in the elderly subjects). There was less agreement with respect to the end of the arousals, however. According to our algorithm, the percent of arousals that ended within ± 2.0 sec of the end indicated by the SHHS scorers were, for the middle-aged subjects, 48% of Stage 2 + Stage 3 arousals and 50% of REM arousals, and for the elderly subjects, 47% of Stage 2 + Stage 3 arousals and 45% of REM arousals.

Approximately half of all arousals were determined to be longer than the durations indicated by the scorers. The subject mean values for arousal durations determined by our algorithm indicated that 48 ± 30% of the middle aged (Stage 2 + Stage 3: 56 ± 28%; REM: 26 ± 38%) and 54 ± 27 % of the elderly (Stage 2 + Stage 3: 52 ± 34%; REM: 22 ± 34%) arousals were longer than marked by the SHHS scorers. NREM + REM arousals lasted on average 9 ± 3% longer in the middle aged subjects and 17 ± 4% longer in the elderly subjects.

4.2. Sample Entropy Values Before versus After Arousals

Because Sample Entropy reflects the relative amounts of high-frequency (which tends to increase Sample Entropy) and low-frequency (which tends to decrease Sample Entropy) power in a signal (Bruce, et al., 2009), it may be used as a generic indicator of changes in the EEG signal. To determine whether there were systematic changes in the EEG signal, Sample Entropy was calculated for each of five 6-sec intervals both before and after each Stage 2 (S-2) and Stage 3 (S-3) arousal. In this analysis alone, the 6-sec interval immediately preceding the arousal was excluded to avoid the influence on Sample Entropy of the delta bursts that frequently occur immediately before arousals in Stage 2, and less frequently in Stage 3, but not in REM (DeCarli et al., 2004).

To facilitate the comparison between middle-aged and elderly subjects for whom Sample Entropy values have been shown to differ significantly in S-2 (Bruce, et al., 2009), Sample Entropy values from each subsequent 6-sec time interval were normalized to the values obtained from the 36-30 sec interval before each arousal. [Fig. 1] Linear regression analysis of Sample Entropy values during the 36 to 6-sec period before arousals indicated a negative slope that was marginally significant for the 133 Stage 2 + Stage 3 middle aged arousals ($p = 0.05$), but not significant ($p = 0.111$) for the 148 Stage 2 + Stage 3 elderly arousals. Arousals, like awakenings (Bruce et. al., 2009), were associated with an abrupt increase in Sample Entropy. (Data not shown.) Post-arousal, Sample Entropy values were initially higher than pre-arousal values, then decreased at each subsequent 6-sec interval with the exception of the final value for the middle-aged subjects. This negative slope was highly significant in the elderly subjects ($p < 0.0001$) but was not significant in the middle-aged

subjects ($p = 0.089$). We did not observe a similar trend for REM arousals, perhaps because very few were available for analysis.

The significance of the apparent increase in Sample Entropy after arousals was determined by dividing subject mean Sample Entropy values for the 30 sec interval immediately after each arousal by mean Sample Entropy values for the 30 sec interval that extended from 36 to 6 sec before each arousal. For both middle-aged and elderly women, these ratios were significantly greater ($p \leq 0.003$) than 1.0 (e.g., Sample Entropy post-arousal was greater than Sample Entropy pre-arousal) for Stage 2 + Stage 3 arousals but not for REM arousals. Taken together, these data indicate a higher state of entropy, suggesting a higher state of arousal, for 30 sec after the end of Stage 2 and Stage 3 arousals in both the middle-aged and elderly subjects

4.3. EEG Power Spectrum Before versus After Stage 2 Arousals

To obtain insights into the mechanisms that might have contributed to the altered cortical state reflected by the Sample Entropy responses, we evaluated the changes in EEG spectral power before and after arousals. We included in this analysis only those Stage 2 arousals neither preceded, nor followed, within 30 sec by a change in sleep stage. A total of 113 arousals in middle-aged subjects and 111 arousals in elderly subjects met these criteria. Stage 3 arousals were not analyzed because of the relatively small number that remained after the removal of those preceded or followed by a sleep-stage change. Although no sleep stage changes were associated with REM arousals in either the middle-aged or the elderly subjects, the relatively small number of REM arousals precluded a meaningful analysis of the power spectrum data before vs. after arousals.

4.4. Median Spectral Power of the EEG Signal Before and After Stage 2 Arousals [Fig. 2]

In view of the significant changes in Sample Entropy described above, we examined the extent to which changes in spectral power extended beyond the duration of the arousal. Because we calculated average power using sliding windows in time, for the 2-sec (or 4 sec, for low delta) period before and after the arousal, power values within 2 (or 4) sec of an arousal are influenced by the shift in power that occurs during the arousal. Beyond these specified intervals, however, the power shift associated with the arousal does not influence the power values. Visual inspection of the spectral power in each of the six frequency bands indicated that power in each band was relatively stable from approximately 36 – 21 sec before an arousal. Accordingly, this 15-sec period was designated as the baseline value for each arousal. The spectral power before and after each arousal was then normalized to the mean baseline power in each frequency band. Because even the normalized power signals displayed significant variability between arousals which appeared to be asymmetrically distributed, we first plotted the median power, plus the 25^{th} and 75^{th} percentiles, for each frequency band point-by-point across time before and after the arousals. [Fig. 2] Pre-arousal signals (time < 0) were synchronized by moving backwards in time from the onset of each arousal. Post-arousal signals (time > 0) were synchronized by moving forwards in time from the end of each arousal.

Both low and high frequency delta powers increased sharply in the 2–3 sec immediately preceding arousals in both age groups, as shown in the plot of the median values. However, we often observed that both delta powers increased during the arousal, and some of that increase may have been captured when the sliding window projected into the arousal. More modest increases in power were observed immediately before the arousal onset in the theta, alpha, sigma and beta frequency bands. A striking increase in both low and high frequency delta bands, beginning approximately 20 sec before the onset of the arousal, occurred in roughly half of the arousals in the middle-aged subjects, leading to the increase in the 75^{th}

percentile levels seen on the plots of median powers. However, this early increase in delta power was not seen in the arousals in elderly subjects.

Post-arousal, median values for both high and low frequency delta remained below pre-arousal levels for most, if not all, of the 36 sec period. Median values for theta, alpha and sigma powers also decreased post-arousal to levels that remained well below pre-arousal values for 30 to 36 sec post-arousal. Median beta power differed from the other frequency bands in several respects. There was little variability in beta power in the 36 sec preceding an arousal, but after the end of the arousal, median beta power remained above pre-arousal levels for ~ 6 sec for both age groups. It seems unlikely that the high beta power seen immediately post-arousal is indicative of a premature termination of the arousal by our algorithm because neither the alpha nor theta powers were increased during this time interval. Furthermore, the durations of arousals as determined by our algorithm were, on average, somewhat longer than the durations determined by the SHHS scorers.

4.5. Median Power Analysis of S-3 and REM Arousals

The relatively small number of acceptable arousals found in REM (middle age = 20; elderly = 11) and in S-3 (middle age = 16; elderly = 12) made it difficult to discern age- or stage-related trends in any frequency band before or after the arousals. In this small sample, low frequency delta power appeared to decrease after REM arousals in the middle-aged subjects. A similar decrease was not seen in the elderly subjects (data not shown).

4.6. Mean Power Analysis of Stage 2 Arousals [Fig. 3]

To compare the two age groups, for each frequency band mean power was calculated for nonoverlapping 3-sec intervals beginning 36 sec before and ending 36 sec after each Stage 2 arousal. With two exceptions the responses were visually similar in the two age groups: in middle-aged subjects, low delta and sigma powers began to increase ~20 sec before the arousal, but they did not increase in the elderly.

To determine the significance of the apparent differences in the power of high and low frequency delta, theta, alpha and sigma bands pre- vs. post-arousal, the average normalized (as described above for median power) values obtained for the 21 sec interval immediately before arousals were compared with values for the 21 sec interval immediately after the arousals using a Mixed Linear Process model as described in Methods. The beta frequency band was not included in this analysis because, with the exception of the 6 sec delay in the return of beta power to baseline post-arousal, pre- and post-arousal values were essentially identical.

Power in the low and high delta and theta frequency bands was significantly higher ($p < 0.0001$) in the 21-sec interval before arousals when compared with the 21-sec interval immediately following the arousals for both the middle-aged and elderly subjects. [Table I] Alpha power was also significantly greater in the pre-arousal period in middle-aged ($p < 0.0001$) and elderly ($p < 0.0002$) subjects, whereas sigma power was greater ($p < 0.0001$) pre-arousal only in the middle-aged subjects.

To determine the time points within the 21-sec window where spectral power differed significantly from baseline values, the average powers in six 7-sec time intervals (three pre- and three post-arousal) (Fig. 3) were calculated. Then the least squares means of the normalized power at each time interval were estimated using the Mixed Linear Model. Time points where the power measure was significantly changed from baseline levels (1.0) were identified [Table I] as discussed below:

Delta Power—In both age groups, there was a significant increase ($p < 0.0021$) in low and high frequency delta power in the 7-sec interval prior to the arousal. In addition, in the middle-aged – but not the elderly - women, both low and high frequency delta powers were significantly greater ($p<0.01$) than baseline values for the intervals 21–14 sec and 14–7 sec before arousals. Post-arousal, low frequency delta power did not differ from the pre-arousal baseline values in the middle-aged subjects and was below baseline only at 7–14 sec post-arousal in elderly subjects. However, high frequency delta power decreased significantly in the 0 – 7 sec interval post-arousal in both age groups and was also below baseline in the 7 – 14 sec interval in the middle-aged women.

Theta Power—Theta power increased significantly only in the 21 – 14 sec pre-arousal interval in the middle-aged subjects. Post-arousal, theta power decreased significantly in the 7 – 14 and the 14 – 21 sec intervals in the middle-aged, and in the 0 – 7 and the 7 – 14 sec intervals in the elderly.

Alpha Power—Relative to baseline, alpha power was significantly increased from 14 – 7 sec before arousals in the middle-aged group, but no increase was seen in the elderly women. Post-arousal, alpha power was significantly lower than baseline values at 7 – 14 and 14 – 21 sec in the middle-aged and at 7 – 14 sec in the elderly.

Sigma Power—In middle-aged women, sigma power was significantly greater than baseline values at each of the three pre-arousal time intervals, and below baseline at 7 14 sec post-arousal. In contrast, no significant changes with respect to baseline were observed in sigma power in the elderly.

4.7. Low Frequency Delta Power Pre-Arousal in Short vs. Long Arousals in Middle-Aged Women

The observation in the middle-aged group (but not in the elderly) that low frequency delta power was significantly greater than baseline in each of the three 7-sec pre-arousal intervals suggested that this prolonged increase in delta power might influence the duration of a subsequent arousal. To explore this possibility, S-2 arousals were separated by duration: short arousals were those that lasted from 3 to < 8 sec ($n = 65$) and long arousals were those lasting from ≥ 8 to 15 sec ($n = 44$). For short arousals, both inter-arousal and intra-arousal variability of low delta power increased dramatically beginning ~21 sec before the arousals, whereas such changes were rare before the long arousals. Superimposed plots of individual arousals (Figure 4) demonstrates the striking change in variability which occurs before short arousals not only between arousals but also across time within individual middle-age arousals. In contrast, such differences were not observed for high delta power. For elderly subjects, for both long and short arousals the typical behaviors were more similar to those associated with long arousals in the middle-aged subjects.

The plot of normalized low frequency delta power in short and in long arousals (Fig. 5) highlights the striking differences between the two age groups (note the different maximum values on the y-axes). The increase in low delta power observed in the 21-sec pre-arousal period in the pooled data from middle-aged women (Fig. 3) is attributable primarily to the low delta power increase that occurs when the arousal is short. In contrast, there are only a few individual cases exhibiting modest increases in delta power before the long arousals in middle-aged subjects (or before any arousal in the elderly). Analysis of the subject mean values for low frequency delta power in short vs. long arousals by a Linear Mixed Model indicated that the Time-by-Duration Interaction effect was significant ($P = 0.0275$). A post hoc comparison of subject means demonstrated that low frequency delta power at 21 – 14 sec pre-arousal was significantly greater ($P = 0.01$) in short vs. long arousals. For the short

arousals, the mean low frequency delta power did not vary significantly during the pre-arousal period. In contrast, for the long arousals, mean low frequency delta power during the 7 – 0 sec pre-arousal period was significantly greater than either the 14 – 7 sec period ($P = 0.006$) or the 21 – 14 sec period ($P = 0.001$).

4. DISCUSSION

Our study of isolated cortical arousals occurring in middle-aged and elderly women found systematic changes in C3A2 EEG signals both preceding and following arousals. Low- and high-frequency delta, theta, and sigma activities began to increase as soon as 21 sec before an arousal in middle-aged subjects. In the elderly, only the delta activities changed pre-arousal, and then only during the last 7 sec preceding the arousal. In both groups the mean powers over 21 sec post-arousal in the delta, theta, alpha, and sigma (middle-aged only) bands were all smaller than pre-arousal. Beta power remained high post-arousal in both age groups and returned to baseline in ~6 sec. Sample Entropy of the EEG signal also remained elevated immediately following the arousal, then decayed back to its baseline level over ~30 sec in both age groups, reflecting the changes in delta and beta powers. Thus, our initial two hypotheses are supported by these findings. We also observed that differences from baseline of the pre- and post-arousal EEG behaviors in elderly subjects were less extensive in time than in middle-aged subjects, principally because of the absence of pre-arousal responses in the elderly. This latter finding also supports our hypothesis that differences between elderly and middle-aged subjects in pre- and post-arousal cortical state may predispose the elderly to additional arousals because the pre-arousal low delta response in the middle-aged subjects may have acted to shorten their arousals.

It is important to our findings that SHHS scorers had identified arousals correctly and that our algorithm had identified the beginning and end of each arousal accurately. Inter-scorer reliability with respect to arousal identification is typically low (Bonnet et al., 2007b) and for the SHHS database, the intrascorer reliability has an intraclass correlation coefficient of 0.54 (Whitney et al., 1998). The potential for scoring errors was likely increased by the fact that the majority of the arousals we studied occurred during Stage 2, whereas arousals are easier to detect during Stages 3 and 4 (Drinnan et al., 1998). In addition, we avoided arousals that occurred within 30 sec of apneas or hypopneas, both of which may provide arousal cues to the scorer (Thomas, 2003). On the other hand, for all analyzed arousals our algorithm identified EEG changes consistent with the ASDA criteria. In addition, the beginnings and ends of arousals were determined to be within 2 sec of those marked by scorers about half of the time; however, our method is less subjective, more precise, and more reproducible (see Appendix). Our arousal durations were on average somewhat longer than the scorers found for the same arousals.

Although a burst of delta activity in the few seconds preceding an arousal has been reported in NREM sleep (De Carli et al., 2004; Halasz, 2004; Togo et. al., 2006; Sforza et al., 2008), our observations extend this finding to much earlier times. In middle-aged subjects, normalized low- and high-frequency delta, and sigma, activities were greater than baseline beginning 21 sec before the arousal. The slow decline of Sample Entropy pre-arousal is likely due to the increase of delta power (Bruce, et al., 2009). The frequency ranges involved are consistent with the occurrence of K-complexes and spindles. It is unclear why these events would increase in number prior to a presumably unanticipated arousal; however, it has been reported that the rate of K-complexes increases in the 10 sec before a Transitory Activation Phase (PAT) arousal in S-2 (but the rate of spindles decreases) (Naitoh et al., 1982). The elderly subjects did not exhibit an elevation of normalized power in these bands until the final 7 sec before the arousal, when both delta activities increased. This finding

may be a consequence of the diminished incidence and amplitude of K-complexes in the elderly (Colrain, 2005; Colrain et al., 2010).

The association of delta power in general, and of K-complexes in particular, with arousals has been vigorously debated in the literature. A burst of delta power just prior to an arousal has been reported (DeCarli et al., 2004; Halasz, 2004; Togo et. al., 2006) as has the presence of one or more K-complexes at this time (Naitoh et al., 1982; Thomas, 2003; Sforza et al., 2008). Furthermore, even isolated K-complexes are associated with signature autonomic events correlated with arousals – i. e., a rise in heart rate and/or blood pressure (Davies et al., 1993; Halasz, 2004; Togo et al., 2006) and a burst of sympathetic nerve activity (Shimizu et al., 1992). By way of contrast, apneas are frequently followed by an arousal, but the majority of apneas are not followed by a K-complex or burst of delta activity (Thomas, 2003) although the amplitude of delta power is reported to increase during the apnea itself (Svanborg and Guilleminault, 1996). The rate of K-complexes increases in the 10 sec before a PAT arousal in S-2 while the rate of spindles decreases (Naitoh et al., 1982); however, the majority of K-complexes without spindles are not followed by an arousal (Colrain, 2005). During a recovery night after sleep deprivation or fragmentation, the rate of spontaneous K-complexes has been reported to increase (Nicholas et al., 2002) or not to change significantly (Sforza et al., 2004) whereas the rate of arousals decreases (De Gennaro et al., 2002; Zavodny et al., 2006). The recent study by Cash, et al., (2009) seems to provide a parsimonious explanation of these observations. By using depth recordings in the cortex of human subjects, these investigators demonstrated that voltage and current patterns during K-complexes and during the down state of the slow (<1 Hz) cortical oscillation were indistinguishable. They proposed that stimuli (both external and internal, or “occult” in their terminology) elicit K-complexes in the cortex, which drives cortical neurons into a down state and transiently reduces their sensitivity to the stimulus. In addition, these K-complexes are associated with autonomic responses that some investigators have identified as “subcortical arousals” (Halasz, 2004). Thus, stimuli may give rise to autonomic responses without signs of EEG arousal, although daytime sleepiness or cognitive impairment correlates only with EEG arousals (Guillminault et al., 2006). Colrain (2005) has presented an elegant discussion of the question of whether these autonomic behaviors should be considered arousals and has concluded that “the K-complex reflects a cortical response to events (external or internal) that may also produce an autonomic response” and that the K-complex “probably serves to prevent a cortical arousal.”

The neurophysiological substrate for parallel activation of autonomic responses and the cortex probably involves the brainstem. Waking involves a persistent cortical up-state without intervening hyperpolarizations of cortical neurons (Steriade et al., 1993), and it is reasonable to assume that an arousal is also associated with a prolonged up-state. Both the brainstem pedunculopontine/lateral dorsal tegmental (PPT/LDT) and locus coeruleus (LC) nuclei can induce a cortical up-state, and the LC can activate responses of the autonomic nervous system via its many projections. The LC itself can be activated both by many types of external stimuli and by projections from the PPT/LDT (Steriade, 2004) It is unclear, however, what mechanisms cause the initial delta burst (and presumed cortical down-state) that is proposed to counteract the effect of a stimulus on cortical neurons (Cash et al., 2009)..

Some investigators have proposed that temporal fluctuations in EEG signals can be described, in some sleep states, as a cyclic phenomenon known as a Cyclic Alternating Pattern (CAP) (Terzano et al., 2001). These “cycles” are identified by characteristic events, some of which are correlated with ASDA arousals. The vast majority (~65–85% in recent studies) of CAP events are A1 events (Ferri, et al., 2006; Smerieri, et al., 2007), which are not arousals by ASDA criteria and would not be included in our analysis. SHHS scorers do

not mark CAP events and it is unclear whether our arousals are part of a CAP; however, we have shown that certain phenomena might occur systematically before a minority of CAP events. It has been proposed that the timing of CAP events may be under the influence of the slow (< 1 Hz) cortical oscillation (Thomas, 2007) or even an infraslow oscillation (Ferri et al., 2005). Any relationship of our findings to CAP may be due to a common low-frequency oscillation driving both. The possibility of such a relationship requires further investigation.

Our findings reveal some interesting differences between middle-aged and elderly subjects with respect to the time course of spectral powers in the 21 seconds preceding an arousal, especially when we considered two groups of arousals based on their durations (3–8 sec and 8–15 sec). For both groups of arousals and both ages, normalized low delta power increases in the 7-sec time interval just before the arousal. Thus, there is a strong impression that a "burst" of low delta power frequently occurs in the last few seconds before any arousal. This low delta activity just before the arousal may be a sleep-preserving response that reduces local sensitivity of cortical neurons to a disturbance (Cash et al., 2009). However, when a burst of low delta activity occurs 14 to 21 seconds before an arousal in middle-aged women, that arousal is more likely to be short. This early response associated with short arousals seems to occur too early to effectively reduce cortical sensitivity at the time of the arousal; however, the elevation of average low delta power for 21 sec preceding an arousal could represent brief bursts of low delta power that occur at variable times before individual arousals, rather than a response that is time-locked to the arousals. The superimposed plots from individual middle-aged short arousals support the suggestion that low delta power does not consistently increase at a pre-determined time pre-arousal. Rather, it increasingly fluctuates in individual arousals beginning ~21 sec before the arousal. These fluctuations could represent slow oscillations in cortical state (or cortical up-states and down-states) that seem to involve the same neural mechanisms as K-complexes (Cash et al., 2009). When arousal stimuli occur in a time period during which slow oscillations of cortical state are minimal or absent, then a longer arousal occurs. The reduced occurrence and amplitude of K-complexes in the elderly probably is related to the lack of such pre-arousal behavior in these subjects since their low delta response is so similar to that of the long arousals in the middle-aged subjects. Our finding is similar to the report that the rate of K-complexes increases in the 10–20 sec before a PAT arousal (Ehrhart et al., 1981) and to the proposal that some external stimuli fail to elicit a K-complex because they occur in an "inappropriate" phase of the slow oscillation (Steriade, 2004). . There must, of course, be other factors which also affect arousal duration such as the strength of a stimulus.

Our hypothesis depends on there being a waxing and waning of the amplitude of the slow oscillation which could explain the increase in between-arousal variability (as evidenced by the 75^{th} percentile tracings in Fig. 2). The slow (<1 Hz) cortical oscillation is less regular in Stage 2 than in deeper sleep (Steriade, 2004;Amzica and Steriade, 2006). Furthermore, Steriade et al., (1993) showed examples from human subjects in which delta power fluctuated substantially over 60 sec and Achermann and Borbely (1997) concluded that delta power oscillated with a period of 20–30 sec in NREM. Unfortunately in the latter two reports delta activity included all EEG components below ~4 Hz so that one cannot be certain that low delta power varied similarly,. In elderly subjects, the diminished rate and amplitude of K-complexes (Crowley et al., 2002) suggests that there may be less difference in cortical sensitivity over time.

Another possibility is that there is an actual stimulus occurring in the 21 to 14 sec period prior to the arousal. Either this stimulus is the one that ultimately causes the arousal, or a later arousing stimulus is coupled to this early one. Supporting this hypothesis is the increase in theta power in the same (21 to 14 sec) time interval, suggestive of an initiated, but aborted, arousal. It is possible that a stimulus continues throughout the 21 seconds,

repeatedly evoking a burst of delta power and eventually “breaking through” the cortical desensitization and causing an arousal; however, tracings from individual arousals do not appear to support the systematic presence of repeated bursts of low delta power pre-arousal. .

The variability in arousal duration may also be related to the timing of the stimulus relative to the phase of the slow cortical oscillation. The amplitudes of somatosensory evoked potentials have been shown to vary with time during this oscillation, being largest when evoked near the down-state to up-state transition (Massimini et al., 2003; Curto et al., 2009). Furthermore, a simple model of cortical neural activity derived from the pre-stimulus EEG activity was able to predict the major part of the variability of the evoked response in the ~150 msec after the stimulus (Curto et al., 2009), implying that the state of the cortex is the primary factor causing this variability rather than differences in transmission of the stimulus. Although the slow oscillation can be generated by the cortex in animals after thalamectomy, one cannot rule out a role for the thalamus in cortical state changes in intact subjects (Massimini et al., 2003). Differences between middle-aged and elderly subjects might be expected if the characteristics of the slow oscillation are different in the elderly. Since average evoked cortical responses have been shown to depend on factors that change cortical state (e. g., vigilance state and sleep state), and the variability of these responses changes with cortical state (Vanderwolf et al., 1987), it is reasonable to assume that the properties of the slow oscillation might change with age. Whether one can extrapolate from these brief (i. e., a few hundred msec) responses to discrete stimuli to predict longer behaviors such as arousals is an important question.

We have demonstrated that after an arousal the central EEG signal returns to its pre-arousal baseline state over a time course lasting some 20–30 sec, as observed in the responses of both the power signals and Sample Entropy. These findings are in agreement with the implications from previous studies (Stradling et al., 1999; Black et al., 2000; Togo et al., 2006), all of which are inconclusive because ensemble averaging was done using a non-EEG event as the point of synchronization. Thus, in those studies the EEG responses reflect averages over EEG arousals of differing lengths, a procedure which would produce an artifactual slowly decaying response. By synchronizing our averaging with the end of the EEG marker of arousal, we avoided this problem.

The mechanistic basis of the slow return to baseline activities after the arousal is unclear although it is similar to the slow return of low-frequency, high-amplitude cortical activity after electrical stimulation of the brainstem or of the amygdala which transiently evokes high-frequency, low-amplitude activity (Kapp et al., 1994; Whalen et al., 1994; Curto et al., 2009). We have also reported a slow return of C3A2 mutual information to its baseline state following arousals, as well as a slow return of coupling between C3A2 and C4A1 EEG signals (Ramanand et al., 2010). Also, it has been shown that the time courses of delta and alpha powers differ during sleep onset (Tagaya et al., 2000; Ferrara et al., 2002), but the time scale is much longer than the current observations. It should be noted that in the present study all activities except beta (and sigma in the elderly) fell to levels below their baseline by 7–14 sec after the arousal. Sforza, et al., (2002) also reported decreases in delta and alpha powers within 10 sec of the onset of a phasic leg movement (PLM) associated with a delta burst or a microarousal; however, these authors focused on EEG responses before and during PLMs and did not further discuss the decreased powers.

We studied fewer than 10% of the arousals per subject because we wished to avoid nearby (i. e., within +/−30 sec) events known or suspected to affect an arousal. We did analyze all arousals that met our criteria including this criterion of separation. It is an open and relevant question whether arousals associated, for example, with obstructive apneas would show

similar behaviors. On the other hand, spontaneous arousals often occur less than 30 sec from another arousal, and we would propose that the later arousal will be altered by the continuing disruption of the cortical state following the earlier arousal. Arousals sometimes occur in groups of 3 or more separated from each other by less than 20 sec, and there is some evidence from piglets (BuSha et al., 2001) that EEG responses differ between the first and subsequent arousals in such groups.

Our findings show that the alteration of EEG spectral powers by the arousal is not completed by the end of the arousal (even when the end is established by a rigorous quantitative method based on EEG spectral powers). These responses are reflected by the Sample Entropy, an index which has been shown to closely reflect the balance of beta and delta powers in EEG signals (Bruce et al., 2009). Sample Entropy was significantly higher, i.e., closer to values seen in the Wake state, after arousals that occurred during Stage 2 and Stage 3, but not during REM, when compared with pre-arousal values in both middle-aged and elderly women. To the extent that Sample Entropy represents a measure of the balance between sleep-promoting and alertness-promoting neural mechanisms, these observations indicate an increase in the level of alertness that extends beyond the SHHS-marked end of the arousal (Bruce et al., 2009). The implication is that the cortex is in an altered state for much longer than is apparent from visual inspection of the EEG. Schwartz, et al. (2006) have reported that the Epsworth Sleepiness Score correlates weakly with the frequency of long arousals but does not correlate with the frequency of short arousals. Thus, our observations of an apparent increase in the duration of an aroused state due to the decrease in delta power and the increase in beta power post-arousal could potentially have a significant impact on quantitative assessments of sleep quality. Underestimation of the durations of the arousals may contribute to the discrepancy between the arousal indices determined by scorers and the perception of sleep quality by individual subjects. The clinical implications of these findings are that other assessment tools may need to be developed to enable clinicians to predict excessive daytime sleepiness more accurately.

CONCLUSIONS

We have shown that spontaneous, isolated, cortical arousals from sleep often last longer than noted by trained human scorers using ASDA criteria. Furthermore, the alteration of cortical state begins ~21 sec before the arousal in healthy middle-aged women in NREM stage 2 sleep and persists for ~14 sec post-arousal. The pre-arousal change is associated with an increase in delta power of the EEG and, for individual arousals, the presence of early pre-arousal low delta power was associated with shorter arousals. We suggest that this apparent attenuation of the effect of the arousing stimulus may be related to the slow (<1 Hz) cortical state oscillation. For healthy elderly women, cortical state changes only in the few seconds prior to the arousal but changes also persist for ~14 sec post-arousal. These prolonged alterations of cortical state due to arousals may contribute to the low correlation between indices of arousals and indices of sleepiness or impaired cognitive function.

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5. APPENDIX: Analysis of EEG Signals

EEG signals were first upsampled to 250 Hz, then lowpass filtered at 25 Hz using a 21-point, FIR filter based on a Hamming window (Figure A1). Next, the signal was downsampled to 50 Hz and passed through six bandpass filters (equiripple filters based on the Parks-McClelland algorithm, maximum stopband gain = −40 dB) in parallel. Each filter selected one of the following six frequency bands: low frequency delta = 0.2–2 Hz; high frequency delta = 2–4 Hz; theta = 4–8 Hz; alpha = 8–12 Hz; sigma = 12–16 Hz; and beta = 16–23 Hz. The mean level was removed from each filter output, and the mean absolute value of each output was calculated over a sliding window of 2-sec duration (4-sec duration for the low frequency delta signal) which advanced through the data in steps of 0.02 sec. Each such “moving average” signal was squared to estimate instantaneous power in the corresponding frequency band.

The onset and termination of the cortical component of an arousal, which had been previously identified by a human scorer, were determined based on comparing the sum of powers in the alpha, beta, and theta bands relative to its level during a preceding 30-sec time interval (from 6 to 36 sec before the scored arousal). (As specified by the ASDA criteria, a sudden increase in any of these bands indicates an arousal.) Individual powers in these three bands were each converted to dB (by calculating 10*log(power)) and the three dB values were summed at each point in time, creating a “summed power signal”. Then a threshold was determined by adding 6 dB to the average summed theta + alpha + beta powers in a 30-sec window covering the interval from 6 to 36 sec before the scored arousal (Figure A2). Finally, the summed power signal was smoothed by processing it through a sliding (in time) median filter with a window length of 3 sec. The onset of an arousal was located when this smoothed signal crossed the threshold and remained above it for more than 3 sec and the arousal ended when the signal fell below the threshold for more than 3 sec. This method was the result of testing numerous combinations of alpha, beta, and theta powers and how to relate them to past activity so that a “sudden increase” would be detectable. The algorithm presented here produced results that were the most consistent with those of the SHHS scorers (although often preceding their onsets slightly) without generating false arousal detections in the 30 seconds preceding a marked arousal, during which the scorers had not identified any arousals.

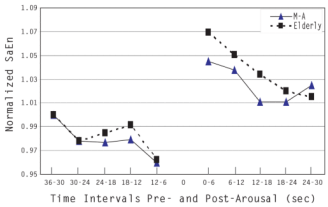

Figure 1.

Linear trend analysis of normalized Sample Entropy (SaEn) values calculated over 6-sec intervals from 36-6 sec before and from 0–30 sec after Stage 2 + Stage 3 arousals in 20 middle-aged (n=133 arousals) and 20 elderly (n=148 arousals) women. The linear decrease in Sample Entropy post-arousal was significant only in the elderly women ($p<0.0001$).

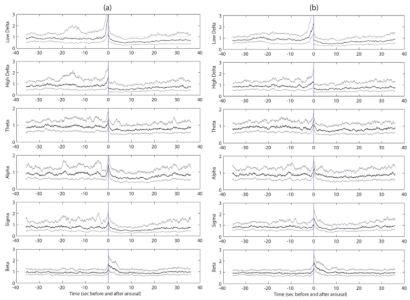

Figure 2.

Median normalized spectral power in 6 frequency bands for 36 sec before and 36 sec after Stage 2 arousals in (a) 20 middle-aged women (n=113 arousals) and (b) 20 elderly women (n=111 arousals). Pre-arousal signals (time < 0) were synchronized by moving backwards in time from the onset of each arousal. Post-arousal signals (time > 0) were synchronized by moving forwards in time from the end of each arousal. The dark solid line represents the median values. At each time point, 75% of the values fall below the upper dashed line and 25% of values fall below the lower dashed line.

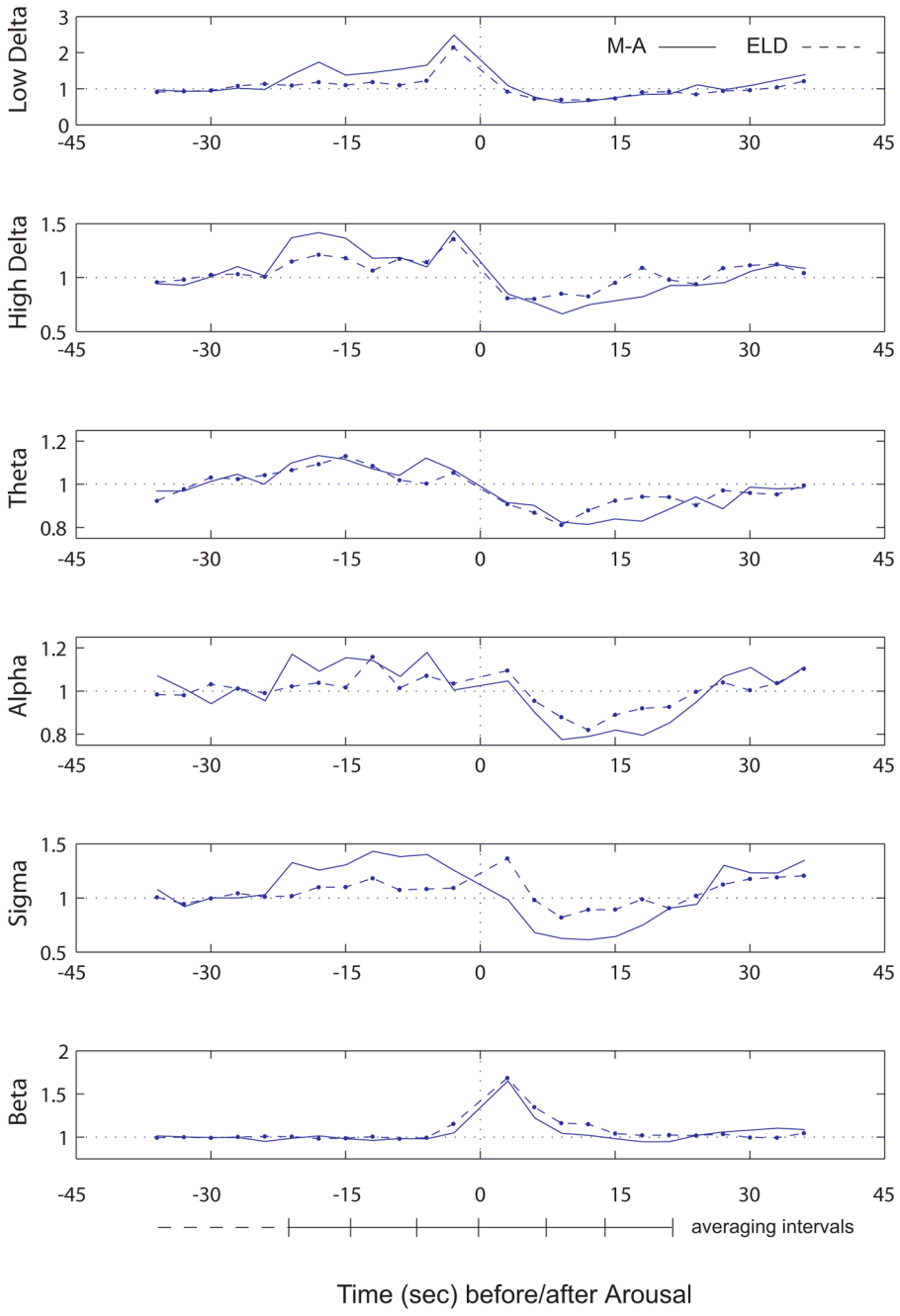

Figure 3.

Mean normalized spectral power calculated over 3-sec intervals before and after Stage 2 arousals (Signals synchronized for ensemble averaging as explained for Figure 2.) in 20 middle-aged women (n=113 arousals) (solid lines) and 20 elderly women (n=111 arousals) (dashed lines). Marker at the bottom of the figure indicates the baseline time period (dashed) and the six 7-sec intervals (solid) over which averaging was done for statistical testing.

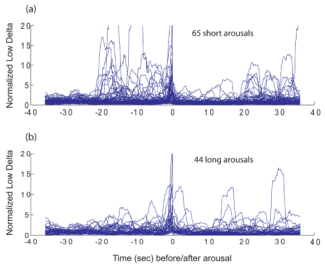

Figure 4.

Normalized low delta power before and after individual arousals in middle-aged subjects. (a) 65 arousals with durations less than 8 sec; (b) 44 arousals with durations between 8 and 15 sec.

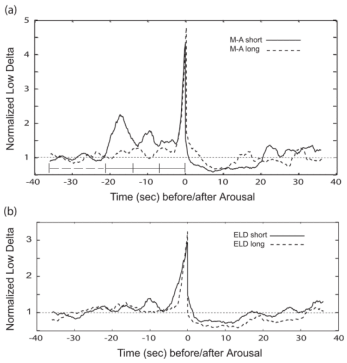

Figure 5.

Mean normalized low delta power before and after arousals for short (solid lines) and long (dashed lines) arousals. (a): middle-aged subjects. The time intervals over which averaging was done for statistical analysis are indicated by the solid bar with vertical tick marks. The long dashed bar indicates the baseline period. (b): elderly subjects.

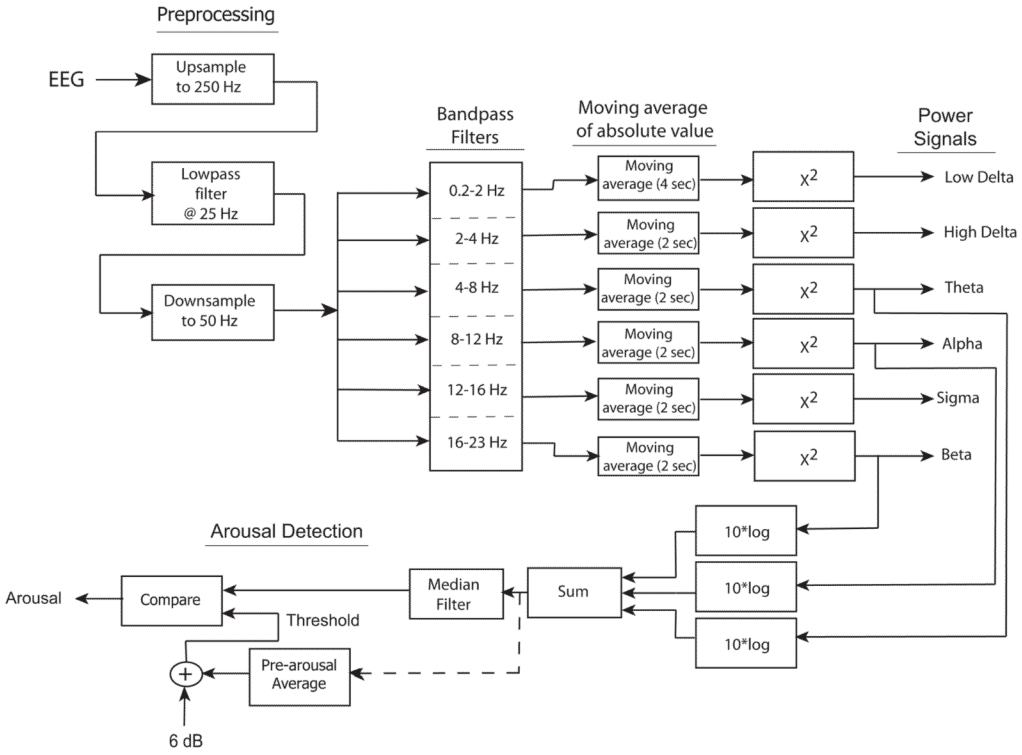

Figure A-1.

Overall scheme for off-line processing of EEG signals for calculating power in 6 frequency bands and for determining the onset and termination of an arousal. Dashed line indicates that the calculation of the threshold was done before the other steps in arousal detection. See text for additional details.

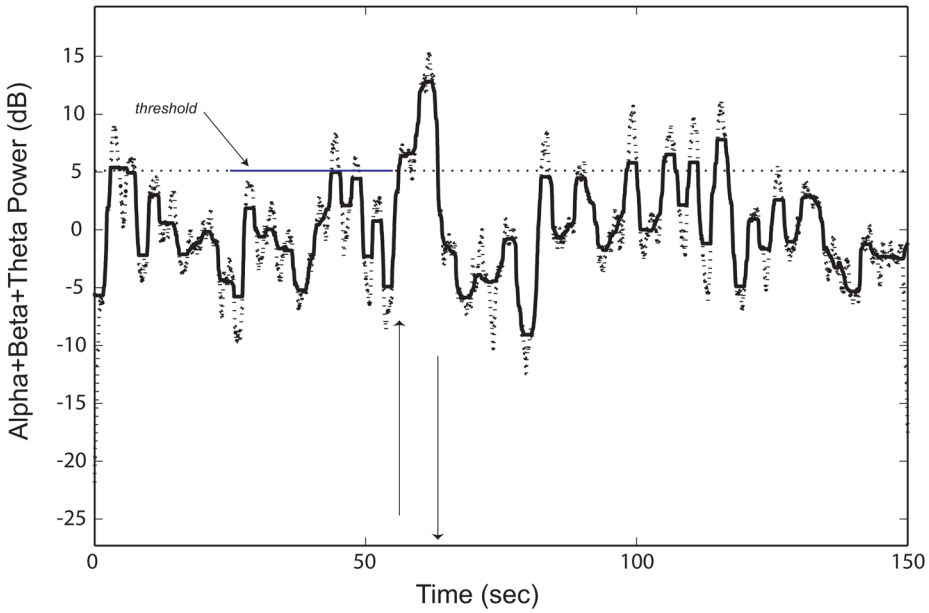

Figure A-2.

The onset and termination of each arousal was determined as described in the text. The dotted black line represents the sum of alpha, theta, and beta powers. The thick line which approximates the dotted line represents the median-filtered sum of powers. The threshold is shown as the horizontal dotted line, which indicates 6 dB above the average power during the time of the short horizontal bar labeled “threshold”. T_{on} (up arrow) and T_{ter} (down arrow) correspond to the times closest to the scored arousal at which the median-filtered signal crosses the threshold for at least 3 sec.

TABLE I

Statistical Results

P-values are given for various statistical tests. Pre-A>Post-A: comparison of average power for 30 sec post-arousal to average power for 30 sec pre-arousal. The remaining columns compare average powers across three time points pre-arousal and post-arousal with baseline power (i. e., 36–21 sec pre-arousal).

			Pre-Arousal			Post-Arousal		
Age	**Spectral Power**	**Pre-A > Post-A**	**21–14 sec**	**14-7 sec**	**7-0 sec**	**0–7 sec**	**7–14 sec**	**14–21 sec**
Middle- Aged	low-delta	< 0.0001	0.0040	0.0097	< 0.0001	NS	NS	NS
	high-delta	< 0.0001	< 0.0001	0.0020	0.0021	0.0052	0.0016	NS
	theta	< 0.0001	0.0036	NS	NS	NS	< 0.0001	0.0004
	alpha	< 0.0001	NS	0.0097	NS	NS	< 0.0001	0.0008
	sigma	< 0.0001	0.0025	< 0.0001	0.0003	NS	< 0.0001	NS
Elderly	low-delta	< 0.0001	NS	NS	< 0.0001	NS	< 0.0046	NS
	high-delta	< 0.0001	NS	NS	< 0.0001	0.0062	NS	NS
	theta	<0.0001	NS	NS	NS	0.0034	0.0029	NS
	alpha	< 0.0002	NS	NS	NS	NS	0.0004	NS
	sigma	NS	NS	NS	NS	NS	NS	NS

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