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Transient Decoupling of Cortical EEGs following Arousals during NREM Sleep in Middle-aged and Elderly Women

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Abstract

Spontaneous cortical arousals in non-REM sleep increase with age and contribute to sleep fragmentation in the elderly. EEG spectral power in the faster frequencies exhibits well-described shifts during arousals. On the other hand, EEG activities also exhibit correlations, which are interpreted as an index of interdependence between distant cortical neural activities. The possibility of changes to the interdependence between cortical regions due to an arousal has not been considered. In this work, using previously recorded C3A2 and C4A1 EEG signals from two groups of adults, middle aged (42–50 years) and elderly (70–80 years) women, we examined the effects of spontaneous arousals in NREM sleep on cortical interdependence. We quantified the auto- and cross-correlations in these signals using mutual information and characterized these correlations in periods before the onset and following the end of arousals. The pre-arousal period exhibited significantly higher interdependence between central regions than that following the arousal in both age groups (middle aged: $p = 0.004$, elderly: $p < 0.0001$). Also, for both EEG signals the auto mutual information had a faster rate of decay, implying lower signal predictability, following the arousal than prior to it (Both age groups, $p < 0.0001$). These results indicate that the state of the cortex is different after, compared to before, the arousal even when the spectral power changes characteristic of an arousal are no longer visible. The findings suggest that the state following an arousal characterized by lower interdependence may resemble a more vigilant period during which the system may be vulnerable to more arousals.

Keywords

Arousals; Sleep; Interdependence; Age; Mutual Information

1 Introduction

Aging, sleep and the interaction between the two have been key fields of research in sleep medicine and health care for many years (Agnew, et al., 1967, Feinberg 1974, Ehlers and Kupfer, 1989). Characteristics of declining sleep quality such as daytime sleepiness, and impaired cognitive and psychomotor function, are commonly reported in the elderly (Bliwise 1993, Blackwell, et al. 2006). Chronic medical or psychiatric health conditions and complications such as sleep disordered breathing (SDB) and periodic limb movement

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disorders (LMD) are also prevalent in this population which may, to a great extent, explain the reported objective and subjective measures of poor sleep quality (Smith and Haythornthwaite 2004, Neikrug and Ancoli-Israel 2009). However, evaluations of polysomnogram recordings (PSG) from healthy subjects ranging in age from young to non-complaining elderly have identified lower sleep efficiency and total sleep time, less slow wave (restorative) sleep, and shifts in the EEG power spectrum apparently unrelated to medical conditions in the older subjects (Carrier, et al. 2001, Dijk, et al. 2001, Vitiello, et al. 2004, Bruce, et al. 2009). Hence while it is unclear whether age by itself causes sleep degradation in the elderly, it is generally accepted that sleep quality parameters show a declining trend with age.

Arousals (AR) which represent brief episodes of awakening during sleep are believed to contribute to sleep fragmentation, especially in older populations, which in turn may cause reduced sleep time (Bonnet, et al. 2007a). According to the definition by the American Sleep Disorders Association (ASDA), an EEG arousal is an abrupt shift in frequency towards faster frequencies such as theta, alpha or beta exceeding 16 Hz but not spindles and lasting between 3 and 15 sec (ASDA 1992). ARs frequently manifest following respiratory disturbances such as apneas and hypopneas, or movements. However, idiopathic or spontaneous arousals occur in sleep of people of all ages. In a study on such physiological arousals with subjects ranging from 10 to over 60 years in age, Boselli et al. (1998) established a significant increase in the number of arousals in nonREM (NREM) stages 1 (S-1) and 2 (S-2) with age. This fact coupled with observed measures of poor sleep quality suggest that excessive occurrence of arousals may be contributing to sleep fragmentation in the elderly (Bonnet and Arand 2007b).

Spontaneous arousal events represent changes in cortical activation due to brief episodes of sleep disruption alone. The power of the EEG spectral bands delta, theta and alpha is subject to changes just prior to and during AR events when compared to background activity (De Carli, et al. 2004, Togo, et al. 2006). While the delta band showed an increase in power prior to and a decrease during an arousal, the faster theta, alpha and beta bands increased in power during the arousal. Spectral power changes in individual neural activities may be accompanied by changes in the interactions between them. The functional organization between cortical regions following the arousal may be strikingly different from that existing during a typical sleep stage in the absence of, or prior to, the occurrence of such an event. The interdependence between EEG signals is interpreted as a measure of the coupling or connectivity between cortical regions underlying them (Stam, 2005). Recently, slow wave synchronization between brain regions during sleep and its link to cognitive processing has been hypothesized (Huber et al., 2004; Ferri et al., 2005). The significance of inter-hemispheric interactions during sleep and increase in slow wave coherence following enhanced sleep pressure suggest a functional and active role in sleep homeostasis and regulation (Tononi and Cirelli, 2003, Vyazovskiy, et al., 2004). Hence, examining the dependencies between signals from spatially distant cortical sites provides valuable information about the effect of arousals on dynamical interactions between the underlying neuronal networks.

Investigating the coordination of underlying neuronal populations and how it is changed by arousals requires the application of multivariate methods to EEG signals. Different measures of connectivity have been introduced and applied extensively to assess the interdependence between brain regions from neural signals in the context of normal waking, sleep, task oriented and pathological brain conditions (Pereda, et al. 2005, Stam, 2005 and references therein). Mutual information (MI), an information-theoretic measure of dependence between signals has found wide application in understanding the information transfer across brain regions under varied conditions of normal and pathological brain functioning (Jeong, et al.

2001, Na, et al. 2002, Na, et al. 2006). Characterizing both linear and nonlinear dependency between two signals, mutual information gives a measure of the amount of information about one signal contained in the other (Fraser and Swinney, 1986). Hence, when applied to two EEG signals, MI gives a measure of dynamical coupling between them. When used to compare a single signal with itself, (auto mutual information, AMI), the rate of decay of MI with time represents how quickly the information is lost from the signal.

In this paper, we report on the effect of spontaneous arousals in non-REM S-2 and S-3 on the interdependence between central regions by applying the MI measure to sleep EEG signals recorded from middle aged (MA) (42–50 years) and elderly (ELD) (71–86 years) women. Our primary objective was to investigate the effect of spontaneous ARs on the connectivity of cortical regions and to test for differences in the behavior of the interdependence between the two age groups. Since an arousal is defined as an abrupt change in signal frequency and thereby a cortical activation, we hypothesized that an AR may cause a lowering in cortical co-ordination which persists after the termination of the arousal.

2 Methods

2.1 Subjects

The study was conducted on previously-existing polysomnogram (PSG) EEG datasets obtained from the NIH-sponsored Sleep Heart Health Study (SHHS) (Quan et al. 1997). The PSG data were recorded using Compumedics P-series Sleep Monitoring system and included: EEGs recorded from leads C3/A2 and C4/A1, a right and a left electro-oculogram (EOG), a bipolar submental electromyogram (EMG), electrocardiogram (EKG), nasal airflow, respiratory excursions of the thorax and abdomen, and finger pulse oximetry. The EEG signals were filtered between 0.48 – 30 Hz with sampling frequency 125Hz. Sleep staging was scored by SHHS personnel at 30 s intervals based on the Rechtschaffen and Kales criteria (1968), and apneas, hypopneas and arousals were marked on the PSGs. From the SHHS database, we initially selected 20 middle-aged (MA) and 20 elderly (ELD) Caucasian women for the present work. Due to contamination of the second EEG channel, one subject in the ELD group was excluded from the analysis. These women did not have clinically-diagnosed sleep-disordered breathing or a history of stroke, were not taking any medications known to interfere with sleep, and did not take frequent naps during the daytime. None were current smokers. Table 1 gives the relevant information for the subjects included in this study.

2.2 Determination of arousal time and duration

Arousal scoring from polysomnogram data is usually based on the guidelines of the Atlas Task Force report published by the ASDA (1992). However, this process remains to date very subjective with low inter- or even intra-scorer reliability scores of AR detection (Drinnan, et al. 1998, Whitney, et al. 1998). Indeed, this method is adequate for the purpose of counting the arousal occurrences in the whole PSG record to compute parameters such as the arousal index. However, for the objectives of this work where understanding the changes occurring just prior to and following an AR were the focus, a robust procedure that helped mark the AR onset and termination times with accuracy was imperative. Briefly, our method relies on the definition of an EEG arousal as a sudden shift of EEG power to higher frequencies and is described in the Appendix in detail. We analyzed scorer marked (based on ASDA arousal scoring criteria), isolated ARs from each subject record that were at least 40 s away from apparent events such as other arousals, apneas, hypopneas and movement. In general, our onset times were within 2–3 seconds of those marked by the scorers. Figure 1 presents the detection of an AR from the EEG signal using our algorithm.

2.3 Mutual Information

Mutual Information, a metric derived from information theory, quantifies the information gained about one random event from observations of another (Fraser and Swinney 1986, Abarbanel, et al. 1993). It measures the linear and nonlinear dependencies existing between two sets of data. Hence, MI is often regarded as the nonlinear counterpart of the standard correlation function. The MI function can be applied to two time series as the Cross Mutual Information (CMI), or to a single data series (Auto Mutual Information, AMI).

Consider $X = \{x_i\}$ and $Y = \{y_j\}$ representing two sets of random observations with probability distribution of amplitudes given by $P_X(x_i)$ and $P_Y(y_j)$, respectively. The average amount of information gained from measurements of X according to Shannon information theory is,

$$H(X) = -\sum_{x_i} P_X(x_i) \log P_X(x_i) \tag{1}$$

This is the *a priori* uncertainty in X existing before any measurements are made. The conditional uncertainty in a measurement of X, given that y_j is the measurement made in Y, is $H(X|Y = y_j)$. The mean conditional uncertainty in measuring X under the condition that Y is known is then

$$H(X|Y) = -\sum_{y_j} P_X(y_j)\, H(X|Y=y_j) = H(X,Y) - H(Y) \tag{2}$$

where,
$$H(X,Y) = -\sum_{x_i,y_j} P_{XY}(x_i,y_j) \log[P_{XY}(x_i,y_j)]$$

The mutual information (MI) between X and Y quantifies the reduction in the uncertainty of X by measurements made on Y and is given as

$$MI(X,Y) = H(X) - H(X|Y) = H(X) + H(Y) - H(X,Y) \tag{3}$$

Using the equations (1) and (2) for single and joint entropies, the Cross Mutual Information (CMI) in (3) can also be expressed as,

$$CMI(X,Y) = \sum_{x_i,y_j} P_{XY}(x_i,y_j) \log\left(\frac{P_{XY}(x_i,y_j)}{P_X(x_i)P_Y(y_j)}\right) \tag{4}$$

Usually, the logarithm in the above relations is taken to the base 2 and information is then expressed in units of bits. By estimating the CMI for signals lagged in time, the CMI can be obtained as a function of the time lag between them. This function gives the average number of bits of X that can be predicted by making measurements of Y.

The estimation of the probability functions in (4) poses a hurdle in estimating the MI function from time series data. Different methodologies have been proposed for MI estimation ranging from the histogram-based to nearest neighborhood estimation of the joint probability function (Cellucci, et al. 2005,Papana and Kugiumtzis 2008). In this work, the histogram method was used to estimate the MI over varying time lags of the signal. The MI value by this method is critically dependent on the choice of the number of bins. Too few

bins will lead to an underestimation of the value, while choosing a very large number to form the histogram leads to an overestimation of the MI estimate. For the data sets that we were analyzing, use of 16 bins was found to give stable estimates of CMI and this number was used through the entire analysis. The CMI function was estimated over time lags of −0.4 s to 0.4 s between the signals. To quantify the interdependence between two signals, the average CMI over a time lag of −0.2 s to 0.2 s (by which time the CMI had fallen to baseline level) was calculated. The variation of the interdependence over time with respect to the AR was further investigated by dividing the 30 s periods of pre- and post arousal segments into 3 non-overlapping segments of 10 s each and computing the mean CMI for these segments by the method described above. This analysis was intended to obtain information on the time scale over which changes in interdependence relative to the AR may be occurring.

Analogous to the definition of the CMI, the Auto Mutual Information (AMI) function tells how many bits on average about a given signal may be predicted by measurements on the time-advanced version of itself. The AMI between $X(t) = \{x_i\}$ and $X(t+\tau) = \{x_{i+\tau}\}$ is,

$$AMI\,(X(t), X(t+\tau)) = \sum_{x_t, x_{t+\tau}} P_{XX_\tau}(x(t), x(t+\tau)) \log\left(\frac{P_{XX_\tau}(x(t), x(t+\tau))}{P_X(x(t)) P_{X_\tau}(x(t+\tau))}\right) \tag{5}$$

In the case of AMI, the rate at which information decays with time is an inverse measure of the predictability of the signal. A higher rate of decay is associated with a quicker loss of predictability of the signal (Abásolo, et al. 2008). The behavior of the AMI curve for the EEG signals prompted us to fit it with an exponential function of the form,

$$AMI(t) = c_0 + c_1 e^{-\lambda t} \cos^2(2\pi f_c\, t) \tag{6}$$

where λ is the decay rate and f_c is the central frequency of the signal. The damped squared cosine equation for MI function is a natural generalization of the damped cosine model for the autocorrelation function of signals. In the case of the broadband data where effects from all the spectral bands are present, the AMI curve was fit in the least squares sense using,

$$AMI(t) = c_0 + c_1 e^{-\lambda t} \text{ with } \cos^2(2\pi f_c t) = 1 \tag{7}$$

With this definition, we may say the central frequency for the broadband signal is the sampling frequency.

2.4 Surrogate data Analysis

The MI quantifies the linear and nonlinear correlations in the signal. The question of whether the estimated CMI detects dependencies other than linear ones between the sleep EEG signals is answered by applying the method of surrogate data analysis (Theiler, et al. 1992, Schreiber and Schmitz 2000). Although the MI between independent signals is zero, the finite size of a data set often causes this lower bound to be greater than zero. The methodology we followed to establish the significance of the CMI values and nature of the interdependence is similar to that of Pereda and coworkers (2001). In this two step procedure, first univariate surrogates, S^1, that retained the linear properties of one of the signals, say E^1, were generated by the iterated amplitude adjusted Fourier transform (iAAFT) method. The CMI between each of these surrogates and the other EEG signal, E^2, was computed. In the case of true interdependence between E^1 and E^2, $MI\,(E^1,E^2)$ will be

always greater than MI (S^1, E^2), because the surrogates are non-correlated with E^2. For the pairs of signals for which significance was thus established, bivariate surrogates, $(S_2)^1$ and $(S_2)^2$, that preserved the linear properties of each of the signals and also the linear cross-correlation between them, were generated by the iAAFT method for the multivariate case. If the signals have nonlinear correlations between them, then the MI between the original (EEG) signals will be greater than that of the surrogates. This difference was detected using a rank order test at a pre-specified significance level, $(1 - \alpha) \times 100$ %. For the one-sided tests in both the univariate and bi-variate cases, we generated $M = \left(\frac{1}{\alpha} - 1\right)$ surrogates. Including the original EEG segments, this gave an ensemble of $\left(\frac{1}{\alpha}\right)$ data sets. The probability that the measure for the EEG signals is the largest in the ensemble of CMI values due to chance is then exactly α. With α = 0.05, the significance level was 95% and M= 19 surrogate sets were generated for the analysis in both cases. As the time lag increased, the EEG signals became more de-correlated, giving small values for the CMI. In the final step we required that the estimated MI for the EEG signals be greater than that for the surrogates for at least 60% of the time lags considered. This condition thus ensured that the higher values of MI due to the interdependence between the signals that was present at short time lags was included in assessing the nature of the interdependence. The tests of significance conducted between the mean CMI and CMI functions of the EEG signals and the surrogates are illustrated in Figure 2.

All the software for the signal analysis including AR onset detection, MI and surrogate analysis was developed and carried out in MATLAB v 7.5.0.342 (R2007b).

2.5 Statistical Analysis

The MI data compiled from analyzing the EEG signals relative to pre-arousal (pre-AR) and post-arousal (post-AR) segments were analyzed separately for the MA and ELD groups to identify statistically significant changes in the interdependence prior to and following an arousal. All statistical analyses were conducted using SAS 9.2 software (SAS Institute Inc., Cary, NC). The PROC MIXED analysis was used to design a one factor analysis with two repeated measures. This model was applied to the mean CMI data from the 10 s interval based analysis, with two fixed factors, STATE (2 levels): pre-AR and post-AR and TIME (3 levels) nested within STATE to test the hypothesis that the mean CMI did not change significantly between the pre-AR and post-AR states. The 3 levels of TIME corresponded to the 10 s period closest to the AR, the mid 10 s interval and the farthest 10 s interval relative to the AR on the pre- and post-sides. In the case of the measure (mean CMI or AMI decay rate, λ) calculated over the whole 30 s interval, the only fixed factor was STATE. Since the number of arousals from each subject was different, the index for each arousal, AR_ID, was nested within the subject, SUBJ_ID. Variance components pertaining to SUBJ_ID, AR_ID, SUBJ_ID by STATE, AR_ID by STATE and SUBJ_ID by STATE(TIME) were included as random factors in the model. The Satterthwaite approximation was used to estimate the degrees of freedom. For the measure of mean CMI over 10 s intervals, a post-hoc Dunnett test comparing the measures at each time point with a baseline level was performed. The baseline level was chosen as that corresponding to the farthest 10 s interval in the pre-AR state. This analysis thus indicated at which time points a significant change to the interdependence occurred with respect to the (arbitrarily) chosen baseline interdependence level that was existing prior to the arousal. For all the analyses, the significance was defined for $p<0.05$.

3 Results

3.1 CMI analysis of EEG

EEG signals of 30 s duration from pre- and post-AR intervals were used to estimate the cross mutual information between them. CMI was estimated as a function of time between the two EEG signals over lags (advance) of −0.4 to 0.4 s. The CMI as a function of time lag for a pre- AR segment from a MA subject is presented in Figure 3. The CMI function was observed to decay to baseline values within lags of 0.2 s between the signals. Hence, the mean CMI over a period of −0.2 to 0.2 s centered on the peak in the CMI function was chosen as a measure of the interdependence between them. This also ensured that changes in CMI due to values of lag (or advance) between signals other than the zero lag, were also taken into account in quantifying the interdependence. The dotted lines represent the CMI estimated between the univariate surrogates of C3A2 EEG and the C4A1 EEG segment, which form a significance threshold for the CMI function between the two EEG signals. The maximum CMI at each time lag for the set of bivariate surrogates is also plotted. In this case, the EEG segments exhibit higher values than the set of bivariate surrogates at over 60% of time lags between −0.2 to 0.2 s and hence cast doubt on the hypothesis of linearity of the interdependence.

3.1.1 Dependence of CMI on spectral power: Simulation study—The observed behavior of the CMI functions and the interdependence values led us to suspect a strong impact of the low frequency delta band on the findings. A simulation study was undertaken to investigate the effect of a dominant frequency band on the observed CMI values. Bivariate normal random numbers with a correlation of 0.6 were filtered into the traditional spectral bands, delta (0.2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–25 Hz). Each EEG signal was simulated by adding the filter outputs after weighting them appropriately so that the maximum power occurred in the delta band. The weights were selected from random selections from a uniform distribution (Bruce et al., 2009). The CMI was estimated over the same time lags used in this study. The mean CMI over −0.2 s to 0.2 s for each pair of signals was plotted against the sum of the relative delta powers in the two signals (Figure 4 (c)) and fit with a straight line indicating an increase in the mean CMI as the delta power increased (R^2=0.77, p<0.001). Moreover, this trend was very strong for values of total relative delta power >1 i.e., when at least one of the signals had over 50% of its power attributable to the delta band.

In order to understand the effect of the dominant spectral band on mean CMI, the analysis was repeated after bandpass filtering (BP filtering) the delta band component from the simulated signals. The signals were bandpass filtered between 4 to 25 Hz using a fourth order elliptic filter of peak to peak ripple of 1 dB and stop band attenuation of 30 dB. The mean CMI was computed for the band pass filtered segments. In general with 2 signals, the following cases of power distribution in the delta band can occur: (i) both signals have low relative delta band powers, (ii) either or both have moderately high relative delta band power ($0.3 \leq P_\delta \leq 0.7$) and (iii) either or both have high delta band powers ($P_\delta > 0.7$). Considering all the cases where at least one of the signals had relatively high delta band power (cases ii and iii) we calculated the difference in mean CMI between the broadband and BP filtered cases. A histogram of this difference is plotted in Figure 4(d). It was observed that the mean CMI was reduced in a majority of cases when the delta band was removed. The few cases where the mean CMI for band pass filtered segments was greater than that for the broadband case can be explained in the following manner. If the second signal had low delta band power to begin with, its power is concentrated in one or more of the faster bands. Once the delta band is filtered out, the faster spectral bands become the dominant ones in the signal due to which the CMI function may have a higher value at small lags causing the mean CMI

to be higher. However in such a case, the CMI decays very quickly in comparison to signals where the delta band is dominant (Figure 4(b)).

Hence, in our analysis of the sleep signals relative to AR events, the CMI analysis was repeated after band pass filtering to remove the low frequency delta component (0.2–2Hz) and restrict the signal to the relevant 2 to 25 Hz frequency range. Figure 3 (b) refers to the same pre- AR segment as in Figure 3(a) and represents the CMI function after bandpass filtering of the signals. The comparison of the changes in interdependence relative to the AR from the broadband and band pass filtered (BP filt.) segments for 10 s duration analysis helped identify changes in the CMI that may be attributable to the dominant low frequency delta component in the sleep EEGs.

3.1.2 Interdependence measures: Analysis of Pre-AR and Post-AR intervals— CMI of EEG signals corresponding to durations of 30 s from the period prior to and following the termination of ARs were computed. The signals were then bandpass filtered between 2 and 25 Hz to remove the dominant low frequency delta band component and the CMI estimation was repeated. The CMI over shorter 10 s windows on the pre- and post-AR sides for the broadband (BB) and bandpass filtered (BP filt.) segments were also computed and the mean CMI calculated in each case. The analysis was carried out on 114 NREM arousals in the MA group and 124 ARs in the ELD subjects.

Figure 5 summarizes the results for the interdependence between the central EEG signals relative to spontaneous ARs for MA (top row) and ELD (bottom row) subjects. It was observed from analysis of 30 s segments that the mean CMI was lower following an AR for both MA and ELD subjects. In the case of MA subjects (Figure 5 (a)), the one factor repeated measures design for the fixed factor STATE gave $F(1, 7.62) = 17.26$, $p = 0.004$ indicating significant differences between the pre-AR and post-AR states for the broadband data. After the band pass filtering, the differences between pre-AR and post-AR interdependence values remained significant with $F(1, 12.8) = 13.10$, $p = 0.0032$. For the 10 s analyses, a second repeated factor, TIME, was nested within STATE. The analysis indicated significantly lower interdependence following an AR compared to before (STATE: $F(1, 9.99) = 26.45$, $p = 0.0004$) and there was also a significant difference across time (TIME: $F(4, 48.3) = 4.77$, $p = 0.0025$). To investigate the effect of the time window on the interdependences, a Dunnett test comparing the mean CMI values at each time point to the interdependence value at the farthest 10 s interval on the pre-AR side was performed. The closest 10 s interval to the AR prior to it and the closest 10 s window to the AR following it showed significant differences from this chosen base line level (Figure 5 (b)). In the case of the 10 s analyses, after filtering out the low frequency delta, both the fixed factors were significant with pre-AR state having higher interdependence than the post-AR state (STATE: $F(1,12.9) = 17.98$, $p=0.001$ and TIME: $F(4,64.3) =3.17$, $p=0.019$). The Dunnett test revealed a significantly lower mean CMI in the first 10 s interval following the AR when compared to the baseline level. Interestingly, the higher CMI observed in the closest 10 s prior to the AR was no longer significantly different from the baseline level on the pre-AR side.

In the case of the ELD subjects, the statistical analysis of the 30 s mean CMI values showed significant differences between pre- AR and post-AR states (STATE: $F(1,123) = 27.4$, $p<0.0001$) with higher interdependence in the pre arousal state. For the bandpass filtered case, this difference was no longer significant (STATE: $F(1,123) = 1.19$, $p = 0.28$). For the 10 s analyses of the interdependence between broadband signals, only the STATE factor was significant indicating higher CMI in the pre-AR state than in the state following an AR (STATE: $F(1,38.8) = 40.63$, $p<0.0001$; TIME: $F(4,38.8) = 1.76$, $p=0.16$). On the other hand, the bandpass filtered signals whose time resolved interdependence values were statistically

assessed indicated significant difference for the STATE ($F(1,123) = 6.75$, $p = 0.01$) and across TIME ($F(4,492) = 2.95$, $p = 0.02$). In this case, the Dunnett test identified significantly lower CMI at the first 10 s interval following the AR when compared to the baseline of the mean CMI at the farthest 10 s interval from the AR on the pre-AR side (Figure 5 (c, d)).

Finally, we analyzed the summed power in high frequencies (theta + alpha + beta) of the EEG signal, which was used to mark the onset and termination of arousals, to check whether it had returned to its pre-arousal values in the post-arousal period. A paired t-test for this spectral measure averaged over 30 s showed a significant decrease post-arousal in comparison to pre-arousal for both age groups (MA: $t=6.45$, $p<0.001$ and ELD: $t=3.92$, $p<0.001$). Table 2 presents the Mean ± SD of the power measure for this analysis.

3.2 Analysis of AMI decay rate of the central EEG signals

The AMI gives the average amount of information of the signal with the time lagged version of itself. Hence, the rate of decay of the AMI function is a measure of how quickly the dependence in the time-shifted signal is lost with increasing time lag. The normalized AMI function estimated for the 30 s duration signals of both C3A2 and C4A1 channels was fit with equation (7) and the decay rate, λ, was determined. A comparison of the AMI decay rates between the pre- and post arousal states can effectively tell if the signal regularity changes due to the intervening arousal event. The fit parameter C_0 was close to 0 (0.03 ± 0.012 for MA and 0.03 ± 0.015 for ELD) and C_1 was close to 1 (0.94 ± 0.031 for the MA, 0.94 ± 0.034 for the ELD).

The significant findings of the analysis of the decay rate parameter for the broadband and band pass filtered signals from the pre and post arousal states of the MA and ELD subject groups are shown in Figure 6. In the case of the MA subjects, the statistical analysis of the decay rate parameter indicated significantly higher values post-AR in comparison to the pre-AR state for both central EEG signals [For C3A2, STATE: $F(1,113)=31.57$, $p<0.0001$ and for C4A1, STATE: $F(1, 15.9)=28.82$, $p<0.0001$]. After the low frequency delta component was removed from the signals, the decay rate parameters were higher for both states in comparison to the broadband signals. However, the differences in λ between pre-AR and post-AR states remained significant for both signals [For C3A2, STATE: $F(1, 13.6) = 8.99$, $p = 0.0098$ and for C4A1, STATE: $F(1, 15.2) = 8.75$, $p = 0.0097$]. Figure 6 (c) represents these results. In Figure 6(d), a box plot of the distribution of paired differences ($\lambda_{\text{Post-AR}} - \lambda_{\text{Pre-AR}}$) for each arousal from the two EEG channels in the broadband and band pass filtered cases is presented. From this, we observed that a majority of the arousals had higher decay rates following vs. preceding an AR for both channels in the broadband as well as band pass filtered cases. Out of 114 ARs analyzed in the MA group, 73% of C3 and 68 % of C4 EEG signals had faster decay rates after the AR than before. After filtering out the low frequency delta component, this was reduced to 66% in the C3A2 and 61 % in the C4A1 segments.

For the elderly group of subjects, the statistical analysis of the decay parameter exhibited highly significant differences for the pre- and post-AR states characterized by faster loss of information following the arousal. For the broadband case, the C3A2 signal had 80% of the 124 analyzed trials with higher values of λ post-AR in comparison to the state prior to arousal ($F(1,13.5) = 46.03$, $p<0.0001$). The C4A1 signal had 82% cases with higher post-AR decay rates ($F(1, 11.8) = 59.07$, $p<0.0001$). After bandpass filtering, the cases with λ higher in the post-AR period than in the pre-AR period were reduced to 74% in the C3A2 channel and to 71% in the C4A1 channel. However, the mean differences between the states remained significant [C3A2, $F(1, 13.9) = 34.06$, $p<0.0001$ and C4A1, $F(1, 9.1) = 29.25$, $p =$

0.0004]. Figure 6 (e, f) depict the changes in the decay rate parameter before and after spontaneous arousals computed for the two central signals of the ELD group.

3.3 Surrogate analysis of the EEG signals

The EEG signals from the pre- and post-arousal states were studied using surrogate methods to first, derive a significance threshold to test the hypothesis of independence between them and second, to test the linearity of the nature of interdependence. As described in the Methods section, the significance threshold was obtained by generating univariate surrogate copies of one signal and estimating the CMI of each surrogate with the other EEG signal. In cases where the EEG signals had significant interdependence, bivariate surrogates of both signals that preserved not only the individual linear properties but also the cross-correlation between them were created. The interdependence between these surrogates was tested against the observed values between the original EEG signals to check if the observed interdependence could be explained by accounting for the linear properties alone. The tests of significance for both cases were described earlier. The results of the surrogate analysis of the test regarding the nature of interdependence are shown in Figure (7) where (a, b) refer to the MA group and (c, d) refer to the ELD subjects. These graphs show the mean CMI (A-CMI) for the EEG segments which pass both tests to reject the hypothesis of linearity of interdependence plotted against the (Mean ± SD) of the CMI from the set of bivariate surrogates for each pair of signals in the pre- AR and post-AR states. A majority of the EEG segments in both the pre- and post-AR states failed to reject the null hypothesis of linearity of the observed interdependence. For the MA subjects, of 112 segments (of the total 114) in the pre-AR state that had significant interdependence between them, 57 qualified as showing interdependence that could not be explained by the linear correlations between them. For the post-AR state, this was about 52% (58 out of 110 segments). For the ELD group, fewer segments indicated a possible nonlinear explanation for the observed interdependence. In the pre-AR state, this was ~46% (47 of 102 segments) and for the post-AR state, only about 34% of the segments exhibited interdependence higher than that for the set of bivariate surrogates (32 of 93 segments). It may be noted that fewer segments from the ELD group passed the test for significant interdependence from the available 124 segments in each state in comparison to the MA subjects. The lower independence between sleep EEG signals exhibited by ELD subjects during typical NREM sleep stages in comparison to middle aged subjects was reported in an earlier work (Ramanand, P., Bruce, M.C., Bruce, E.N., Mutual Information Analysis of EEG Signals Indicates Age-Related Changes in Cortical Interdependence during Sleep in Middle-aged vs. Elderly Women, under review).

4 Discussion

This paper investigated the effect of spontaneous AR events on the interdependence of cortical activity during NREM sleep. A significantly higher cross mutual information between C3A2 and C4A1 EEG signals was observed in the pre-arousal state in comparison to the post arousal state, implying that the strength of interaction between cortical regions was lower following the termination of the arousal. The lowered coupling between central cortical regions in the post-AR state was exhibited by signals of 30 s duration and also by a more time resolved analysis in which the 30 s interval was divided into three consecutive 10 s intervals. The analysis of the decay rate of the AMI function which gives a measure of irregularity of the individual signals indicated that both the central EEG signals exhibited greater irregularity following an AR. Interestingly, all the findings were qualitatively the same for NREM arousals in the MA and ELD subject groups.

The low correlation between scorers in arousal detection has been reported widely (Bonnet, et al. 2007). The present study required that the AR onset and durations be accurately determined. We used a method recently reported by our group to monitor the changes in a

summed power function of the theta, alpha and beta (>16Hz) frequencies in the C3A2 signal and noted the sudden rise of these frequencies over a suitably defined threshold to mark the beginning of an arousal. Our objective in developing this algorithm was not the identification of all the arousal events in a sleep EEG record; rather a more precise determination of the beginning and ending of the arousals which were *already* scored by sleep experts in each record was desired. In general, if the ending of an arousal is prematurely marked, there is a possibility of the arousal event being carried over into the analysis period. In the time resolved analysis in particular this may affect the estimated values of interdependence in the first 10 s window following the arousal. However, most of our arousals were longer than those marked by scorers (by visual methods) and hence, the possibility of a carryover of the arousal event into the subsequent analysis period is unlikely. For the present work, we chose arousals from NREM sleep stages 2 and 3 which were at least 40 s away from apparent disruptive events such as apneas, hypopneas, movements and other arousals in time.

The interdependence measure, chosen as the mean of the CMI function over an interval of −0.2 s to 0.2 s was compared between the pre-AR and post-AR EEG segments. Using simulated EEG signals, we demonstrated that this measure may be affected by the power of a dominant spectral band in the signals. Removal of this band caused the interdependence to be lower in magnitude in general. In the case of sleep signals, the low frequency delta band (0.2– 2 Hz) tends to dominate the EEG signals. Moreover, our recent work on the spectral power analysis of sleep EEG signals prior to and following NREM arousals showed significantly higher values of low frequency delta power within 3 s of the start of an arousal in both ELD and MA subjects (Bruce, M.C., Bruce, E.N., Hayes, D., “Sleep fragmentation in older women: an analysis of EEG activity before and after spontaneous cortical arousals”, under review). This prompted us to assess whether the observed changes in interdependence will hold even after removal of this dominant band. On repeating the CMI analysis for the signals after band pass filtering between 2 to 25 Hz, we observed that the post-AR state was again characterized by significantly lower interdependence values. More remarkable was the finding that higher interdependence observed in the closest 10 s interval prior to the AR for broadband data was no longer significant in the filtered data. This led us to believe that the higher interdependence between EEG signals just prior to the AR may be attributable to delta bursts that have been mentioned in arousal literature (De Carli, et al. 2004). The presence of delta bursts was visually confirmed in the case of many of our analyzed arousals as well. The link between delta bursts and stimuli-induced or spontaneous arousals is still unclear (Poyares, et al. 2002). Some researchers have suggested that the delta bursts occurring right before the arousals may be counteractive measures to arousal stimuli to maintain sleep and represent the struggle between the sleep promoting and vigilance promoting mechanisms at play (Halász, et al. 2004).

The decay rate of the AMI as a function of the elapsed time between observations of a signal provides insight into the predictability of the signal. The decay rate gives a measure of how quickly information about the current state of a signal is lost. The AMI decay rate was significantly higher for both the EEG signals following the arousal than prior to it implying that after the AR both signals evolved more irregularly than before. This result is in agreement with our related work where the Sample Entropy, a measure of signal irregularity estimated at intervals of 6 s, was found to be significantly higher for 5 consecutive intervals post-AR than in the pre-AR state (Bruce et al., under review). Recently, a correlation between approximate entropy, another irregularity measure closely related to the sample entropy, and the AMI rate of decrease was shown for EEG background activity (Abásolo, et al. 2008) providing grounds for equivalent interpretation of the findings related to the nature of irregularity of the analyzed signals. The abrupt shift to faster frequencies during an AR may be introducing greater randomness to the signal thereby causing the post-AR state to be

less regular than before. There is also the possibility that the two signals may be affected differently by the arousal, and the response of the neuronal populations that are represented by the two signals may be different, due to which the shared information between them following the AR tends to be lower than before.

Although the number of arousals during sleep increases with age, their role in sleep fragmentation is still being debated (Bliwise 1993, Bonnet and Arand, 2007b). The situation is further confounded by factors such as the greater incidence of disordered breathing- and movement-related events during sleep with age and other age-related, possibly physiological, changes in sleep architecture and spectral changes in sleep EEG making it difficult to differentiate the root causes of declining sleep quality with age (Stepanski 2002). In this paper, we studied two groups of women - middle aged and elderly - with a higher incidence of arousals than young adults, and attempted to assess the differences in the response of their cortical activity to apparently spontaneous arousals. Changes to the interdependence between EEG signals indicate functional reorganization of the cortical regions underlying them. The arousal may represent an abrupt, yet transient, input that disrupts the existing coordination between the neuronal networks. The interdependence may thus act as a marker of arousal events and their persistent effect on the inter-hemispheric connectivity may hold clues to changes to the homeostatic nature of sleep in the two groups. Both the middle aged and elderly age groups exhibited similar responses in the interdependence to the AR event. The mean CMI between central regions was lower in magnitude for the elderly group in general when compared to the MA group. We have reported this for typical NREM and REM stages of sleep in a recent communication (Ramanand et. al., under review). This pointed to greater decoupling of central brain regions in ELD subjects during sleep. However, a common response of lower interdependence and higher AMI decay rate following the termination of AR in comparison to before was observed in both age groups.

The surrogate analysis of the pre and post arousal segments indicated that only a few of the analyzed segments had dependencies that could not be fully explained by accounting for linear correlations between them. The ELD subjects had more segments that failed to pass the threshold of significance, again pointing to the lowered coordination in sleep of elderly women. The surrogate analysis of the interdependence measure of EEG signals from pre-AR and post-AR states indicated ~ 47% of all the segments analyzed (pooled numbers from both subject groups) as exhibiting dependencies not fully explained by linearity. This makes measures such as mutual information that quantify both linear and nonlinear dependencies advantageous to the analysis of EEG signals. A possible cause for finding so many segments was due to a majority of the analyzed events being in NREM S-2. Shen and colleagues have reported that among all sleep stages, nonlinear character of EEG signals is exhibited most frequently in S-2 (Shen, et al. 2003).

In general, lighter sleep stages and wake state are associated with lower cortical coupling (Guevara, et al. 1995, Ferri, et al., 2005). The period following arousal termination is scored as a particular sleep stage based on the EEG signals having returned to some ‘apparently normal’ background activity when the visual characteristics of arousals are no longer present. Hence, the finding that the cortical co-ordination remains lowered for up to 30 s following a spontaneous arousal is highly relevant. It is possible that for a short time following the arousal, lowered coupling may be similar to that in a more vigilant state making the sleep state more susceptible to further arousals. Also, the disturbing effect of the AR may last longer than previously thought. Our analysis of the summed power in the theta, alpha and beta frequencies averaged over 30s in the pre- and post-arousal periods indicated that there are systematic spectral changes occurring during the period following arousals. Hence, in conjunction with interdependence measures, spectral analysis may be informative

in understanding the dynamics of the system following spontaneous arousals during sleep. On the other hand, since correlation between sites is independent of the amplitude of their activities, the spectral changes in a single signal (and/or both signals) by themselves may not be sufficient to explain the observed changes in the co-ordination between them.

The behavior of central interdependence with respect to arousals appears to be the same in both middle aged and elderly subject groups and supports the idea of a more gradual effect of aging on observed sleep EEG parameters (Colrain, et al. 2008). While the arousal index has been reported to increase with age (Bonnet and Arand 2007), the response of the system to an arousal event may well remain the same across age. The above scenario may be complicated by the occurrence of events related to sleep disordered breathing or periodic limb movement disorders which also increase with age. A neural network analysis of the depth of sleep based on EEG signals during abnormal breathing events, e.g., apnea and hypopnea, have indicated lower sleep depth following the termination of these events (Stradling, et al. 1999). In so much as arousals often terminate these breathing events in sleep, such studies may well pertain to the cortical activation associated with arousals. It remains an open question whether ARs associated with breathing events such as apneas and hypopneas will exhibit the same changes in interdependence as those from spontaneous arousals.

A limitation of this study was the inclusion of NREM arousals selected from all sleep cycles of the night. Delta band spectral power is known to change over the course of the entire night (Pracka and Pracki 1996, Darchia, et al. 2007). However the range in the observed interdependence values for the ARs although from different cycles of the night for each subject was not large. Hence, we do not think that the interdependence measures were significantly affected by the sleep cycles. A more time resolved analysis of the interdependence measure may provide a more exact time frame for the changes relative to the AR. We chose 30 s duration of signal because it corresponds to the time window frequently used in sleep scoring and related literature. Also, the histogram method used for estimation of mutual information provides accurate estimates for reasonably long data sets. Measures of connectivity derived from EEG signals such as coherence are subject to problems related to volume conduction and common reference which may inflate (or in some cases, reduce) the actual measures between signals recorded over short distances on the scalp (Nunez, et al. 1997). These effects are probably minimal in our case which had signals referenced to the ears and from the central EEG channels that are adequately spaced apart (Barry, et al. 2005). This study was based on EEG signals recorded from the homologous central brain electrodes. However, inter-regional differences in state- and frequency related spectral powers and coherence/synchronization measures have been reported (Werth et al., 1997, Ferri et al., 2005). Hence, different topographical patterns of interdependence with respect to arousals may result when EEGs from other brain regions such as frontal or parietal are studied.

In conclusion, we found that the sleep state following a spontaneous arousal exhibits lowered interdependence between central EEG signals in comparison to the state existing previously. This finding may be explained to some extent by greater randomness and irregular time evolution of the two signals after an arousal. We suggest that an AR causes a subtle decrease in the existing interdependence of cortical regions for a short time following it, causing the state to resemble a more vigilant state, thus making it more susceptible to arousals or even awakenings. This study suggests a strong possibility for an arousal to affect the sleep state not only during the length of its duration but even *afterwards*. In the case of excessive arousal occurrences, the integrative effect of the heightened vigilance during and following the arousals over the course of the whole night may likely have an effect on consolidated sleep time. We surmise that a better understanding of the effect of arousals on

sleep state and cortical activation might provide links to the possible connection of their excessive occurrence to sleep fragmentation and quality.

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APPENDIX

Method for precise determination of the onset and end of arousals

A 2.5 minute EEG segment with the AR onset marked (by visual scoring) at 60 s was selected and first upsampled to 250 Hz. It was then low pass filtered at 25 Hz using a 21-point, FIR filter based on a Hamming window. Finally, the signal was downsampled to 50 Hz. The signal was filtered into 6 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. This was performed using 6 band pass filters in parallel based on the Parks-McClellan algorithm and the signal was passed through the filters forwards and backwards to eliminate phase distortions. Spectral power was calculated in each frequency band after removal of the mean level and calculating the mean squared value of the output signal over windows of 2 s sliding over the data by 0.02 s. For the low frequency delta band alone, the duration of the sliding window was 4 s. In keeping with the EEG arousal definition, the powers in the theta, alpha and beta bands were summed and smoothed using a sliding median filter with a window length of 3 s. This signal plotted across time from the start of the analysis window was observed with respect to a threshold level. The threshold was determined as 6 dB above the mean of the summed power signal over a 30 s period. The AR onset was determined to occur when the summed power signal increased above this threshold and the time point at which it dropped below the same threshold was marked as the termination.

References

Abarbanel HDI, Brown R, Sidorowich JJ, Tsimring LSh. The analysis of observed chaotic data in physical systems. Rev. Mod. Phys 1993;65:1331–1392.

Abásolo D, Escudero J, Hornero R, Gómez C, Espino P. Approximate entropy and auto mutual information analysis of the electroencephalogram in Alzheimer's disease patients. Med. Biol. Eng. Comput 2008;46:1019–1028. [PubMed: 18784948]

Agnew HW Jr, Webb WB, Williams RL. Sleep patterns in late middle age males: An EEG study. Electroenceph. clin. Neurophysiol 1967;23:168–171. [PubMed: 4166697]

American Sleep Disorders Association (ASDA) Atlas Task Force Report. EEG arousals: scoring rules and examples; Sleep. 1992. p. 173-184.

Barry RJ, Clarke AR, McCarthy R, Selikowitz M. Adjusting EEG coherence for inter-electrode distance effects:an exploration in normal children. Int. J. Psychophysiol 2005;55:313–321. [PubMed: 15708644]

Blackwell T, Yaffe K, Ancoli-Israel S, Schneider JL, Cauley JA, Hillier TA, Fink HA, Stone KL. Study of Osteoporotic Fractures Group. Poor sleep is associated with impaired cognitive function in older women: the study of osteoporotic fractures. J. Gerontol. A. Biol. Sci. Med. Sci 2006;61:405–410. [PubMed: 16611709]

Bliwise DL. Sleep in normal aging and dementia. Sleep 1993;16:40–81. [PubMed: 8456235]

Bonnet MH, Doghramji K, Roehrs T, Stepanski EJ, Sheldon SJ, Walter AS, Wise ML, Chesson A. The scoring of arousals in sleep: reliability, validity and alternatives. J. Clin. Sleep Med 2007a;3:133–145. [PubMed: 17557423]

Bonnet MH, Arand. DL. EEG arousal norms by age. J Clin Sleep Med 2007b;3(3):271–274. [PubMed: 17561594]

Boselli M, Parrino L, Smerieri A, Terzano MG. Effect of age on EEG arousals in normal sleep. Sleep 1998;21(4):361–367.

Bruce EN, Bruce MC, Vennelaganti S. Sample entropy tracks changes in electroencephalogram power spectrum with sleep state and aging. J Clin Neurophysiol 2009;26:257–266. [PubMed: 19590434]

Carrier J, Land S, Buysse DJ, Kupfer DJ, Monk TH. The effects of age and gender on sleep EEG power spectral density in the middle years of life (20–60 years old). Psychophysiology 2001;38:232–242. [PubMed: 11347869]

Cellucci CJ, Albano AM, Rapp PE. Statistical validation of mutual information caluculations: comparison of alternative numerical algorithms. Phys. Rev. E 2005;71 066208.

Colrain IM, Crowley KE, Nicholas CL, Afifid L, Bakera FC, Padilla M, Turlington SR, Trinder J. Sleep evoked delta frequency responses show a linear decline in amplitude across the adult lifespan. Neurobiol Aging. 2008 In Press. doi:10.1016/j.neurobiolaging.2008.06.003.

Darchia N, Campbell IG, Tan X, Feinberg I. Kinetics of NREM delta EEG power density across NREM periods depends on age and delta band designation. Sleep 2007;30(1):71–79. [PubMed: 17310867]

De Carli F, Nobili L, Beelke M, Watanabe T, Smerieri A, Parrino L, Terzano MG, Ferrillo F. Quantitative analysis of sleep EEG microstructure in the time-frequency domain. Brain Res. Bull 2004;63:399–405. [PubMed: 15245767]

Dijk DJ, Duffy JF, Czeisler CA. Age-related increase in awakenings: impaired consolidation of nonREM sleep in all circadian phases. Sleep 24:565–577. [PubMed: 11480654]

Drinnan MJ, Murray A, Griffiths CJ, Gibson GJ. Interobserver variability in recognizing arousal in respiratory sleep disorders. Am. J. Respir. Care Med 1998;158:358–362.

Ehlers CE, Kupfer DJ. Effects of age on delta and REM sleep parameters. Electroenceph clin Neurophysiol 1989;72:118–125. [PubMed: 2464482]

Feinberg I. Changes in sleep cycle patterns with age. J Psychiatr. Res 1974;10:283–306. [PubMed: 4376564]

Ferri R, Rundo F, Bruni O, Terzano MG, Stam CJ. Dynamics of the EEG slow-wave synchronization during sleep. Clin. Neurophysiol 2005;116:2783–2795. [PubMed: 16253553]

Fraser AM, Swinney HL. Independent coordinates for strange attractors from mutual information. Phys. Rev. A 1986;33:1134–1140. [PubMed: 9896728]

Guevara MA, Lorenzo I, Arce C, Ramos J, Corsi-Cabrera M. Inter- and intrahemispheric EEG correlation during sleep and wakefulness. Sleep 1995;18(4):257–265. [PubMed: 7618024]

Halász P, Terzano M, Parrino L, Bódizs R. The nature of arousal in sleep. J. Sleep Res 2004;13:1–23.

Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. Nature 2004;430:78–81. [PubMed: 15184907]

Jeong J, Gore JC, Peterson BS. Mutual Information analysis of the EEG in patients with Alzheimer's disease. Clin. Neurophysiol 2001;112:827–835. [PubMed: 11336898]

Na SH, Jin S-H, Kim SY. The effects of total sleep deprivation on brain functional organization: Mutual information analysis of waking EEG. Int. J. Psychophysiol 2006;62:238–242. [PubMed: 16837091]

Na SH, Jin S-H, Kim SY, Ham B-J. EEG in schizophrenic patients: mutual information analysis. Clin. Neurophysiol 2002;113:1954–1960. [PubMed: 12464333]

Neikrug AB, Ancoli-Israel S. Sleep Disorders in the Older Adult: A Mini-Review. Gerontology. 2009 In press. DOI: 10.1159/000236900.

Nunez PL, Srinivasan R, Westdorp AF, Wijesinghe RS, Tucker DM, Silberstein RB, Cadusch PJ. EEG coherency: I. Statistics, reference electrode, volume conduction, Laplacians, cortical imaging, and interpretation at multiple scales. Electroencephalogr. Clin. Neurophysiol 1997;103:499–515. [PubMed: 9402881]

Papana A, Kugiumtzis D. Evaluation of mutual inforamtion estimators on nonlinear dynamic systems. Nonlinear Phenomena in Complex Systems 2008;11(2):225–232.

Pereda E, Gamundi A, Rial RV, Gonzalez J. Assessment of changing interdependencies between human electroencephalograms using nonliear methods. Physica D 2001;148:147–158.

Pereda E, Quian Quiroga R, Bhattacharya J. Nonlinear multivariate analysis of neurophysiological signals. Prog. in Neurobiol 2005;77:1–37.

Poyares D, Guilleminault C, Rosa A, Ohayon M, Koester U. Arousal, EEG spectral power and pulse transit time in UARS and mild OSAS subjects. Clin. Neurophysiol 2002;113:1598–1606. [PubMed: 12350436]

Pracka D, Pracki T. Spectral analysis in cyclic changes of human sleep evaluation. Acta Neurobiol. Exp 1996;56:255–258.

Quan SF, Howard BV, Iber C, Kiley JP, Nieto FJ, O'Connor GT, Rapoport DM, Redilne S, Robbins J, Samet JM, Wahl PW. The Sleep Heart Health Study: design, rationale, and methods. Sleep 1997;20(12):1077–1085. [PubMed: 9493915]

Rechtschaffen, A.; Kales, A. A manual of standardized terminology, techniques and and scoring system for sleep stages of human subjects. Washington DC: US Government Printing Office, National Institute of Health Publication; 1968.

Schreiber T, Schmitz A. Surrogate time series. Physica D 2000;142:346–382.

Shen Y, Olbrich E, Achermann P, Meier PF. Dimensional complexity and spectral properties of the human sleep EEG. Clin. Neurophysiol 2003;114:199–209. [PubMed: 12559226]

Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-relate? Insights from longitudinal and cognitive-behavioral clinical trials literature. Sleep Med. Rev 2004;8:119–132. [PubMed: 15033151]

Stam CJ. Nonlinear dynamical analysis of EEG and MEG: Review of an emerging field. Clin. Neurophy 2005;116:2266–2301.

Stepanski EJ. The effect of sleep fragmentation on daytime function. Sleep 2002;25(3):268–276. [PubMed: 12003157]

Stradling JR, Pitson DJ, Bennett L, Barbour C, Davies RJO. Variation in the arousal pattern after obstructive events in obstructive sleep apnea. Am. J. Respir. Crit. Care Med 1999;159:130–136. [PubMed: 9872830]

Theiler J, Euband S, Longtin A, Galdrikian B, Farmer DJ. Testing for nonlinearity in time series: the method of surrogate data. Physica D 1992;58:77–94.

Togo F, Cherniack NS, Natelson BH. Electroencephalogram characteristics of autonomic arousals during sleep in healthy men. Clin. Neurophysiol 2006;117(2):2597–2603. [PubMed: 17011823]

Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. Brain Res. Bull 2003;62:143–150. [PubMed: 14638388]

Vitiello MV, Larsen LH, Moe KE. Age-related sleep change. Gender and estrogen effects on the subjective-objective sleep quality. J. Psychosom. Res 56:503–510. [PubMed: 15172206]

Vyazovskiy V, Achermann P, Borbély AA, Tobler I. Interhemispheric coherence of the sleep electroencephalogram in mice with congenital callosal dysgenesis. Neuroscience 2004;124:481–488. [PubMed: 14980397]

Werth E, Achermann P, Borbély AA. Fronto-occipital power gradients in human sleep. J. Sleep Res 1997;6:102–112. [PubMed: 9377529]

Whitney CW, Gottlieb DJ, Redline S, Norman RG, Dodge RR, Shahar E, Surovec S, Nieto FJ. Reliability of scoring respiratory disturbance indices and sleep stages. Sleep 1998;21:749–757. [PubMed: 11286351]

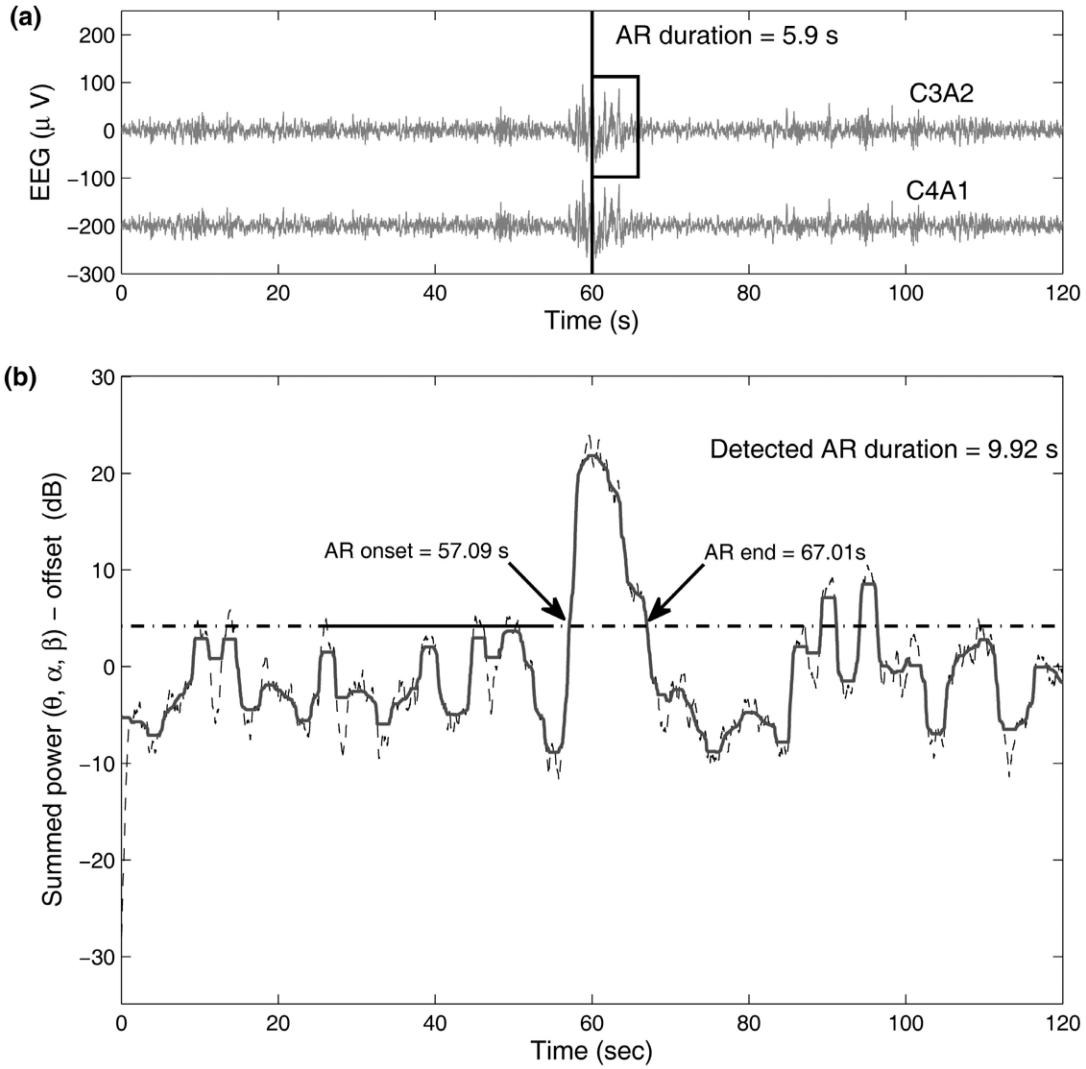

Figure 1.

Description of the method for precise determination of the AR onset and duration. Top panel shows the EEG signals indicating the scorer marked AR at 60 s with duration of 5.9 s. In the lower panel, the signal of the summed powers in theta, alpha and beta bands is compared to the threshold level (marked in bold) to determine the onset time as 57.1 s (3.1 s earlier than the scorer's onset time) with a duration of 9.92 s.

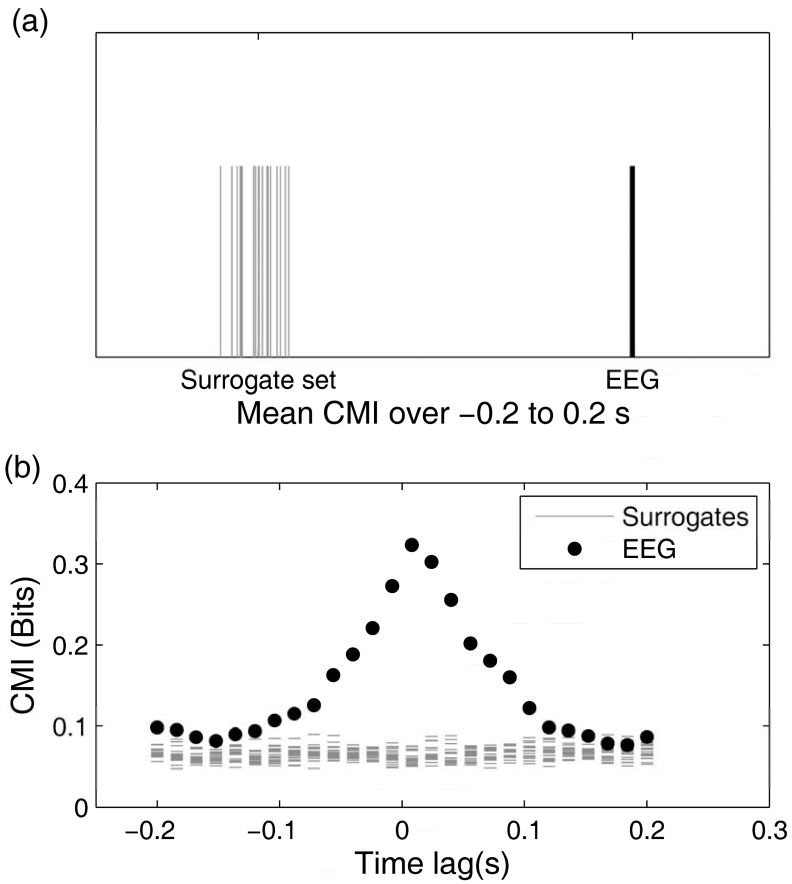

Figure 2.

The EEG signals and surrogates (both uni- and bi-variate) are tested by rank based tests according to which, the mean CMI of the EEG signals over −0.2 to 0.2 s must be greater than all the values for the surrogates (a) and the individual CMI estimates at each time lag should be higher than that for the surrogates at a minimum of 60% of the time lags considered (b).

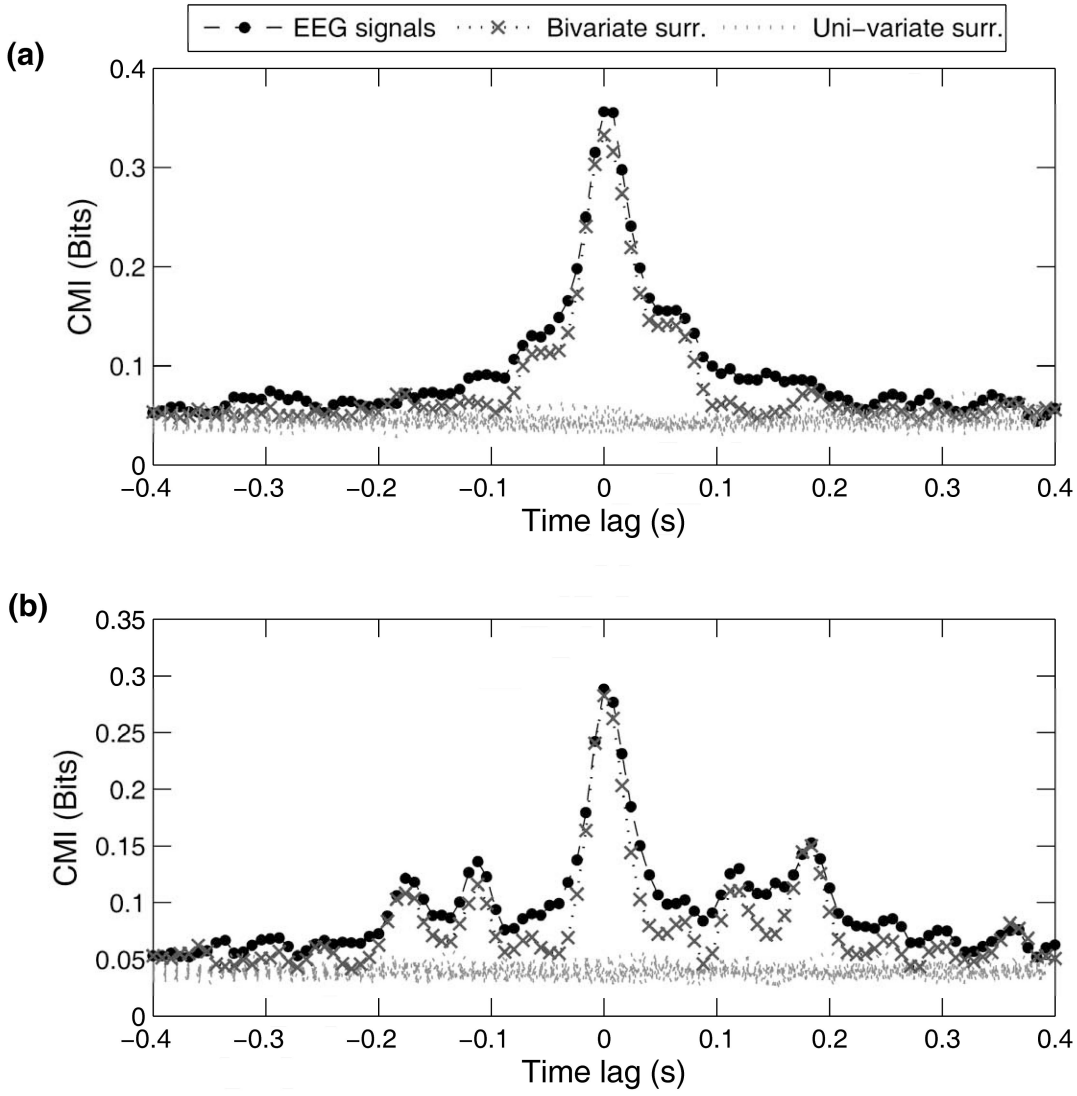

Figure 3.

Representative CMI functions between the EEG signals along with the CMI estimated with univariate surrogates and bivariate surrogates that are used for the surrogate analysis testing the significance and the nature of the estimated interdependence. The top panel (a) is for a pre-AR segment from a MA subject. Panel (b) refers to the same segment after band pass filtering between 2 to 25 Hz. For the bi-variate case, the maximum CMI from the surrogate set (19 values) at each time lag is plotted.

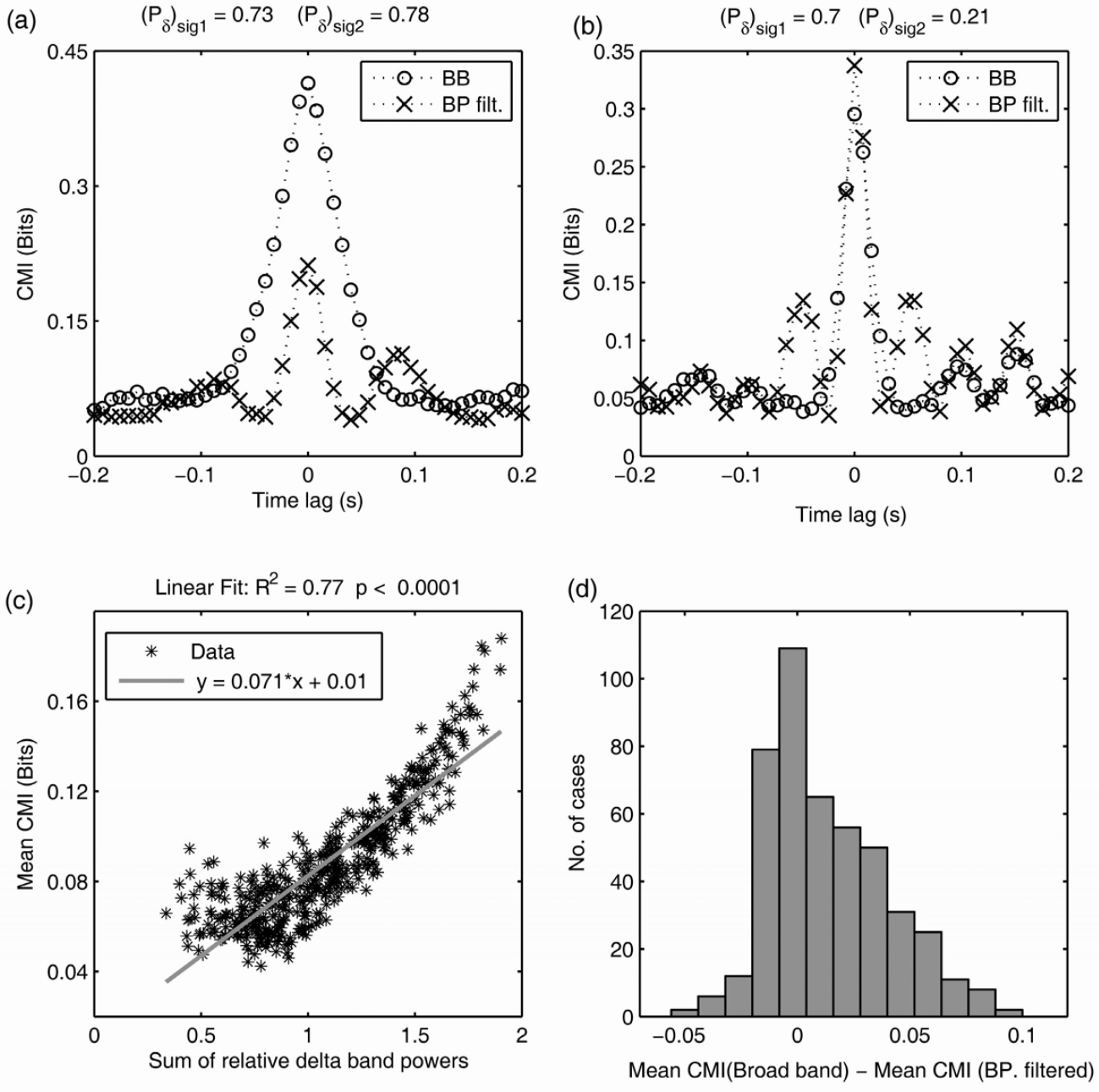

Figure 4.

Comparison of mean CMI from simulated signals before and after filtering of the dominant spectral band. (a) and (b) respectively refer to examples of estimated CMI function for which the signals both have high delta band powers and where only one of the signals has high delta band power. In (c), the variation of interdependence value with the sum of delta band powers of the two signals is plotted. (d) shows the distribution of the difference in mean CMI between the broadband and BP filtered signals.

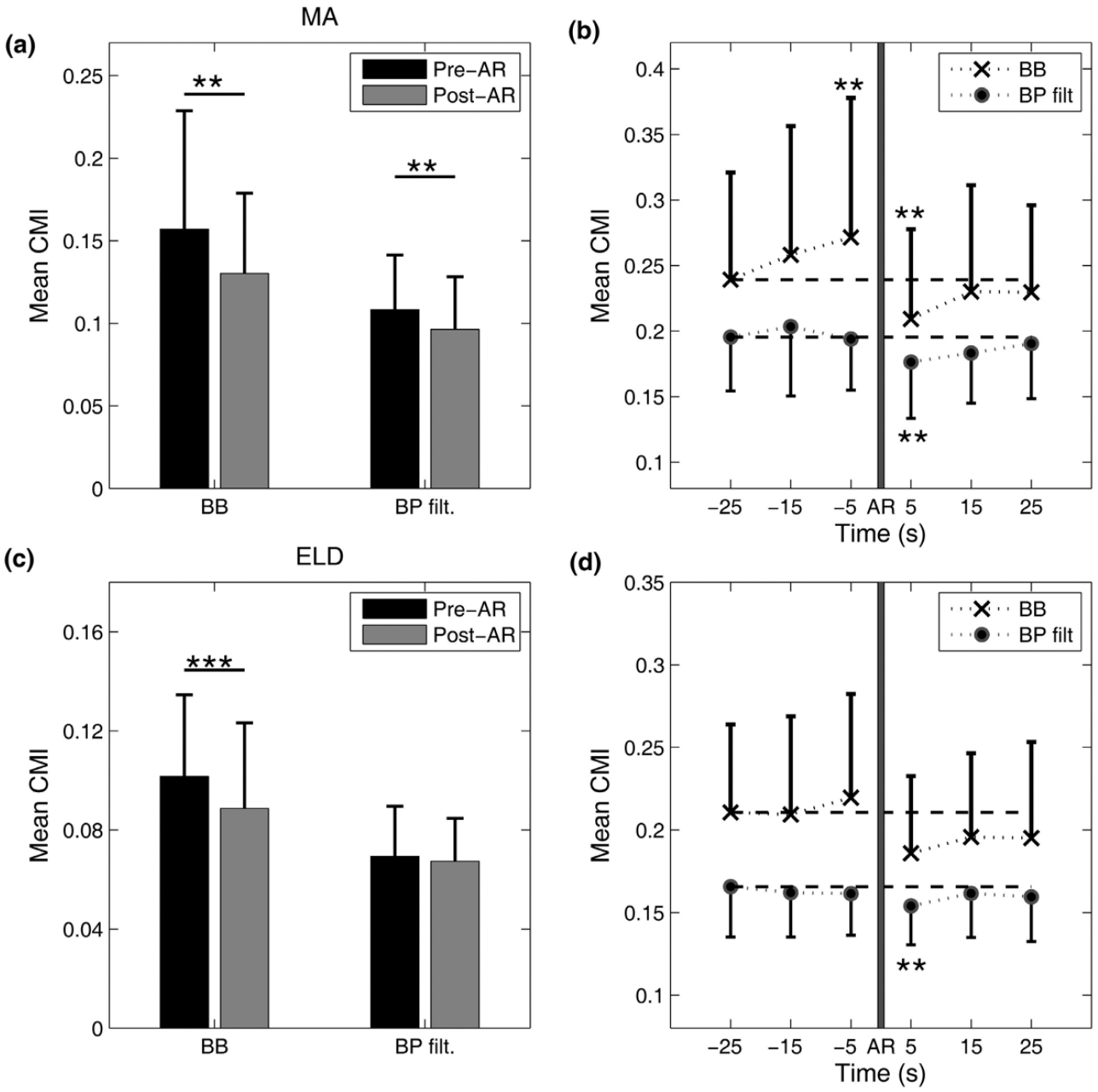

Figure 5.

Analysis of the mean CMI measure for 30 s (left column) and 10 s (right column) durations between pre- and post- AR signals is presented. Results from MA subject data are in (a) and (b) and from ELD group in (c) and (d). The error bars represent the standard deviation for the mean CMI in each case. Statistical significances are denoted by asterisks: *, $p<0.05$, ** $p<0.005$, *** $p<0.0001$.

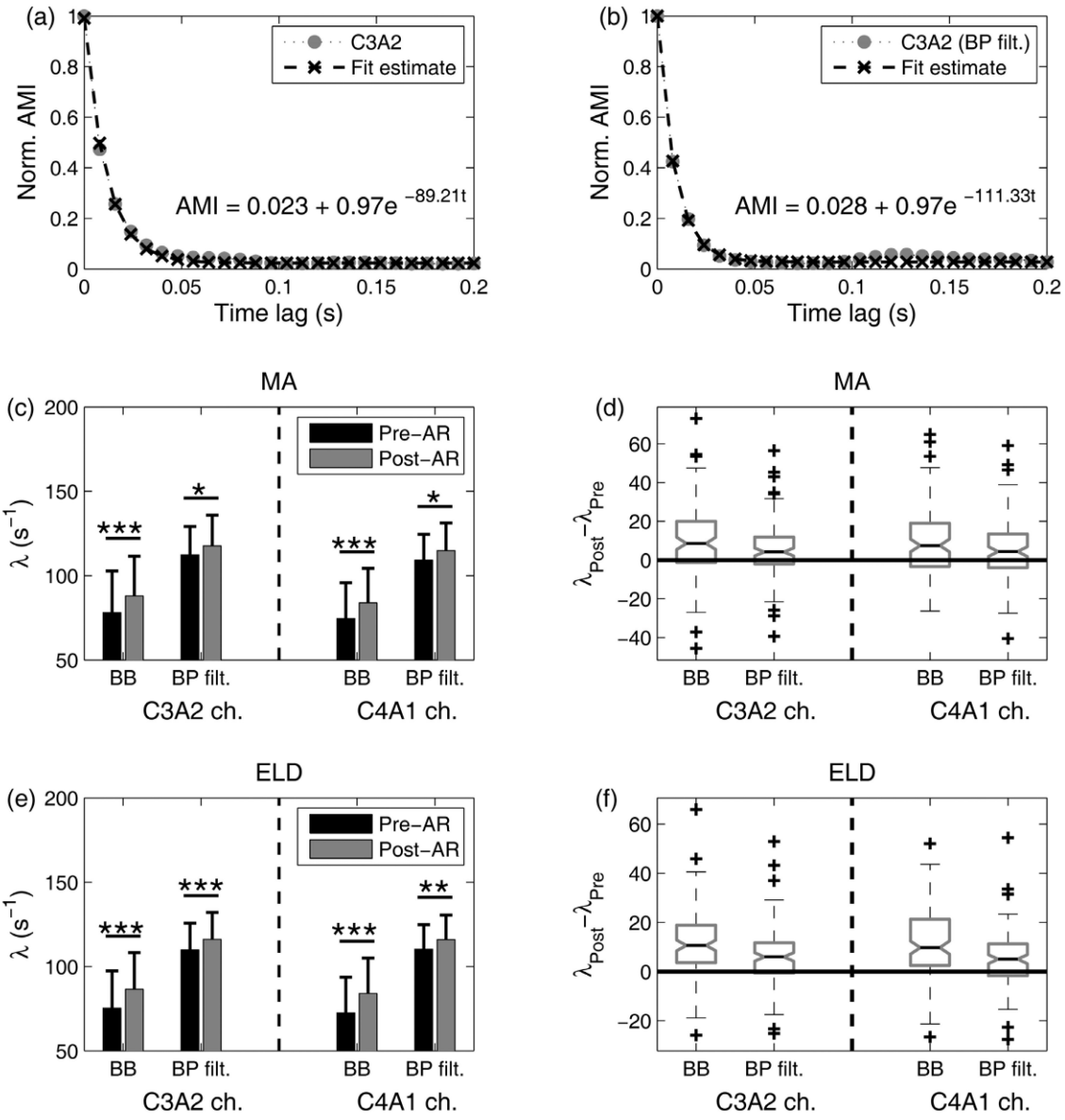

Figure 6.

Analysis of the AMI for the pre- and post-AR EEG segments. The fit applied to the normalized AMI function to determine the decay rate parameter, λ is presented in (a) and (b) for a representative broadband and band pass filtered segment. The mean values of λ for the two central channels for broadband (BB) and bandpass filtered (BP filt.) cases are shown in (c) for the MA and in (e) for the ELD groups. The error bars represent the SD. The statistically significant changes are marked by asterisks,*p<0.05, ** p<0.005, *** p<0.0001. The box plots in (d) and (f) show for the MA and ELD subjects resp., the paired difference in λ between post-AR and pre-AR state for each arousal. Horizontal lines are drawn at the lower quartile, median and upper quartile values with whiskers extending up to 1.5 times the inter-quartile range. The outliers are marked by the '+' symbol.

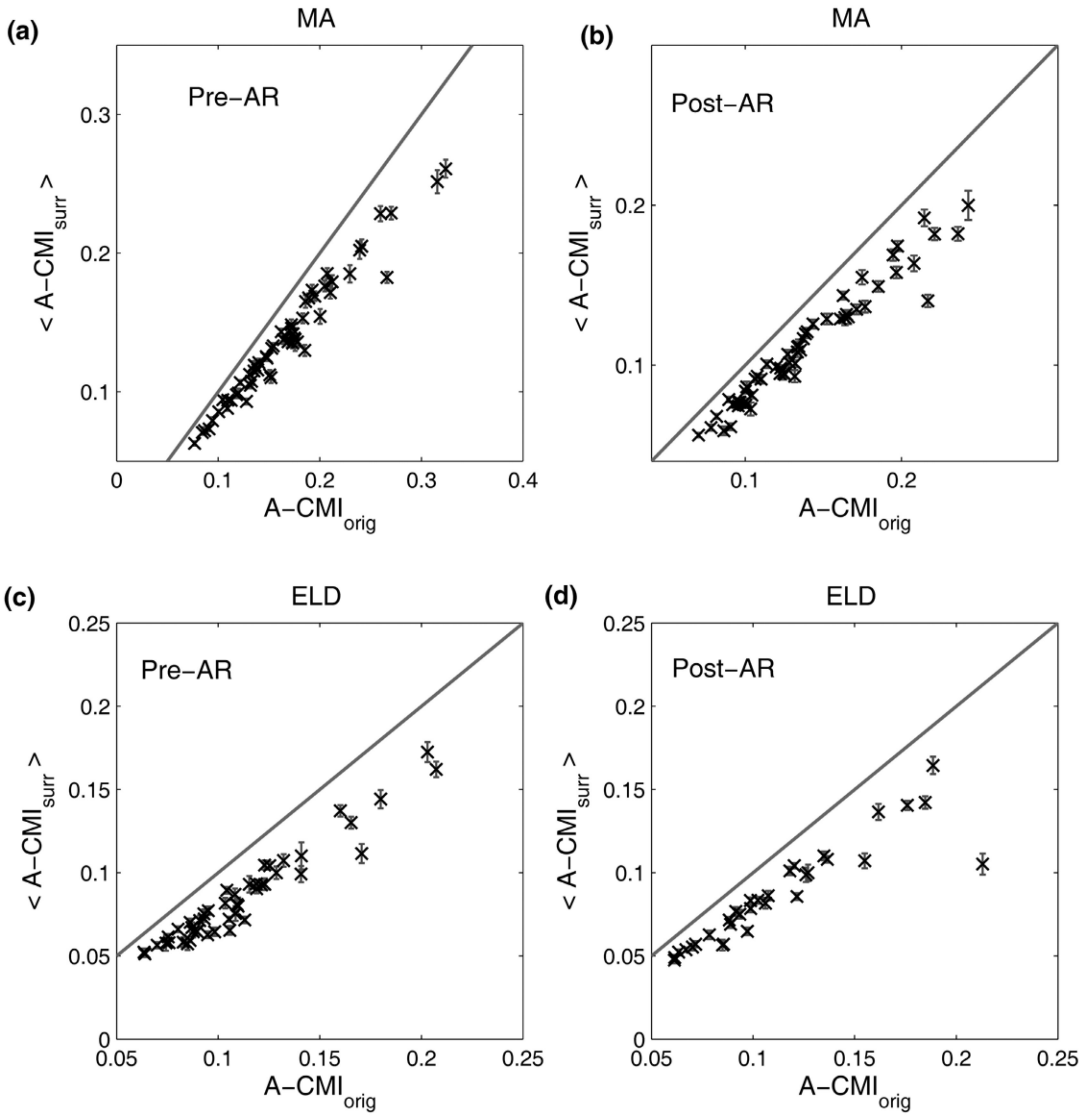

Figure 7.

The surrogate data analysis for the pre-AR and post-AR EEG segments from MA (a, b) and ELD (c, d) subjects. The mean CMI for the EEG segments ($A\text{-}CMI_{orig}$) is plotted against the average over the interdependence values for the set of bivariate surrogates ($ï\_CMI_{surr}>$) for segments identified as exhibiting nonlinear nature of interdependence. The error bars are the SD over the set of surrogate interdependence values. The line of equality is also drawn.

Table 1

Characteristics of the study sample

		Middle aged (MA)	Elderly (ELD)
Number of subjects		20	19
Age	Mean ± SD	47.2 ±1.99	78.3 ± 3.8
	Range	42–50	71–86
Apnea-Hypopnea Index (AHI)	Mean ± SD	1.48 ± 2.48	2.42 ± 2.55
	Range	0–9.18	0–9.72
Arousal Index (AI)	Mean ± SD	19.64 ± 11.17	17.15 ± 9.05
	Range	7.0 – 41.6	5.7 – 33.2
No. of NREM arousals		114	124

All subjects had body mass index ≤ 30

Table 2

The (Mean± SD) of the summed spectral power in theta, alpha and beta bands averaged over 30 s intervals for each arousal in the elderly (ELD) and middle aged (MA) subjects.

	Mean over 30 s of the summed power (P_{theta}+P_{alpha}+P_{beta}) in dB	
	Pre_AR	**Post_AR**
MA ***	20.77± 5.31	19.44 ± 5.02
ELD ***	22.57 ± 4.71	21.79 ± 4.25

*** P<0.001