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A Fundamental Question about the Application of High-Density Electroencephalography and Time-Series Analysis in Examining Synchronous Networks During Sleep – Does the Use of Different Referencing and Data Preprocessing Methods Really Matter?

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ABSTRACT

This study tested whether different referencing and data preprocessing strategies would influence the results of electroencephalographic network analyses. Data were collected from two volunteers during the last 60 seconds of the second and fourth rapid-eye-movement epochs using a 256-channel electroencephalographic system and prior to correlation analyses, were preprocessed by varying combinations of techniques, including referencing/re-referencing (vertex, average mastoid, and common average), bandpass filtering, differencing, and autoregressive integrative moving average (ARIMA) modeling. The findings suggest that using different methods to eliminate temporal structures, noise, and extraneous signals embedded in a time series does not substantially influence the results of subsequent network analyses. However, ARIMA parameters should be carefully chosen to ensure that all or almost all 256 EEG time series can be preserved after the ARIMA prewhitening procedure. In contrast to the analogous correlation networks between different data preprocessing protocols, different referencing can lead to significantly dissimilar correlation patterns. Specifically, the use of a common average reference moderates the overall strength of a connectivity network, while vertex referencing and mastoid referencing may respectively underestimate the strength of connections over the central and mastoid regions. All in all, it appears that the combination of average referencing, filtering, and differencing provides a relatively reliable protocol for dense EEG network analysis.

Keywords: ARIMA, functional connectivity, dense array EEG, synchronous cortical activity, rapid eye movement

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INTRODUCTION

Numerous studies have been performed concerning the functional connectivity during sleep. They typically compared intrahemispheric and interhemispheric electroencephalographic (EEG) connectivity across sleep stages, frequency bands, and subjects (e.g., Jurysta, Van Wettere, Lanquart, Linkowski, & Marinazzo, 2013; Kurth, Achermann, Rusterholz, & LeBourgeois, 2013; Lázár et al., 2010; Lévillé et al., 2010; Sakellariou et al., 2016). Nevertheless, only two studies (Langheim et al., 2011; Yu, 2015a) have attempted to construct synchronous networks during sleep by applying time-series statistics in analyzing data acquired with a dense array EEG system. This is partly because a synchronous network cannot be properly established without a recording system that can thoroughly visualize the distribution of electrical potentials generated by different regions of the brain. In contrast to a typical connectivity study, which entails only a minimum of four index EEG electrodes, the system employed by Langheim et al. (2011) and Yu (2015a) can gauge 256 channels covering almost the entire head surface. By plotting significant partial correlations of all 32,640 possible pairs of the 256 electrodes, Langheim et al. identified a cluster of positive interactions in the right parieto-occipital region during rapid-eye-movement (REM) sleep. Yu (2015a), on the other hand, calculated non-partial correlations, which resulted in positive connections over the antero-fronto-central and occipito-temporo-cerebellar regions.

The study of functional connectivity necessitates certain data preprocessing procedures, such as re-referencing and removal of artifacts or extraneous signals by means of bandpass filtering. Langheim et al. utilized Box-Jenkins autoregressive integrative moving average (ARIMA) modeling to remove the underlying trend embedded in each EEG time series, thereby obtaining stationary data such that the statistical properties of the time series, such as mean and variance, remain constant over time. Although the ARIMA modeling method can reduce autocorrelations and spurious correlations resulting from the common trends or predictability of

temporal structures, its use may not be compatible with the routine EEG filtering procedure. Both signal filtering and ARIMA modeling are prewhitening tactics, which draw on a transfer function in separating target signals from noise or unwanted signals. Langheim et al. argued that prewhitening data that have already been prewhitened can cause model instability and renders subsequent correlation analyses unreliable. Therefore, they applied ARIMA modeling in raw data rather than filtered data.

However, bandpass filtering, which can effectively attenuate many artifacts associated with spontaneous sleep, is virtually an essential preprocessing procedure for sleep research. In view of that, Yu (2015a) used differencing – one of the three ARIMA components – rather than the full ARIMA forecasting method to suppress EEG temporal structures. This allows the use of filtering while avoiding model instability resulting from repeated modeling. In establishing dense EEG networks, researchers have been employing different data preprocessing protocols. Langheim et al. (2011) introduced the use of ARIMA modeling without filtering to generate stationary time series; some other researchers (e.g., Jalili & Knyazeva, 2011a, b) filtered their data without considering trend removal and Yu (2015a) attempted to combine both maneuvers.

In a similar vein, different researchers have been using different EEG referencing approaches. In Langheim et al.'s (2011) study, all data were referenced to the default electrode Cz placed at the vertex. On the other hand, Yu (2014, 2015a) recommended applying a common average reference (the average of all 256 or 257 electrodes) in sleep research for more accurate localization of waveforms. Indeed, the superiority of common average referencing over other types of EEG referencing has been discussed by many researchers (e.g., Alhaddad, 2012; Dien, 1998; Ludwig et al., 2009). Both the Cz and common average referencing approaches represent a significance departure from the American Academy of Sleep and Medicine's (AASM; Iber, Ancoli-Israel, Chesson, & Quan, 2007) standard montage, which is made up of three EEG, two EOG, and one EMG channels, all being referenced to the mastoid (M) electrode.

These divergent referencing and preprocessing strategies raise a fundamental question as to whether in network analyses, they would alter the connectivity pattern being investigated. If this is the case, neural networks identified by different researchers using different referencing and preprocessing methods cannot be directly compared and certain standard protocols should be established for dense EEG network research. The primary purpose of the study presented here was to answer this question. Langheim et al. proposed an optimal ARIMA model, which comprised 40 AR orders ($AR = 40$), one differencing order ($I = 1$), and one MA order ($MA = 1$). Nonetheless, Yu (2015a) found that a considerable number of time series could not be fitted by the ARIMA (40, 1, 1) model. Likewise, although it is a popular practice

for researchers to extract 60-second data from the entire epoch of a sleep stage for analysis, processing data of this time length with the AASM's recommended sampling rate of 500 Hz in dense array EEG research can be expensive in terms of computation time. The second purpose of the present study was to explore alternative ARIMA parameters that might provide a proper fit to 60-second, 30-second, and 15-second sleep EEG data.

METHOD

Two volunteers' (Subject 1: male, 23 years old; Subject 2: female, 21 years old) sleep was monitored by a high-density electroencephalographic system. The sensor net is composed of 256 index electrodes, covering

Figure 1: Two-dimensional projection of sensor net layout

almost the entire head (see Figure 1), including areas on both cheeks (e.g., E243, E247, E251) and around both eyes (e.g., E46, E54, E252). Data were sampled at 500 Hz and were referenced to the vertex (Cz) electrode. Raw EEG data that were collected during the last 60 seconds of the second (REM2) and fourth (REM4) REM episodes of the second laboratory night and were relatively devoid of ocular and other artifacts were analyzed using the MATLAB and R statistical packages. In addition to the raw datasets, the data were also re-referenced to the common average of 257 electrodes (256 index electrodes and the vertex electrode) and to the average of the two mastoid electrodes, were preprocessed by ARIMA modeling, and/or were bandpass filtered at 0.3-45Hz for comparisons. Referencing to the mastoid electrode on either side as recommended by the AASM is apparently not a good option for network analysis in that it would create a systematic crescendo of electrical amplitude toward the opposite side of the head. This bias, however, can be corrected by averaging the two mastoid electrodes of the sensor net (average mastoid reference). In this study, synchronous networks were examined using correlation coefficients – that is, the classic measure of connectivity. The detailed protocol for the high-density EEG method in sleep research can be found in Yu's (2014, 2015a, 2015b, 2016a) previous reports.

Analyses

ARIMA modeling

The ARIMA (40, 1, 1) model was fitted into 256 15-second, Cz referenced, unfiltered time series

extracted from Subject 1's REM2 in an attempt to generate residuals (see Table 1). Residuals of 10 channels' data could not be computed because of the AR component could not be fitted into the time series. The same model was applied to 11 other sets of 256 time series. This resulted in an average of 10.3 unfitted channels for each set. Three other ARIMA models with different AR orders (30, 20, and 10) but the same differencing (1) and MA orders (1) were examined. The ARIMA (20, 1, 1) and ARIMA (10, 1, 1) models could provide a proper fit to virtually all 256 time series for both subjects, both REM periods, and all three time lengths. By way of comparison, the ARIMA (40, 1, 1) and (20, 1, 1) models were also applied to Subject 1's REM4 256 60-second time series that were re-referenced to the average of the left and right mastoid channels and to the average of 257 channels. The results for these mastoid referenced and average referenced data were even more drastic. The numbers of unfitted channels for ARIMA (40, 1, 1) prewhitening were 47 and 51, those for ARIMA (20, 1, 1) prewhitening being 2 and 1.

Using R's auto-arma function to search for the best parameters for the two subjects' REM2 and REM4 data yielded AR range = 0-5, I = 1 or 2, and MA range = 0-5. The best I parameter for 98.5% channels was 1. The modes of AR and MA orders were 5 (40.7% of channels) and 3 (27.5% of channels), respectively. In addition to 3, 5 was also identified as the best MA order for 23.9% of channels. In view of these auto-arma results, ARIMA (5, 1, 5) and (5, 1, 3) models were employed to generate residuals for the 12 sets of 256-channel data. As shown in Table 1, the ARIMA (5, 1, 3) model provided a better fit than did the ARIMA (5, 1, 5) model.

Table 1: Numbers of Unfitted Channels of Different ARIMA Models (Cz Reference)

ARIMA parameters	S1						S2					
	REM2			REM4			REM2			REM4		
	15s	30s	60s	15s	30s	60s	15s	30s	60s	15s	30s	60s
40, 1, 1	10	19	10	11	11	15	13	16	8	5	1	5
30, 1, 1	13	16	6	10	5	12	2	1	0	5	1	0
20, 1, 1	0	0	1	0	0	0	1	0	0	0	0	1
10, 1, 1	0	0	0	0	0	0	0	0	0	0	0	0
5, 1, 5	3	0	0	2	0	0	9	3	0	4	3	2
5, 1, 3	1	0	0	2	0	0	2	0	0	0	0	0

Figure 2: Autocorrelation functions (ACF) for Cz referenced 60-s data obtained from Electrodes 224 (F4), 183 (C4), and 150 (O2) during Subject 1's REM4

Figure 2: Autocorrelation functions (ACF) for Cz referenced 60-s data obtained from Electrodes 224 (F4), 183 (C4), and 150 (O2) during Subject 1's REM4 (Continued)

Autocorrelations and Cross-Correlations

Figure 2 presents the autocorrelation functions for the 60-s data recorded by F4 (E224), C4 (E183), and O2 (E150) electrodes during Subject 1's REM4. The number of lags was set to 25, corresponding to 50ms. Before ARIMA preprocessing, all 25 lags for the three channels' data showed a very large autocorrelation coefficient (see Panels A-C); after ARIMA preprocessing, the

autocorrelation coefficient for all the lags was close to 0.0 (see Panels D-U). This effect was peculiarly evident for ARIMA (40, 1, 1), (30, 1, 1), and (20, 1, 1) modeling, which completely eradicated the trends and autocorrelation structures in the EEG time series (see Panels D-L). In a similar vein, ARIMA preprocessing, especially using the AR orders 40, 30, and 20, greatly suppressed the cross-correlations beyond ± 1 lags (4ms) between the three

Figure 3: Cross-correlation functions (CCF) for Cz referenced 60-s data obtained from Electrodes 224 (F4), 183 (C4), and 150 (O2) during Subject 1's REM4

Figure 3: Cross-correlation functions (CCF) for Cz referenced 60-s data obtained from Electrodes 224 (F4), 183 (C4), and 150 (O2) during Subject 1's REM4 (Continued)

electrodes (see Figure 3). This ARIMA transformation procedure increased the 0-lag cross-correlation coefficient (CC^0) between F4 and C4 but decreased the CC^0 between C4 and O2.

Of the six ARIMA models presented in Table 1, the ARIMA (20, 1, 1) model appeared to comprise the best parameters for EEG preprocessing because it effectively

removed temporal structures to the extent very similar to the ARIMA (40, 1, 1) and ARIMA (30, 1, 1) models with virtually no unfittable channels. The ARIMA (10, 1, 1) or ARIMA (5, 1, 3) might constitute an alternative model for prewhitening in certain situations despite the autocorrelation and cross-correlation results that the ARIMA (20, 1, 1) model was more potent for eliminating trends.

Comparing Electroencephalographic Connectivity and Networks between Different References and Data Transformation Methods

Table 2 lists the standard AASM derivations (see Column 1, F3 to O2) and nine other electrodes placed on the neuroanatomical regions particularly relevant to sleep research (see Column 1, FT7 to TP10). For example, vertex sharp waves, which signify the transition to Stage 1 sleep, emanant from the central region of the cortex. Likewise, BA37 and BA40 are thought to be critical for the process of dream-image formation (see Yu, 2001a, 2001b, 2003, 2006, 2007, 2016b, for the neuroanatomical correlates of dreaming sleep). Tables 3-8 shows the correlation matrices of Subject 1's REM4 data obtained with these selected channels. The data were referenced to the Cz electrode, the average of all 257 electrodes, or the average of the two mastoid electrodes and were preprocessed by either ARIMA (40, 1, 1) or ARIMA (20, 1, 1) transformation before correlations were computed.

Varying the AR order did not appear to alter the correlation patterns. For example, the seven largest correlation coefficients in the two Cz reference matrices preprocessed respectively by the ARIMA (40, 1, 1) and ARIMA (20, 1, 1) models were the same (see Tables 3 & 4). The similar also applied to the average-referenced (see Tables 5 & 6) and mastoid-referenced data (see Tables 7 & 8). Since the residuals for some channels could

not be generated by the ARIMA (40, 1, 1) modeling, the correlations for these unfitted channels could not be computed. This to some extent affected the correlation patterns; for instance, O1's robust correlation with O2 and P7 in the ARIMA (20, 1, 1) average reference matrix could not be demonstrated in the ARIMA (40, 1, 1) average reference matrix.

In contrast to the similar correlation matrices comparing the two ARIMA prewhitening configurations, the correlation patterns varied substantially across the three references. The O1-P7 electrode pair was the only one of the seven largest correlation coefficients shared by the three referenced datasets (see Tables 3, 5, & 7). The Cz-referenced data exhibited the largest correlation coefficients in the connections of the inferoposterior temporal (mastoid) electrodes with the orbitofrontal and occipitotemporal electrodes (see Tables 3 & 4), the correlation coefficient for the C3-C4 connection being the smallest. On the other hand, the largest correlation coefficients for the average-referenced (see Tables 5 & 6) and mastoid-referenced data (see Tables 7 & 8) clustered around the central and posterior electrodes.

The use of the average mastoid reference resulted in the methodological artifact that the two mastoid electrodes (TP9 & TP10) were inversely and perfectly correlated and had an exact opposite coefficient with other electrodes. Moreover, the average mastoid reference tended to diminish the strength of correlations for the mastoid electrodes. Both the Cz and average

Table 2: Electrode Positions and Corresponding Neuroanatomical Regions

10-20 position	Electrode number	Brodmann area	Neuroanatomical area
F3	E36	BA8	Intermediate frontal
F4	E224	BA8	Intermediate frontal
C3	E59	BA1-4	Central
C4	E183	BA1-4	Central
O1	E116	BA18	Parastriate
O2	E150	BA18	Parastriate
FT7	E62	BA47	Orbitofrontal
FT8	E211	BA47	Orbitofrontal
CP3	E66	BA40	Supramarginal
CP4	E164	BA40	Supramarginal
P7	E96	BA37	Occipitotemporal
P8	E170	BA37	Occipitotemporal
Cz	Reference	BA4	Vertex
TP9	E94	BA20, BA21	Mastoid/inferoposterior temporal
TP10	E190	BA20, BA21	Mastoid/inferoposterior temporal

Table 3: Correlation Matrix for Cz Referenced, ARIMA (20, 1, 1) Preprocessed, 60-s Data Extracted from Subject 1's REM4

	F3	F4	C3	C4	O1	O2	FT7	FT8	CP3	CP4	P7	P8	TP9
F4	.327												
C3	.320	.162											
C4	.188	.309	.128										
O1	.223	.187	.282	.234									
O2	.185	.206	.199	.289	.417								
FT7	.423	.271	.348	.209	.343	.264							
FT8	.288	.380	.195	.354	.290	.312	.335						
CP3	.269	.146	.393	.141	.312	.234	.335	.186					
CP4	.168	.257	.143	.393	.255	.324	.206	.332	.154				
P7	.282	.194	.348	.223	.468	.356	.400	.278	.377	.228			
P8	.200	.239	.188	.334	.359	.421	.267	.361	.203	.349	.317		
TP9	.315	.235	.317	.244	.468	.366	.447	.367	.330	.239	.483	.345	
TP10	.261	.303	.211	.336	.376	.401	.338	.473	.220	.335	.345	.438	.420

Note. The 7 largest correlation coefficients are bolded.

Table 4: Correlation Matrix for Cz Referenced, ARIMA (40, 1, 1) Preprocessed, 60-s Data Extracted from Subject 1's REM4

	F3	F4	C3	C4	O1	O2	FT7	FT8	CP3	CP4	P7	P8	TP9
F4	.317												
C3	.315	.154											
C4	.179	.300	.122										
O1	.212	.176	.276	.226									
O2	.175	.195	.193	.282	.410								
FT7	.415	.259	.341	.199	.333	.254							
FT8	.279	.370	.188	.347	.282	.303	.326						
CP3	.264	.140	.391	.137	.308	.231	.330	.181					
CP4	.159	.247	.137	.388	.247	.318	.196	.324	.150				
P7	.271	.181	.342	.214	.461	.348	.390	.267	.373	.218			
P8	.189	.228	.181	.326	.350	.414	.256	.350	.199	.342	.305		
TP9	.304	.221	.309	.233	.460	.356	.437	.357	.325	.229	.474	.333	
TP10	.250	.291	.203	.328	.367	.393	.327	.465	.215	.327	.334	.429	.409

Note. The 7 largest correlation coefficients are bolded.

Table 5: Correlation Matrix for Average Referenced, ARIMA (20, 1, 1) Preprocessed, 60-s Data Extracted from Subject 1's REM4

	F3	F4	C3	C4	O1	O2	FT7	FT8	CP3	CP4	P7	P8	TP9
F4	.187												
C3	.253	.090											
C4	.087	.252	.160										
O1	-.007	-.020	.186	.118									
O2	-.027	.042	.113	.215	.330								
FT7	.198	-.031	.148	-.086	.058	-.040							
FT8	-.038	.173	-.073	.165	-.020	.068	-.074						
CP3	.197	.073	.417	.171	.229	.156	.137	-.076					
CP4	.071	.201	.181	.413	.154	.265	-.079	.146	.189				
P7	.073	-.019	.282	.106	.388	.236	.153	-.069	.325	.129			
P8	-.044	.065	.065	.250	.223	.350	-.072	.145	.091	.282	.147		
TP9	-.003	-.082	.104	-.016	.309	.165	.186	.011	.138	-.003	.331	.107	
TP10	-.090	.041	-.051	.128	.150	.236	-.046	.255	-.030	.141	.074	.297	.159

Note. The 7 largest correlation coefficients are bolded.

Table 6: Correlation Matrix for Average Referenced, ARIMA (40, 1, 1) Preprocessed, 60-s Data Extracted from Subject 1's REM4

	F3	F4	C3	C4	O1	O2	FT7	FT8	CP3	CP4	P7	P8	TP9
F4	.186												
C3	.249	.089											
C4	.085	.251	.156										
O1	-	-	-	-									
O2	-.027	.041	.113	.215	-								
FT7	.198	-.031	.147	-.086	-	-.040							
FT8	-.036	.173	-.071	.166	-	.067	-.073						
CP3	.193	.072	.414	.167	-	.156	.135	-.074					
CP4	.069	.200	.178	.411	-	.264	-.078	.147	.185				
P7	.071	-.021	.283	.104	-	.236	.153	-.070	.326	.127			
P8	-.042	.064	.066	.250	-	.351	-.070	.142	.092	.281	.147		
TP9	.000	-.080	.107	-.013	-	.166	.185	.011	.140	-.001	.333	.107	
TP10	-.087	.042	-.047	.130	-	.237	-.045	.253	-.025	.144	.075	.295	.158

Note. Note. The 7 largest correlation coefficients are bolded. The ARIMA (40, 1, 1) model could not be fitted into O1 data.

Table 7: Correlation Matrix for Average-Mastoid Referenced, ARIMA (20, 1, 1) Preprocessed, 60-s Data Extracted from Subject 1's REM4

	F3	F4	C3	C4	O1	O2	FT7	FT8	CP3	CP4	P7	P8	TP9
F3													
F4	.481												
C3	.511	.394											
C4	.403	.488	.414										
O1	.270	.235	.379	.304									
O2	.253	.282	.315	.385	.419								
FT7	.492	.331	.427	.264	.257	.179							
FT8	.312	.426	.242	.389	.136	.223	.237						
CP3	.466	.370	.584	.408	.402	.333	.404	.217					
CP4	.389	.452	.424	.573	.326	.421	.258	.368	.416				
P7	.374	.284	.488	.333	.496	.342	.380	.148	.508	.341			
P8	.257	.314	.291	.424	.306	.453	.164	.301	.292	.445	.261		
TP9	.069	-.054	.114	-.069	.150	-.041	.164	-.145	.125	-.073	.218	-.132	
TP10	-.069	.054	-.114	.069	-.150	.041	-.164	.145	-.125	.073	-.218	.132	-1.000

Note. The 8 largest correlation coefficients are bolded.

Table 8: Correlation Matrix for Average-Mastoid Referenced, ARIMA (40, 1, 1) Preprocessed, 60-s Data Extracted from Subject 1's REM4

	F3	F4	C3	C4	O1	O2	FT7	FT8	CP3	CP4	P7	P8	TP9
F4	-												
C3	-	.391											
C4	-	.486	.408										
O1	-	.235	.376	.302									
O2	-	-	-	-	-								
FT7	-	.329	.425	.262	.255	-							
FT8	-	.426	.241	.388	.138	-	.237						
CP3	-	.367	.581	.402	.399	-	.402	.217					
CP4	-	.450	.419	.570	.324	-	.256	.368	.409				
P7	-	.283	.485	.329	.494	-	.379	.149	.506	.338			
P8	-	-	-	-	-	-	-	-	-	-	-		
TP9	-	-.054	.112	-.071	.147	-	.162	-.144	.124	-.075	.216	-	
TP10	-	.054	-.112	.071	-.147	-	-.162	.144	-.124	.075	-.216	-	-1.000

Note. The 7 largest correlation coefficients are bolded. The ARIMA (40, 1, 1) model could not be fitted into F3, O2, and P8 data.

references identified relatively strong connections between the TP9 and O1 electrodes, between the TP9 and P7 electrodes, and between the TP10 and P8 electrodes but all these could not be captured by the mastoid reference. Overall, the correlation coefficients for the Cz-referenced and mastoid-referenced data were larger than those for the average-referenced data, except for the connections between the C3, C4, CP3, and CP4 electrodes and the mastoid connections.

Six full matrices (2 ARIMA models by 3 references) for Subject 1's REM4, each of which comprised 32,640 possible correlation coefficients (256 by 255/2 sensor pairs), were analyzed. The z score for the differences in the correlation coefficients between the Cz reference ARIMA (20, 1, 1) and ARIMA (40, 1, 1) matrices ranged between 2.4909 (between E145 and E228 sensors) and -3.2171 (between E101 and E146 sensors), with the effect size q between 0.0203 and -0.0263 (see Table 9). Of the 32,640 possible correlation coefficients, 3,720 (11.4%) could not be computed because of unfitted channels, 25,381 (77.76%) correlation coefficients for the ARIMA (20, 1, 1) residuals were larger than those for the ARIMA (40, 1, 1) residuals, and 3,539 (10.84%) correlation coefficients for the ARIMA (20, 1, 1) residuals were smaller than those for the ARIMA (40, 1, 1) residuals. The Bonferroni corrected alpha value of .05 is 1.5319×10^{-6} (256 by 255/2 sensor pairs), which is equivalent to the z score of ± 4.8070 . In other words, there were no significant differences in the correlation coefficients between the two Cz reference ARIMA matrices. In a similar vein, no significant differences were found for the average-referenced and mastoid-referenced datasets (see Table 9).

The z score for the differences in the correlation coefficients between the average reference ARIMA (20, 1, 1) and Cz reference ARIMA (20, 1, 1) matrices ranged between -63.383 and 47.897, with the effect size q between -0.518 and 0.391 (see Table 10). Of the 32,640 possible correlation coefficients, 255 (0.78%) could not be computed because of 1 unfitted channel (E138). Over 86% correlation coefficients of the average reference matrix were significantly smaller than their Cz reference counterparts, with the effect size of 35.45% comparisons

being medium ($q < -0.3$) or large ($q < -0.5$). By contrast, only 6.89% correlation coefficients were significantly larger in the average reference matrix than in the Cz reference matrix, with only 72 (0.22%) comparisons showing a medium effect size of $q > 0.3$. All these electrodes with a medium effect size were within a radius of 4 electrodes from the Cz electrode (E7-E9, E17, E43-E45, E53, E60, E79-E81, E88-E90, E100, E101, E129-E132, E142-E144, E155, E185, E186, E198, and E207). In other words, all the largest positive differences between the average reference and Cz reference correlation matrices surrounded the central region. Similar differences were observed in the comparison between the average and mastoid reference matrices; that is, 92.55% of correlation coefficients were significantly smaller in the former than in the latter. Moreover, all 39 (0.12%) positive differences with a medium effect size involved the connections of the mastoid sensors E94 (with 12 other posterior electrodes) and E190 (with 27 other posterior electrodes).

The rank orders of the Cz reference ARIMA (20, 1, 1) and ARIMA (40, 1, 1) correlation matrices were highly correlated, Spearman's rho (r_s) = 0.9986, $p < .001$ (see Table 11). Both the Cz reference ARIMA correlation matrices showed a rank-order correlation coefficient larger than 0.9 with the correlation matrix generated by the data referenced to Cz and preprocessed by a bandpass filter of 0.5 to 45 Hz and by 1 order of differencing. They also had a medium-large rank-order correlation coefficient (> 0.7) with the Cz correlation matrix preprocessed only by bandpass filtering. All four Cz correlation matrices, however, were correlated relatively weakly with the correlation matrix built upon raw data (r_s values between 0.2 and 0.5). The exact same rank-order correlation pattern was noted for the average reference matrices and for the mastoid reference matrices. The correlation matrix for the average-referenced, filtered, and differenced dataset exhibited a medium-to-large r_s value with all other correlation matrices, except the three correlation matrices derived from the raw data. By contrast, all the rank-order correlations between the Cz and mastoid reference matrices were weak.

Table 9: Differences between ARIMA (20,1,1) and ARIMA (40,1,1) Correlation Matrices

	z	q	Invalid correlations due to incomputable channels	Positive differences	Negative differences
Cz (20,1,1) - Cz (40,1,1)	2.4909 (E145 and E228) to -3.2171 (E101 and E146)	0.0203 to -0.0263	3,720 (11.4%)	25,381 (77.76%)	3,539 (10.84%)
Average (20,1,1) - Average (40,1,1)	2.5023 (E101 and E90) to -3.2814 (E101 and E146)	0.0204 to -0.0268	11,934 (36.56%)	9,816 (30.07%)	10,890 (33.36%)
Mastoid (20,1,1) - Mastoid (40,1,1)	2.1948 (E101 and E90) to -3.0132 (E89 and E146)	0.0179 to -0.0246	10,905 (33.41%)	12,022 (36.83%)	9,713 (29.76%)

Note. Cz = Cz referenced correlation matrix, Average = Common average referenced correlation matrix, Mastoid = Average-mastoid referenced correlation matrix, (40, 1, 1) = ARIMA (40, 1, 1) preprocessed correlation matrix, (20, 1, 1) = ARIMA (20, 1, 1) preprocessed correlation matrix

Table 10: Differences between Average Reference, Cz Reference, and Mastoid Reference Correlation Matrices

	z	q	Invalid correlations due to incomputable channels	Positive differences/ significant differences/ medium or large effect sizes	Negative differences/ significant differences/ medium or large effect sizes
Average (20,1,1) - Cz (20,1,1)	-63.383 to 47.897	-0.518 to 0.391	255 (0.78%)	3,265 (10.00%)/ 2,449 (6.89%)/ 72 (0.22%)	29,120 (89.22%)/ 28,196 (86.38%)/ 11,570 (35.45%)
Average (20,1,1) - Mastoid (20,1,1)	-53.817 to 50.319	-0.439 to 0.411	763 (2.34%)	727 (2.23%)/ 354 (1.08%)/ 39 (0.12%)	31150 (95.44%)/ 30207 (92.55%)/ 7568 (23.19%)

Note. Cz = Cz referenced correlation matrix, Average = Common average referenced correlation matrix, Mastoid = Average-mastoid referenced correlation matrix, (20, 1, 1) = ARIMA (20, 1, 1) preprocessed correlation matrix

DISCUSSION

This study explored optimal ARIMA parameters for prewhitening sleep EEG time series of various lengths and tested whether different referencing and data preprocessing strategies would influence the correlation patterns in dense-array EEG network analyses. The ARIMA (40, 1, 1) model employed by Langheim et al. did not seem to be appropriate for generating time-series residuals from the present data, with a failure rate being as high as 20% of EEG sensors. Although varying the AR order by itself did not alter the correlation patterns and the differences between the ARIMA (40, 1, 1) and ARIMA (20, 1, 1) correlation matrices were not significant, the high failure rate of generating ARIMA (40, 1, 1) residuals indeed rendered subsequent connectivity analyses unreliable in that some connections between critical

regions for sleep, such as those between the parastriate region and the occipitotemporal junction, could not be detected.

Of the six ARIMA models investigated, the ARIMA (20, 1, 1) model was the best for sleep EEG prewhitening because it effectively removed time structures to the extent very much like the ARIMA (40, 1, 1) and ARIMA (30, 1, 1) models with virtually no unfittable channels for both early and late REM periods and different time lengths. It is important to note, nonetheless, that as indicated by the large rank-order correlation coefficients, the correlation matrices of the ARIMA prewhitened time series highly resembled those of the data preprocessed by bandpass filtering and differencing or even by bandpass filtering alone. This suggests that the use of different data preprocessing methods does not substantially influence the results of subsequent network

Table 11: Spearman Correlation Coefficients Comparing the 256-channel Correlation Matrices between Different Referencing and Preprocessing Approaches

	Cz (20,1,1)	Cz (40,1,1)	Cz raw	Cz filtered	Cz filtered & differenced	Average (20,1,1)	Average (40,1,1)	Average raw	Average filtered	Average filtered & differenced	Mastoid (20,1,1)	Mastoid (40, 1, 1)	Mastoid raw	Mastoid filtered
Cz (40,1,1)	0.9986													
Cz raw	0.3110	0.3121												
Cz filtered	0.7311	0.7407	0.4156											
Cz filtered & differenced	0.9407	0.9492	0.3336	0.8273										
Average (20,1,1)	0.5257	0.5454	0.2553	0.4897	0.5623									
Average (40,1,1)	0.5194	0.5398	0.2507	0.4870	0.5580	0.9995								
Average raw	0.3524	0.3511	0.9547	0.4100	0.3616	0.2536	0.24778							
Average filtered	0.4148	0.4263	0.3418	0.5507	0.4930	0.7703	0.7601	0.3601						
Average filtered & differenced	0.6162	0.6343	0.2966	0.5816	0.6804	0.9387	0.9340	0.3141	0.8572					
Mastoid (20,1,1)	0.2897	0.3087	0.0812	0.1353	0.2769	0.7865	0.7847	0.0673	0.6251	0.7329				
Mastoid (40,1,1)	0.2896	0.3091	0.0800	0.1378	0.2786	0.7890	0.7879	0.0652	0.6212	0.7342	0.9997			
Mastoid raw	-0.2133	-0.2061	0.0441	-0.0995	-0.1792	0.1353	0.1351	-0.0470	0.1755	0.1140	0.3303	0.3307		
Mastoid filtered	0.0640	0.0783	0.1725	0.2106	0.1184	0.5702	0.5644	0.1136	0.7191	0.5740	0.7325	0.7298	0.4896	
Mastoid filtered & differenced	0.2418	0.2602	0.0447	0.0702	0.2549	0.6642	0.6610	0.0466	0.6084	0.6773	0.9248	0.9232	0.3261	0.7359

Note. Cz = Cz referenced correlation matrix, Average = Common average referenced correlation matrix, Mastoid = Average-mastoid referenced correlation matrix, (40, 1, 1) = ARIMA (40, 1, 1) preprocessed correlation matrix, (20, 1, 1) = ARIMA (20, 1, 1) preprocessed correlation matrix, raw = calculated based on raw data, filtered = calculated based on filtered data, differenced = calculated based on differenced data

analyses so long as all EEG time series can be preserved after the preprocessing procedures.

In contrast to the analogous correlation matrices comparing different data preprocessing protocols, the correlation patterns varied substantially across the Cz-referenced, mastoid-referenced, and average-referenced datasets. The present findings demonstrate that the use of the common average reference significantly reduces overall correlation coefficients in a network, while Cz referencing and mastoid referencing suppress respectively the strength of connections over the central and mastoid regions. This systematic bias can be somewhat ascribed to a small variance in the time series obtained by electrodes placed near to the Cz and mastoid reference electrodes.

Using different references can dramatically alter the visualization of waveforms and the amplitudes of EEG waves. Figures 4-6 show the topographic plot of an epoch with a vertex sharp wave extracted from Subject 1's REM4 using the three references. The vertex sharp wave with the highest negative polarity is clearly localized at the Cz region in the average reference plot (see Figure 4). The negative polarity gradually diminishes with increasing distance from the center of the head. The similar can also be observed in the mastoid reference plot but the amplitude range is widened such that the high negative amplitude is picked up by more electrodes in the mastoid reference plot than in the average reference plot (see Figure 5). In the topographic plot for the Cz reference, this vertex wave creates a distorting image of a sharp positive wave appearing in all peripheral electrodes except a few electrodes over the central region (see Figure 6). The overall variation in amplitude is smaller in the average reference plot than in the other two reference plots. On the other hand, the amplitude is flattened over the central region for the Cz reference and over the two mastoid regions for the mastoid reference. These characteristics of the three referencing methods, as suggested by the present study, are also reflected in the correlation patterns.

The present study demonstrates that the use of the average mastoid reference would result in the methodological artifact of the two mastoid electrodes

being inversely and perfectly correlated. Moreover, the average mastoid reference tends to diminish the strength of correlations for the electrodes in the mastoid regions. Since the inferior temporal cortex is in the vicinity of the mastoid region (the mastoid process is part of the temporal bone), utilizing the mastoid electrodes as a reference would reduce the sensitivity for detecting activities in the region which is believed to play an important role in the neural network of sleep. Accordingly, the AASM's standard guideline which recommends configuring the mastoid electrode as a reference electrode is probably unsuitable for dense EEG network research. Furthermore, as demonstrated by the present analyses, researchers can somehow manipulate the

resultant network by using different referencing methods for analysis, for example, suppressing the connectivity over the inferior temporal region. This is alarming for sleep EEG network research; researchers should be cautious about the limitations and systematic bias of each referencing approach. The correlation matrix for the average-referenced, filtered, and differenced dataset was found to have an overall strongest rank-order correlation with other correlation matrices, the rank-order correlations between the Cz and mastoid reference matrices being weak. Taken together, it appears that the combination of average referencing, filtering, and differencing can constitute a relatively reliable protocol for dense EEG network analysis.

Figure 4: Average reference topographic plot of a vertex sharp wave detected in Subject 1's REM4

Figure 5: Average mastoid reference topographic plot of a vertex sharp wave detected in Subject 1's REM4

Figure 6: Cz reference topographic plot of a vertex sharp wave detected in Subject 1's REM4

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