



The long term effects of extreme low birth weight on visual attention memory process and functional connectivity of the brain.

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Abstract: Being born at extremely low birth weight (ELBW) and being born prematurely may result in impaired development of brain. The objectives of this study are to examine the long term impact of ELBW on visual working memory process using the event related potentials (ERPs) elicited during the visual attention experiment. The ERP amplitudes and wavelet-based magnitude squared coherence (MSC) function computed for adults survived from ELBW and for adults born with normal birth weight (NBW) were compared to each other. The time-frequency based method of wavelet coherence analysis proved useful in detecting various time-varying MSCs with optimal time-frequency resolution. The two-way ANOVA statistical test revealed significant difference in amplitude of ERP components and in MSC function between matching and non-matching trials for NBW group of subjects. However for ELBW group of subjects, the two-way ANOVA could not reveal significant difference level between matching and non-matching trials. The considerable loss in the significance level for the group of ELBW subjects indicate that ELBW may produce long term impact on the visual memory process and functional connectivity of the brain.

Keywords: EEG, volume conduction effects, alcoholism, coherence function.

1. **INTRODUCTION**

Extreme low birth weight (ELBW) and being born prematurely can affect the development of the brain and electroencephalography (EEG) which are electric potentials produced inside the brain has been found useful in detecting these changes. Various studies using the visual analysis have reported unique EEG profile of ELBW (< 1000 gm) group of newborns as compared those who were born with normal birth weight (Dreyfus-Brisac, 1962; Lindsley, 1939; Smith, 1941; Miskovic *et al.*, 2009; Sommers *et al.*, 2011). These changes were mostly increased occipital EEG activity around 3 to 5 Hz in group of ELBW newborns as compared to the group of normal birth weight (NBW) newborns.

In addition to the visual analysis of EEG, various signal processing tools have been used in order to examine the EEG signals. Among them, the most commonly used method is the power spectral density function. The power spectral density describes the distribution of energy (variance) in signal and usually estimated by taking the square of the magnitude of the Fourier transform of the signal. The change in power spectral density of ELBW group of newborns as compared to the power spectral density of NBW group have been reported in literature.

These studies report increased power spectral density in theta and delta band in ELBW newborns

whose age ranges from one week to several weeks (for reviews, see, e.g., Grieve *et al.*, 2008; Bell *et al.*, 1991; Guzzetta *et al.*, 2011)

The coherence function is another signal processing tool which has been frequently used in EEG analysis for examining the correlation between different regions of the brain. For example, it is being used in the detection of the epileptogenic focus from epilepsy patients (Mormann *et al.*, 2000), identification of neuroanatomic pathways for a seizure propagation (Sherman *et al.*, 1997), alcoholic disorders (Debruin *et al.*, 2006) as well as for the detection of various cognitive disorders (Klein *et al.*, 2006; Marosi *et al.*, 1992)

Relatively, few studies have examined effects of ELBW on EEG coherence function. Also *et al.* (2004) examined increased EEG coherence in a group of ELBW group of newborns (2 to 4 weeks of age) between frontal and occipital electrodes and lower coherence between central and occipital electrodes. Various studies have reported more short inter-electrode distance coherence spectra in ELBW group of newborns and more long inter-electrode distance coherence spectra in NBW group of infants (Grieve *et al.*, 2008; Miskovic *et al.*, 2009; Gonzalez *et al.*, 2011). This typical coherence spectra examined in newborns affected by ELBW have also been reported for adults who were born at ELBW (Miskovic *et al.*, 2009).

The literature reported on EEG of subjects survived from the ELBW have been limited to the frequency domain analysis of EEG signals. On the other hand both time and frequency-domain analysis of EEG signals is important because most of EEG signals encounter in nature are time-varying and may contain important information both in time and frequency domain. In addition to this, the volume conduction effects due to uncorrelated sources (VCUS) present in the brain, have been ignored while interfering the results of study based on the effects of ELBW on coherence function. The VCUS effects can introduce the biased estimates into the true value of coherence function. Moreover, previous studies have not included cognitive tasks such as visual working memory tasks, etc in order to examine whether the EEG spectral aberrations have functional significance.

In view of the above mentioned limitations in the existing literature, the main objectives of this study were to examine the long term effects of ELBW on the visual working memory and functional connectivity (coherence function) of the brain keeping in account the effects of volume conduction. The ERPs elicited during the visual attention experiment and recorded from the young adults survived from the ELBW were used for this purpose. In order to examine the long term impact of ELBW on visual working memory, amplitudes of ERPs computed for a group of ELBW were compared to those of adults who were born with NBW.

In addition to this, the wavelet-based MSC was used in order to examine the effect of ELBW on functional connectivity of the brain. The advantage of using wavelet transform is that it allows time-frequency analysis at optimal time-frequency resolution. Unlike the previous studies on the effects of ELBW on coherence function in which VCUS effects has not been taken into account, this study has examined the MSC function with minimum VCUS effects.

2. MATERIAL AND METHODS

The subjects were divided into two groups. The extremely low birth (ELBW) group of young adults born with the birth weight less than 1000 g between 1980 and 1986 who were selected from a random sample of 400 newborns registered at neonates intensive care unit of Kings College Hospital London. Of these 400 newborns, 180 were survived to hospital discharge. Out of these 180 group of young adults, we were able to access and record EEG data of 79 young adults. The normal birth weight group of young adults were selected from the random sample of registered newborns at newborn care unit of Kings

College London. The age of subjects in both groups of NBW and ELBW ranged from 22 to 25 years at the time of experiment. All subjects in each group were carefully monitored by neurologist and no sign of any neurological disorder was diagnosed. The subjects of same age limit (22 to 25 years), same sex (male), same race as well as those who were right-handed users were selected in each group.

EEG recording

An event-related potential (ERP) is an EEG signal which results due to some thought or perception when subject is instructed to respond to some visual or audio stimulus. The ERPs for this study were recorded in the laboratory of the Centre for Cognition and Neuroimaging at Brunel University and the 10-20 system for the recording of ERPs was used in this study. Subjects were asked to avoid unnecessary movements in order to avoid artefacts caused due to the movement of various body parts. The bandpass filter of 0.02-50 Hz was also used in order to minimize artefacts caused due to the movement of the body. ERPs were recorded in a sound attenuated and radio frequency shielded room in order to avoid artifacts caused due to external sources such as electromagnetic radiation coming from outside the recording room. Subjects, who were sitting one meter away from the computer screen, were shown different pictures of objects selected from the Snodgrass and Vanderwart (1980) picture set in three different ways: (1) two same pictures were shown (2) two different pictures were shown (3) one single picture was shown. The task of the subject was to recognize whether two pictures which appeared with the time interval of 1.7s. are same or different. The trials with same picture stimuli and different picture stimuli are called matching and non-matching trials respectively. The subjects were asked to show their respond by pressing the mouse key. Three main wave forms in recorded event related potentials were observed. These waveforms mostly appeared around 100-125 ms, 160-190 ms, and 220-260 ms. In this study these waves forms are called ERP components A_1 , A_2 , and A_3 respectively.

EEG signal processing

Wavelet coherence function

The wavelet transform of discrete time series $x(n)$ is

$$X_n^x(a, b) = \frac{1}{\sqrt{a}} \sum_{n=1}^N x(n) \psi_{a,b}^*(n) \quad (1)$$

where asterisk symbol denotes the conjugate operation. For $a = 1$ and $b = 0$, $\psi_{a,b}(n)$ is called the mother wavelet, where a and b are the scale and the translation parameters respectively. As scale a changes, the shape of the mother wavelet is

compressed or stretched to cover different frequency ranges and by varying translation parameter b , the mother wavelet is displaced in time. In this way, the wavelet transform provides a time-frequency description of the signal $x(n)$. The Morlet mother wavelet

$$\psi(n) = \frac{1}{\pi} e^{\frac{t^2}{2}} e^{i\omega_0 t} \quad (2)$$

with nondimensional frequency $\omega_0 = 6$ was chosen in this study, because it provides a scale of the wavelet nearly equivalent to Fourier period (Paul, 2004), thus providing an optimum definition in the frequency domain. Given two time series $x(n)$ and $y(n)$ with wavelet transforms $X_n^x(a, b)$ and $Y_n^y(a, b)$, the wavelet cross-spectrum $W_n^{xy}(a, b)$ and the wavelet auto-spectra $W_n^{xx}(a, b)$ and $W_n^{yy}(a, b)$ are given by

$$W_n^{xy}(a, b) = X_n^x(a, b) \cdot Y_n^{*x}(a, b) \quad (3)$$

$$W_n^{xx}(a, b) = X_n^x(a, b) \cdot X_n^{*x}(a, b) \quad (4)$$

$$W_n^{yy}(a, b) = Y_n^y(a, b) \cdot Y_n^{*y}(a, b) \quad (5)$$

The wavelet coherence is given by

$$\gamma_n^{xy}(a, b) = \frac{W_n^{xy}(a, b)}{\sqrt{W_n^{xx}(a, b) \cdot W_n^{yy}(a, b)}} \quad (6)$$

The square of the absolute value of wavelet coherence is called here MSC. Equation (6) shows that values of coherence and MSC is unity for all values of two time series, however computation of MSC using the average estimates based on the segments of original time series produces meaningful results between one and zero. This method makes sense for stationary time series or frequency domain analysis of coherence function. This study uses the method of (Zhan *et al.*, 2006) which is based upon the estimation of cross and auto spectra for each individual trial separately and then MSC value is estimated by using a average value of these cross and auto spectra into the square of the absolute value of Equation (6).

ERP analysis

The number of repeated trials must be sufficient to cause ERPs to be clearly distinguishable from unrelated background EEG. This is because, ERPs compared to background EEG are very small in magnitude, therefore ERPs are enhanced when many trials are averaged together. The signal to noise ratio is thus improved in proportion to the square root of the number of trials averaged. Therefore, the ERP data chosen for this research consists of the large number of repeated trials, i.e., at least 100 trials per subject.

Statistical considerations

The group difference

The statistical significance of difference between EEG activities of ELBW and NBW group of subjects using ERP amplitudes and MSCs was estimated using the two-way ANOVA test for each frequency band. The ERPs and MSC values were normalized using the logarithmic and Fisher's Z transformation respectively. The estimated MSC around the sample length of 100-200ms appeared to be less affected by VCUS effects as it showed dependence on both time and frequency for most of subjects. In addition to this, MSC was analyzed for three different frequency regions $\theta(4 - 8\text{Hz})$, $\alpha(8 - 13\text{Hz})$, and $\beta(13 - 30)$. These three different frequency regions are known theta, alpha, and beta frequency bands in EEG literature. Therefore in order to access the MSC difference using the two way ANOVA test, the average of MSC across the sample length of 100-200ms and across the alpha, beta and theta frequency bands was used in this study.

Confidential interval of MSC

The statistical significance of time-frequency MSC was examined by the confidence intervals. In Fourier MSC, confidential interval is set by assuming that two time series are stationary and Gaussian distribution is used to approximate the probability density of data. However such an assumption cannot be used for time-frequency methods of MSC. Therefore, statistical significance of time-frequency MSC was assessed by using the method of Gish and Cochran (1988) which is not based on stationary assumption of EEG signals. It is given by the following relation,

$$P_t = 1 - (1 - t)^{R-1}, \text{ where } 0 \leq t \leq 1 \quad (7)$$

where t is the detection threshold, R is the number of repeated trials, and P_t is the desired level of confidence. For a 95 % confidence interval,

$$1 - (1 - t)^{R-1} = 0.95 \quad (8)$$

Or

$$t_{95\%} = 1 - 0.05^{\frac{1}{R-1}} \quad (9)$$

Any estimate of these coherence less than the $t_{95\%}$ was not considered as the significant value.

3

RESULTS AND DISCUSSION

The position of the electrodes was organized accordingly to the 10-20 system for the recording of ERPs. The frontal region consisted of F3, F4, F7, F8, the parietal region consisted of PZ, P3, P4, the temporal region consisted of T5, T6, and the occipital region consisted of O1 and O2. At all electrodes, the

two-way ANOVA could not reveal significant group differences in the amplitude of ERP components A_1 , A_2 , and A_3 between groups of ELBW and NBW subjects performing either matching or non-matching trials. Since A_3 reflects visual working memory process, it might be suggested that ELBW does not necessarily produce long term effects on visual working memory process. The amplitude of ERP components A_2 and A_3 during matching and non-matching trails for the NBW and ELBW are shown in (Table 1). The two-way ANOVA analysis revealed significant group difference in ERP components A_2 and A_3 for NBW group of subjects which is consistent to the previous studies performed on subjects having no neurological and cognitive disorders (Zhang *et al.*, 1995). However as shown in Table 1 that no significant group difference in ERP components A_2 and A_3 for ELBW group of subjects was examined which might be due to the effects of ELBW.

The volume conduction effects from various uncorrelated sources (VCUS) present in the brain

introduce an artificial MSC into the true value of MSC (Nunez *et al.*, 1997). The issue of VCUS effects is important in this study, because effects of ELBW on MSC for short inter-electrode distance have been reported in literature without keeping in account the issue of VCUS effects whereas VCUS effects tend to be maximum when inter-electrode distance tends to be minimum. Therefore this study, using the characteristics of VCUS effects as discussed in literature, has eliminated the values of MSCs affected by the VCUS effects (for reviews on VCUS effects, see, e.g.; Srinivasan *et al.*, 1998; Srinivasan, 1999; Nunez *et al.*, 1997). In addition to this, the time-frequency analysis of coherence function proved to be useful in examining the time-domain characteristic of VCUS effects. It was found that coherence which is independent of frequency is also independent of time. This result proved to be useful in detecting coherences affected by volume conduction effects especially those which existed at one frequency and therefore could not be detected using the frequency domain characteristics only.

Table 1: The amplitude of ERP components A_2 and A_3 (mean \pm SD) for various positions of electrode and results of ANOVA analysis for the group of NBW and ELBW subjects performing matching and non-matching trials.

A_2	F3	F4	F8	P3	P4	PZ	T5	T6	O1	ANOVA F P
ELBW MT NMT	0.72 \pm 0.21 0.63 \pm 0.16	0.89 \pm 0.21 0.67 \pm 0.16	0.53 \pm 0.25 0.52 \pm 0.16	0.53 \pm 0.25 0.49 \pm 0.11	0.54 \pm 0.26 0.52 \pm 0.23	0.61 \pm 0.21 0.56 \pm 0.11	0.49 \pm 0.25 0.42 \pm 0.25	0.48 \pm 0.24 0.42 \pm 0.19	0.32 \pm 0.25 0.32 \pm 0.26	0.993 ..321
NBW MT NMT	0.93 \pm 0.18 0.75 \pm 0.22	0.96 \pm 0.20 0.72 \pm 0.25	0.73 \pm 0.21 0.59 \pm 0.30	0.79 \pm 0.21 0.57 \pm 0.26	0.81 \pm 0.22 0.65 \pm 0.32	0.93 \pm 0.21 0.69 \pm 0.29	0.75 \pm 0.27 0.60 \pm 0.37	0.83 \pm 0.26 0.63 \pm 0.38	0.51 \pm 0.24 0.40 \pm 0.36	8.450 005*
A_3										
ELBW MT NMT	0.43 \pm 0.29 0.40 \pm 0.26	0.44 \pm 0.26 0.39 \pm 0.26	0.37 \pm 0.27 0.34 \pm 0.20	0.36 \pm 0.25 0.34 \pm 0.22	0.45 \pm 0.26 0.37 \pm 0.22	0.50 \pm 0.26 0.38 \pm 0.30	0.37 \pm 0.27 0.36 \pm 0.15	0.40 \pm 0.26 0.35 \pm 0.19	0.36 \pm 0.16 0.30 \pm 0.23	0.673 0.422
NBW MT NMT	0.50 \pm 0.25 0.36 \pm 0.26	0.51 \pm 0.25 0.34 \pm 0.23	0.43 \pm 0.25 0.33 \pm 0.28	0.49 \pm 0.23 0.35 \pm 0.30	0.63 \pm 0.27 0.44 \pm 0.23	0.68 \pm 0.28 0.51 \pm 0.41	0.54 \pm 0.33 0.37 \pm 0.31	0.60 \pm 0.34 0.39 \pm 0.35	0.33 \pm 0.33 0.17 \pm 0.38	4.235 0.043

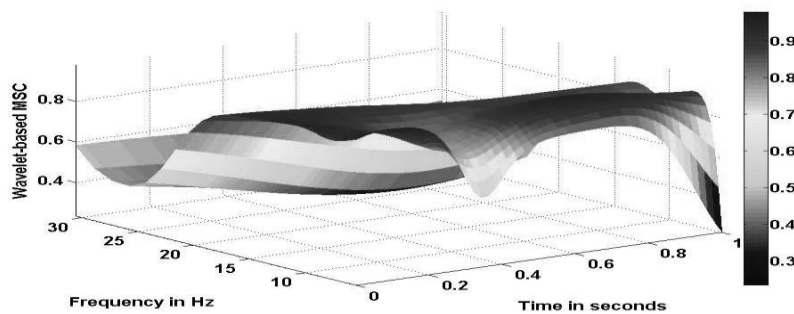


Fig. 1: The frequency independent part of MSC affected by VCUS effects around 10Hz to 20Hz is also independent of time indicating that MSC due to the VCUS effects is independent of both time and frequency.

MSC values and two-way ANOVA scores for the NBW and ELBW group of subjects performing matching and non-matching trials are shown in Table 2. NBW group of subjects exhibited significant difference in MSCs between matching and non-matching trials for the frontal and parietal regions of the brain. However as shown in Table 2 and similar to the results obtained for the amplitudes of A_2 and A_3 , the two way ANOVA revealed significant drop in the

statistical significance of group difference in MSCs between matching and non-matching trials.

As shown in Table 3, there is no significant difference in MSCs between ELBW subjects and NBW subjects performing either matching or non-matching trials. The results obtained in this study showed that ELBW does not necessarily produce significant effects on functional connectivity of the brain.

Table 2: The difference in MSCs between matching and non-matching trials for both NBW and ELBW group of subjects.

Bands Subjects		F3-F7	F4-F8	F3-F4	P4- PZ	P3-PZ	ANOVA	
							F	P
θ	ELBW	1.25±0.10	1.28±0.11	1.26±0.08	1.26±0.09	1.27±0.08	2.852	0,094
	MT	1.21±0.09	1.23±0.12	1.23±0.11	1.21±0.11	1.250.10		
	NMT	1.10±0.11	1.10±0.09	1.11±0.07	1.10±0.08	1.07±0.08		
NBW	MT	1.04±0.05	1.03±0.08	1.05±0.08	1.03±0.07	1.04±0.06	18.415	0.001*
	NMT							
α	ELBW	1.21±0.09	1.24±0.08	1.22±0.08	1.23±0.08	1.24±0.09	2.436	0.123
	MT	1.18±0.09	1.20±0.12	1.19±0.10	1.18±0.11	1.22±0.07		
	NMT							
NBW	MT	1.07±0.10	1.07±0.08	1.08±0.05	1.10±0.07	1.04±0.07	17.010	0.000*
	MT	1.01±0.03	1.01±0.07	1.02±0.07	1.07±0.05	1.01±0.05		
	NMT							
β	ELBW	1.20±0.08	1.22±0.08	1.20±0.06	1.20±0.07	1.22±0.07	2.545	0.124
	MT	1.15±0.09	1.17±0.12	1.17±0.10	1.15±0.10	1.20±0.10		
	NMT							
NBW	MT	1.05±0.10	1.05±0.08	1.06±0.05	1.05±0.07	1.03±0.07	15.221	0.005*
	MT	1.01±0.03	1.00±0.07	1.01±0.07	0.97±0.05	1.01±0.05		
	NMT							

The asterisk symbol indicates the significant value of P for the 0.05 level of significance

Table 3: The difference in MSCs based on ELBW and NBW group of subjects performing matching and non-matching trials for different frequency bands.

Frequency bands	Subjects	F3-F7	F4-F8	F3-F4	P4- PZ	P3-PZ	ANOVA	
							F	P
θ	MT	1.18±0.10	1.22 ±0.11	1.20±0.09	1.20±0.10	1.21± 0.10	2.514	0.117
	LBW	1.16±0.10	1.18±0.12	1.18±0.10	1.16±0.10	1.20±0.11		
	NBW							
	NMT	1.16±0.10	1.17±0.12	1.17±0.11	1.15±0.10	1.19±0.09	2.801	0.099
	LBW	1.18±0.10	1.21±0.10	1.19±0.10	1.19±0.10	1.20±0.09		
	NBW							
α	MT	1.33±0.10	1.36±0.10	1.34±0.09	1.35±0.09	1.35±0.08	3.150	0.080
	ELBW	1.29±0.10	1.31±0.13	1.30±0.11	1.29±0.11	1.32±0.11		
	NBW							
	NMT	1.59±0.10	1.16±0.11	1.16±0.12	1.14±0.10	1.18±0.10	2.414	0.137
	ELBW	1.17±0.12	1.20±0.11	1.19±0.11	1.18±0.13	1.19±0.12		
	NBW							
β	MT	1.36±0.10	1.37±0.10	1.16±0.04	1.12±0.06	1.06±0.06	2.721	0.098
	ELBW	1.25±0.13	1.30±0.12	1.06±0.10	1.11±0.14	1.01±0.12		
	NBW							
	NMT	1.20±0.07	1.22±0.10	1.22±0.10	1.20±0.10	1.24±0.08	2.862	0.105
	ELBW	1.24±0.08	1.27±0.09	1.25±0.06	1.25±0.07	1.26±0.06		
	NBW							

4. CONCLUSION

This study examines the long-term effects of ELBW on the visual working memory process and on the functional connectivity of the brain using

amplitude analysis of event related potentials and wavelet-based MSC function respectively. The results show that ELBW may produce long term effects on visual working memory process and functional

connectivity of the brain. In order to minimize VCUS effects on MSC function, VCUS effects were also examined in time-frequency domain. It was found that MSC due to VCUS effects do not depend on both time and frequency.

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