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Master of Statistics: Biostatistics

Masterproef

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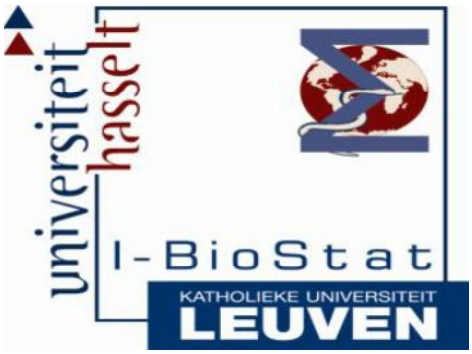

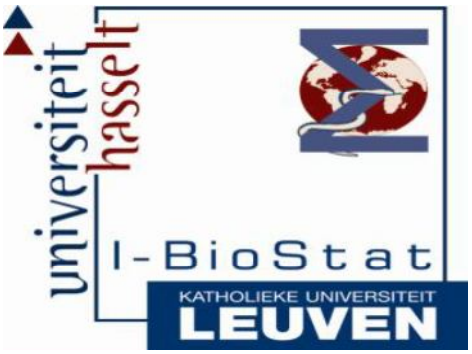

Impact Of Exposure To Prenatal Maternal Stress On Infant Cognitive Development

By

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Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Science in Biostatistics of Hasselt University

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Abstract

These days, many women are experiencing stress at time of pregnancy due to emotional, physical, and social changes in their life. Stress during pregnancy is risk factors having adverse impact for mothers and children. If a mother is stressed, anxious or depressed during pregnancy, her child is at increased risk for having a range of problems, including emotional problems, conduct disorder, and impairment of cognitive development. In this study, we focus on investigating the effect of mother's anxiety during pregnancy trimester 1 on ERP.

Two month after birth infant's ERP were measured four times from six electrode brain locations. Considering this, measurements from the same subject expected to be correlated over stimulus blocks and over locations. Linear mixed model with Kronrcker direct product covariance structure were employed to take into account the dependence of measurements within and between locations from the same infant. The results of the study reveals an overall decreasing responses and also significant effect of mother's anxiety and IBQ2 (Negative affect). As conclusion IBQ2 and Mother's anxiety have negative impact on infants cognitive development.

KEY WORDS: ERP; Stress; pregnancy; linear mixed model; Habituation; Sensitization; IBQ.

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1. Introduction

Stress (also including anxiety and depression) during pregnancy and its associated impact on the child after birth has been a concern for psychiatrists and other health related disciplines, especially behavioural medicine, health psychology, and social epidemiology, for more than a decade (Schetter and Tanner, 2012). The concept of stress, according to Glover (1997), is a complex term that encompasses a large number of states such as mild stress, distress, anxiety, and depression that can be experienced as a result of a range of phenomena including daily trouble, dysfunctional relationships, and adversity.

According to the World Health Organization (2000), depression (or stress) is common and affects about 121 million people worldwide. The occurrence of the disorder is particularly high among women. For instance, Kessler *et al* (1993) indicated that the prevalence of depression in women is about 20% compared to men, of which about 10% with the initial episode occurring in childbearing year.

These days many women are experiencing physical and psychological changes as a result of the many factors involved in pregnancy such as emotional, physical, and social changes that cause stress (Chang, Chen, & Huang, 2008). Pregnancy is also an individual experience that elicits a range of responses that ranges from very negative to very positive. The wide range of responses are due to the complexity of the process such as physical, emotional, psychological and social changes that occur in the woman's personality due to the life experiences of the individual and the cultural expectation of one's society. The experience of anxiety by pregnant women has an impact on their baby's health and pending lifestyle change (Chang *et al.*, 2008).

Recent studies indicate that constant stress, depression and anxiety of mothers could cause damaging effects on infant development during pregnancy as well as in the postnatal period. For instance, Schetter and Tanner (2012) stated that anxiety, depression, and stress during pregnancy are risk factors having adverse impacts and/or outcomes for mothers and children. Explaining further, they pointed out that anxiety in pregnancy is associated with shorter gestation and has adverse implications for fetal neurodevelopment and child outcomes. In addition, (Chang *et al.*,

2008) argued that if a mother is stressed, anxious or depressed during pregnancy, her child is at increased risk for having a range of problems, including emotional, conduct disorder, and impairment of cognitive development.

According to Mennes, M *et al*. (2009) Physiological measures, such as Event-Related Potentials (ERP), are more closely related to underlying biological processes compared to complex behavioural measures. The use of physiological measures can provide an important impetus for research into the mechanisms of the relationship between antenatal maternal anxiety and later development. One way to do this is by measuring ERP during stimulus repetition.

The ERP is an average electroencephalogram (EEG) response from the repeated stimuli measures brain response that is the direct result of an external event. More formally, it is any stereotyped electrophysiological response to stimulus. The study of the brain in this way provides a non-invasive means of evaluating brain functioning. During repetition of the same stimulus a typical phenomenon can be observed: Habituation, defined as a decrease in response to a stimulus when that stimulus is presented repeatedly (Kandel *et al.* 2000 and Rankin *et al.* 2008) and Sensitization , has opposite effects to habituation. It is defined as an enhanced response to stimuli after the presentation of stimulus (Kandel *et al.* 2000).

This study focuses on habituation/sensitization of brain response/ ERP over different stimuli blocks. The main objective of this project is to assess whether there is habituation/ sensitization over repeated stimulus presentation. In addition, the study assesses whether habituation/ sensitization of ERP over stimulus blocks is different for electrode location (central (c) Vs frontal (f) and left (3) Vs right (4) Vs centre (z)) and also, whether a mother's state anxiety during pregnancy trimester1and the temperament (IBQ (infant behavioural question)) of infant's contribute to habituation/sensitization.

Organization Of The Paper

The report is organized as follows. Section 2 and 3, we discuss the material and methods of the study. In section 4, results of the data are illustrated. Finally, general discussions and conclusions are given in section 5.

2. Material And Methods

This part describes data set used in the analysis of this project. A brief overview of the methods used to analyze the data and the motivations behind the chosen method will be presented.

2.1. Data Description

The data set used in this study was obtained from Tilburg university; Prenatal Early Life Stress project in Tilburg (PELS).

Participants

For the PELS project, a total of 190 pregnant women had been recruited. Of these women, 178 women were recruited before their 15^{th} weeks of pregnancy, and 12 women were between 15^{th} and 23^{rd} weeks of their pregnancy. In each pregnancy trimester1 to 3 (T1 to T3), the women filled out questionnaires regarding their feelings and state of mind. One of the questionnaire was the state trait Anxiety Inventory (Spielberger), of which the sum scores of the questionnaire filled out during the first trimester was used to represent mother's state of anxiety in trimester_1 (T1). The questionnaire consists of 20 items which can be rated on a scale from 1 (never) to 4 (always).

Two months after giving birth, the mother and their infants (N=91 participants) were invited to the baby lab for postnatal observations (T4). Of the 91 women who visited the lab for testing when their infants were aged two months, only 85 women had filled out the questionnaires at T1. The information gathered from 15 infants was excluded from analysis due to crying (N=2), excessive movements/ artefacts (N=9), and technical problems (N=4) during testing. Therefore, only 70 infants and their mothers were participated in the experiment.

During this lab visit, the mother's filled out a questionnaire about their infants' temperament: the Infant Behavioural Questionnaire (IBQ). The IBQ consists of three subscales: positive affectivity, negative affectivity and effortful control, which can be rated on a scale from 1 (not at all/ almost never) to 7 (very much/ almost always) and does not apply (NA), which was used when the baby had not been in the situation described in the last seven days. The mean score of the items for each of the three subscales were used to represent the infant’s temperament. The

means were calculated by dividing the sum of all numerical item responses for a given scale, with the number of items receiving a numerical response. The means do not include items marked "does not apply (NA)" or “items receiving no response” in determining the number of items.

Stimuli

At T4 the infants were administered an auditory oddball paradigm. The stimulus sequences of this project consisted of 4 types of sounds: one standard and three deviants each with 10 millisecond (ms) rise and fall times and of 200 ms duration. All stimuli had an intensity level of 75 decibel (dB) and, except for the inter-stimulus interval (ISI)-deviant events (see below), they were delivered at a uniform 300 ms inter-stimulus interval (ISI; offset-to-onset interval). The standard was a complex tone constructed from the 3 lowest partials. The fundamental frequency was 500 Hz and the intensity of the second and the third partials was 6 and 12 dB lower, respectively, than that of the first one. One deviant was identical to the standard sound, but it was preceded by 100 ms instead of 300 ms silence (‘ISI-deviant’). The other two deviant types were white noise segments (‘white noise’) and environmental sounds (‘novel sounds’, 150 different ones), such as dog barking or a door-bell ringing. Each novel sound was delivered only once during the experiment to maintain novelty throughout. Sounds were presented in random order with the restriction that both white noise and novel sounds were always preceded by at least two standard sounds or a combination of a standard sound and an ISI-deviant. In addition, consecutive ISI-deviants were always separated from each other by at least two standards or by a standard combined with either a white noise or novel sound.

In totally, 1500 stimuli were delivered to each 70 infants, consisting of 1050 standard sounds together with 150 deviants of each type. The stimuli were divided into five blocks of 300 stimuli each and presented with short breaks in between.

Procedure

The infants were tested at the developmental psychology lab at Tilburg university (the Baby lab), in a dimly light and sound-attenuated room. The monitored behaviour in combination with the EEG signal was used to determine the state of alertness during each stimuli blocks: awake or

asleep. Only data recorded during those stimulus blocks in which the infant was either awake or asleep throughout the whole period were analyzed.

Data Acquisition And ERP Measurements

EEG was recorded with Biosemi Active Two amplifiers with 512 Hz sampling rate, using a head cap with 64 electrode locations placed according to the revised version of the international 10-20 system. Reference electrodes were placed on the left and right mastoids. Off-line, the EEG signals were filtered with a 1 to 30 Hz band-pass filter (slope 24 dB) and a 50 Hz notch filter.

The ERP was created from an average brain responses of the first 75 (out of the first 100 stimuli (block1A)) and last 75 (out of the last 100 stimuli (block1B)) standard sounds that were presented in the first block and first 75 (out of the first 100 stimuli (block5A)) and last 75 (out of the last 100 stimuli (block5B)) standard sounds that were presented in block five for six electrode locations (C3, Cz, C4, F3, Fz, and F4). For analysis of this project we only used data recorded during those stimulus blocks in which the infant was either awake or asleep throughout the whole stimulus blocks (as described above). Additional to the above criteria, infants should have 75 artefact-free responses to be included in the first part of the analysis and 50 artefact-free responses for the second part of the analysis in each stimuli block mentioned above. The analysis is based on 26 infants that satisfied the above criteria.

The outcome of interest was the average brain response /ERP measured four times (block1A, block1B, block5A and block5B) from six electrode locations for each infant. Mother's state of anxiety during pregnancy trimester_1 and IBQ: surgency (positive affect), negative affect and effortful control of the infant are the baseline covariates.

Table 1: Description of outcome and covariates.

Variable	Symbol	Description
Response		
Event Related Potential	ERP	The average brain response for stimulus presented in each stimuli block. Measured from six brain locations over 4 stimulus blocks.
Covariates		
Mother's anxiety	Moanxiety	Mother's anxiety measured during pregnancy trimester 1. Using questionnaire.
Infants Behavioural Question	IBQ	provides information about the temperament of the child. This questionnaire was filled by their mother's and consist of three subscales - : IBQ1- surgency (positive affect), IBQ2- negative affect and IBQ3- effortful control.
Location		Brain location (frontal (F) and central (C))
Sub-location		Brain location (left (3), medial (z) and right (4))
Stimulus block: block1A : block1B : block5A : block5B	Stimuliblock1 Stimuliblock3 Stimuliblock13 Stimuliblock15	There are 4 stimuli blocks that the brain response were measured. block1A and block1B belongs to block one and stimuli block5A and block5B belongs to block five. Block one and block five described briefly in part of stimuli sub topic.

3. Methods

3.1. Exploratory Analysis

The first step in any model-building process, is exploring the data to get some insight. In this step, we used graphs that expose the patterns relevant to the scientific question.

3.2. Statistical Analysis

Given that repeated measurements were taken from each subject over two repeated factors, two intra-subject correlations have to be taken into account when analyzing the data set. We therefore, use methods that take the correlations into account. The methods we employed in our analysis are briefly explained below.

3.2.1. Spatio-Temporal Data Analysis

Longitudinal imaging studies are moving increasingly to the forefront of medical research due to their ability to characterize patio-temporal features of biological structures across the lifespan. Modeling the correlation pattern of these types of data can be immensely important for proper analyses. Accurate inference requires proper choice of the correlation model. Multivariate repeated measures studies are characterized by data that have more than one set of correlated

outcomes or repeated factors. Spatio-temporal data fall into the more general category since the outcome variables are repeated in both space and time. The Kronecker product correlation structure is proposed for multivariate repeated measures data in which the correlation between measurements for a given subject is induced by two factors (space and time). The patio-temporal model takes into account two types of covariance patterns among measurements from the same subject: there are dependences (1) among measurements from different locations (locations on the infant's brain), and (2) among measurement from different stimulus blocks (within location). The approach considered is to fit a model with a direct product covariance structure to specify the within subject variance-covariance matrix. The Kronecker product is used to combine the factor specific correlation structures into an overall correlation model.

$$\boldsymbol{Y_i} = \boldsymbol{X_i}\boldsymbol{\beta} + \boldsymbol{Z_i}\boldsymbol{b_i} + \boldsymbol{\varepsilon_i}$$

Where, $\boldsymbol{Y_i}$ is the *ni*-dimensional continuous response (ERP) vector for subject i, $\boldsymbol{X_i}$ and $\boldsymbol{Z_i}$ $(ni\ x\ P)$ and $(ni\ x\ l)$ dimensional matrices of known covariates, respectively, $\boldsymbol{\beta}$ is a p-dimensional vector containing the fixed effects, $\boldsymbol{bi}$ is an l- dimensional vector containing the random effects $\boldsymbol{b_i} \sim \boldsymbol{N}(\boldsymbol{0}, \boldsymbol{D})$, and $\boldsymbol{\varepsilon_i}$ is an $ni-$dimensional vector of residual components $\boldsymbol{\varepsilon_i} \sim \boldsymbol{N}(\boldsymbol{0}, \boldsymbol{\Omega_i})$. $\boldsymbol{D}$ is a general $(l\ x\ l)$ covariance matrix for the random effects. $\boldsymbol{\Omega}$ is the $(pq\ x\ pq)$ variance covariance matrix.

$$\boldsymbol{\Omega}_{pq \times pq} = V_{p \times P} \otimes \Sigma_{q \times q}$$

Where, $\boldsymbol{V}$ and $\boldsymbol{\Sigma}$ respectively are p by p and q by q positive definite matrices and $\otimes$ stands for the Kronecker product. The matrix $\boldsymbol{\Sigma}$ represents the variance covariance matrix of repeated measures for a given location. The matrix $\boldsymbol{V}$ represents the variance covariance matrix between measurements on all locations at a given stimuli block. It is assumes that this does not depend on the particular stimuli block and is the same for all stimulus blocks. Mathematical formulation of Kronecker product covariance matrix are given in appendix E. Observations from different infants are assumed to be independent and observations within infant are expected to be correlated. For more explanation, we refer to Naik, D. N. and Rao, S. S. (2001).

4.Results

This section contains two subsections. The first subsection presents results from the data set that contains infants who had 75 artifact free response for 100 stimulus presented in each stimuli block and the second subsection is for data set from infants who had 50 artifact free response for 100 stimulus presented in each stimuli block.

4.1. 75 Artifact Free Response

In this subsection we present results from the exploratory data analysis and statistical modelling on ERP data from 75 artifact- free brain responses.

4.1.1.Exploratory Data Analysis

To get more insight into the structure of the data individual and mean profile plots were used. We started with individual profile plot of ERP with stimuli block to illustrate the between-subject and within-subject patten. Stimuli blocks1 corsponds to Block1A, stimuli block3 corsponds to Block1B, stimuli block13 corsponds to Block5A and stimuli block15 corsponds to Block5B.

Figure 1 shows individual profiles for location C3. The between-subjects variability seems less but, there is considerable within-subjects variability. From the other plots (presented in appendix A), it was observed that the individual profile plots have similar patterns as location C3.

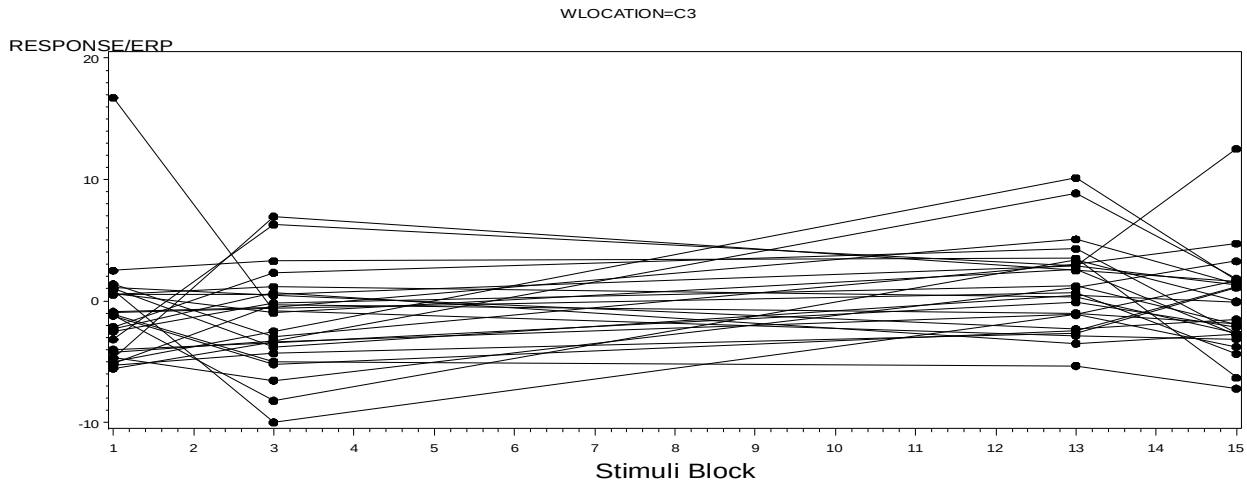

Figure 1:Individual profile plot of ERP for location C3.

In order to see the average evolution of the ERP over stimulus blocks and to have some idea of what the mean structure for each location looks like, a plot of the average evolution over

stimulus blocks was depicted. In addition, to see the average evolution within location and sub-location, different locations and sub-locations were considered. Thus, the average evolution of the mean over stimuli blocks and for each six locations and sub-locations (central vs. frontal and right , left and medial) are presented in Figures 2, 3, 4 and 5 respectively. The average evolution plot indicates that there is positive response in stimuli block13 compared to the other stimulus blocks. The other three stimulus blocks have closer negative average response. Moreover, the negativity response increases somewhat from stimuli block1 in comparison to stimuli blocks3. This is an indication of the presentation of sensitization. In the last block, the positivity response to stimuli block13 changes into a negativity response in the stimuli block15. It is difficult to say this is habituation or sensitization but, ignoring the sign the average response in stimuli block15 is higher than that of average response for stimuli block13, which hints at sensitization. From this, we could say that there is sensitization within blocks but, if we see the plot there seems to be habituation across blocks. Because the negativity in stimuli block3 is larger than the negativity in the stimuli block15, the same thing is observed in stimuli block1 and stimuli block13.The average evolution for each of the six locations is presented in Figure 3. Location Cz seems to have higher negative response in all stimuli blocks than all the other locations. Except for Cz, the response on the other electrode locations have quite similar average response.

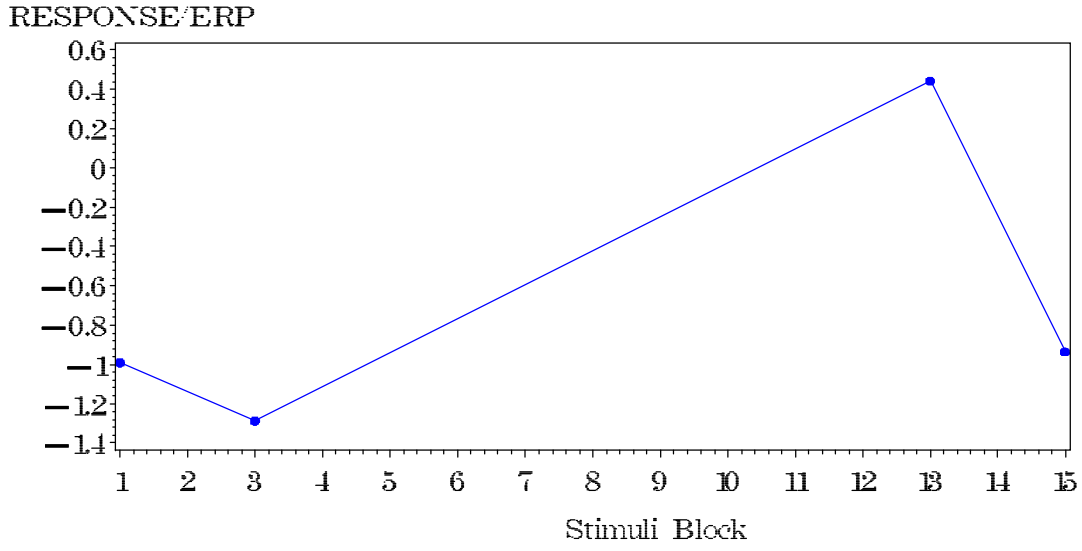

Figure 2: Average evolution plot of ERP.

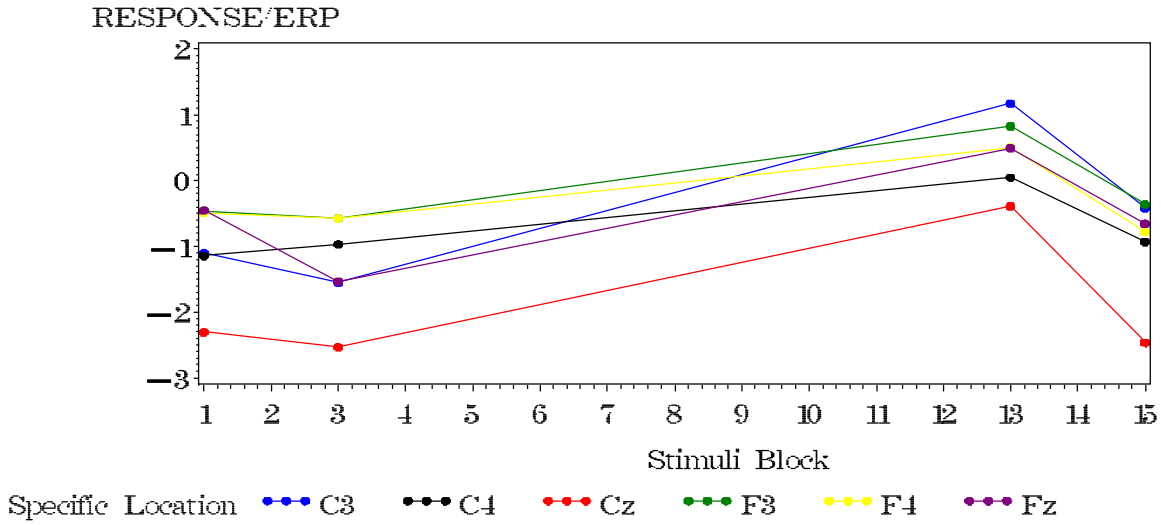

Figure 3: Average evolution plot of ERP by specific location.

The average evolution of the ERP by sub-location are presented in Figure 4. As we could see, the negative brain response appears in all stimulus blocks except for stimuli block13 in both locations (frontal and central). Moreover, the negative response is higher in central than frontal parts of the brain.

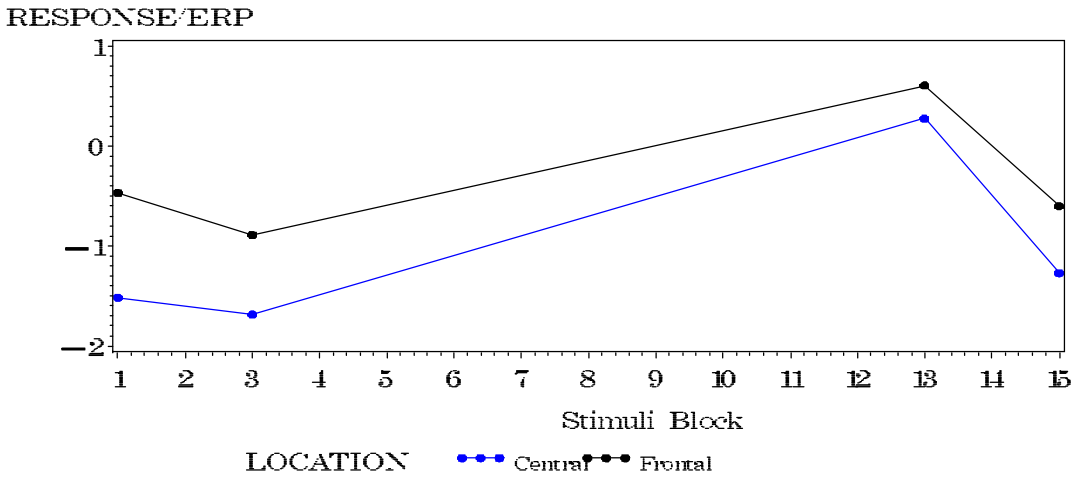

Figure 4:Average evolution of ERP by locations.

Figure 5 shows the average evolution of ERP by sub-locations: left, medial and right. There is high negative response for stimuli in medial part of brain electrode sub-location than the other sub-locations in each stimuli block except for stimuli block13. In stimuli block13 there is high positive brain response in left brain electrode sub-location than the other sub-location: right and centre.

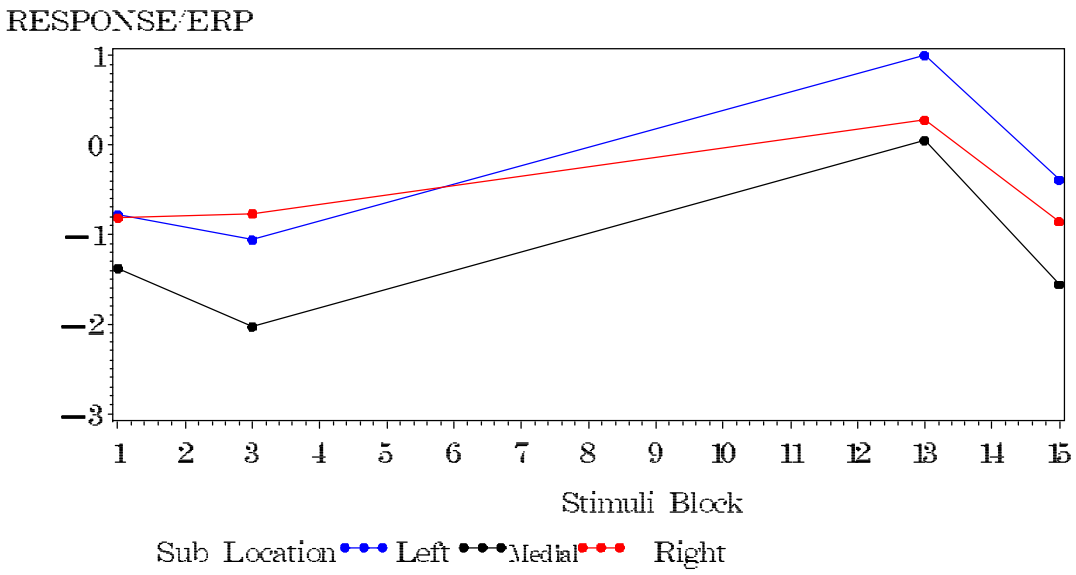

Figure 5: Average evolution of ERP by sub-locations.

4.1.2.Spatio-Temporal Data Analysis

Model Reduction

We begin the formulation of the model by selecting the preliminary structures for the residual covariance and for the mean using a saturated model that contained all covariates and all possible interactions of interest. In general, the saturated model takes the form:

$$
\begin{aligned}
y_{ijkl} = \ & \alpha + \beta_1 stimuli\ block_l + \beta_4 location_j + \beta_5\ sublocation_k + \beta_7 IBQ1 + \beta_8 IBQ2 \\
& + \beta_9 IBQ3 + \beta_{10} mother'sAnxiety + \beta_{11}(location * sublocation)_{jk} \\
& + \beta_{13}(location * stimuli\ block)_{jl} + \beta_{16}(sublocation * stimuli\ block)_{kl} \\
& + \beta_{22}(sublocation * mother'sAnxiety)_k \\
& + \beta_{24}(location * mother'sAnxiety)_j \\
& + \beta_{25}(stimuli\ block * mother'sAnxiety)_l + \beta_{28}(IBQ1 * stimuli\ block)_l \\
& + \beta_{31}(IBQ2 * stimuli\ block)_l + \beta_{34}(IBQ3 * stimuli\ block)_l \\
& + \beta_{37}(IBQ1 * location)_j + \beta_{38}(IBQ2 * location)_j + \beta_{39}(IBQ3 * location)_j \\
& + \beta_{40}(IBQ1 * sublocation)_k + \beta_{42}(IBQ2 * sublocation)_k \\
& + \beta_{44}(IBQ3 * subocation)_k + \beta_{46}(IBQ1 * stimuliblock * location)_{jl} \\
& + \beta_{49}(IBQ2 * stimuliblock * location)_{jl} \\
& + \beta_{53}(IBQ3 * stimuliblock * location)_{jl} \\
& + \beta_{56}(IBQ1 * stimuliblock * sublocation)_{kl} \\
& + \beta_{62}(IBQ2 * stimuliblock * sublocation)_{kl} \\
& + \beta_{68}(IBQ3 * stimuliblock * sublocation)_{kl} \\
& + \beta_{74}(stimuliblock * location * mother'sAnxiety)_{jl} \\
& + \beta_{77}(stimuliblock * sublocation * mother'sAnxiety)_{kl} \\
& + \beta_{83}(mother'sAnxiety * location * sublocation)_{jk} \\
& + \beta_{85}(stimuliblock * location * sublocation)_{jkl} \\
& + \varepsilon_{ijkl} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \qquad I
\end{aligned}
$$

Where, y_{ijkl} is ERP measurement at stimuli block l $(l = 1,3,13,15)$ for infant i $(i = 1,2,\ldots..26)$ at j[th] brain location $(j = 1,2)$, within sub-location $k(k = 1,2,3)$.

Taking model I as our saturated model, we tried to obtain the most plausible residual covariance structure and the most parsimonious mean structure using a likelihood ratio test. In modeling these data as explained in section2 of the report, we need to take into account two types of covariance patterns among measurements from the same subject: there are dependences among measurements in the same location over different stimuli blocks, and among measurements from different locations. The approach considered fit a model with a direct product covariance structure to specify the within subject variance-covariance matrix from six locations, thus to examine the between and within location correlation.

The approach assumes unstructured (UN) covariance structure for between location measurements, but for within location (over different stimulus blocks) measurements we can compare AR(1), UN and CS. We compared the direct product covariance of unstructured with unstructured and unstructured with compound symmetry (CS). The CS assumes the same

covariance between pairs of measurements within location. The model with UN ⊗UN covariance structure did not converge. The model with UN ⊗ CS structure was used to fit the data and CS was used to account within location covariance for the remainder of the analysis.

Modeling The Mean Structure

In order to find the most parsimonious model, a backward selection procedure was used to drop covariates that were not statistically significant. Higher order interaction effects were evaluated followed by the main effects evaluation and the insignificant results were removed. So as to reduce the mean structure under the maximum likelihood estimate method, we then used likelihood ratio statistics (LRT) to test whether the dropped covariates as a whole were significant in the model or not by comparing the saturated model with final reduced model as shown in Table 2. Covariate IBQ1, IBQ3, the three way interaction among stimuli blocks, IBQ and location, stimuli blocks, IBQ, and sub-location, stimuli blocks, location and sub-location, mother's anxiety, location and sub-location and mother's anxiety, stimuli blocks and sub-location, were found to be insignificant. The two way interactions between IBQ and location, IBQ and sub-location, stimuli blocks and sub-location, IBQ1 and stimuli blocks and finally IBQ3 and stimuli blocks were also insignificant. Here, we tested the null hypothesis that β=0 where β is vector of all parameters for the covariates under investigation.

Table 2:Likelihood ratio tests for mean structure.

ML Log Likelihood Statistics						
Saturated Model		Reduced Model		Statistics	Df	P-Value
-LogL	#Pars	-LogL	#Pars			
2055.5	89	2131.7	18	76.2	71	0.6850

From Table 2 we can see that the reduced model fits the data well and hence the final model for the response variable ERP is:

$$y_{ijkl} = \alpha + \beta_1 stimuliblock_l + \beta_4 location_j + \beta_5\, sublocation_k + \beta_7 IBQ2 + \beta_8 mother'sAnxiety + \beta_9 (IBQ2 * stimuliblock)_l + \beta_{12} (location * sublocation)_{jk} + \beta_{14} (sublocation * mother'sAnxiety)_k + \beta_{16} (stimuliblock * mother'sAnxiety)_l \quad \ldots\ldots II$$

Results parameter estimates and standard errors, obtained from fitting the final model *II* are presented in Table 3. There is a significant interaction effect of location with sub location. The interaction effect of baseline covariate mother's anxiety during pregnancy with stimulus blocks was also found to be significant. The interaction effect of mother's anxiety during pregnancy in stimuli block1 have significant effect as compare to stimuli block15 in ERP (*p-value*=0.0014). The interaction effect of IBQ2 with stimulus blocks was also found to be significant.

Table 3: Parameter estimates (standard errors) obtained from fitting model *II*.

Effect	Estimate (S.Error)	P-Value
intercept	6.5951 (3.3167)	0.0501
stimuliblock1	-16.6429 (4.5772)	0.0005
stimuliblock3	-10.2049 (4.5772)	0.0288
stimuliblock13	3.6004 (4.5772)	0.4340
location(central)	-0.2784 (0.3300)	0.4027
left	-1.7193 (0.5960)	0.0059
medial	-0.1539 (0.6247)	0.8064
IBQ2(negative affect)	-0.5350 (0.6724)	0.4286
motanxiety	-0.1529 (0.0559)	0.0076
IBQ2*stimuliblock1	1.8436 (0.9345)	0.0522
IBQ2*stimuliblock3	1.3304 (0.9345)	0.1587
IBQ2*stimuliblock13	-0.5547 (0.9345)	0.5546
location*left	0.1076 (0.3553)	0.7633
location*medial	-1.0981 (0.3365)	0.0019
motanxiety*left	0.0564 (0.0165)	0.0014
motanxiety*centre	0.0029 (0.0173)	0.8634
motanxiety*stimuliblock1	0.2542 (0.0766)	0.0014
motanxiety*stimuliblock3	0.1253 (0.0766)	0.1062
motanxiety*stimuliblock13	0.0126 (0.0766)	0.8689

Since the interaction effect of mother's anxiety with stimulus blocks and sub-location was found to be significant with p-value = 0.0042 and 0.0025 respectively, the marginal interpretation of the mother's anxiety would depend on the interaction term. The interaction effect of baseline covariate IBQ2 by stimulus blocks was also found to be significant with p-value 0.0419. This indicates that the marginal effect of stimulus blocks depends on mother's anxiety and IBQ2.

As can be seen from Table 3 the effect of mother's anxiety was highly significant in stimuli block1 as compared to stimuli block15. Based on the contrast and estimate table (appendix C), there is high response in stimuli block1 as compare to other stimulus blocks, except stimuli block3. The contrast between stimuli block1 and stimuli block3 was insignificant. From this we could say there is overall decreasing brain response/ERP.

The same result was obtained for the interaction effect of IBQ2 and stimulus blocks, there is significant effect of IBQ2 in stimuli block1 as compare to stimuli block15. The covariance matrices for the within and between location are presented in appendix E (a).

The predicted estimates do approximate the observed values fairly well as shown in Figure 6, indicating that the model described the data very well.

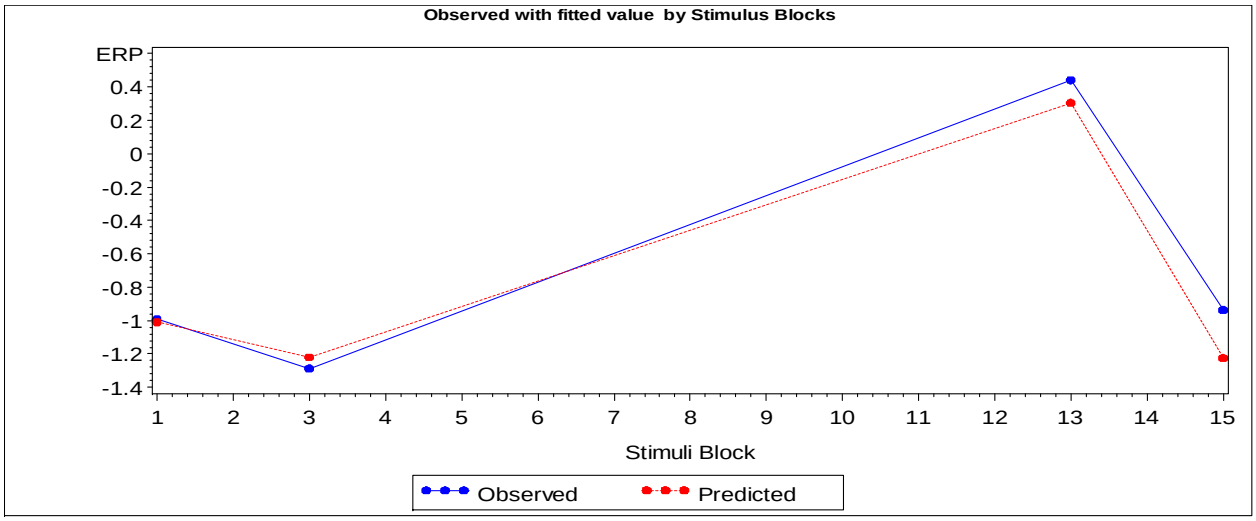

Figure 6:Predicted mean profile (broken line) and observed mean (continuous line).

4.2. 50 Artifact Free Response

similar to section 4.1 this subsection we present the analysis for ERP data from 50 artifact free brain responses. Results from exploratory analysis and statistical modeling are presented.

4.2.1.Exploratory Data Analysis

As we did in the previous subsection we started exploring the individual profile and mean structures using plots.

Figure 7 shows the individual profiles for location C3. The between-subjects variability seem less but, there is considerable within-subjects variability. From the other plots (presented in appendix B), it was observed that the individual profile plot have similar patterns as location C3.

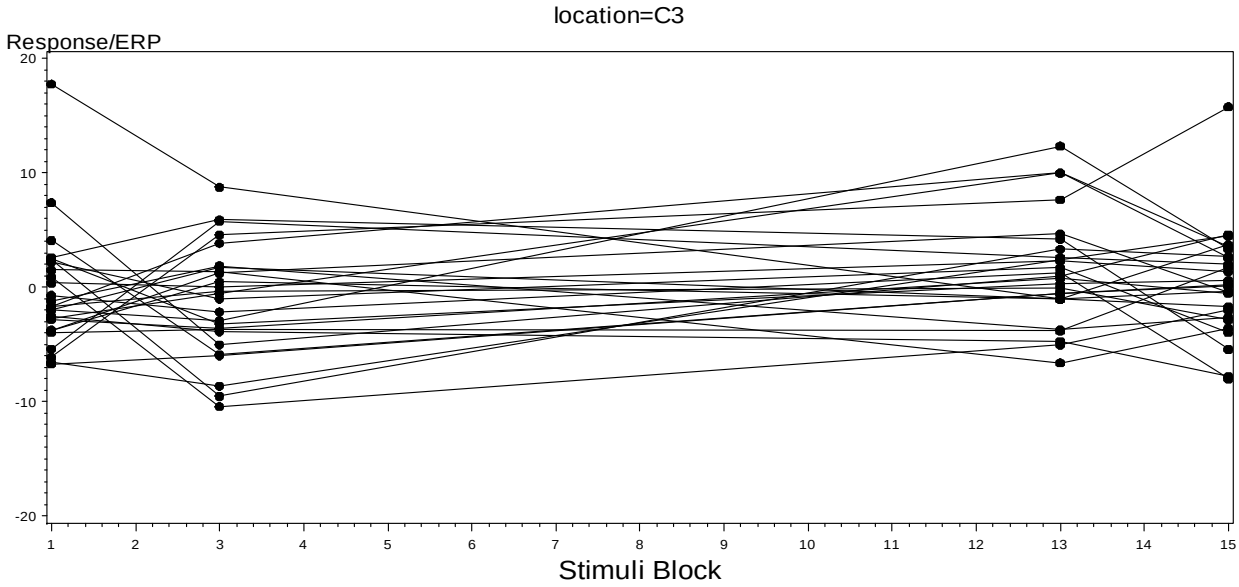

Figure 7:Individual profile plot of ERP for location C3.

In order to see the average evolution of ERP over stimuli blocks and to have some ideas how the mean structure for each location looks like, a plot of the average evolution over stimulus blocks was depicted. In addition to see the average evolution within location and sub-location, different locations and sub-locations were considered. Thus, the average evolution of the mean over stimulus blocks and for each of the six locations and sub-locations (central Vs. frontal and right , left and medial) are presented in Figures 8, 9, 10 and 11 respectively. The average evolution plot in Figure 8 indicates that there is negative response in all stimulus blocks except for stimuli block13. Moreover, the negativity response increases somewhat from stimuli block1 in comparison to stimuli blocks3. This indicate the presentation of sensitization. the same thing is observed as we observed in section one analysis, that the positive response to stimuli block13 changed into a negative response in the stimuli block15, so it is difficult to say this is habituation or sensitization but, ignoring the sign the average response in stimuli block15 is seem to have closer average response in stimuli block13 so, it is difficult to say this is habituation or sensitization. from this we could say that, there is sensitization within block one. Moreover, we

could say habitation observed across blocks because, the negative response in stimuli block3 is larger than the negative response in the stimuli block15.

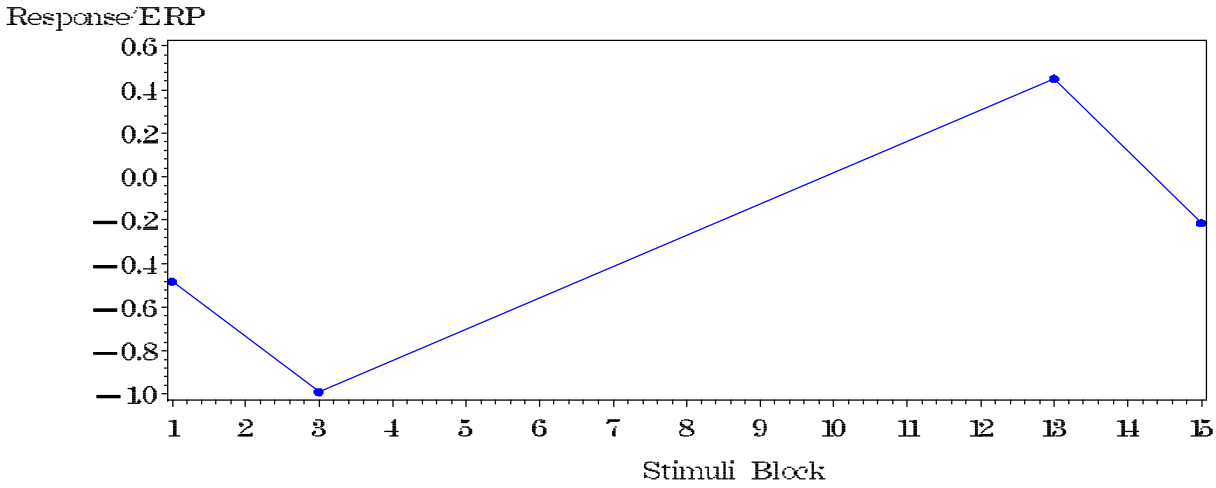

Figure 8: Average evolution plot of ERP.

Figure 9 shows the plot of average evolution for each location. Location Cz seem to have higher negative response in all stimulus blocks. Except for the Cz, the response on the other electrode location have quite similar average response.

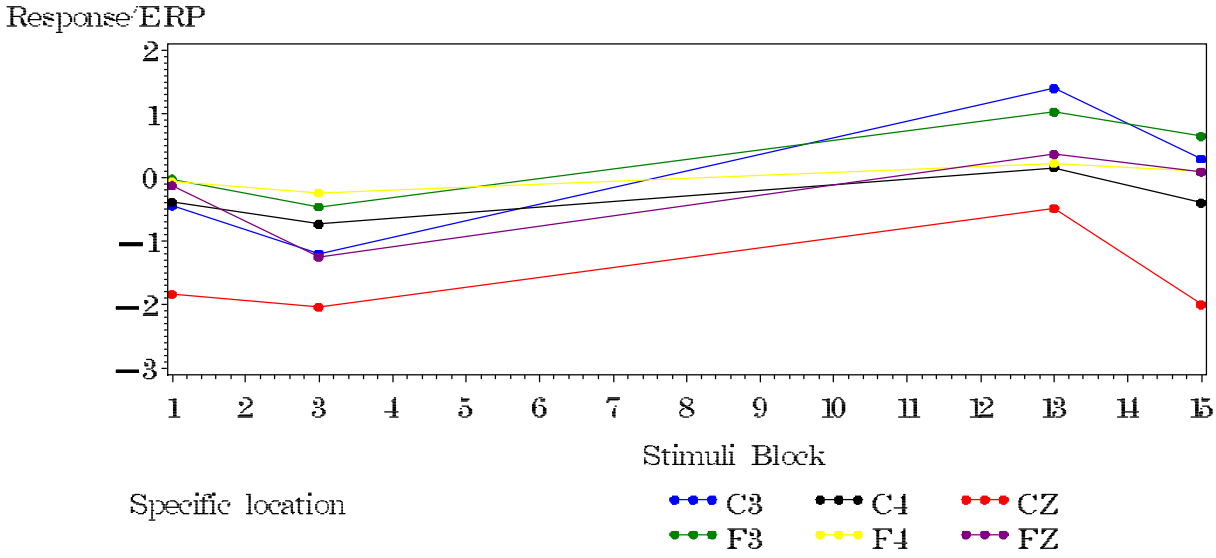

Figure 9: Average evolution plot of ERP by location.

In Figure 10, the average evolution of ERP by sub-location are presented. As we could see the higher negative brain response occurred in stimuli block3 for both location but, it is higher in central electrode brain location than the frontal.

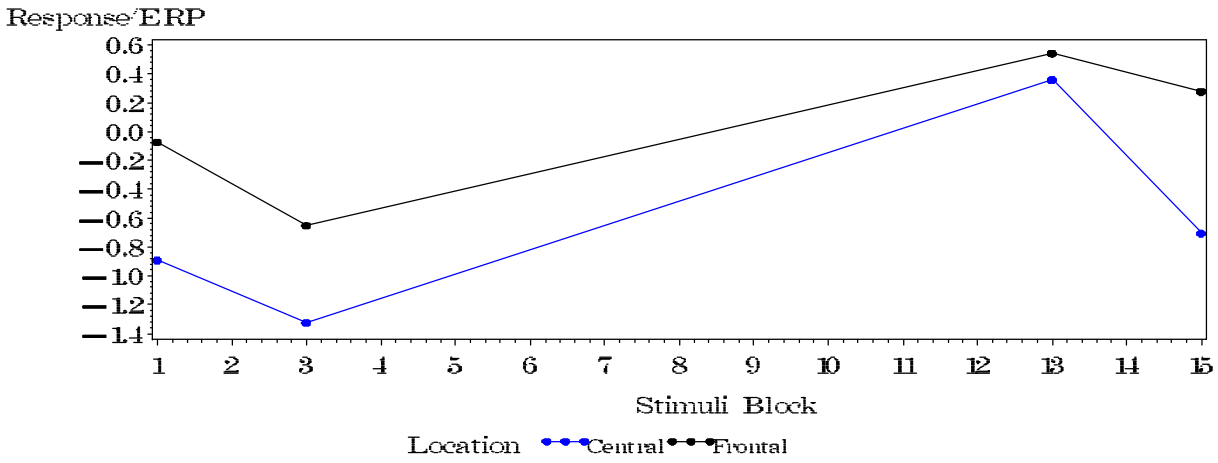

Figure 10: Average evolution plot of ERP by location.

Figure 11 shows the average evolution of ERP by sub-location: left, medial and right. There is high negative response for stimuli in medial part of brain electrode sub-location than the other sub-location in each stimulus blocks except for stimuli block13. In stimuli block13, there is high positive brain response in the left brain electrode sub-location than the other sub-locations: right and centre.

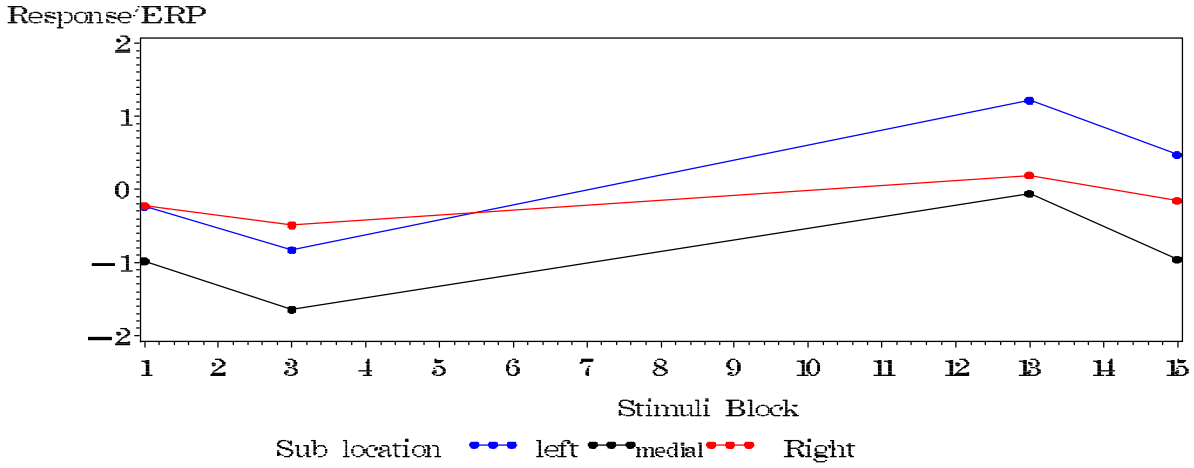

Figure 11: Average evolution of ERP by sub-location.

4.2.2. Spatio-Temporal Data Analysis

We adopted the same steps as section 4.1.2 one and ended up with the same final model.

Model Reduction

We begin the formulation of the model by selecting the preliminary structures for the residual covariance and for the mean using a saturated model that contained all covariates and all possible interaction of interests as we did in section 4.1.2. The saturated model takes the form:

$$
\begin{aligned}
y_{ijkl} &\\
= \ & \alpha + \beta_1 stimuli\ block_l + \beta_4 location_j + \beta_5\ sublocation_k + \beta_7 IBQ1 + \beta_8 IBQ2 + \beta_9 IBQ3 \\
& + \beta_{10} mother'sAnxiety + \beta_{11}(location * sublocation)_{jk} \\
& + \beta_{13}(\ location * stimuli\ block)_{jl} + \beta_{16}(sublocation * stimuli\ block)_{kl} \\
& + \beta_{22}(sublocation * mother'sAnxiety)_k + \beta_{24}(location * mother'sAnxiety)_j \\
& + \beta_{25}(stimuli\ block * mother'sAnxiety)_l + \beta_{28}(IBQ1 * stimuli\ block)_l \\
& + \beta_{31}(IBQ2 * stimuli\ block)_l + \beta_{34}(IBQ3 * stimuli\ block)_l + \beta_{37}(IBQ1 * location)_j \\
& + \beta_{38}(IBQ2 * location)_j + \beta_{39}(IBQ3 * location)_j + \beta_{40}(IBQ1 * sublocation)_k \\
& + \beta_{42}(IBQ2 * sublocation)_k + \beta_{44}(IBQ3 * subocation)_k \\
& + \beta_{46}(IBQ1 * stimuliblock * location)_{jl} + \beta_{49}(IBQ2 * stimuliblock * location)_{jl} \\
& + \beta_{53}(IBQ3 * stimuliblock * location)_{jl} + \beta_{56}(IBQ1 * stimuliblock * sublocation)_{kl} \\
& + \beta_{62}(IBQ2 * stimuliblock * sublocation)_{kl} + \beta_{68}(IBQ3 * stimuliblock * sublocation)_{kl} \\
& + \beta_{74}(stimuliblock * location * mother'sAnxiety)_{jl} \\
& + \beta_{77}(stimuliblock * sublocation * mother'sAnxiety)_{kl} \\
& + \beta_{83}(mother'sAnxiety * location * sublocation)_{jk} \\
& + \beta_{85}(stimuliblock * location * sublocation)_{jkl} \\
& + \varepsilon_{ijkl} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \qquad\qquad III
\end{aligned}
$$

Where, y_{ijkl} is ERP measurement at stimuli block l $(l = 1,3,13,15)$ for infant i $(i = 1,2,\ldots..26)$ at j[th] brain location $(j = 1,2)$, within location $k(k = 1,2,3)$.

Taking model III as our saturated model, we tried to obtain the most plausible residual covariance structure and the most parsimonious model using a likelihood ratio test. In modeling these data, as we did in section 4.1.2, we need to take into account two types of covariance patterns among measurements from the same subject: there are dependences among measurements in the same location over different stimulus blocks, and among measurements from different locations. The approach considered to fit a model with a direct product covariance

structure to specify the within subject variance-covariance matrix from six locations, thus to examine the between and within location correlation.

The approach assumes an unstructured (UN) covariance structure for between location measurement, but for within location (over different stimuli block) measurement we can compare AR(1), UN and CS. We compared the direct product covariance of unstructured with unstructured and unstructured with compound symmetry (CS). The CS assumes the same covariance between pairs of measurements within location. The model with UN ⊗UN covariance structure did not converge. The model with UN ⊗ CS used to fit the data and we use CS to account within location covariance for the remainder of the analysis.

Modeling The Mean Structure

In order to find the most parsimonious model, a backward selection procedure was used to drop covariates that were not statistically insignificant. Higher order interaction effects were evaluated followed by the main effects evaluation and the insignificant were removed. So as to reduce the mean structure under the maximum likelihood estimate method, we then used likelihood ratio statistics(LRT) to test whether the dropped covariates as a whole were significant in the model or not by comparing the saturated model with final model as shown in Table 4 . Covariate IBQ1, IBQ2, the three way interaction among stimuli block, IBQ and location, stimuli block, IBQ and location, stimuli block, location and sub-location, mother's anxiety, location and sub-location and mother's anxiety, stimuli block and sub-location, and also, the two way interaction between IBQ and location, IBQ and sub-location, stimuli block and sub-location, IBQ1 and stimuli block and finally, IBQ3 and stimuli block were found insignificant. Here, we tested null hypothesis that $\beta=0$ where β is vector of all parameter for the covariates under test.

Table 4: Likelihood ratio tests for mean structure.

ML Log Likelihood Statistics						
Saturated Model		Reduced Model		Statistics	D.f	P-Value
-LogL	#Pars	-LogL	#Pars			
2184.1	89	2304.6	18	120.5	71	0.9997

This shows the reduced model fits well and the final model for the response variable ERP was then:

$$y_{ijkl} = \alpha + \beta_1 stimuliblock_l + \beta_4 location_j + \beta_5\, sublocation_k + \beta_7 IBQ2 + \beta_8 mother'sAnxiety + \beta_9 (IBQ2 * stimuliblock)_l + \beta_{12}(location * sublocation)_{jk} + \beta_{14}(sublocation * mother'sAnxiety)_k + \beta_{16}(stimuliblock * mother'sAnxiety)_l \quad \ldots\ldots IIII$$

Results obtained from fitting final model *IIII* are presented in Table 5. There is a significant interaction effect of location with sub-location. The p-value for interaction effect of baseline covariate mother's anxiety during pregnancy with stimuli block is in borderline. The interaction effect of IBQ2 with stimuli block was found to be significant.

Table 5:Parameter estimates (standard errors) obtained from fitting model *IIII*.

Effect	Estimate (S.Error)	P-Value
intercept	8.8614 (4.2265)	0.0397
stimuliblock1	-19.1339 (5.9446)	0.0020
stimuliblock3	-9.2188 (5.9446)	0.1259
stimuliblock13	-3.3611 (5.9446)	0.5738
location(central)	-0.2674 (0.3680)	0.4712
left	-2.0939 (0.7309)	0.0063
medial	-1.1902 (0.7109)	0.1009
IBQ2 (negative affect)	-1.5650 (0.8609)	0.0735
moanxiety	-0.0729 (0.0706)	0.3056
IBQ2*stimuliblock1	3.1062 (1.2137)	0.0129
IBQ2*stimuliblock3	2.0191 (1.2137)	0.1011
IBQ2*stimuliblock13	1.2744 (1.2137)	0.2977
location*left	0.1710 (0.3970)	0.6687
location*medial	-1.0385 (0.3955)	0.0115
moanxiety*left	0.0680 (0.0204)	0.0017
moanxiet*medial	0.0298 (0.0196)	0.1372
moanxiet*stimulibloc1	0.1779 (0.0995)	0.0786
moanxiet*stimuliblock3	0.0209 (0.0995)	0.8345
moanxiet*stimuliblock13	-0.0450 (0.0995)	0.6523

The parameter estimates and standard errors from the final model are shown in Table 5. Since the interaction effect of mother's anxiety with stimuli blocks and sub-location was found to be significant. The marginal interpretation of the mother's anxiety would depend on the interaction

term. The interaction effect of baseline covariate IBQ2 by stimuli blocks also found to be significant with p-value 0.0524. This indicates that marginal effect of stimulus blocks depends on mother's anxiety and IBQ2.

As can be seen in Table 5 the effect of mother's anxiety was difficult to say significant in stimuli block1 as compare to stimuli block15 with borderline p-value=0.0786. The interaction effect of IBQ2 and stimulus blocks was significant, there is significant effect of IBQ2 in stimuli block1 as compare to stimuli block15. Based on the estimate table (Appendix D), there is high response in stimuli block1 as compare to other stimuli block15, the comparisons between stimuli block1 and 3 and 1 and 13 were insignificant. This may indicate that it is difficult to make decisions (comparisons) based on small average responses. But, since the difference between response stimuli in block1 and 15 were significant this may be an indication of decrease in brain response/ERP. The covariance matrices for the within and between location are presented in appendix E (b).

The predicted estimates does not approximate the observed values fairly well as shown in Figure 12, this is may be the insignificant interaction effect of mother's anxiety with stimulus blocks not removed from the model.

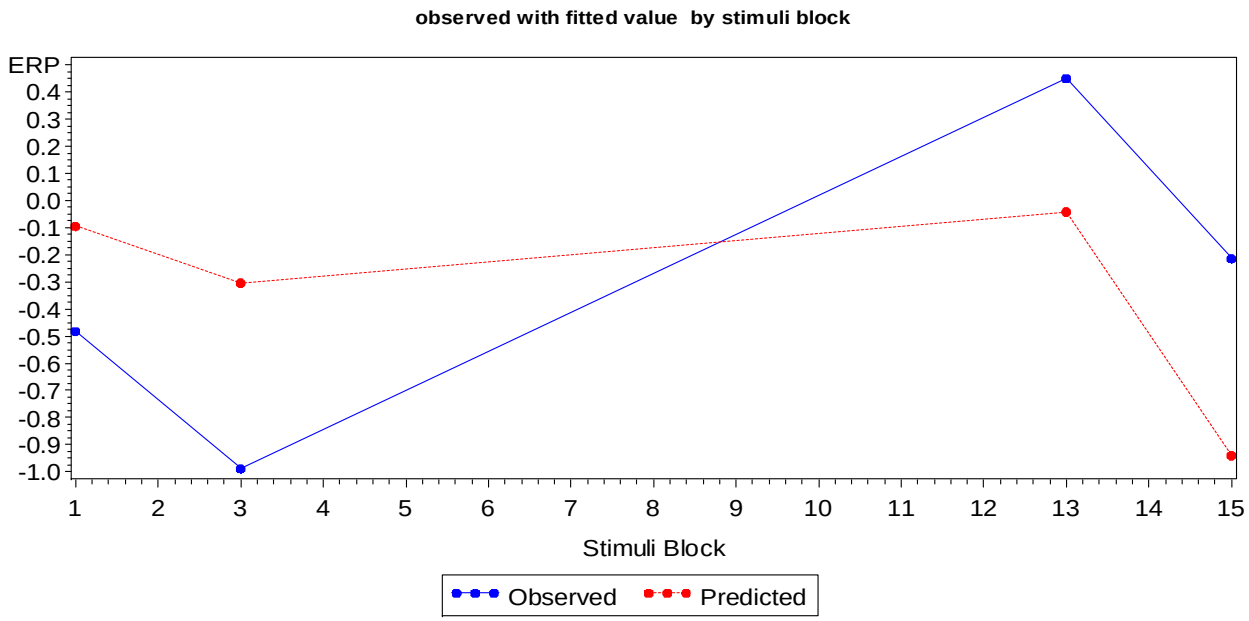

Figure 12::Predicted mean profile (broken line) and observed mean (continuous line)

5.Discussions And Conclusions

For many years and still now stress during pregnancy and its implication on born infants was dealt within different disciplines in health. To examine the impact stress in this study data set from Tilburg University was used, particularly from the project of Prenatal Early Life Stress in Tilburg (PELS). For the study, analysis of ERP obtained from 75 articat free response for 100 stimuli presented in each stimulus blocks were discussed in the first part of the result and analysis of ERP from 50 artifact free brain response for 100 stimuli presented in stimulus block. In both sections the same steps were followed to select the most parsimonious covariance and mean structure and ended up the same final model.

From the exploratory analyses we observed that there seemed to occur less between-infant variability and considerable within-infant variability. The average evolution of ERP by stimulus blocks showed that the brain response was more negative after stimuli block1 to stimuli block3; this indicates that the presentation of sensitization and then, decreased at stimuli block13; this indicate habituation and finally, increased again at stimuli block15 this also indicate sensitization. From the plots of the average evolution of ERP over stimulus blocks by location we observed that there is more negative brain response over central than frontal brain areas. In order to capture the evolution depicted by the exploratory analysis, linear mixed model with direct product covariance structure (that accounts for the correlation from two repeated factors within subject) was proposed and implemented in to the data set. A likelihood ratio test was used to find the most parsimonious covariance and mean structure. The results showed that there is a significant interaction effect of mother's anxiety during trimester1, IBQ2 with stimuli blocks on ERP. So, this indicates that IBQ2 and mother's anxiety contribute to habituation and/or sensitization.

From the result of exploratory and statistical analysis we concluded that within each block there is increasing response which indicates the presentation of sensitization, but across the block there is decreasing of response which indicate the presentation of habituation across block. Based on the estimate table (appendix C and D), there is significant difference between response in stimuli block1 as compare to other stimulus blocks15, this may indicate overall decreasing of response. Since, the effect of the stimuli blocks depends on exposure to prenatal maternal anxiety and temperament of the infant, we concluded that they contribute to habituation/sensitization.). As conclusion IBQ2 and Mother's anxiety have negative impact on infants cognitive development.

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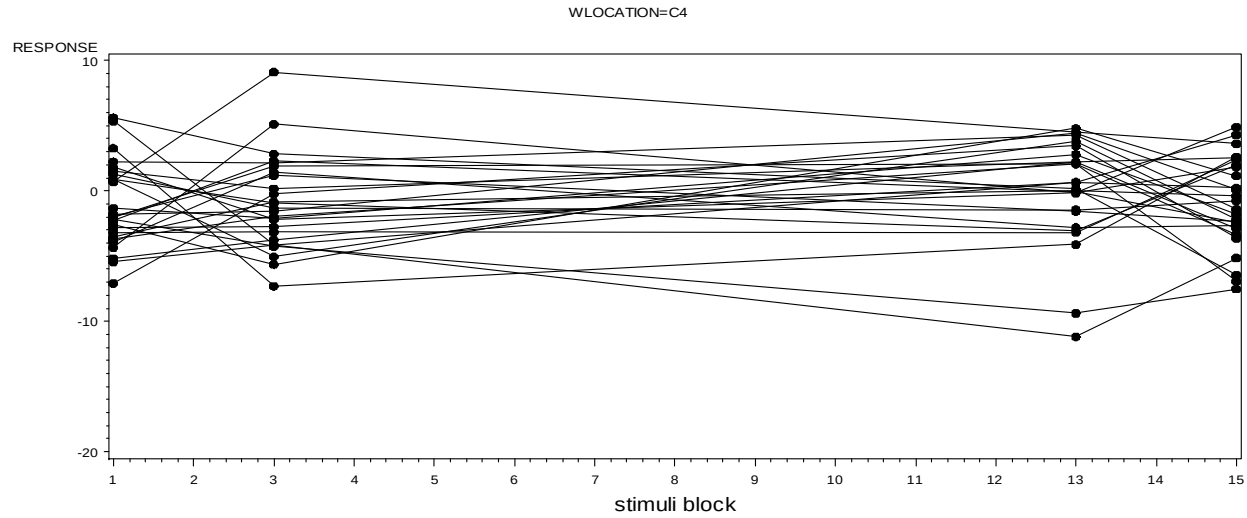
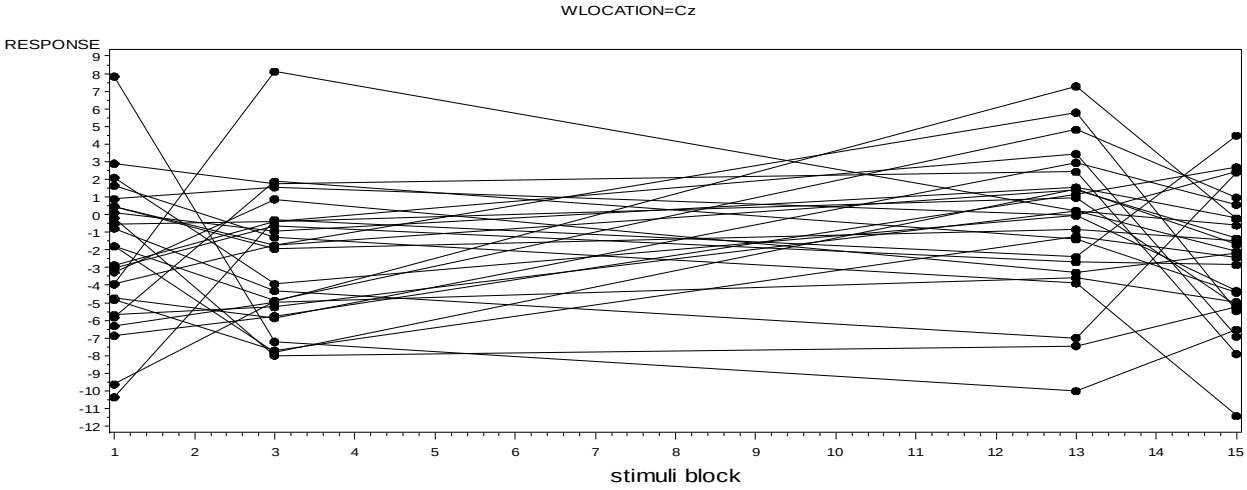
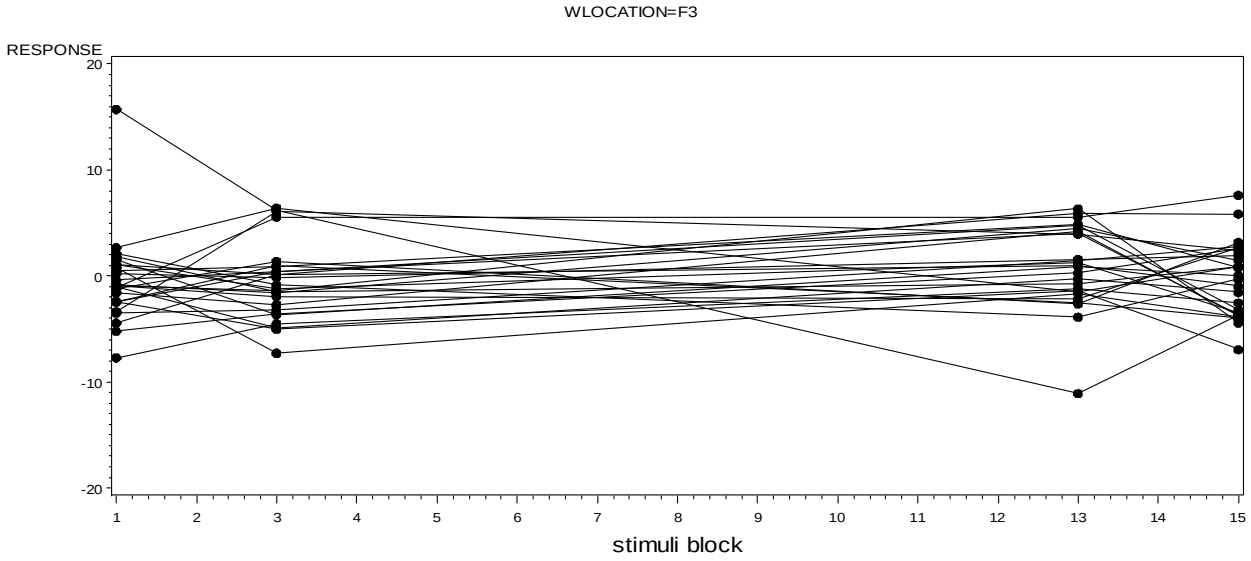
Appendix

A, Individual profile plot of ERP for 75 artifact free response.



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RESPONSE
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10
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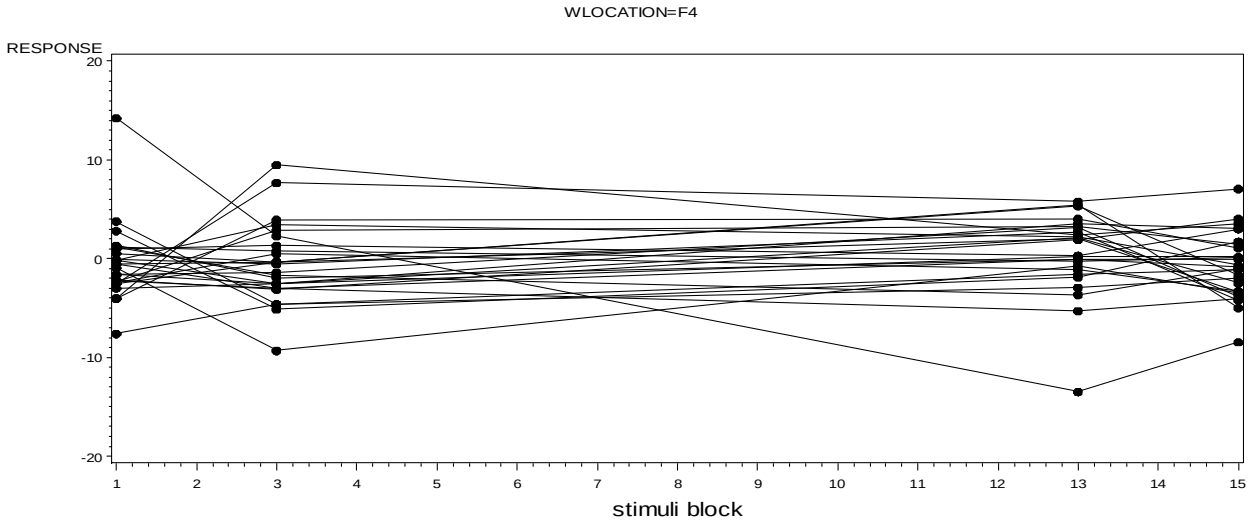
3
4
5
6
7
8
9
10
11
12
13
14
15
stimuli block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0
-10
-20
1
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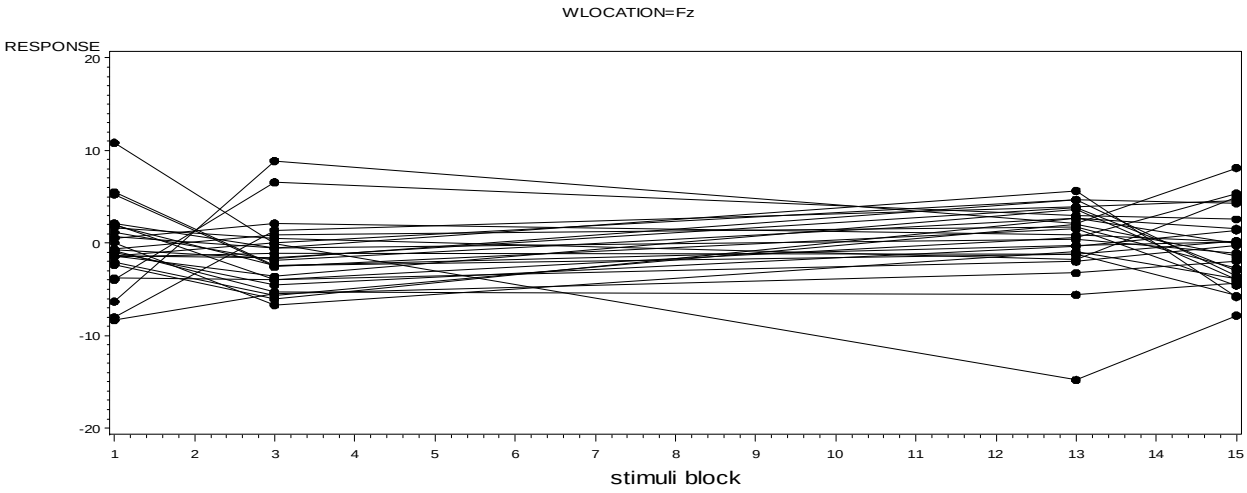
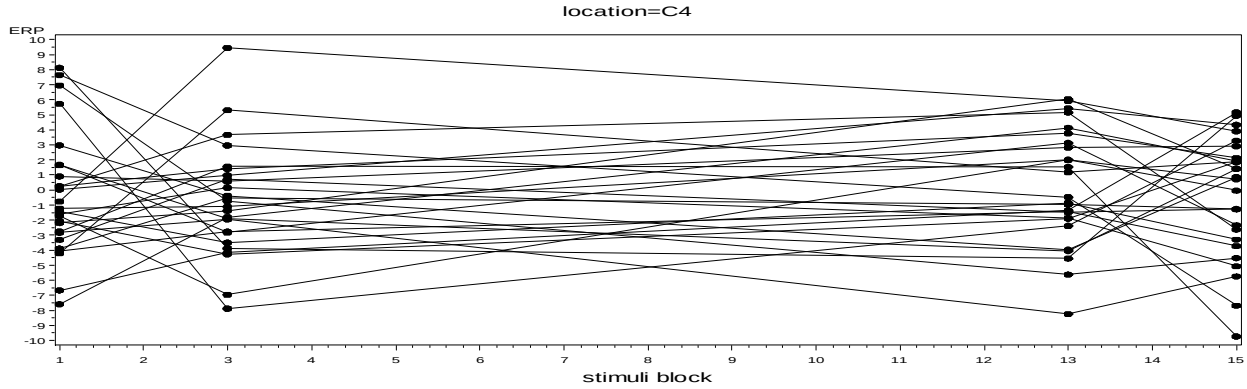
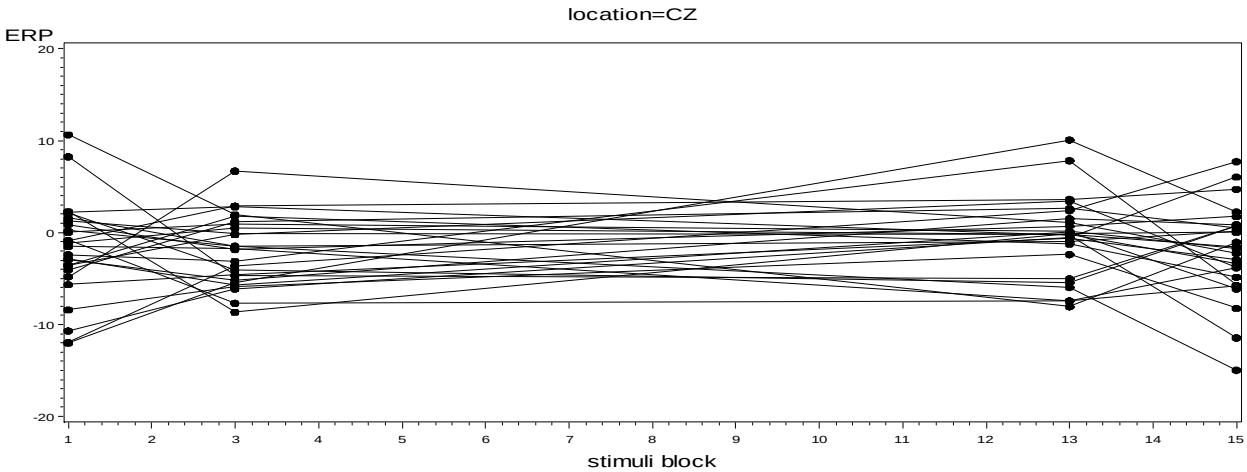
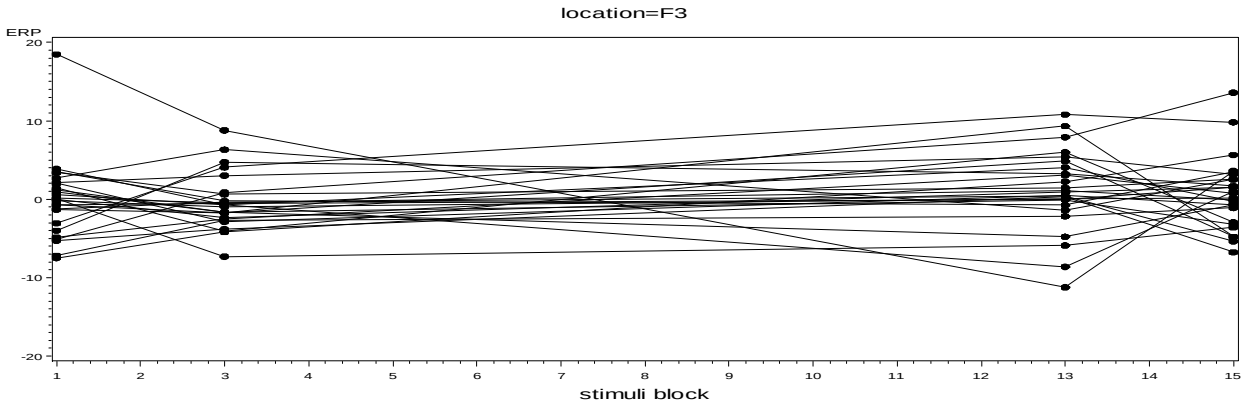
3
4
5
6
7
8
9
10
11
12
13
14
15
stimuli block



B, Individual profile plot of ERP for 50 artifact free response.



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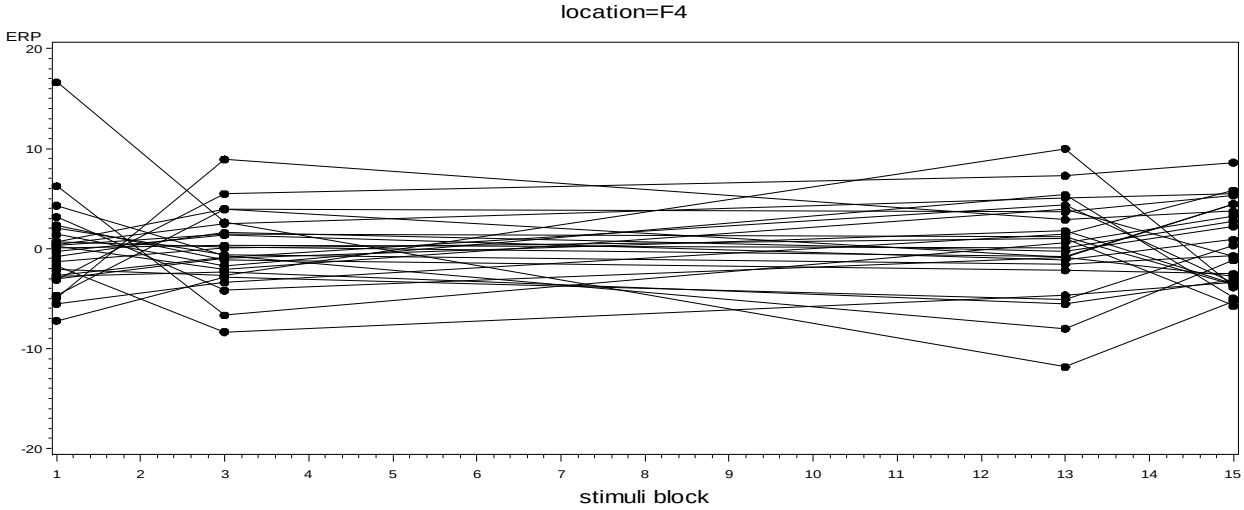
ERP
20
10
0
-10
-20
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
stimuli block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ERP
20
10
0
-10
-20
1
2
3
4
5
6
7
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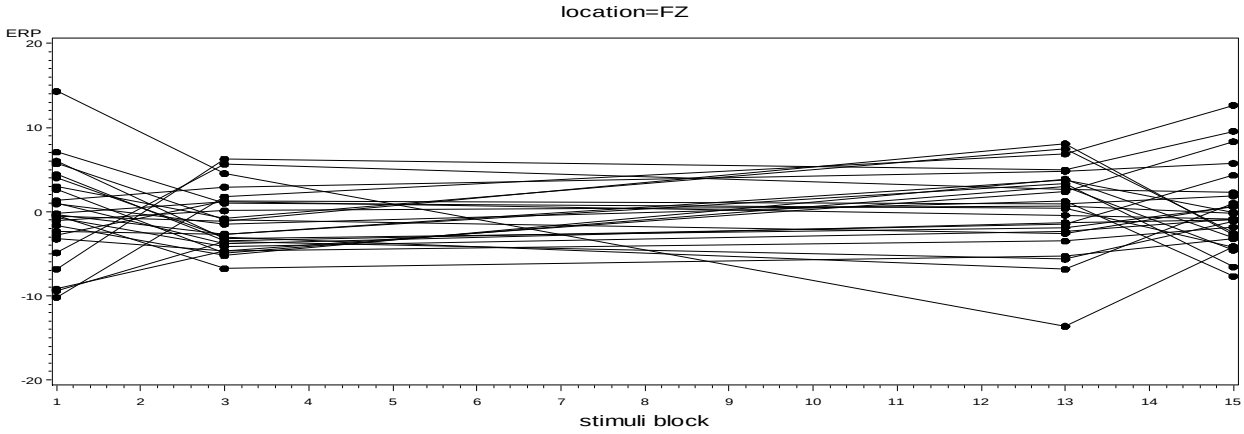
9
10
11
12
13
14
15
stimuli block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ERP
20
10
0
-10
-20
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
stimuli block

C, Parameter estimate of estimate statement (parameter estimate for the difference of response in each stimuli).

parameter	Estimate	p-value	95% confidence interval	
stimuliblock1-stimuli block3	0.3210	0.4887	-0.5980	1.2401
stimuliblock1-stimuli block13	1.3199	0.0055	0.4008	2.2389
stimuliblock1-stimuli block15	1.0489	0.0259	0.1298	1.9679

D, Parameter estimate of estimate statement (parameter estimate for the difference of response in each stimuli).

Parameter	Estimate	P-Value	95% confidence interval	
stimuliblock1-stimuli block3	0.6188	0.2706	-0.4919	1.7296
stimuliblock1-stimuli block13	1.0217	0.0709	-0.0890	2.1325
stimuliblock1-stimuli block15	1.6483	0.0042	0.5376	2.7591

E, Direct product covariance structure

For simplicity, let assume we have two spaces and the unstructured (UN) space covariance is can be written as $V = \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{21} & \sigma_2^2 \end{pmatrix}$, where, σ_1^2 is variance of measurement error at first space and space two measurement error variance is σ_2^2 . let assume we have three time points and the within space correlation structure can be handled by compound symmetry and can be written as $\Sigma = \begin{pmatrix} 1 & \rho & \rho \\ \rho & 1 & \rho \\ \rho & \rho & 1 \end{pmatrix}$ with parameter ρ . From these two set of matrices, we can construct the within subject matrix, a direct product covariance structure (Galecki 1994).

$$V \otimes \Sigma = \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{21} & \sigma_2^2 \end{pmatrix} \otimes \begin{pmatrix} 1 & \rho & \rho \\ \rho & 1 & \rho \\ \rho & \rho & 1 \end{pmatrix}$$

$$= \begin{pmatrix} \sigma_1^2 & \sigma_1^2\rho & \sigma_1^2\rho & \sigma_{12} & \sigma_{12}\rho & \sigma_{12}\rho \\ \sigma_1^2\rho & \sigma_1^2 & \sigma_1^2\rho & \sigma_{12}\rho & \sigma_{12} & \sigma_{12}\rho \\ \sigma_1^2\rho & \sigma_1^2\rho & \sigma_1^2 & \sigma_{12}\rho & \sigma_{12}\rho & \sigma_{12} \\ \sigma_{21} & \sigma_{21}\rho & \sigma_{21}\rho & \sigma_2^2 & \sigma_2^2\rho & \sigma_2^2\rho \\ \sigma_{21}\rho & \sigma_{21} & \sigma_{21}\rho & \sigma_2^2\rho & \sigma_2^2 & \sigma_2^2\rho \\ \sigma_{21}\rho & \sigma_{21}\rho & \sigma_{21} & \sigma_2^2\rho & \sigma_2^2\rho & \sigma_2^2 \end{pmatrix}$$

The covariance structure for the first and second subsection analysis are given below in

a) The unstructured (UN) location covariance (V) and Compound symmetry (CS) within location correlation structure for analysis of 75 average response of ERP.

$$\begin{pmatrix} 13.3370 & 8.4850 & 8.1865 & 8.6714 & 9.1992 & 8.9569 \\ 8.4850 & 12.6513 & 8.1834 & 5.3554 & 8.1963 & 6.3283 \\ 8.1865 & 8.1834 & 11.2081 & 6.2541 & 8.0973 & 7.6866 \\ 8.6714 & 5.3554 & 6.2541 & 11.6319 & 10.4380 & 10.2101 \\ 9.1992 & 8.1963 & 8.0973 & 10.4380 & 13.1764 & 10.8043 \\ 8.9569 & 6.3283 & 7.6866 & 10.2101 & 10.8043 & 12.0676 \end{pmatrix}$$

, is UN covariance matrix for six locations.

$\Sigma = \begin{pmatrix} 1 & 0.0342 & 0.0342 & 0.0342 \\ 0.0342 & 1 & 0.0342 & 0.0342 \\ 0.0342 & 0.0342 & 1 & 0.0342 \\ 0.0342 & 0.0342 & 0.0342 & 1 \end{pmatrix}$, is CS within location covariance matrix.

b) The unstructured (UN) location covariance (V) and Compound symmetry (CS) within location correlation structure for the analysis of 50 average response of ERP.

$$V = \begin{pmatrix} 25.0952 & 16.7264 & 14.0748 & 17.9679 & 16.7223 & 15.6089 \\ 16.7264 & 20.5640 & 12.5005 & 12.2195 & 14.7948 & 10.8821 \\ 14.0748 & 12.5005 & 16.2646 & 11.8338 & 13.8439 & 12.3272 \\ 17.9679 & 12.2195 & 11.8338 & 20.5803 & 17.8490 & 17.3669 \\ 16.7223 & 14.7948 & 13.8439 & 17.8490 & 20.8957 & 17.3358 \\ 15.6089 & 10.8821 & 12.3272 & 17.3669 & 17.3358 & 19.0215 \end{pmatrix}$$

, is UN covariance matrix for six locations.

$$\Sigma = \begin{pmatrix} 1 & 0.0064 & 0.0064 & 0.0064 \\ 0.0064 & 1 & 0.0064 & 0.0064 \\ 0.0064 & 0.0064 & 1 & 0.0064 \\ 0.0064 & 0.0064 & 0.0064 & 1 \end{pmatrix},$$ is CS within location covariance matrix.

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Richting: **Master of Statistics-Biostatistics**
Jaar: **2012**

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Datum: **14/09/2012**