Title page

Prenatal Exposure to Antiepileptic Drugs and Early Processing of Emotionally Relevant Sounds

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Abstract

Introduction. Prenatal exposure to antiepileptic drugs (AED) is associated with developmental compromises in verbal intelligence and social skills in childhood. Our aim was to evaluate whether a multi-feature Mismatch Negativity (MMN) paradigm assessing semantic and emotional components of linguistic and emotional processing would be useful to detect possible alterations in early auditory processing of newborns with prenatal AED exposure.

Material and methods. Data on AED exposure, pregnancy outcome, neuropsychological evaluation of the mothers, information on maternal epilepsy type, and a structured neurological examination of the newborn were collected prospectively. We compared a cohort of 36 AED exposed and 46 control newborns at the age of two weeks by measuring MMN with a multi-feature paradigm with six linguistically relevant deviant sounds and three emotionally uttered sounds.

Results. Frontal responses for the emotionally uttered stimuli *Happy* differed significantly in the exposed newborns compared to the control newborns. In addition, responses to sounds with or without emotional component differed in newborns exposed to multiple AEDs compared to control newborns or to newborns exposed to only one AED.

Discussion. Our study implies that prenatal antiepileptic drug exposure may alter early processing of emotionally and linguistically relevant sound information.

Keywords

Evoked potentials, Epilepsy, Newborn, Fetal, Pregnancy, Intrauterine

Abbreviations

AED Antiepileptic Drug, MMN Mismatch Negativity, ERP Evoked Response Potential, VPA Valproic acid, CBZ Carbamazepine, OXC Oxcarbazepine, LEV Levetiracetam, LTG Lamotrigine, TPM Topiramate, CZP Clonazepam, PWE Pregnant women with epilepsy, EEG Electroencephalography, HNNE Hammersmith Neonatal Neurological Examination, CA Conceptional age, GA Gestational age

1. *Introduction*

Approximately 0.3-07% of pregnant women in Western countries have a diagnosis of epilepsy. Most of them receive antiepileptic medication during pregnancy [1-3]. The adverse effects of prenatal antiepileptic drug (AED) exposure have been vigorously studied during the last decades. Prenatal exposure to AEDs is associated with both structural and functional teratogenic effects [4-6]. The most prominent effects have been observed with valproic acid (VPA) which is associated with decreased verbal intelligence [4, 7, 8], and an elevated risk of autism spectrum disorders [9].

Cortical processing can be measured by event-related potentials (ERPs) extracted from the electroencephalogram (EEG) already in neonates. ERP measurement is an economical and non-invasive technique that provides repeatable and quantitative information with high temporal resolution. Auditory processing has been examined by using Mismatch negativity (MMN) response [10] and these responses can be detected already during neonatal period and also in preterm newborns [11-15]. Altered MMN responses are observed in infants and children suffering from several neural and developmental conditions including dyslexia or autism spectrum disorder [16-22]. More specific alterations in cortical responses have been observed in different age groups. Dyslexic adults seem to have impaired pitch discrimination [19, 23], whereas autistic children have modified MMN responses for pitch and phoneme-category changes [17, 18]. Moreover, ERPs measured in term or preterm newborns may already have predictive value for the later development [14, 20, 21].

In addition to phonetic changes, MMN responses to changes in the emotional components of the sounds have been investigated. Autistic children and adults are shown to have impaired discrimination of emotional speech prosody [24, 25]. Altered auditory processing of emotional information has been detected in young people with conduct disorder symptoms [26]. Orientation to emotionally salient speech may be altered in patients with bipolar disorder and job burnout [27, 28]. Recently a multi-feature MMN paradigm to compare semantic and emotional components of linguistic and emotional processing in newborns has been developed [13, 29].

Taken together, prior literature suggests that the long-term developmental compromises after prenatal exposure to AEDs is mainly observed in areas of verbal intelligence and social skills [4, 9, 30, 31]. To test whether early precursors of these

developmental compromise could also be detected in newborns after fetal exposure, we used the recently established multi-feature MMN paradigm that allows combined assessment of emotional and linguistic processing in the newborn period.

2. *Material and methods*

2.1. General aspects

The study was conducted at the Helsinki University Hospital in collaboration with Finnish Institute of Occupational Health and University of Helsinki Cognitive Brain Research Unit. The ethics committee of the Helsinki University Hospital has approved the study. All mothers signed a written informed consent during pregnancy. The study protocol followed the Declaration of Helsinki. Recruitment process was prospective and included background information, exposure data, pregnancy outcome data, and mothers' neurocognitive evaluation. The process is represented in detail in a previous publication [32]. The examinations were carried out between April 2010 and May 2014. Examiners were blinded to the exposure status of the newborns.

2.1. Cohort

The original cohort included 56 newborns with prenatal AED exposure and 67 control newborns. AEDs used during pregnancies were valproic acid (VPA), carbamazepine (CBZ), oxcarbazepine (OXC), levetiracetam (LEV), lamotrigine (LTG), topiramate (TPM), and clonazepam (CZP). Due to newborn related issues we were not able to extract ERP epochs form five of the exposed and six of the control newborns. In

addition, we missed ERP data due to lack of reference electrode (eight exposed newborns) or due to inadequate trigger data or artefacts (7 exposed and 15 control newborns). Therefore, a full data set was obtained from 36 exposed and 46 control newborns. Of the exposed newborns, 25 were exposed to only one AED (Monotherapy group), and 11 newborns to more than one AED (Polytherapy group). Exposure status of the monotherapy group is shown see in Table 1. Polytherapy combinations were (number of newborns in the group): LTG + LEV (1), CBZ + LEV (3), OXC + LEV (1), OXC + GBP (1), LTG + OXC + CZP (1), LTG + LEV + CZP (3), LTG + TPM + CLB (1). In the monotherapy group, mean dosages and mean serum concentrations during the first trimester were: OXC 825 mg (27 umol/l), LTG 280 mg (7.7 umol/l), VPA 740 mg, (total serum concentration 283 umol/l, free serum concentration 24 umol/l), and LEV 825 mg.

Of background variables (Table 2), the exposed newborns had lower mean birth weight the unexposed newborns. The difference in Apgar scores was due to one outlier, and vanished if we left this outlier out. Mothers of the AED group tended to have higher educational level and lower performance IQ level than the mothers of the control group. Background information is revealed in detail in Table 2.

Neurological status of the newborns were assessed by Hammersmith Neonatal Neurological Examination [33] at the CA of 41 to 42 weeks. As observed before when analysing the entire cohort [32], the exposed newborns of this subcohort had slightly lower limb and axial tone than the control newborns. The mean Compound Optimality Score Tone for exposed newborns of the subcohort was 5.9 and for

controls 7.1 (p = 0.003), and the mean Total Optimality Score 23.9 and 25.4 (p = 0.029). Neurological findings were reported in detail in our previous publication [32].

2.2. MMN

EEG signals were collected by using NicOne EEG amplifier at sampling frequency of 250 or 500 Hz and EEG caps with 20-32 sintered Ag/AgCl electrodes positioned according to the International 10-20 standard. For sleep state assessment, we included channels for chin EMG, ECG, eye movements, and respiratory sensors. The sleep state of trace alternant or quiet sleep was determined visually by using NicoletOne Reader software by consensus agreement (MV and SV) when needed.

MMN recordings were assessed with the multi-feature mismatch negativity paradigm during either trace alternant or quiet sleep. A standard stimulus (pseudo-word /ta-ta/), six types of *linguistically relevant deviant stimuli* (vowel duration, vowel change, intensity changes (+/-6dB), frequency changes (+/-25.5Hz) and three types of *emotionally uttered stimuli* (happy, angry, sad) were performed as explained in full detail in previous publications from Pakarinen et al [29] and Kostiainen et al [13]. The stimuli were presented via a loudspeaker located at a distance of approximately 1 meter. The MMN data were collected from the frontal (F3, Fz, F4), central (C3, Cz, and C4), and occipital (Oz) electrodes. The Oz was used as a reference electrode. As the paradigm for emotional stimuli was only introduced after the recruitment had already started, the first 18 recordings lacked the emotional stimuli.

Intervals between 100–200 ms and 300–500 ms were considered descriptive for the brain responses and the averaged value of the signal within these latency windows was collected. The mean amplitude values from frontal electrodes were averaged together as electrode line *F* and from central electrodes as electrode line *C*. The mean values were calculated for each infant and each stimulus type for both time windows. To obtain standard-subtracted mean amplitudes, amplitude of standard stimulus was subtracted from the mean value in each electrode lines (*F* and *C*).

Epochs with signal values larger than +/- 150μV at any channel, or response average larger than +/- 10 microvolts at an individual electrode, were considered to be artefactual. Artefactual epochs were rejected, and individual artefactual ERP responses were left out from the averages.

2.3. Statistical analysis

To compare the ERPs of AED exposed and unexposed newborns, the mean standard-subtracted ERP amplitudes of frontal and central signals were computed for the given time windows.

Both latency windows (100–200 ms and 300-500 ms) were tested separately. For group comparisons, we used independent-sample t-test (2-tailed) for continuous variables, and Chi-square test for independence, or if the expected frequency was less than five, Fisher's Exact test, for categorical variables.

When evaluating whether gender affected the mean amplitudes, we applied one-way analysis of variance (ANOVA), and when evaluating the effect of age and

conceptional age on the brain responses, we applied the analysis of covariance (ANCOVA). In cases with multiple comparisons, we applied Bonferroni correction.

3. *Results*

3.1. AED group

Standard-subtracted mean amplitudes, both *emotionally uttered stimuli* and *linguistically relevant deviant stimuli,* in the exposed and unexposed newborns are shown in Table 3 and Figure 1.

The mean amplitude of the emotional variant *Happy* in the late latency window from the frontal electrode line was found to significantly differ between the groups: the exposed newborns showed positive polarity (2.08 uV, SD +/- 3.03) while the controls showed negative polarity (-1.30 uV, SD +/- 4.35 p = 0.04). To evaluate the impact of age and conceptional age (CA) on the reaction to the stimulus, we conducted one-way between-groups analysis of covariance (ANCOVA) by using age and CA of the newborn as covariates. Exposure status was the independent variable and standard-subtracted mean amplitude was the dependent variable. After adjusting for age and CA, there were still no significant differences between AED and control groups for any other stimuli or latency window than emotional variant *Happy* in the late latency window from the frontal electrode line (p = 0.04).

Commented [MV1]: Sampsalta 11_2018 käsite ”frontal electrode line” kuulostaa neurofysiologille pahalta.
toki siinä viiva=line, mutta kun tehdään aivotutkimusta niin siinä ei ole viiva vaan signaali.
Siis ERP/EEG/signal from the frontal electrode/brain area/tmv.

Tämä tulee pitkin paperia, ehkä voisi kaikki vaihtaa?

3.2. Polytherapy and Monotherapy groups

Newborns with exposure to more than just one antiepileptic drug (polytherapy group) had significantly more positive standard-subtracted mean amplitudes than control newborns in the early latency window for emotional variant *Angry* in the frontal line (Polytherapy group 4.26 uV, SD +/-2.41, Control group 0.29 uV, SD +/-3.45, $p = 0.01$). The polytherapy group also differed significantly from the control group with regard to early positive frequency deviants in both frontal and in central electrode lines (frontal electrodes: Polytherapy group -1.02 uV, SD +/-0.89, Control group 0.83 uV, SD +/-2.60, $p < 0.001$, and central electrodes: Polytherapy group -1.12uV, SD +/-1.97, Control group 0.45 uV, SD +/-2.09, $p = 0.03$). We observed similar statistically significant findings when we compared standard-subtracted mean amplitudes of the polytherapy and monotherapy groups with each other though monotherapy group as itself did not differ significantly from the control group.

When different monotherapy groups were compared to each other and to the control group, we did not find significant differences in standard-subtracted mean amplitudes (ANOVA).

A summary of the statistically significant findings is outlined in Table 4.

4. *Discussion*

Our results suggest that prenatal antiepileptic drug exposure may affect early processing of emotionally relevant linguistic information. Earlier studies have shown that auditory evoked potentials are linked to language functions, and they may specifically predict language impairments [34]. There has been an association between MMN amplitudes and performance in cognitive tests [35], and the intensity

of auditory evoked potentials have been shown to correlate with attention [36]. Atypical processing of the emotional sounds has been observed in patients with autism spectrum disorders [24] [25]. These together are compatible with the idea that the present findings might reflect an early precursor of developmental challenge caused by AED exposure.

Our study is in line with previous studies showing no major adverse effects on verbal development in association with prenatal OXC, CBZ, LEV, or LTG exposure [4, 7, 8]. Our study was initially motivated by the earlier findings that intrauterine VPA exposure leads to later risk of verbal and social compromise [37]. Epilepsy patients with VPA medication have shown to have decreased P300 amplitudes when compared to epilepsy patients with CBZ medication, epilepsy patients without medication, or healthy controls [38]. Delayed and smaller MMN responses (N270) have been observed in epilepsy patients compared to the responses of healthy controls [38].

The main limitation of our study was the relatively small number of exposed newborns in each monotherapy group, particularly VPA group (Table 1). MMN data was further limited due to artefact or incomplete electrode settings, and data from emotionally uttered stimuli was limited as the paradigm for emotional stimuli was only introduced after the first 18 recordings of all MMN data. Thus, the number of the newborns exposed to any particular AED was too few to evaluate the impact of an individual medication. We cannot exclude the possibility that individual drugs might have, either adverse or protective, effects on neonatal auditory processing.

There are several strengths in this study. The background information including exposure data was collected prospectively. During all measurements and analyses,

the researchers were blinded for the exposure status of the child. Furthermore, MMN recordings were conducted during the same sleeping state (quiet sleep) and during limited time range (conceptual age) thus eliminating the effects of sleeping states and maturation on the quality of the MMN response [39-42].

In our cohort, there was a trend toward lower mean performance intelligence quotient in women with epilepsy than in women without epilepsy (Table 2) which could be explained by lower processing speed of the mothers with epilepsy [43]. However, the percentage of the women having either tertiary or secondary education was higher among women with epilepsy. Higher educational level might be due to neuropsychological evaluation included in neurological follow-up thus enabling earlier and/or more intensive educational support, or due higher motivation to show one's capacity despite living a life with a chronic disease. Aspects regarding both strengths and limitations regarding enrollment and background data collection are discussed in more detail in our previous publication [32].

MMN paradigms are applied to several clinical approaches to increase understanding of disease mechanisms of many neurodevelopmental, neuropsychiatric, and neurological disorders, or to serve as biomarkers for risk of these disorders [44]. In particular, MMN responses have been used to explore the relationship between auditory processing and developmental disorders. It remains seen whether the deviant responses to sad and angry stimuli in frontal lines of the polytherapy group in our study (Table 4), have correlation to later susceptibility to depression or anxiety disorders. MMN might provide a noninvasive bedside method for detection functional neurotoxicity associated with fetal drug exposure, and thus offer the possibility of early supportive measures [45, 46].

Together with other neuroscience techniques, auditory ERP responses have supported the idea of continuity in the development of language starting from the early precursors of language in the first year of life to full blown linguistic abilities [47]. Fetal AED exposure has shown to interfere with several developmental events in rodent brain including apoptosis and myelination [44[48]. These particular developmental phenomena are reflected in evoked potentials [49]. Functional toxicity of fetal AED exposure seen in previous studies [4] may thus have origin in disturbing neonatal developmental “building blocks” [48, 50].

By investigating auditory responses already as early as the neonatal time period, we were able to focus on the effects fetal exposure and minimize the effect of imminent environmental confounders encountered in long term follow up studies. Subtle drug-related alterations in auditory processing measured in the newborn period may lead to developmental compromises later in life. This remains unanswered in the present study, and will require further follow-up of the cohort.

5. *Conclusions*

Prenatal exposure to antiepileptic drugs may affect auditory processing of emotionally relevant information. This may be detected within the first postnatal weeks. The clinical relevance and possible applications of evaluating early auditory processing still require further research.

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Disclosure

None of the authors have potential conflicts of interest to be disclosed.

Figure Captions

Figure 1. Standard-subtracted mean amplitudes Frontal lines.

The waveforms of the standard-subtracted mean amplitudes of the newborns exposed to antiepileptic drugs (AED, red line) and control newborns (blue dotted line) from Frontal (F) electrode lines. Reactions to each emotional variant and each deviant are illustrated in separate figures: *Happy, Sad, Angry, Vowel change, Vowel duration, Positive Intensity Change, Negative Intensity Change, Positive Frequency Change, and Negative Frequency Change.*

Figure 2. Standard-subtracted mean amplitudes Central lines.

The waveforms of the standard-subtracted mean amplitudes of the newborns exposed to antiepileptic drugs (AED, red line) and control newborns (blue dotted line) from Central (C) electrode lines. Reactions to each emotional variant and each deviant are illustrated in separate figures: *Happy, Sad, Angry, Vowel change, Vowel duration, Positive Intensity Change, Negative Intensity Change, Positive Frequency Change, and Negative Frequency Change.*

Table 1. AED exposure

	OXC*/CBZ* N (%)	VPA* N (%)	LTG* N (%)	LEV* N (%)	TPM* N (%)	Polytherapy N (%)	All N (%)
All enrolled	19 (35)	5 (9)	8 (15)	7 (13)	1 (2)	14 (25)	55^ (100)
ERP data available	9 (25)	5 (14)	5 (14)	6 (17)	0 (0)	11 (31)	36 (100)

OXC= Oxcarbazepine, CBZ= Carbamazepine, VPA= Valproic acid, LTG= Lamotrigine, LEV= Levetiracetam, TPM= Topiramate. *Monotherapy**.** ^Exposure status is not available for one newborn

Table 2. Background information

	AED (n=46)	Controls (n=36)	Sig. (AED vs. Controls^)

GA* (weeks, mean (range, SD))	40.2 (37.9-42.3, +/-1.15))	40.3 (38.4-42.1, +/-1.11)	0.67
CA during ERP (weeks, mean)**	42.3 (40.4-44.4, +/-0.94)	42.2 (40.0-43.7, +/-0.86)	0.81
Age during ERP (weeks, mean)	2.1 (0.58-0.40, +/-1.04)	2.0 (0.0-4.85, +/-1.04)	0.65
Enrollment (GA* weeks, mean)	7.35 (3-24, +/-3.75)	10.00 (5-15, +/-7.07)	0.36
Educational level of the mother (primary/secondary/tertiary)	34%/57%/9%	64%/30%/7%	**0.05**
Age of the mother (mean, yrs)	31.5 (24.0-41.0, +/-4.36)	31.7 (21.0-38.0, +/-3.66)	0.82
Smoking during the third trimester (%)	3%	0%	0.53
Neuropsychology of the mothers			
VIQ[#] (mean)	111 (69-137, +/-13)	115 (103-133, +/-9)	0.25^^
PIQ [##](mean)	116 (62-132, +/-13)	123 (102-138, +/-10)	**0.05^^**
Executive problems (no problems/slight problems)	72%/28%	87%/13%	0.46
Gender (Male %)	64%	69%	0.58
Apgar at 1 min (mean)	9.0 (7-10)	8.5 (2-10)	**0.02**
Folic acid amount during the 1st trimester (mean, mg)	2.9 (0.3-5.0, +/-1.75)	3.3 (0-8.0, +/-2.29)	0.42
Birth Weight (grams)	3480 (2490-4555, +/-465)	3714 (2808-4800, +/-474)	**0.03**
Hemoglobin of the newborn	167 (127-199, +/-19)	166 (127-214, +/-22)	0.93

*GA = Gestational Age (weeks), **CA =Conceptional Age (weeks), [#]=Verbal Intelligence Quotient, [##] =Performance Intelligence Quotient, ^ T-test, Pearson's Chi-Square test or Fisher's Exact test, ^^After discarding one outlier mother with VIQ 69 and PIQ 62 the p- value for VIQ is 0.42 and for PIQ 0.12 (mean VIQ: AED 112, control 114 and mean PIQ: AED 117, control 122)

Table 3. Standard-subtracted mean amplitudes of AED exposed and control newborns

Stimulus	AED/100-200 ms uV (min, max, SD)	Control/100-200 ms uV (min, max, SD)	p*	AED/300-500 ms uV (min, max, SD)	Control/300-500 ms uV (min, max, SD)	p*
Emotional variants						
Happy **/ta-ta:/**						
Frontal	0.72 (-5.79, 4.74, +/-3.14)	-0.25 (-11.25, 10.95, +/- 4.69)	0.33	2.08 (-3.93, 8.32, +/- 3.03)	-0.13 (-14.93, 9.36, +/- 4.35)	**0.04**
Central	0.51 (-5.03, 3.67, +/- 2.19)	0.21 (-6.61, 6.88, +/- 2.97)	0.65	0.44 (-6.08, 3.80, +/- 2.21)	-0.24 (-14.89, 6.90, +/-3.14)	0.32
Sad **/ta:-ta:/**						
Frontal	-0.38 (-7.26, 7.63, +/-4.21)	-0.59 (-8.28, 11.45, +/- 4.34)	0.86	1.57 (-6.35, 12.13, +/-4.99)	1.27 (-11.42, 14.41, +/-5.44)	0.83
Central	0.46 (-0.39, 7.73, +/-2.76)	0.04 (-6.05, 7.67, +/- 2.63)	0.57	1.01 (-6.66, 6.18, +/- 3.04)	0.30 (-11.14, 11.50, +/- 4.25)	0.45
Angry **/ta-ta/**						
Frontal	-0.25 (-10.05, 7.59, +/-4.49)	-0.29 (-7.02, 6.47, +/- 3.45)	0.97	0.48, (-5.16, 4.47, +/- 2.77)	1.28 (-8.55, 21.05, +/-5.01)	0.41
Central	0.45 (-4.35, 7-08, +/-2.89)	0.15 (-8.16, 11.26, 3.30)	0.71	0.39 (-2.43, 7.22, +/- 2.14)	1.53 (-5.11, 18.57, +/-4.07)	0.14
Deviants						
Vowel change **/ta-to/**						
Frontal	-0.34 (-4.00, 3.75, +/-1.88)	0.26 (-5.33, 7.69, +/- 2.28)	0.19	0.03 (-2.83, 3.12, +/- 1.58)	0.34 (-4.52, 5.91, +/- 2.26)	0.47
Central	-0.24 (-2.82, 3.03, +/- 1.17)	-0.02 (-4.93, 4.90, +/- 1.88)	0.53	0.27 (-2.78, 3.98, +/- 1.36)	-0.02 (-2.34, 3.82, +/-1.28)	0.33
Vowel duration **/ta-ta:/**						
Frontal	-0.10 (-2.42, 5.82, +/-1.71)	0.12 (-5.36, 7.04, +/- 2,58)	0.64	0.07 (-290, 3.73, +/- 1.59)	-0.65 (-5.01, 3.13, +/-1.90)	0.07
Central	-0.05 (-2.62, 3.21, +/-1.36)	-0.02 (-4.50, 6.56, +/- 2.06	0.94	0.08 (-2.18, 2.80, +/- 1.15)	-0.36, (-4.28, 3.83, +/-1.50)	0.13
Frequency (positive) **/ta-ta/**						
Frontal	0.22 (-3.95, 4.81, +/-2.40)	0.83 (-5.45, 6.21, +/- 2.60)	0.27	-0.11 (-5.82, 6.21, +/-2.50)	0.12 (-486, 5.61, +/- 2.30)	0.67
Central	-0.21 (-4.18, 3.30, +/- 1.91)	0.45 (-5.15, 6.07, +/- 2.09)	0.13	0.07 (-2.40, 5.63, +/- 1.72)	0.07 (-5.54, 4.57, +/-2.03)	1.00
Frequency (negative) **/ta-ta/**						
Frontal	0.33 (-5.48, 8.40, +/-2.90)	0.29 (-10.34, 12.20, +/- 3.66)	0.95	-0.18 (-4.96, 7.59, +/-2.99)	0.15 (-5.15, 4.58, +/-2.06)	0.57

Central	0.14 (-3.24, 6.115, +/-1.94)	0.44 (-7.10, 9.28, +/-2.67	0.56	-0.23 (-3.93, 8.32, +/-3.03)	0.29 (-3.76, 5.64, +/-1.72)	0.19
Intensity (positive) **/ta-ta/**						
Frontal	0.30 (-6.16, 5.58, +/-2.62)	-0.08 (-11.35, 8.09, +/- 4.05)	0.60	-0.16 (-5.94, 5.86, +/-3.07)	-0.01 (-5.40, 8.85, +/-2.83)	0.82
Central	-0.002 (-5.95, 2.50, +/-1.91)	0.11 (-9.27, 8.11, +/-3.04)	0.84	0.13 (-3.10, 4.29, +/-1.93)	0.49, (-4.44, 7.21, +/-2.13)	0.43
Intensity (negative) **/ta-ta/**						
Frontal	0.34 (-5.87, 8.79, +/-3.59)	0.73 (-4.00, 10,82, +/-3.00)	0.61	1,21 (-3.84, 6.97, +/-2.33)	0.34 (-7.10, 6.37, +/-3.02)	0.14
Central	-0.46 (-5.14, 3.73, +/-2.13)	0.29 (-3.54, 5.09, +/-2.06)	0.12	0.47 (-2.76, 4.20, +/-1.56)	0.09 (-11.09, 5.61, +/-2.76)	0.43

Table 4. Outlines of significant differences in standard-subtracted mean amplitudes

Comparisons	**AED vs. Controls**		**Mono vs. Controls**		**Poly vs. Controls**		**Mono vs. Poly**	
Stimulus	100-200 ms	300-500 ms	100-200 ms	300-500 ms	100-200 ms	300-500 ms	100-200 ms	300-500 ms
Emotional variants								
Happy /ta-ta:/								
Frontal	#	**0.04**	#	#	#	#	#	#
Central	#	#	#	#	3	#	#	**0.08**
Sad /ta:-ta:/								
Frontal	#	#	#	#	**0.06**	#	**0.02**	#
Central	#	#	#	#	#	#	#	#
Angry /ta-ta/								
Frontal	#	#	#	#	**0.01**	#	**0.02**	#
Central	#	#	#	#	#	#	**0.06**	**0.04**
Deviants								
Vowel change /ta-to/								
Frontal	#	#	#	#	**0.06**	#	**0.01**	#
Central	#	#	#	#	#	#	#	#
Vowel duration /ta-ta:/								
Frontal	#	**0.07**	#	#	#	#	#	#
Central	#	#	#	#	#	#	#	#
Frequency (positive) /ta-ta/								
Frontal	#	#	#	#	**<0.001**	#	**0.005**	#
Central	#	#	#	#	**0.03**	#	**0.06**	**0.10**
Frequency (negative) /ta-ta/								
Frontal	#	#	#	#	#	#	#	#
Central	#	#	#	#	#	#	#	#
Intensity (positive) /ta-ta/								
Frontal	#	#	#	#	#	#	#	#
Central	#	#	#	#	#	#	#	#
Intensity (negative) /ta-ta/								
Frontal	#	#	#	#	#	#	#	#
Central	#	#	**0.06**	#	#	#	#	#

P-values (t-test) 0.05 - 0.1 are represented with blue, < 0.05 with red, > 0.1 with #.
AED = newborns exposed to antiepileptic drugs
Mono = newborns exposed to one drug
Poly = newborns exposed to more than one drug

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