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ORIGINAL ARTICLE

Somatosensory and auditory processing in opioid-exposed newborns with neonatal abstinence syndrome: a magnetoencephalographic approach

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Abstract

Objective: Opioid exposure during pregnancy is a potential risk factor for the developing central nervous system of the fetus. We studied evoked responses in buprenorphine-exposed newborns who displayed neonatal abstinence syndrome (NAS) to elucidate the possible alterations in functioning of the somatosensory and auditory systems.

Methods: We compared somatosensory (SEFs) and auditory evoked magnetic fields (AEFs), recorded with magnetoencephalography (MEG), of 11 prenatally buprenorphine-exposed newborns with those of 12 healthy newborns. Peak latencies, source strength and location of SEFs or AEFs were recorded.

Results: AEFs were present in all buprenorphine-exposed newborns without significant differences from those of healthy newborns. In contrast, though no group level differences in SEFs existed, at individual level the response deviated from the typical neonatal morphology in four buprenorphine-exposed newborns.

Conclusions: Although buprenorphine exposure during pregnancy does not seem to cause constant deficiencies in somatosensory or auditory processing, in some newborns the typical development of somatosensory networks may be – at least transiently – disrupted.

Keywords

Auditory evoked magnetic field, buprenorphine, magnetoencephalography, neonatal abstinence syndrome, somatosensory evoked magnetic field

History

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Introduction

Neonatal abstinence syndrome (NAS) is a withdrawal syndrome of newborns after prenatal exposure to substances, most commonly opioids. NAS is characterized by clinical signs and symptoms of hyperirritability, respiratory distress, gastrointestinal dysfunction, and autonomic symptoms [1,2]. The withdrawal symptoms may affect the early mother–infant attachment [1], which is known to be important for later emotional development – other long-term health effects of NAS remain unclear.

In humans, neurophysiologic studies in opioid-exposed newborns have shown prolonged latencies in certain auditory brainstem responses and disturbances in the sleep–wake cycle: increase of active sleep (AS) with concomitant reduction of quiet sleep (QS) [3,4]. The disturbances of sleep in newborns with NAS (sleep deprivation, disorganization, and fragmentation) associate with the severity of the withdrawal [5]. In mouse pups, prenatal opioid exposure reduced branching and length of dendrites in neocortical pyramidal cells at the primary somatosensory cortex [6]. The effect of these morphological changes on neuronal function remains undetermined, however.

Electrical activity of the brain can be measured with electroencephalography (EEG) and magnetoencephalography (MEG). MEG records the weak extracranial magnetic fields generated by neuronal activity, mainly in the cerebral sulci, with millisecond temporal accuracy. Compared with EEG, MEG is less distorted by the differences in the resistive properties of the tissues between the active cortical source and the measurement device [7]. To date, no MEG studies of opioid-exposed newborns exist. MEG has, however, previously served to test the functioning of somatosensory cortical areas in preterm infants at risk for neurodevelopmental impairment [8].

We aimed at determining whether the somatosensory (SEFs) and auditory evoked magnetic fields (AEFs) of buprenorphine-exposed newborns with NAS differ from those of non-exposed healthy newborns. The brain electrical activity of newborns with NAS has not been previously studied in response to somatosensory or auditory stimulation,

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though these newborns have been described to be sensitive to external stimuli and decreasing sensory stimulation is generally recommended for supportive treatment of NAS [1,2]. We hypothesized that opioid exposure during pregnancy would cause changes in the function of cortical neurons, which may be reflected as differences in SEFs and AEFs in buprenorphine-exposed newborns compared to non-exposed healthy newborns.

Patients and methods

Subjects

The subjects were 2–30 days old prenatally buprenorphine-exposed, full-term newborns diagnosed with NAS born between March 2007 and November 2008 in tertiary maternity clinics, Department of Obstetrics and Gynaecology, Women's Hospital, Helsinki University Central Hospital (HUCH). Urine samples for drug screen were routinely collected from the newborns of opioid-using mothers and 37 newborns were positive for buprenorphine. A pediatrician informed mothers of 19 buprenorphine-exposed newborns about the study and successfully enrolled 15 of them. The MEG studies took place at the BioMag Laboratory (HUCH) in Helsinki. Three newborns did not fall asleep during the three-hour time slot. One newborn's data were excluded because of problems with the stimulus. Consequently, 11 newborns (eight males and three females) were successfully measured. The mothers of the studied newborns had histories of opioid abuse. During pregnancy, they were on buprenorphine replacement therapy ($n = 6$) or misused buprenorphine. Some mothers on buprenorphine replacement therapy may have had additional buprenorphine misuse during pregnancy.

In addition to a positive buprenorphine screen, two newborns screened positive for benzodiazepines and one for amphetamine. During pregnancy, all the mothers smoked and three had used alcohol. None of the newborns had been so far diagnosed with fetal alcohol spectrum disorders (FASD). The opioid withdrawal symptoms were evaluated in the neonatal ward using Finnegan scoring. [9] Newborns with Finnegan scores >8 three times successively or >12 two times successively were treated with an oral morphine hydrochloride mixture. Of the 11 buprenorphine-exposed newborns, five received oral morphine hydrochloride after birth and four of them were still on oral morphine hydrochloride therapy during the MEG measurement.

Altogether 12 healthy full-term newborns (age 1–3 days; four males and eight females) were recruited into the control group from the Department of Obstetrics and Gynaecology, HUCH, between June 2007 and April 2008. Some data of the healthy newborns is included in a previous publication for other purposes [10]. None of the mothers of the healthy newborns had a history of substance abuse (tobacco, alcohol or drugs).

The clinical characteristics [mean (range)] of 11 patients and 12 control newborns were – age: 12.3 days (3–30) versus 1.6 days (1–3)*, gestational age: 40.5 weeks (38.1–42.3) versus 40.4 weeks (39.0–41.7), postmenstrual age (gestational age plus chronological age): 42.2 weeks (39.7–44.7) weeks versus 40.7 weeks (39.3–42.0)**, birth weight: 3324 g (2500–3920) versus 3635 g (3110–4318), Apgar 1 min: 8.2 (1–9) versus 9.2 (9–10), umbilical artery pH: 7.24 (7.14–7.30) versus 7.24 (7.12–7.42) (Independent samples Student's t-test, $^*p = 0.001$, $^{**}p = 0.005$).

Procedure

MEG was recorded in a magnetically shielded room (Euroshield Ltd., Eura, Finland) with a whole-head helmet-shaped MEG sensor array with 306 sensors: 204 planar gradiometers and 102 magnetometers (Elekta Neuromag, Helsinki, Finland). EEG, with one to three silver-silver chloride disposable electrodes placed at F4, P4, Cz, or P3, and electrooculography (EOG), from two electrodes, one above the left and the other below the right eye canthi, were recorded simultaneously with MEG. The reference electrode was on the left mastoid and the ground electrode on the forehead. EEG and MEG signals were bandpass filtered at 0.03–257 Hz. The sampling rate was 1002 Hz.

In the beginning of the recording session, an individual Cartesian coordinate system was defined with a three-dimensional digitizer (Polhemus). The x-axis connected the preauricular points, (positive values towards the right ear), the y-axis connected the x-axis and nasion (positive values towards the nose) and the z-axis was perpendicular to the xy-plane (positive values upwards). Four position indicator coils were attached on the newborn's head. The coil positions were determined with the digitizer relative to the anatomical landmarks. If necessary, the newborn was fed before placing him/her on a bed next to the MEG device, which was in supine position. The newborn lay with left hemisphere downwards over the occipital part of the adult-sized helmet. One or two researchers were in the room with the newborn. A researcher held the tactile stimulus on the newborn's index finger, observed the newborns behavior, and coded the alertness and the presumed sleep stage onto trigger channels linked to the raw data file. The measurement session lasted from two to three hours. The stimulation and recording started when the newborn fell asleep and finished when the newborn woke up. All measurements were conducted during natural sleep and no sedation was used.

Stimuli

The tactile and auditory stimuli were alternating in the same recording session. The interstimulus interval between different modalities was 1 s and, consequently, between the same modality 2 s. For more details of the stimulation setup, see the work by Pihko et al. [10]. The tactile stimulus was a gentle tap on the skin of the tip of the newborn's right index finger given by a thin elastic membrane expanded by pressurized air (Somatosensory Stimulus Generator, 4-D Neuroimaging Inc., San Diego, CA). The auditory stimuli were delivered to the newborn's right ear via a plastic tube and an earpiece at ~75 dB SPL. The auditory stimuli were utterances of separated vowels a: and i: read by a Finnish adult female. Both vowel sounds lasted 300 ms and they were delivered within a semi-random sequence so that 85% of the auditory stimuli (standards) were the vowel [a:], and 15% were deviants [i:]. After a deviant, there were always at least two standards before the next deviant. In the present study, only responses to the standards will be discussed.

Analysis

To eliminate possible magnetic artifacts, the MEG data were preprocessed with a Spatiotemporal Signal Space Separation method (tSSS) [11] of the MaxFilter© software (Elekta Neuromag, Helsinki, Finland) using a correlation limit of 0.98 and a 4-s time window, thereby suppressing frequencies below 0.25 Hz. After tSSS, the data were carefully examined visually before offline averaging according to sleep stages, excluding periods with movement artifacts. MEG, EEG, EOG, and behavioral coding were used to determine the sleep stage. Only periods of QS free of movement artifacts were selected for further analysis. The sleep stage was characterized as QS when the infant lay eyes closed and had a regular respiration pattern, MEG/EEG showed high-voltage low-frequency activity or tracé alternant and there were no rapid eye movements in the EOG [12] Approximately 300 tactile responses were averaged for each newborn.

The location, strength, and orientation of the active neural sources were estimated with the equivalent current dipole (ECD) model. The ECDs were calculated using data from an individually chosen subset of MEG sensors close to the measured hemisphere and showing clear responses. The baseline was a 100-ms period before the stimulus. Single dipoles with 1-ms intervals were modeled around the visually determined peaks and the ECD with the greatest dipole moment was chosen for further analysis. The selected dipoles had a dipolar field pattern and goodness-of-fit values exceeding 70%.

Statistics

As AEFs of newborns are known to correlate with postmenstrual age (PMA) [13,14] and in our study the healthy newborns had significantly lower PMA than the patients (Student's t-test $p = 0.005$), the AEF parameters (peak latency, source strength, and source location) were first correlated against PMA with simple regression (or Spearman's rho when the data did not follow the normal distribution). When the values of a certain parameter were not dependent on PMA, the values of patients against those of healthy newborns were compared using a mixed 2×2 analysis of variance (ANOVA), with group (patients/controls) as a between-subjects factor, and response (auditory: M250/M550) as a within-subjects factor. When a significant correlation with PMA existed, analysis of covariance (ANCOVA) was applied, with PMA added as a covariate to the ANOVA design above. In contrast to AEFs, SEFs are not significantly dependent on PMA in the neonatal period [15] and thus the SEF characteristics were compared using ANOVA. Mann–Whitney U test was used when the data did not follow normal distribution.

Results

Auditory evoked magnetic fields

The first main auditory response, M250 (mean latency 289 ± 36 ms), was detected in all 11 patients and 8/12 controls (272 ± 36 ms). It was generated by a dipolar source modeled with an ECD pointing superiorly in 10 patients and 7 controls (Figure 1, Table 1). In one patient and one control the ECD pointed downwards. The ECD location (with respect to the anatomical landmarks defining the coordinate frame) roughly correlated with the known location of the primary auditory cortex on the superior temporal gyrus. A later response, M550, was detectable in all 11 patients (mean latency 583 ± 75 ms) and 7/12 controls (545 ± 76 ms) (Figure 1, Table 1). It was generated by a dipolar source pointing superiorly (inferiorly in the two infants in whom the M250 pointed inferiorly). The M550 source was located 3.4 ± 7.3 mm more posterior [ANOVA, main effect for response: $F(1,16) = 5.5$; $p = 0.03$] and 2.7 ± 5.6 mm inferior [ANOVA, main effect for response: $F(1,16) = 4.6$; $p = 0.046$] to the M250 source. No auditory responses were detected in four controls.

When the AEF source parameters were plotted against PMA, a significant correlation with PMA was found for

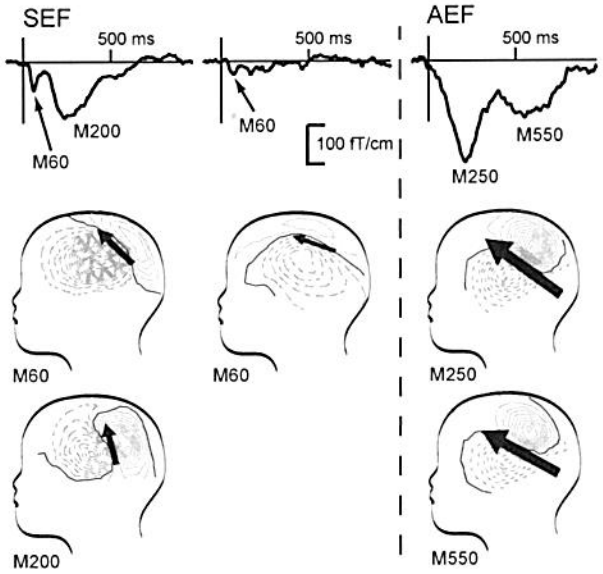

Figure 1. Waveforms from one gradiometer channel showing the somatosensory (SEF) (M60 and M200) and auditory evoked field (AEF) responses (M250 and M550) in representative buprenorphine-exposed newborns. On the left, typical somatosensory responses with both M60 and M200, in the middle, M60 is present but M200 response from SII is missing. Below are shown the corresponding isofield contour maps with approximate locations on a schematic head. The solid lines represent magnetic flow entering the head and dashed lines flow exciting the head. The arrows, with lengths proportional to ECD strength, display the source location and orientation.

Table 1. AEF parameters in controls and patients: number of newborns showing the indicated response (n), response peak latency, source strength and location in head coordinates.

	Controls		Patients	
AEFs	M250	M550	M250	M550
n	8	7	11	11
Peak latency (ms)	272 ± 36	545 ± 76	289 ± 36	583 ± 75
Source strength (nAm)	9.0 ± 9.0	9.8 ± 12.5	16.1 ± 11.9	24.4 ± 12.3
X (mm)	-24 ± 8	-25 ± 7	-33 ± 7	-28 ± 5
Y (mm)	7 ± 7	1 ± 16	-2 ± 10	-4 ± 7
Z (mm)	46 ± 9	41 ± 11	48 ± 10	46 ± 11

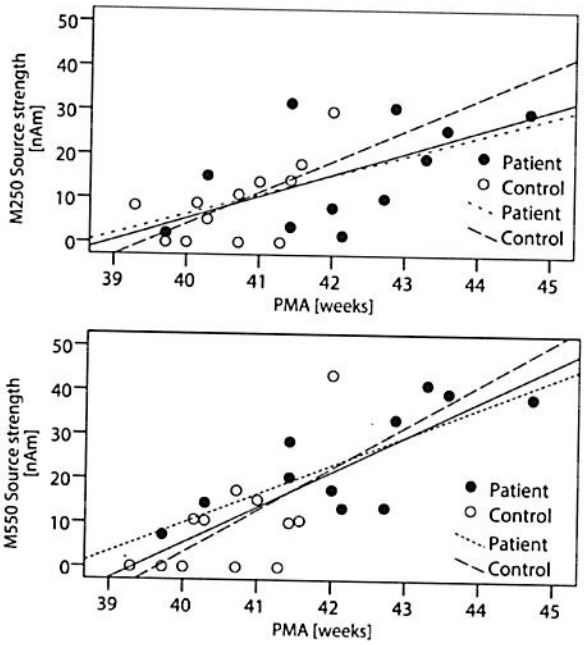

Figure 2. Correlation of the AEF source strength with PMA. Above M250 peak and below M550 peak. The solid line shows overall correlation with the two groups combined. The PMA effect is similar in patients and controls.

Table 2. SEF parameters in controls and patients: number of newborns showing the indicated response (n), response peak latency, source strength and location in head coordinates.

SEFs	Controls		Patients	
	M60	M200	M60	M200
n	12	11	10	7
Peak latency (ms)	63 ± 10	249 ± 109	65 ± 12	242 ± 40
Source strength (nAm)	9.8 ± 4.7	15.2 ± 10.9	8.1 ± 4,5	9.2 ± 8,9
X (mm)	−20 ± 6	−23 ± 9	−21 ± 5	−25 ± 8
Y (mm)	5 ± 7	4 ± 9	−1 ± 10	−4 ± 9
Z (mm)	64 ± 10	51 ± 16	70 ± 6	60 ± 6

source strengths of M250 (Pearson's $R = 0.64$, $p = 0.001$) and M550 ($R = 0.78$, $p < 0.001$) (Figure 2). ANCOVA, where the PMA effect was accounted for, showed no significant difference in AEF source strength between the patients and controls. No correlation with PMA was found for AEF peak latencies or locations and ANOVA showed no latency differences between the patients and controls.

Somatosensory evoked magnetic fields

The first SEF response, M60, was present in all control infants (mean latency 63 ± 10 ms) and 10/11 patients (65 ± 12 ms). The underlying ECD, located on the primary somatosensory cortex (SI), pointed anteriorly (Figure 1, Table 2). A later response from the secondary somatosensory cortex (SII), M200, was detected in 11/12 controls (249 ± 109 ms) and 7/11 patients (242 ± 40 ms) (Figure 1, Table 2). The M200 ECD pointed upwards. M60 and M200 responses did not differ significantly between groups in source strength, peak latency or ECD location (ANOVA/Mann–Whitney U).

Discussion

In contrast to our original hypothesis, we found no group level differences in peak latency, source strength, or location of SEFs or AEFs between buprenorphine-exposed and non-exposed healthy newborns. The general morphology and peak latencies of the SEFs and AEF in both groups were in accordance with the existing literature for healthy newborns. However, at the individual level, in four of the buprenorphine-exposed newborns, the secondary somatosensory cortex response was absent.

Animal models of prenatal opioid exposure are scarce. In one study, prenatal heroin exposure reduced branching and length of layer II/III pyramidal cells of the primary somatosensory areas in mouse pups [16]. Whether such structural changes occur in human newborns with NAS is unclear. Though MEG represents activity of the neocortical pyramidal cells, we did not observe differences in somatosensory or auditory evoked fields at the group level. However, in clinical circumstances, many factors such as drug dose and misuse of other substances than opioids may hamper group level effects.

Former studies imply that abnormal somatosensory evoked responses from SI [17,18] or SII [19] predict future neuromotor abnormalities in at-risk newborns. Auditory event-related potential characteristics at birth can be associated with later language development and reading abilities [20]. Our study found no group level differences between the buprenorphine-exposed versus non-exposed newborns in SEFs or AEFs that could suggest general deficits of the basis for developing appropriate auditory and sensorimotor skills. Previous studies have suggested that after controlling for confounding environmental factors (social position, child maltreatment, care-taker psychiatric co-morbidity etc.), the outcome of opioid-exposed children does not differ significantly from that of non-exposed controls [21,22]. In one research, after controlling for covariates, prenatally buprenorphine-exposed 3-year-old children scored lower on child responsiveness and involvement on the Bayley Cognitive and Language scales than control children, but the standardized scores were mostly within the normal range [23].

In our study, the strength of auditory responses was dependent on age in agreement with earlier studies. The amplitude and polarity of auditory evoked response depend on age in neonatal era [13,14] and M250 grows in amplitude up to 3-months age [24,25]. Thus, the missing AEFs in four of the youngest healthy infants may be explained by their age. By contrast, SI and SII responses, which are detectable in over 90% of healthy newborns, do not significantly change with PMAs between 37 and 43 weeks [15]. The SII response was missing in four buprenorphine-exposed newborns, but only one control newborn. At the individual level, the lack of M200 in prematurely born infants has been formerly associated with motor-related developmental problems at 2 years follow-up [19]. Though we do not have such outcome data of our study group, the prognostic value of absence of the M200 response is of interest for future studies.

In summary, our study revealed that auditory or somatosensory processing in the cerebral cortex in buprenorphine-exposed newborns with NAS does not significantly differ from that of healthy newborns when measured with MEG.

The magnetoencephalographic approach indicated no clear disturbances at group level in the prerequisites of the buprenorphine-exposed newborns for successful auditory learning and neuromotor development. More research must be pursued to clarify the interrelation between structural changes detected in animal models, the effects of socio-economic factors, and the symptoms observed in human newborns and older children exposed to opioids during pregnancy.

Declaration of interest

The authors report no declarations of interest. This study was supported by the Foundation for Pediatric Research, Helsinki, and the aivoAALTO research project of Aalto University.

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