Developmental Cognitive Neuroscience 30 (2018) 60–69

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: www.elsevier.com/locate/dcn

Consequence of intraventricular hemorrhage on neurovascular coupling evoked by speech syllables in preterm neonates

Mahdi Mahmoudzadeh[a,b,*], Ghislaine Dehaene-Lambertz[c], Guy Kongolo[d], Marc Fournier[a], Sabrina Goudjil[d], Fabrice Wallois[a,b]

[a] INSERM U1105, Université de Picardie, CURS, Amiens, France
[b] INSERM U1105, Unit Exploration Fonctionnelles du Système Nerveux Pédiatrique, South University Hospital, Amiens, France
[c] Cognitive Neuroimaging Unit, CEA DSV/I2BM, INSERM, CNRS, Université Paris-Sud, Université Paris-Saclay, NeuroSpin Center, 91191 Gif/Yvette, France
[d] INSERM U1105, Neonatal ICU, South University Hospital, Amiens, France

ARTICLE INFO

Keywords:
Electroencephalogram (EEG)
Functional Near Infrared Spectroscopy (fNIRS)
Intraventricular hemorrhage
Neurovascular coupling
Preterm

ABSTRACT

Intraventricular Hemorrhage (IVH) is the leading cause of neurological and cognitive impairment in preterm neonates with an incidence that increases with increasing prematurity. In the present study, we tested how preterm neonates with IVH react to external stimulation (i.e. speech syllables). We compared their neural responses measured by electroencephalography (EEG), and hemodynamic responses measured by functional near-infrared spectroscopy (fNIRS), with those of healthy preterms. A neural response to syllables was observed in these infants, but did not induce a vascular response in contrast with healthy neonates. These results clearly demonstrate that the cerebral vascular network in IVH preterm neonates was unable to compensate for the increased metabolism resulting from neuronal activation in response to external stimulation. Optical imaging is thus a sensitive tool to identify altered cerebral hemodynamic in critically ill preterms before behavioral changes are manifested or when only minor abnormalities on other functional monitoring techniques such as EEG are visible. We propose that a multi-modal approach provides unique opportunities for early monitoring of cognitive functions and opens up new possibilities for clinical care and recommended practices by studying the difficulties of the premature brain to adapt to its environment.

1. Introduction

Efficient brain functions depend on the integrity of the neural system that processes and produces information and the vascular system that provides oxygen and other energetic substrates. They also rely on the functionality of the fine tuning between the two systems as defined by the neurovascular coupling. Intraventricular hemorrhage (IVH) is the most common neurovascular complication of prematurity. It can be considered as a model of an alteration of the vascular system at this early period of development. It occurs very early, during the first 3 days of life. The etiopathogenesis of IVH is complex, but mainly involves fragility of the capillaries in the germinal matrix (GM), which are sensitive to anoxic mechanisms. IVH is graded from I to IV, according to the degree of bleeding and extension from the germinal matrix in which the first bleeding into the cerebral parenchyma occurs. Accumulation of blood inside the ventricles (grade I and II) can lead to ventricular distension (grade III) and rupture of the ventricular walls, resulting in extension of bleeding inside the parenchyma (grade IV) (Larroque et al., 2003). Infants with IVH have a lower and poorly regulated cerebral blood flow (Alderliesten et al., 2013; Perlman et al., 1983; Van Bel et al., 1987).

Although hemodynamic responses evolve in the course of development (Colonnese et al., 2008; Nourhashemi et al., 2017), a neurovascular coupling (NVC) can be observed with Near Infrared Spectroscopy (NIRS) in early premature neonates in different physiological conditions including spontaneous bursts of ongoing cortical activity (Roche-Labarbe et al., 2007) and in response to external stimulation in different domains: nociception (Bartocci et al., 2006; Maimon et al., 2013), somatosensory (Bartocci et al., 2006), visual (Colonnese et al., 2010) and auditory perception (Bisiacchi et al., 2009). It is also seen in epileptic discharges in premature (Wallois et al., 2010). As intraventricular Haemorrhage (IVH) affects the neurovascular coupling to spontaneous bursts of cortical activities (Roche-Labarbe et al., 2007), it might also impact the vascular supply following external stimulation and may be part of the negative consequences of IVH on cognitive development. Impairments of higher cognitive functions, including language (Magill-

* Corresponding author at: INSERM U1105, EFSN pediatriques, CHU Sud, Avenue Laennec, 80054 Amiens Cedex, France.
E-mail address: mahdi.mahmoudzadeh@u-picardie.fr (M. Mahmoudzadeh).

https://doi.org/10.1016/j.dcn.2018.01.001
Received 27 March 2017; Received in revised form 17 November 2017; Accepted 4 January 2018
Available online 05 January 2018

Evans et al., 2002), are common in IVH premature. Therefore it is mandatory to develop new approach to address the efficiency of the neuro-vascular interactions at this early stage of development considering the strong cognitive impact that might have such a precocious dysfunction.

In our previous work using both High Density EEG (HD-EEG) and High Density functional Near Infrared Spectroscopy (HD-fNIRS), we have shown that 28–30 wGA healthy neonates already process several dimensions of speech. They react to a change of phoneme (ba vs. ga) and to a change of voice (male vs. female) by an increase in the neurovascular coupling, using parallel networks within the superior temporal regions and extending into the inferior frontal regions (Mahmoudzadeh et al., 2013; Mahmoudzadeh et al., 2017) with a very similar pattern to that observed in full-term neonates (Pena et al., 2003; Telkemeyer et al., 2009), older infants (Hyde et al., 2010) and adults (Celsis et al., 1999). We therefore used our experimental paradigm in a small group of eight 28–32 wGA neonates with high-grade IVH to examine whether severely injured premature vascular networks are able to react to exogenous quas i ecologic stimulation and how the two arms of the neurovascular system adapt to stimulation when the vascular system is altered. We recorded the neural response by high-density EEG and the vascular response by optical imaging while these infants were listening to speech syllables. We compared the results to previously published results obtained in age-matched healthy preterms (Mahmoudzadeh et al., 2013; Mahmoudzadeh et al., 2017). We hypothesized that during the risk period for IVH, immature germinal matrix which is richly supplied with microvessels lack tight neurovascular junctions. Thus, cerebral hemodynamic response might be unable to adapt to exogenous stimulation in infants with IVH.

2. Materials and methods

2.1. Participants

Eight preterm neonates (6 males; mean gestational age (GA) at test: 30.5 weeks GA, Table 1) with high-grade (III or IV) intraventricular hemorrhage were tested at a median postnatal age of 7 days (range 1–36) and compared to previously published data obtained in 12 healthy preterm neonates by optical topography (8 Males, mean GA at test: 30.7 weeks GA ± 1.5) and in 19 healthy preterm neonates by Event–Related–Potentials (ERPs) (11 males; mean GA at test: 30.4 weeks GA ± 1.4) (Mahmoudzadeh et al., 2013; Mahmoudzadeh et al., 2017). The patients were recruited as IVH grade III and IV based on the grading of severity of Germinal Matrix–Intraventricular Hemorrhage (GM-IVH) by Ultrasound Scan. MRI was not preformed because of ethical issue due to the challenge to move clinically instable neonates to the MRI for pure research reasons as the MRI is not in the vicinity of the neonatal unit. While MRI has the advantage of superbly displaying soft tissue contrast differentiation and the exact extent and site of brain injury, transcranial ultrasonography can be performed at the bedside, and is a relative sensitive brain imaging method to assess lesions and tissue vascularisation. (Lagercrantz et al., 2010). As it is the common case, clinical EEG of the preterms with IVH was abnormal (except one neonate, see Table 1). The altered background activities associated with intraventricular hemorrhages have been classically demonstrated (i.e. occurrence of Positive Rolandic Sharp Waves, or Positive Temporal Spike and also the normal “tracé discontinu” background pattern is sometimes replaced by burst suppression).

ERP and optical topography were obtained successively in each IVH infant in random order. The data for one IVH preterm were discarded, as no useful functional data were obtained due to poor positioning of the optical probe. The parents were informed on the goals of the study and provided their written informed consent. The study was approved by the local ethics committee of Amiens University Hospital (CPP Nord-Ouest II) according to the guidelines of the Declaration of Helsinki of 1975 (ref ID-RCB 2008-A00728-47).

2.2. Experimental paradigm

Four syllables (/ba/and/ga/, produced by male and female speakers) were matched for intonation, intensity, total duration (285 ms), prevoicing and voiced formant transition duration (40/45 ms) (Mahmoudzadeh et al., 2013; Mahmoudzadeh et al., 2017). They were presented at a comfortable hearing level (≈70 dB) via speakers placed at the infant’s feet, by series of four (Stimulus Onset Asynchrony = 600 ms) according to a block design (20 s of stimulation followed by 40 s of silence) for a total duration of 108 min. Each block comprised 20 syllables (five 4-syllable trials separated by an inter-trial interval of 1600 ms (Fig. 1B)). The design comprised three types of blocks in which the responses to a change of voice (male *vs.* female) and a change of phoneme (ba *vs.* ga) could have been analyzed. However, given the weak response in each individual and the small number of infants, we focused on the main response to syllables and we merged all blocks and all types of trials as a lack of a significant response to a change of syllable in these conditions can be related to a weak statistical power rather than to a genuine deficit. The sleep state was checked during EEG analysis based on the EEG cardiac and respiratory features by the experienced clinical neurophysiologist (F.W.) (Wallois, 2010).

2.3. HD-ERP recording

EEG was recorded at the bedside using Ag/AgCl surface electrodes and a nasion reference at a sampling rate of 2048 Hz, amplified by A.N.T® (Enschede, The Netherlands) and DC–50 Hz filtered. The impedance of electrodes was kept below 5 kΩ. The number of electrodes (31–61) was determined by the infant’s head circumference in order to maintain a regular inter-electrode space (center-to-center) of about 1.5 cm. Four caps were used to cover the range of head circumferences observed at this age. In all infants, a minimum of 31 electrodes were placed on the classical 10–20 points and supplementary electrodes were

Table 1
Clinical features of the IVH infants tested.

Infant No.	Gender	GA at birth (weeks)	GA at test (weeks)	Birth Weight (g)	EEG	Apgar 1 min	Apgar 5 min	Brain US	Delivery	Presentation	Clinical conditions (Etiology)
1	M	29 4/7	30	1330	A	6	6	IVH3	Cesarean	–	Twin
2	M	25 4/7	28 5/7	950	A	3	5	IVH3	Vaginal	Cephalic	metrorrhagia
3	M	27 2/7	32	1160	A	8	8	IVH3	Cesarean	–	PROM, chorioamnionitis
4	F	30 3/7	31 6/7	1450	N	9	10	IVH3 Bilateral	Cesarean	transverse	placenta praevia, AFH
5	M	31 1/7	31 4/7	1080	A	10	10	IVH4	Cesarean	Cephalic	Twin
6	F	27	32 1/7	995	A	0	5	IVH4	Vaginal	Breech	Twin, Preeclampsia
7	M	26 5/7	29 2/7	1000	A	3	6	IVH4/3	Vaginal	–	Twin
8*	M	28 3/7	29	1200	A	8	9	IVH3	Vaginal	Cephalic	Twin

M: Male, F: Female, GA: Gestational Age, EEG: ElectroEncephaloGram, Cranial US: Cranial ultrasound, N: Normal, A: Abnormal, RPH: RetroPlacental Hematoma, PROM: Premature Rupture Of Membranes. AFH: Acute fetal hypoxia (* subject was removed from optical imaging study).