

Characterization of the Sensorimotor Rhythm in 4-Month-Old Infants Born at Term and Premature

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Abstract The sensorimotor rhythm (SMR) is an electroencephalographic rhythm associated with motor and cognitive development observed in the central brain regions during wakefulness in the absence of movement, and it reacts contralaterally to generalized and hemibody movements. The purpose of this work was to characterize the SMR of 4-month-old infants, born either healthy at term or prematurely with periventricular leukomalacia (PVL). Two groups of infants were formed: healthy and premature with PVL. Their electroencephalograms (EEGs) were recorded in four conditions: rest, free movement, right-hand grasping and left-hand grasping, in order to explore general reactivity to free movement and contralateral reactivity in hand-grasping conditions. Associations between SMR, and cognitive and motor performance were analyzed. The

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healthy infants showed a SMR between 5.47 and 7.03 Hz, with clear contralateral reactivity to free movement and right-hand grasping. However, the premature infants with PVL did not show enough electroencephalographic characteristics to evidence the presence of SMR. Poor performance, characteristic of children with PVL, was related to low-frequency SMR, while good performance was associated with a higher frequency rhythm in the left hemisphere. The presence of SMR in the group of healthy infants could be considered a sign of health at this age. Thus, poor SMR evidence in the EEG of infants with PVL is probably a sign of brain immaturity or brain dysfunction. Our results provide data on infant SMR development that is needed to design neurofeedback protocols for infants with PVL.

Keywords Sensorimotor rhythm · Healthy infants · Premature infants · Periventricular leukomalacia · Brain development · Brain injury

Introduction

Premature birth, low birth weight, asphyxia, infections during pregnancy, and birth trauma, are risk factors for neurodevelopmental impairments, such as major cognitive deficits and motor disability (Khwaja and Volpe 2008; Mulas et al. 2000; Volpe 2009). Brain injury in premature infants consists primarily of periventricular leukomalacia (PVL) and is frequently accompanied by neuronal and axonal disease; this constellation has been termed encephalopathy of prematurity (Volpe 2009). The neuropathological correlates of this encephalopathy involve lesions in the cerebral white matter and many cortical and subcortical brain structures, such as the thalamus (Ligam et al. 2009; Volpe 2009), basal ganglia, cerebral cortex, brain stem and cerebellum (Volpe 2009). Many infants with encephalopathy of prematurity show paroxysmal activity in their electroencephalogram (EEG), and some of them develop epilepsy (Staudt et al. 1984; Volpe 2001).

In the early 70s, Dr. Sterman discovered that cats trained with operant conditioning of the sensorimotor rhythm (SMR), also termed SMR neurofeedback (NFB), were resistant to hydrazine-induced seizures. This unexpected finding led to a controlled study which proved that 25% of the trained animals were completely protected from crisis induced by hydrazine and in the other 75%, the crisis occurred with a latency twice as long as in the control group. Therefore, independently of the causes of hypersynchronous discharges, this NFB could reduce the neuronal excitability of relevant tissues, block the impact of transient neuronal discharges, and stabilize the characteristics of the different functional states; the authors concluded that NFB that positively reinforces SMR could be an effective therapeutic intervention (Sterman 2000). Sterman and Friar (1972) published the first scientific article describing the use of NFB to treat a clinical condition in humans. Subsequently, it was found that NFB is a useful tool in the treatment of epilepsy (Sterman and Egner 2006) with level 4 efficacy, according to the Guidelines for the Evaluation of the Clinical Efficacy of Psychophysiological Interventions (La Vaque and Hammond 2002).

The SMR, also known as the central or mu rhythm, is an electroencephalographic rhythm observed in the absence of movement during wakefulness, and it is present in early developmental stages of human and other mammalian species (Pineda 2005). The SMR has been recorded in central regions in children and adults (Marshall et al. 2002; Niedermeyer 2004; Pineda 2005; Smith 1939) in dominant frequencies in the ranges of 8-13 and 15-25 Hz (Pineda 2005); this rhythm has also been observed in frontocentral regions in infants from 6 months of age in a frequency band of 6-9 Hz (Marshall et al. 2002; Orekhova and Stroganova 2007; Stroganova et al. 1999). SMR is considered the idling state of the sensorimotor cortex (Niedermeyer et al. 2004), is reactive to generalized movement (Pfurtscheller et al. 2000), and presents contralateral reactivity to movement or somatosensory stimulation of a hemibody (Harii 2006; Niedermeyer 2004; Pineda 2005). The SMR has been strongly related to motor (Marshall et al. 2002; Pfurtscheller et al. 2000; Smith 1939) and cognitive development (Marshall et al. 2002; Sterman 2000); it appears to exhibit mirroring properties (Cuevas et al. 2014; Pineda 2005). However, SMR has never been studied in preterm infants with PVL.

Katona's treatment has proven to be a useful method to prevent the progression of motor and cognitive deficits in infants at risk of brain damage (Harmony et al. 2016; Katona 1988). The goal of this therapy is the neurohabilitation of infants with risk factors for brain damage, by establishing basic motor patterns (Katona 1988). It is based on the concept of plasticity of the young nervous system and it consists in the repetition of therapeutic maneuvers which place the infant in specific corporal positions (Porras and Harmony 2007). These positions activate basic motor patterns that generate new patterns and conducts. The objective of using this method is to reduce the expression of abnormalities in development that could arise as a consequence of a pre or perinatal risk factors. Harmony et al. (2016) showed in children at 6–7 years old with perinatal brain damage very significantly higher percentage of children with normal outcome in treated (90%) than in nontreated (38%) groups.

We propose that NFB treatment that positively reinforces SMR increase could enhance the therapeutic effects of Katona's treatment when the two are co-administered. For this reason, the main goals of this work are to test the presence of SMR and to evaluate whether SMR is related to cognition at 4 months of age.

Methods

The Ethics Committee of the Instituto de Neurobiología of the Universidad Nacional Autónoma de México (UNAM) approved this study, which also complies with the Ethical Principles for Medical Research Involving Human Subjects established by the Declaration of Helsinki. Informed written parental consent for participation in this study was obtained from the parents of all participants.

Participants

In the Neurodevelopment Research Unit of the Neurobiology Institute, from the Universidad Autónoma de México, newborn infants that have been exposed to brain damage risk factors in the prenatal and perinatal stages are diagnosed and enter an early neurohabilitation program. Early diagnosis is a crucial part of the research at this unit, and newborns are studied with different instruments. The infants in this study are part of this research unit and some of them were diagnosed with prematurity and PVL by magnetic resonance imaging when they first entered the program.

The EEGs of 27 infants were recorded at 4 months of age, 13 were healthy subjects and 14 were preterm infants with PVL. Three of the subjects from the healthy control group were eliminated because they do not complete all evaluation. Three healthy subjects and four premature subjects with PVL were eliminated because there were too few segments free of artifacts after editing the EEG. Two infants with PVL were eliminated because they presented other brain alterations besides PVL.

Two groups of infants were studied: a healthy control group of seven participants (CTL Group) and a group of eight preterm infants with PVL (EXP Group); infants belonging to EXP Group received Katona therapy. Tables 1 and 2 show the main characteristics of these two groups.

In the CTL group, all infants were born at term (37 or more weeks of gestational age) and all weighed over 2.5 kg at birth. Infants did not have any antecedent of brain damage and showed normal brain structure in magnetic resonance imaging scans obtained before 2 months of age. Regarding MDI and PDI of the Bayley scale, only one infant showed a low score in MDI with the remaining children of this group showing normal scores. Infants of the CTL group also showed normal values for the EEAS.

In contrast, all premature infants (average gestational age of 32.25 weeks) in the EXP group had antecedents of risk for brain damage, and weights at birth lower than 2.5 kg. Magnetic resonance images showed abnormal findings in almost all infants of the EXP group. White matter (PVL) and grey matter lesions were observed and considered moderate damage. Infants found in the imaging study to have large cysts were not included. The age of premature infants was corrected considering 39 weeks as the age they should born.

Assessment Instruments

Bayley Scale of Infant and Toddler Development, version II (BSITD II): this scale (Bayley 1993) evaluates neurodevelopment of young children, ages from 1 to 42 months, through three indices: mental (MDI), physical (PDI) and behavioral (BDI). It was applied by the experimented psychologists Milene Roca-Stappung and Minerva Moguel-González, the two first authors of this paper.

Table 1 Characteristics of the control group

Evaluation of Selective Attention Scale (EEAS: *Escala de Evaluación de la Atención Selectiva*): EEAS, developed by Gutiérrez-Hernández and Harmony-Baillet (2007) and standardized for the Mexican population (Gutiérrez-Hernández et al. 2017), is a test that evaluates selective attention in infants 6 months and younger; this scale contains a total of 46 items grouped by age and distributed into two subscales, 32 items in the visual subscale and 14 items in the auditory subscale.

Comparison of the Non-EEG Measures Between Groups

When statistical comparisons between groups were performed using a multivariate permutation analysis (Galán et al. 1997), infants of the CTL group showed significantly greater gestational age (p < 0.001), higher weight at birth (p < 0.001) and higher scores in auditory attention from EEAS (p=0.02) than infants of the EXP group. No significant differences were observed in indices from the Bayley scale or scores of visual attention from EEAS. Apgar at birth of the EXP group was significantly lower (p=0.03), and Apgar at 5 min showed a tendency to be lower (p=0.07) than Apgar measures of the CTL group.

Procedures

EEG Recording

Referential EEG recordings were obtained using the appropriate cap (ElectroCapTM, International Inc.; Eaton, Ohio)—depending on the size of the infant's head—with 19 electrodes distributed according to the 10/20 international system (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz) with

Iden	Gestational age	Weight at birth	Apgar	Anteced- ents of risk	Clinical	MRI	Bayley scale			EEAS	
					exam at birth		MDI	PDI	BDI	Visual	Auditory
CON1	37	2520	9/9	Twin	Normal	Normal	75	80	82	48	23
CON11	38	3525	8/9	None	Normal	Normal	91	89	80	52	25
CON12	38	2820	9/9	None	Normal	Normal	91	95	83	51	26
CON14	37	3140	8/9	None	Normal	Normal	93	115	77	64	28
CON15	40	3250	8/9	None	Normal	Normal	91	89	87	55	28
CON18	39	3480	9/9	None	Normal	Normal	111	89	79	46	28
CON19	40	3120	10/10	None	Normal	Normal	95	95	86	56	28
Mean	38.43	3079.28					92.43	93.14	82.00	53.14	26.57
Standard deviation	1.27	315.26					10.50	10.87	3.65	5.96	1.99

MDI, PDI, and BDI mental, physical and behavioral developmental indices of the BSITD II, EEAS Escala de Evaluación de la Atención Selectiva

Incli	Gestational age	Weight at birth	Apgar	Gestational age Weight at birth Apgar Antecedents of risk	Clinical exam at birth	MRI	Bayle	Bayley scale		EEAS	
							MDI	PDI	BDI	Visual	Visual Auditory
EXP3	32	1930	8/9	Premature rupture of mem- branes, sepsis	Normal	† Subarachnoid space	119	109	77	60	27
EXP4	36	2475	8/9	Pre-eclampsia, hyperbiliru- binemia	Axial hypotonia	↑ Subarachnoid space, ↑LV, ↓↓CC	93	95	LL	21	8
EXP7	33	1330	8/9	Pre-eclampsia, acute fetal dis- tress, hyperbilirubinemia	Generalized hypertonia	Generalized hypertonia Leukomalacia, UCC, intraven- tricular hemorrhage	83	84	75	56	26
EXP8	35	1200	8/9	Severe pre-eclampsia, acute fetal distress	Generalized hypotonia	Leucoencephalopathy, intra- ventricular hemorrhage	51	54	64	38	14
EXP18	33	2050	6/8	Hyperbilirubinemia, Sepsis, anemia	Generalized hypotonia	Subarachnoid space, intra- ventricular hemorrhage	83	94	86	50	27
EXP21	29	1315	8/L	Severe pre-eclampsia, acute fetal distress, hyponatremia, pneumonia, anemia	Generalized hypotonia	Leukomalacia, †LV	76	06	81	53	24
EXP25	28	1350	7/8	Premature rupture of mem- branes, pneumonia	Generalized hypotonia	Generalized hypotonia Intraventricular hemorrhage	76	98	82	60	19
EXP27	32	1500	8/9	Twin, oligohydramnios hyper- bilirubinemia	Generalized hypotonia		85	75	82	57	25
Mean	32.25	1643.75					88.50	88.50 87.38 78.0 49.38	78.0		21.25
Standard deviation	2.71	454.87					19.18	19.18 16.77	6.68	6.68 13.50	7.01

linked earlobes as the reference. EEG recordings were obtained using a MedicidTM IV system (*Neuronic Mexicana, S.A.*; Mexico) with differential amplifiers and the Track Walker TM v5.0 data system. Amplifier characteristics were: gain of 20,000; low-pass filter at 0.5 Hz; high-pass filter at 100 Hz. Electrode impedance was below 10 k Ω . EEG was sampled every 5 ms and edited off-line. Recordings took place in a soundproof, dimly lit room. Infants sat on a baby car seat during all recording sessions.

The EEG was recorded under four different experimental conditions for each subject: visual attention and immobility (NM), freely moving activity (M), visual attention and right-hand grasping (R), and visual attention and left-hand grasping (L). Under the first condition, the infant maintained his/her visual attention on a baby mobile; in the second condition, the infant manipulated different toys with both hands; during the third and fourth conditions the infant maintained his/her attention on a baby mobile while he/she was grasping a toy/or the experimenter's finger with the right or the left hand, respectively. Each condition was registered for at least 6 min in order to get at least 30 s of artifact-free EEG recording.

EEG Analyses

The EEG was visually analyzed to eliminate segments that were contaminated with any artifact activity and/or had alpha activity in the occipital leads (Stroganova et al. 1999). If rhythmic activity was observed in occipital leads of any EEG segment, the segment was excluded from the analyses to avoid confusion between alpha rhythm propagation and mu rhythm. On average, 26 segments of artifact-free recording under each condition were used for the analyses. Segment length was 1.28 s.

The analyses were performed off-line. The data were fast Fourier transformed to obtained cross-spectral

matrices, and absolute power (AP) was calculated for every 0.78 Hz in the frequency range of 3.90–8.59 Hz (3.90, 4.68, 5.46, 6.25, 7.03, 7.81 and 8.59 Hz). Only F3, F4, C3, C4, Fz and Cz leads were considered for the EEG analysis, because of the topography of the rhythm we were looking for.

Permutation tests (Good 2005) were used to compare variables obtained by subtracting AP log values of the M, R or L condition from the AP log value of the NM condition in each group. The three variables employed in this study were: $\Delta PM = AP(NM) - AP(M)$, $\Delta PR = AP(NM) - AP(R)$, and $\Delta PL = AP(NM) - AP(L)$. Because SMR occurs in the absence of movement and is suppressed when there is movement of or pressure to limbs, positive ΔPM differences were classified as SMR activity. Also, movement of or grasping with one hand could reduce SMR in the contralateral hemisphere; therefore, positive ΔPR or ΔPL was also classified as SMR activity.

Relationship Between SMR and Cognition

For each lead and frequency included in this analysis, the correlation coefficients between the estimated power values and the scores obtained by the behavioral tests (Bayley indices and EEAS subscale scores) were calculated. Since the sample size was small, and it was not possible to assume linear relationships between the variables, the Spearman's rank correlation method was used in this step.

Each BSITD index or EEAS subscale score was correlated with EEG absolute power in the no-movement condition (Table 3) or in the difference $\Delta PM = [NM - M]$ (Table 4), considering each frequency (3.90, 4.68, 5.46, 6.25, 7.03, 7.81, and 8.59 Hz) and each lead (F3, F4, C3, C4, Fz, Cz) separately.

Table 3 Spearman correlation between behavioral tests and AP during NM condition

Test	Subscale	Frequency	F3	F4	C3	C4	Fz	Cz
Bayley Scales of Infant and Toddler Development	Mental Raw Index	3.90			r = -0.59 p = 0.0268	r = -0.67 p = 0.0090		r = -0.57 p = 0.0337
		4.68				r = -0.72 p = 0.0038		r = -59 p = 0.0259
		5.46				r = -0.63 p = 0162		r = -0.57 p = 0.0328
	Physical Raw Index	3.90				r = -0.69 p = 0.0065		r = -0.57 p = 0339
		4.68			r = -0.63 p = 0.0161	r = -0.67 p = 0.0084		r = -0.60 p = 0.0238
		5.46			r = -0.56 p = 0.0369	r = -0.56 p = 0.0353		r = -0.55 p = 0.0435

Test	subscale	frequency	F3	F4	C3	C4	Fz	Cz
Bayley	Mental	6.25	r = 0.63				r = 0.56	
Scales of	Normalized		p = 0.0165				p = 0.0392	
Infant and	Index	7.03	r = 0.58				•	
Toddler			p = 0.0308					
Development	Mental Raw	3.90				r = -0.68		r = -0.59
	Index					p = 0.0079		p = 0.027
		4.68				r = -0.74		
						p = 0.0027		
		5.46				r = -0.61		
						p = 0.0204		
		7.03	r = 0.60					
			p = 0.0220					
	Physical	7.03	r = 0.57					
	Normalized		p = 0.0316					
	Index							
	Physical	3.90				r = -0.64		r = -0.59
	Raw Index					p = 0.0131		p = 0.024
		4.68				r = -0.66		
						p = 0.0110		
		5.46				r = -0.56		
						p = 0.0387		
		7.03	r = 0.55					
			p = 0.0406					
	Behavioral							
	Raw							
	Index							
	Motor Quality							
	Attention	7.03			r = 0.53			
					p = 0.0490			
Evaluation of Selective	Visual							
Attention	Auditory	5.46	r = 0.55					
Scale	-		p = 0.0356					

 Table 4
 Spearman correlation between behavioral tests and AP during [NM – M] condition

Results

Presence or absence of SMR

Statistical results are shown in Fig. 1. Healthy, 4-monthold infants showed significant positive ΔPM differences ($p \le 0.05$) in central regions: in C3 at frequencies between 5.46 and 7.03 Hz, in C4 at 6.25 Hz, and in Cz at 6.25 and 7.03 Hz. Also, healthy infants showed significant positive ΔPR differences ($p \le 0.05$) in Fz at 5.46 Hz and in the leads of the left hemisphere, F3 at 6.25 Hz and C3 in frequencies between 4.68 and 6.25 Hz. No significant positive ΔPR values were observed in the right hemisphere, nor were significant positive differences observed when ΔPL was analyzed. Interestingly, there were no significant negative differences.

Figure 2 shows a characteristic EEG record of a healthy 4-month-old infant. Rhythmic activity is observed in central leads when the infant is immobile and attending the toy. This activity disappeared with free movement and was attenuated in the right hemisphere (C4) when the infant grasped with the left hand.

Preterm infants with PVL and 4 months of corrected age did not show any significant values ($p \le 0.05$) in either ΔPM , ΔPR or ΔPL (see Fig. 1).

Relationship Between SMR and Cognition

In Table 3, significant Spearman correlations between BSITD-II (and EEAS) and AP during the NM condition are shown. Significant correlations, all negative, were only observed in central leads between raw MDI and PDI from the BSITD and AP calculated for 3.90, 4.68 and 5.46 Hz. On the other hand, significant Spearman correlations between BSITD-II and EEAS and AP using the difference [NM - M] are shown in Table 4. In general, significant correlations were mainly concentrated in leads F3 and C4; correlations that involved F3, C3, and Fz were positive, while correlations that involved C4 and Cz were all negative. In addition, negative correlations associated with lower frequencies, as observed during the NM condition, and positive correlations with the [NM - M] difference were found in higher frequencies.

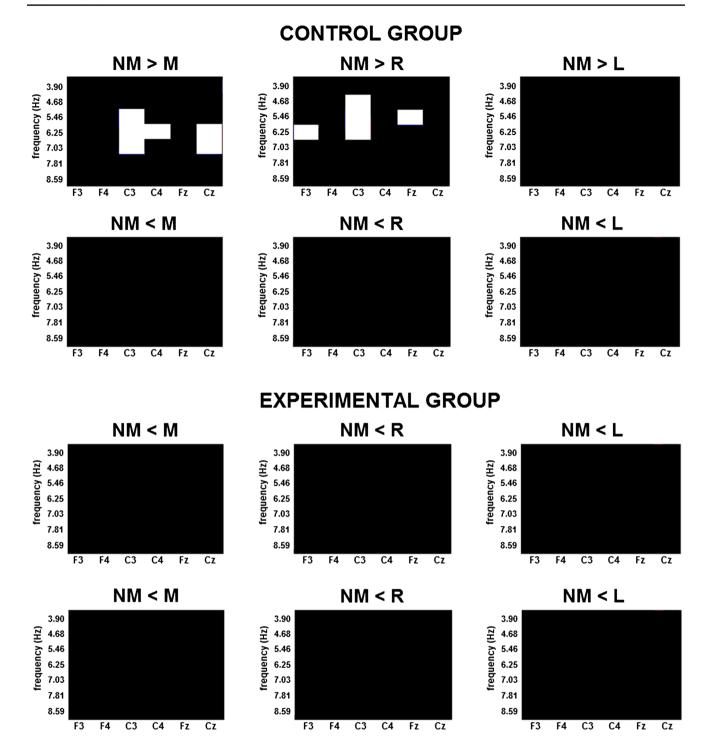


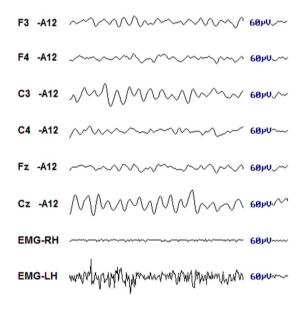
Fig. 1 Comparison of EEG Absolute Power (AP) between no-movement (NM) condition and the remaining conditions in 4-month-old at term and preterm infants. Leads of EEG recordings are represented on the X axis, and frequencies are shown in the Y axis. *White rectangles* show significant positive differences, i.e., EEG activity in the no-movement condition was greater than that in the other conditions

(*NM* no-movement, *M* movement, *R right*-hand grasping, *L left*-hand grasping). Observe that in the Control Group AP in NM condition was significant higher than M (in C3 at 5.46–7.03 Hz, C4 at 6.25 Hz, and Cz at 6.25–7.03 Hz) and R (in F3 at 6.25 Hz, C3 at 4.68–6.25 Hz, and Fz at 5.46 Hz). No other significant differences were observed

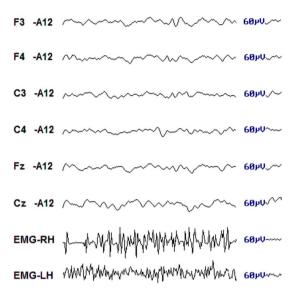
No movement

F3 -A12	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	60µV,~~
F4 -A12	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	60yV~~~
C3 -A12	\sim	60yV
C4 -A12	$\$	60yV~~~
Fz -A12	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	60yV,~~
Cz -A12	·//····//	60⊬ √√∕∽
EMG-RH	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	60yŲ
EMG-LH	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	60µV~~~

Left hand grasping







Right hand grasping

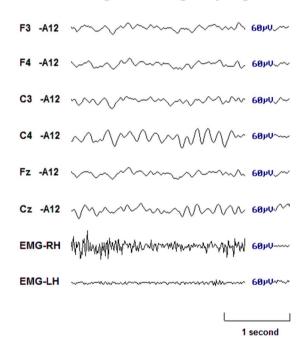


Fig. 2 EEG record of a healthy 4-month-old male at term. Note the rhythmic activity in the "No movement" condition, mainly in central leads (*upper left*), that disappears with "Movement" (*upper right*).

Note also, the contralateral reactivity of this rhythmic activity: C4 reduction with left-hand grasping (*bottom left*) and C3 reduction with right-hand grasping

Discussion

The main purpose of this work was to characterize SMR in 4-month-old infants, either healthy or premature with PVL. According to Steriade, an electroencephalographic rhythm is defined as regularly recurring waveforms of similar shape and duration, and associated with a specific range of frequencies, topography, reactivity and morphology (Niedermeyer 2004). During wakefulness, there is a rhythmic activity at a frequency around 7 Hz in central leads in 4-month-old infants (Smith 1939) and an increase of the relative power in these same leads in a range between 6 and 7 Hz at 5 months of age and between 7 and 8 Hz at 10 months old, which seems to be independent of the classical alpha rhythm at posterior sites (Marshall et al. 2002); these data suggest that the frequency of SMR increases during development. This activity was interpreted as SMR in all cases. Stroganova et al. (1999) observed rhythmic activity in an attention (and no-movement) condition with a peak around 7 Hz at pre-central sites in 7- to 12-month-old infants. They suggested that this was the central or mu rhythm, because it was reduced in a condition of darkness in which alpha rhythm increased.

In the present work, all EEG activity in central or frontal leads in the frequency range between 3.90 and 8.59 Hz that was reactive to movement was classified as SMR. Although previous studies in infants showed that the SMR was present after 6 Hz, our study explored lower frequencies, because some of the infants studied were affected by prematurity and PVL.

An important contribution of this experiment is the attempt to demonstrate the characteristic contralateral reactivity of this rhythm to muscle activity. Healthy 4-monthold infants showed reactivity to free movement in the range of frequencies between 5.46 and 7.03 Hz for all the central leads considered, while reactivity to right-hand grasping was observed in leads of left hemisphere and midline (mainly at C3 in frequencies between 4.68 and 6.25). This suggests that reactivity to free movement is very strong over central regions, while contralateral reactivity of SMR remains unclear. This contralateral reactivity was only observed as a power reduction in the left hemisphere when subjects grasped with their right hands, also involving midline leads, and was not observed when participants grasped with their left hands.

The frequency of the electroencephalographic rhythms was reported to increase during development (Niedermeyer 2004). In addition, recent evidence supports the hypothesis that thalamo-cortical connectivity becomes more specific with maturation due to axonal retraction and elimination of collaterals throughout development and aging (Fair et al. 2010), which may consequently influence this frequency.

On the other hand, preterm infants with PVL and 4 months of corrected age showed no evidence of SMR, because the activity observed during the no-movement condition did not show reactivity to free movement, or to left or right grasping. When they were compared with healthy infants of the same age, a very poor response to manipulation of the SMR was evident. Infants with PVL are known to present many abnormalities, such as smaller volume of subcortical areas or/and hypomyelination of different cerebral structures, because of brain injury (Volpe 2009). Injury to cerebral white matter characterizes PVL (Xydis et al. 2006; Volpe 2009), and it results in neuronal and axonal disease in many cortical and subcortical regions (Volpe 2009). The thalamus is widely affected by this injury; infants with PVL show a 40% volume decrease in this cerebral area (Volpe 2009). It has been suggested that the mu rhythm or SMR has a thalamic origin (Egner and Sterman 2006; Hughes and Crunelli 2005); therefore, differences between healthy and preterm infants with PVL in the SMR characterization were expected. Unexpectedly, premature infants with PVL did not show evidence of SMR at 4 months; this dramatic finding might be due to damage of cortical and subcortical regions as well as white matter lesions, especially impaired oligodendrocyte maturation (Volpe et al. 2011).

When we explored whether there was an association between SMR and mental, motor or behavioral development using the BSITD, or between SMR and selective attention as evaluated by EEAS, negative correlations were found between BSITD MDI and PDI and AP of SMR at 3.90, 4.68 and 5.46 Hz at C4 and Cz, while positive correlations were observed between MDI or PDI of BSITD and absolute power of SMR at 6.25 and 7.03 Hz, involving F3, C3, and Fz. In addition to the association between SMR and motor behavior, SMR has been related to social and cognitive processes, such as imitation and language (Cuevas et al. 2014), and SMR NFB has been used to reduce signs and symptoms of Attentional Deficit Hyperactivity Disorder (Kerson 2013; Lubar 1997). Beauregard and L'evesque (2006) showed that the function of the brain circuits mediating selective attention and response inhibition could be normalized in ADHD children by treating with SMR NFB. In healthy subjects, NFB reinforcing SMR increase has demonstrated a general attention-enhancing effect (Egner and Gruzelier 2004).

Preterm infants with PVL obtained the lowest scores in BSITD and EEAS, suggesting that SMR at higher frequencies in leads of the left hemisphere is related to better performance in behavioral tests. One might then conclude that the adequate target for SMR feedback should be the highfrequency SMR in left leads in order to improve motor and/ or cognitive abilities; however, these preliminary results are not yet conclusive to set NFB protocol recommendations.

Conclusion

We show evidence that SMR is present in healthy infants at 4 months of age. This is the first time that SMR has been studied in infants with PVL and at risk of its well-known motor sequelae. The absence of SMR at 4 months in these infants is an important finding that reflects the abnormality of their motor functions. Further investigations are needed to gain a better understanding of this phenomenon, because SMR must be present in order to positively reinforce an SMR increase, which would be a useful tool to treat braindamaged infants who are receiving Katona's treatment. We expect that with maturation, healthy infants will also present SMR reduction in the left grasping condition. We also expect that at 6–8 months of corrected age signs of SMR will be observed in infants born preterm with PVL.

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Compliance with Ethical Standards

Conflict of interest The authors declare that there is no conflict of interest.

References

- Bayley, N. (1993). Bayley scales of infant development, manual (2nd edn., pp. 1–3, 46–51, 227–230). USA: The Psychological Corporation.
- Beauregard, M., & L'evesque, J. (2006). Functional magnetic resonance imaging investigation of the effects of neurofeedback training on the neural bases of selective attention and response inhibition in children with attention-deficit/hyperactivity disorder. Applied Psychophysiology and Biofeedback, 31, 3–20. doi:10.1007/s10484-006-9001-y.
- Cuevas, K., Cannon, E. N., Yoo, K., & Fox, N. A. (2014). The infant EEG mu rhythm: Methodological considerations and best practices. *Developmental Review*, 34, 26–43. doi:10.1016/j. dr.2013.12.001.
- Egner, T., & Gruzelier, J. H. (2004). EEG biofeedback of low beta band components: Frequency-specific effects on variables of attention and event-related brain potentials. *Clinical Neurophysi*ology, 115, 131–139.
- Egner, T., & Sterman, M. B. (2006). Neurofeedback treatment of epilepsy: From basic rationale to practical application. Futuredrugs. *Expert Review of Neurotherapeutics*, 6, 247–257.
- Fair, D., Bathula, D., Mills, K. L., Costa-Dias, T. G., Blythe, M. S., Zhang, D., Snyder, A. Z., Raichle, M. E., Stevens, A. A., Nigg, J. T., & Nagel, B. J. (2010). Maturing thalamocortical functional connectivity across development. *Frontiers in Systems Neuroscience*, 18, 4–10.
- Galán, L., Biscay, R., Rodríguez, J. L., Pérez-Abalo, M. C., & Rodríguez, R. (1997). Testing topographic differences between event related brain potentials by using non-parametric combinations of permutation tests. *Electroencephalography and Clinical Neurophysiology*, 102, 240–247.
- Good, P. (2005). Permutation, parametric and bootstrap test of hypothesis. (3rd edn.), New York: Springer.
- Gutiérrez-Hernández, C., Harmony, T., Avecilla-Ramírez, G., Barrón-Quiroz, I., Guillén-Gasca, V., Trejo-Bautista, G., &

Bautista-Olvera, M. (2017). Infant scale of selective attention: A proposal to assess cognitive abilities. *Revista Evaluar, 17*, 96–108.

- Gutiérrez-Hernández, C. C., & Harmony-Baillet, T. (2007). Evaluación conductual de la atención selectiva visual y auditiva en lactantes con factores de riesgo de daño cerebral. *Revista de Neuropsicología*, 2, 3–9.
- Harii, R. (2006). Action—perception connection and the cortical mu rhythm. *Progress in Brain Research*, 159, 253–260.
- Harmony, T., Barrera-Reséndiz, J. E., Juárez, M. E., Carrillo-Prado, C., Pedraza, M. C., Asprón, A., Hinojosa, M., Fernández, T., & Ricardo-Garcell, J. (2016). Longitudinal study of children with perinatal brain damage in whom early neurohabilitation was applied. Preliminary report. *Neuroscience Letters*, 611, 59–67. doi:10.1016/j.neulet.2015.11.013.
- Hughes, S. W., & Crunelli, V. (2005). Thalamic mechanisms of EEG alpha rhythms and their pathological implications. *The Neuroscientist*, 11, 357–372.
- Katona, F. (1988). Developmental clinical neurology and neurohabilitation in the secondary prevention of pre- and perinatal injuries of brain. In P. M. Vietze & H. G. Vaugham (Eds.), *Early identification of infants with developmental disabilities*. Philadelphia: Grune & Stratton.
- Kerson, C. (2013). Collaborative neurofeedback group. A proposed multisite double-blind randomized clinical trial of neurofeedback for ADHD: need, rationale, and strategy. *Journal of Attention Disorders*, 17, 420–436.
- Khwaja, O., & Volpe, J. (2008). Pathogenesis of cerebral white matter injury of prematurity. Archives of Disease in Childhood—Fetal and Neonatal Edition, 93, F153–F161.
- La Vaque, T. J., & Hammond, D. C. (2002). Template for developing guidelines for the evaluation of the clinical efficacy of psychophysiological interventions. *Applied Psychophysiology and Biofeedback*, 2, 273–281.
- Ligam, P., Haynes, R. L., Folkerth, R. D., Liu, L., Yang, M., Volpe, J. J., & Kinney, H. C. (2009). Thalamic damage in periventricular leukomalacia: Novel pathologic observations relevant to cognitive deficits in survivors of prematurity. *Pediatric Research*, 65, 524–529.
- Lubar, J. F. (1997). Neocortical dynamics: Implications for understanding the role of neurofeedback and related techniques for the enhancement of attention. *Applied Psychophysiology and Biofeedback*, 22, 111–126.
- Marshall, P. J., Bar-Haim, Y., & Fox, N. A. (2002). Development of the EEG from 5 months to 4 years of age. *Clinical Neurophysi*ology, 113, 1199–1208.
- Mulas, F., Smeyers, P., de Téllez Meneses, M., & Menor, F. (2000). Leucomalacia periventricular: Secuelas neurológicas, radiológicas y repercusiones neuropsicológicas a largo plazo. *Revista de Neurología*, 31, 243–252.
- Niedermeyer, E. (2004). Basic principles, clinical applications, and related Fields. In E. Niedermeyer & F. Lopes da Silva. (Eds.), *Electroencephalography* (pp. 156–160). New York: Lippincott Williams and Wilkins.
- Niedermeyer, E., Goldszmidt, A., & Ryan, D. (2004). "Mu rhythms status" and clinical correlates. *Clinical EEG and Neuroscience*, 35, 84–87.
- Orekhova, E. V., & Stroganova, T. A. (2007). EEG and infant states. In M. Haan. (Ed.), *Infant EEG and event-related potentials. Studies in developmental psychology* (pp. 251–281). New York: Academic Press.
- Pfurtscheller, G., Neuper, C., & Krausz, G. (2000). Functional dissociation of lower and upper frequency mu rhythms in relation to voluntary limb movement. *Clinical Neurophysiology*, 111, 1873–1879.

- Pineda, J. A. (2005). The functional significance of mu rhythms: Translating "seeing" and "hearing" into "doing". *Brain Research Reviews*, 50, 57–68.
- Porras, K. E., & Harmony, T. (2007). Neurohabilitación: Un método diagnóstico y terapéutico para prevenir secuelas por lesión cerebral en el recién nacido y el lactante. *Boletín Médico del Hospital Infantil de México*, 64, 125–135.
- Smith, J. R. (1939). The "occipital" and "pre-central" rhythms during the first 2 years. *The Journal of Physiology*, 7, 223–226.
- Staudt, F., Benda, G. J., Howieson, J., & Engel, R. C. (1984). Seizures in premature and newborn infants under 2500 grams birth weight. *Klinische P\u00e4diatrie*, 196, 293–297.
- Sterman, M. B. (2000). Basic concepts and clinical findings in the treatment of seizure disorders with EEG operant conditioning. *Clinical Neurophysiology*, 31, 45–55. Review.
- Sterman, M. B., & Egner, T. (2006). Foundation and practice of neurofeedback for the treatment of epilepsy. *Applied Psychophysiology and Biofeedback*, 31, 21–35.
- Sterman, M. B., & Friar, L. (1972). Suppression of seizures in an epileptic following sensorimotor EEG feedback training.

Electroencephalography and Clinical Neurophysiology, 33, 89–95.

- Stroganova, T. A., Orekhova, E. V., & Posikera, I. N. (1999). EEG alpha rhythm in infants. *Clinical Neurophysiology*, 110, 997–1012.
- Volpe, J. J. (2001). Neurology of the newborn (4th edn.). Philadelphia: WB Saunders.
- Volpe, J. J. (2009). Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *The Lancet Neurology*, 8, 110–124.
- Volpe, J. J., Kinney, H. C., Jensen, F. E., & Rosenberg, P. A. (2011). Reprint of "The developing oligodendrocyte: Key cellular target in brain injury in the premature infant". *International Journal* of Developmental Neuroscience, 29, 565–582. doi:10.1016/j. ijdevneu.2011.07.008.
- Xydis, V., Astrakas, L., Drougla, A., Gassias, D., Andronikou, S., & Argyropoulou, M. (2006). Myelination process in preterm subjects with periventricular leukomalacia assessed by magnetization transfer ratio. *Pediatric Radiology*, *36*, 934–939.