The effects of preterm infant massage on brain electrical activity

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AIM Early intervention programmes based on the manipulation of the extra-uterine environment have been used in preterm infants with the aim of improving development and functional outcome. Infant massage, among them, has proved effective for weight gain and reduced length of stay in the neonatal intensive care unit. We have recently shown that infant massage accelerates brain maturation of low-risk preterm infants without brain abnormalities as measured by global parameters of electroencephalography (EEG) activity. In the present study we further analyse the same cohort of preterm infants, testing the hypothesis that massage determines changes in EEG spectral activity, a highly sensitive index of brain maturation.

METHOD Infants were randomly allocated to a massage or comparison group. Intervention consisted of standard care only (comparison group) or standard care plus infant massage (massage group). Massage was started at around 10 days after birth and was provided for 12 days during a 2-week period. EEG was performed at around 1 and 4 weeks, i.e. before and after intervention. Spectral EEG analysis was performed on 80 seconds of active sleep, applying the fast Fourier transform on the signal obtained from eight monopolar derivations.

RESULTS The modification in global EEG spectral power between the two assessments was significantly different for the two groups, especially for the delta band activity; the spectral power did not change in massaged infants although, not surprisingly, it decreased significantly in the comparison group, as shown by previous studies.

INTERPRETATION We propose that massage intervention affects the maturation of brain electrical activity and favours a process more similar to that observed *in utero* in term infants.

Preterm birth is increasingly recognized as a complex condition resulting from the interaction of multiple genetic, biological, and environmental risk factors, which potentially contribute to neonatal complications and neurodevelopmental abnormalities.[1] Among the primary goals of care of the preterm infant is the prevention of further exposure to noxious environmental stimulations, with its potential for being detrimental to later development.[2] An additional goal is to promote a supportive care environment based on positive stimulations aimed at reducing the gap between the *in utero* and the intensive care environments.[3]

Early intervention programmes based on the manipulation of the extra-uterine environment, among them infant massage therapy, have been used in preterm infants with the aim of optimizing the infant's sensory experience and thus potentially improving development and functional outcome.[4] Infant massage is a form of systematic tactile stimulation by human hands, consisting in a gentle, slow stroking of each part of the body in turn. It is often combined with other forms of stimulation such as kinaesthetic stimulation (e.g. passive extension/flexion movements of the arms and legs), talking, or eye contact.[5] A recent systematic review of the effects of infant massage in preterm infants concluded that there were positive effects on weight gain and reduced length of stay in the neonatal intensive care unit, but that the evidence of long-term benefit was still weak and did not warrant wider use of massage without further research.[5] Very little is known about the possible mechanisms of effect of massage on early brain development.

In a recent study in preterm infants we have reported a significant effect of massage on the maturation of visual function, in line with the findings of a parallel study in a rat model.[6] We

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found a larger latency shortening of the most prominent peak of flash visual evoked potentials, N300, between pre- and post-massage assessments in massaged babies, relative to a comparison group, associated with an increase of behavioural visual acuity persisting beyond 3 months of post-term age. We also performed a visual analysis of electroencephalography (EEG) activity and reported a much larger degree of shortening of the inter-burst intervals during quiet sleep between pre- and post-massage assessments in massaged babies, relative to a comparison group. More recently, acceleration of brain maturation as measured with different EEG parameters was also reported in healthy preterm infants undergoing skin-to-skin contact, a different kind of neurodevelopmental intervention.[7]

These findings are consistent with the numerous reports of different EEG characteristics in preterm infants at term age compared with term newborns (i.e. at comparable post-conceptional age), which suggest an effect of extra-uterine life on EEG maturation. One of the most studied aspects of EEG maturation concerns the modifications of EEG spectral power, a quantitative measure of the energy of bioelectrical activity that tends to decrease in preterm infants from birth to term age.[8] In the present study we further analyse the effects of infant massage on the same cohort of preterm infants as our previous study, testing the hypothesis that this type of intervention can affect the maturation of brain electrical activity as assessed by EEG spectral analysis, a quantitative measure of EEG activity that in preterm infants is highly sensitive to brain maturation.[9]

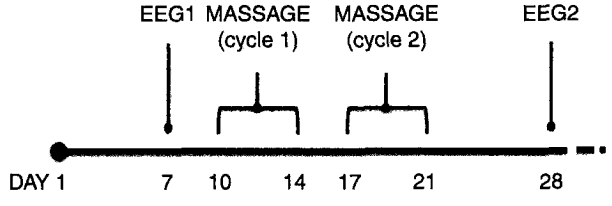

Figure 1: The study protocol. Timings of EEG and massage sessions are shown.

METHOD

Participants

Twenty newborns with a gestational age between 30 and 33 weeks, admitted to the Neonatal Unit of the University Hospital of Pisa, Italy, were consecutively recruited for the study from November 2005 to August 2007. Inclusion criteria were (1) birthweight between the 25th and 75th centile, (2) birth length greater than the 10th centile, and (3) no or minor abnormalities on brain ultrasound (transient flare, mild isolated ventricular dilation). Infants with genetic anomalies, congenital heart malformations, central nervous system dysfunction, or medical conditions primarily related to immaturity, such as respiratory distress syndrome, hyaline membrane disease, apnoea, elevated bilirubin, and hypoglycaemia and hypocalcaemia, were excluded.

After parental consent was obtained, each participant was randomized into the massage or comparison groups by drawing from a container a sealed and unlabelled envelope. To avoid contamination and to optimize resource allocation, the process of selection of a new participant for enrolment was suspended until the previous participant had completed the post-training assessment. When the process of recruitment was reopened, the first participant, based on date of birth, meeting the inclusion criteria and consenting to the study was recruited. Written informed parental consent was obtained in all cases. The study was approved by the Ethics Committee of the Stella Maris Foundation and Pisa University Hospital.

Massage therapy

Massage therapy was started on postnatal day 10 (±1). Sessions were performed three times a day for two blocks of 5 days each, separated by a 2-day interval (Fig. 1). Each massage session was performed approximately 60 minutes before feeding, and at least 2 hours after the completion of the previous stimulation. Each treatment session consisted of 10 minutes of tactile stimulation, followed by 5 minutes of kinaesthetic stimulation. During tactile stimulation, the infant was placed prone and was given moderate-pressure stroking with the flats of the fingers of both hands (Fig. 2a). Head, neck, shoulders, buttocks, and both legs and arms were massaged. For the kinaesthetic phase, the infant was placed in a supine position. Pas-

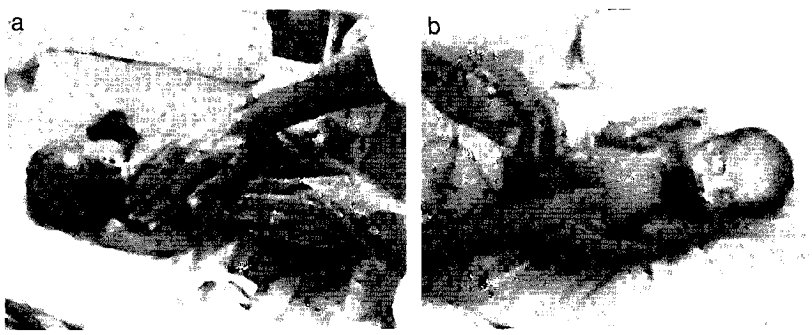

Figure 2: The two phases of massage therapy. (a) Prone phase: tactile stimulation of shoulders and back with moderate pressure stroking with the flats of the fingers of both hands. (b) Supine phase: kinaesthetic stimulation through passive flexion/extension movements of the lower limbs.

sive flexion/extension movements of the limbs in sequence were applied (Fig. 2b).

Pre-massage (T_0) and post-massage (T_1) EEG

EEG was performed at the bedside using a portable digital EEG system (Micromed System Plus; Micromed, Mogliano Veneto, Italy). EEGs were recorded before the massage therapy, at around 1 week of age (±1d), and after the massage therapy, at around 4 weeks of age (±2d; Fig. 1). In participants randomized in the comparison group, EEGs were performed at the time points. Recordings were obtained from eight active electrodes (Fp1–2, C3–4, O1–2, T3–4 of the international 10–20 system) and one reference electrode (Fz) applied to the scalp using adhesive paste. EEG was recorded for at least 40 minutes and included all states of sleep. A low-pass filter was set at 70 Hz and a high-pass filter at 0.3 Hz. A sampling rate of 256 Hz was used for digitization.

For the spectral EEG analysis, four segments of 20 s were selected from the parts of EEG where medium/high voltage slow waves without artefacts were continuously observed during active sleep.[8] Selection of EEG segments was made by careful visual inspection using bipolar montage by one of the authors with extensive experience in neonatal EEG (AG), blind to group allocation. Active sleep was chosen for the analysis as (1) spectral power during active sleep in preterm infants was reported to have a significant correlation with gestational age and other indexes of brain maturation[10] and (2) active sleep is the phase of continuous activity that is generally the least affected by movement artefacts.[11]

Signal processing was performed using the manufacturer's software (Micromed software Analyzer; Micromed). Amplitude spectral analysis was performed applying the fast Fourier transform on the signal obtained from eight monopolar derivations (Fp1, Fp2, C3, C4, T3, T4, O1, O2). The square root of EEG power analysed by fast Fourier transform algorithm, expressed in microvolts, was used for the analyses. The spectrum was divided into the main four frequency bands: delta, 0.5 to 4.0 Hz; theta, 4.5 to 7.5 Hz; alpha, 8.0 to 11.0 Hz; beta, 15.5 to 25.0 Hz. The performance of spectral analysis was improved by pre-processing the signal by de-trending (removal of any direct current component), tapering (windowing of the signal), and overlapping (consecutive epochs of 2s were overlapped by 1s). Global absolute power was measured by averaging the values of all electrodes. Local absolute power was measured for each lobe by averaging the values of paired homotopic monopolar derivations (e.g. C3 and C4).

Statistical analysis

Statists were analysed using the Statistical Package for the Social Sciences (SPSS, version 14.0; IBM SPSS, Chicago, IL, USA). Within-group differences were analysed by a paired-sample *t*-test, unadjusted.[12,13] Between-group differences were analysed by a two-way analysis of variance for repeated measures with time (pre- vs post-massage) and participant group (massaged vs comparisons) as factors. Levine's test was used to assess equality of variances.[14] The level of significance was set at $p<0.05$.

RESULTS

Within-group analysis

The results of the within-group analysis of spectral power variation between T_0 and T_1 are shown in Table I.

Infants in the comparison group showed a significant variation of global absolute power in delta and alpha bands. In the same band, a significant decrease of absolute power was also observed when considering topographical variations in all regions, with the exception of delta band variations in the occipital leads. No significant variations were observed for the theta and beta bands, neither for the global nor for the local spectral power.

Massaged infants showed no significant variations of global absolute power in any of the four frequency bands explored. When assessing topographical variations of spectral power a significant increase was observed in the central regions for delta and theta bands, whereas a significant decrease was observed in the temporal regions for delta and alpha bands.

Between-group analysis

Repeated measures analysis of variance was used to assess the effect of time (pre- vs post-massage) and participant group (massaged vs comparisons) on global and local EEG spectral power (Fig. 3).

The interaction between time and participant group was significant for the global spectral power in the delta band ($F_{1,15}=4.7$, $p=0.046$), for the local spectral power from the central leads in the delta band ($F_{1,15}=15.8$, $p=0.001$), and in the beta band ($F_{1,15}=4.8$, $p=0.044$) (Fig. 3). This was due to the significant decrease of EEG spectral power in non-massaged infants relative to massaged infants between T_0 and T_1.

DISCUSSION

Our results show a significant difference in spectral power during active sleep between newborns who underwent massage therapy and those who did not. In particular, the variation of global EEG power between T_0 and T_1 was significantly different between the two groups for the slow 0.5 to 4 Hz frequencies, owing to a reduction of delta power in comparison infants relative to massaged infants. This difference is especially observed in the central regions, where the variation of delta power is significantly different between the two groups. In the same regions, significant differences were also observed for the beta band. A general confirmation of these findings was also obtained from the within-group analysis, which showed a significant reduction in the comparison group of global and central EEG power in the delta frequencies. Overall, these findings support the assumption that infant massage modifies sleep EEG power spectral density in preterm newborns.

Lower spectral values for all frequency bands, in particular for the delta band, have been consistently reported in preterm infants at term age compared with term newborns (i.e. at a comparable post-conceptional age), which has been interpreted as related to the effect of extra-uterine life.[15,16] This interpretation is supported by the observation that in preterm infants EEG spectral power tends to decrease from birth to

Table 1: Results of the paired-sample *t*-test between T_0 and T_1 on the two groups

	0.5–4Hz					4.5–7.5Hz					8–13Hz					13.5–30Hz				
	Tot	F	C	T	O	Tot	F	C	T	O	Tot	F	C	T	O	Tot	F	C	T	O
Massaged (n=10)																				
T_0	42.6	27.3	35.6	52.9	51.2	18.6	15.1	17.4	21.2	20.2	16.4	14.2	15.0	19.6	17.5	27.2	24.4	26.0	30.9	28.4
	(3.5)	(3.2)	(5.4)	(7.1)	(5.0)	(0.7)	(3.8)	(2.2)	(1.0)	(1.1)	(0.7)	(1.0)	(1.1)	(0.6)	(0.7)	(3.4)	(5.3)	(5.1)	(4.4)	(4.2)
T_1	42.8	25.9	40.0	44.1	51.3	19.2	14.2	20.2	21.0	21.0	15.7	12.6	15.2	17.2	17.3	27.3	22.7	25.8	29.2	33.1
	(1.9)	(2.5)	(6.7)	(5.7)	(5.1)	(0.6)	(1.9)	(0.7)	(0.6)	(1.3)	(0.3)	(0.4)	(0.3)	(0.3)	(1.6)	(1.6)	(2.3)	(2.9)	(3.5)	(6.4)
p	0.83	0.79	0.21	0.09	0.92	0.29	0.45	0.009[a]	0.76	0.31	0.62	0.31	0.78	0.039[a]	0.89	0.91	0.16	0.79	0.49	0.08
Controls (n=10)																				
T_0	40.3	26.0	39.9	45.2	45.2	18.5	14.7	18.3	21.1	19.9	16.3	13.0	16.2	19.1	17.0	25.7	21.1	26.5	27.1	28.0
	(1.3)	(3.3)	(3.8)	(5.1)	(5.2)	(0.7)	(4.1)	(0.4)	(2.3)	(0.9)	(0.4)	(2.6)	(0.6)	(1.6)	(0.4)	(2.5)	(5.3)	(3.7)	(2.5)	(3.1)
T_1	34.1	19.6	30.8	44.5	44.5	17.2	11.9	18.0	19.6	18.7	13.0	10.1	13.2	15.8	14.9	23.0	18.5	21.6	25.1	26.3
	(1.6)	(0.9)	(2.9)	(7.6)	(7.6)	(5.5)	(2.9)	(4.4)	(4.4)	(5.4)	(0.9)	(0.7)	(2.6)	(3.2)	(2.2)	(4.2)	(4.4)	(4.9)	(6.0)	(6.3)
p	0.018[a]	0.003[a]	0.012[a]	0.07	0.79	0.13	0.06	0.68	0.39	0.47	0.027[a]	0.1	0.08	0.11	0.31	0.42	0.56	0.06	0.47	0.54

Tot, total of all leads; F, frontal leads; C, central leads; T, temporal leads; O, occipital leads. Sample size was 10 for each group for all analyses. Mean values (SD) in microvolts at T_0 and T_1; p values are shown. [a] $p<0.05$.

term age, in particular for the delta and, less prominently, the beta frequencies.[8,17] Also, preterm infants born at different gestational age have undistinguishable EEG power at similar postnatal age, suggesting that energy reduction is related to postnatal age (and thus to the duration of extra-uterine life) rather than gestational age.[18]

Taken together, these findings reinforce the hypothesis that one of the electrophysiological correlates of extra-uterine experience is the reduction of EEG spectral power, but they do not clarify whether this phenomenon is the expression of a positive process of brain maturation, owing to the anticipated stimulation of extra-uterine environment, or rather the negative effect of precocious exposition to a non-physiological condition. Several pieces of evidence support this latter assertion. For example, the condition of a reduced EEG spectral power in preterm infants with low birthweight was reported to be associated with transient brain disorders, as in case of systemic hypotension with reduced brain perfusion[19] or in perinatal asphyxia.[20] More importantly, specific neonatal EEG-sleep measures for either healthy preterm or term infants, including a reduction of spectral EEG energies, were found to correlate with lower developmental quotients at both 1 and 2 years of age.[21] Scher et al.[16] interpreted the relative low spectral power in preterm infants at term as the effect of a functional alteration in brain development related to the untimely exposure to the extra-uterine environment; in particular they propose that the extra-uterine environment could be inadequate to support the maturation of the thalamocortical network, resulting in an impoverishment of neuronal aggregates in this network, with the consequence of the reduction of the oscillatory potentials. A possible effect at the level of intracortical circuitry and corticothalamic inputs cannot be excluded.[22]

We feel there is evidence suggesting that a higher EEG spectral power, in particular in the delta band, in preterm infants approaching term age is the expression of a positive phenomenon, likely to be at least partly related to a more advanced maturational stage of corticothalamic and intracortical circuits in terms of increased synaptic density, connectivity, and function. However, the question remains whether these changes can be induced by environmental enrichment, such as massage therapy. In animal studies, environmental enrichment enhances plasticity in cortical and hippocampal circuits.[23] At the cellular level, enrichment enhances synaptic density[24] and induces expression of factors involved in synaptic plasticity, such as brain-derived neurotrophic factor or insulin-like growth factor 1.[25] Very recent work in adults demonstrated a direct link between exploratory behaviour, cortical expression of brain-derived neurotrophic factor, and spectral power of slow wave activity, supporting the notion that sleep EEG is heavily influenced by the richness of preceding wakefulness.[26] Environmental enrichment also affects insulin-like growth factor 1. In the same massaged infants of the present study we reported a significant increase of it relative to comparisons, suggesting that environment may act to modulate the level of endogenous factors involved in brain growth regulation.[6] Consistent with our findings, an increase of insulin-like

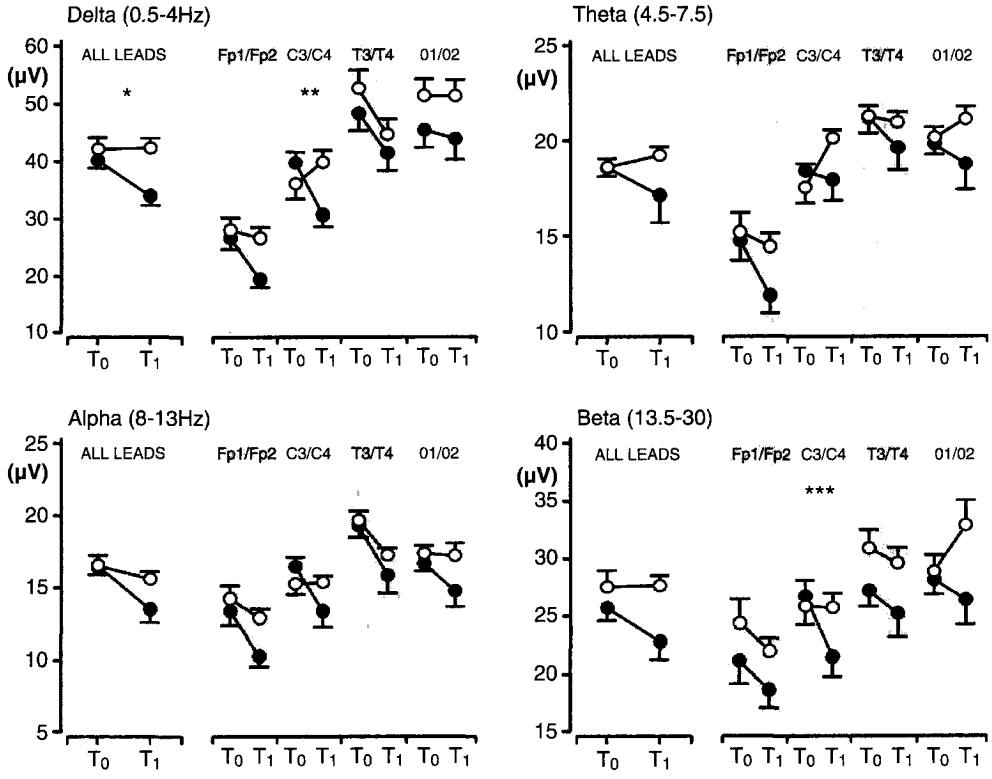

Figure 3: Global and local spectral power (SEM) at T_0 and T_1 in massaged (open circles) and control infants (filled circles). The four frequency bands are shown. Asterisks indicate significant interaction between time and participant group with the two-way analysis of variance (*p=0.046; **p=0.001; ***p=0.044).

growth factor 1 was also recently reported by Field et al.[27] in massaged preterm infants.

The effect of massage in our cohort showed a topographic distribution. The increase of local absolute power of delta and beta band activity was limited to the central regions. The interpretation of these findings is not clear. Regional patterns of sleep EEG modification after local activation of brain regions during wakefulness have been reported both in the animal model and in humans.[28,29] In preterm infants, some reports show reduced white matter development in several frontal lobe projections compared with healthy term infants imaged at the same post-menstrual age.[30,31] Interestingly, Als et al.[32] studied a group of preterm infants enrolled in a neurodevelopmental intervention (NIDCAP) trial, reporting higher relative anisotropy in frontal white matter and increased coherence between frontal and occipital brain regions. Altogether these findings may suggest that in preterm infants the maturation of the connectivity of the central regions is sensitive to the exposition to extra-uterine environment and can be effectively modulated by early intervention. A multidisciplinary approach integrating neuroimaging and neuropysiological studies will be helpful in clarifying this hypothesis.

There are several limitations to our study. First, the number of participants studied was small. It should be noted, however, that in most of our analyses the group variance was low, suggesting that significant differences were not related to the results of a few outliers. Also, the limited number of electrodes used did not allow a high spatial discrimination and therefore a good localization of the activities that were different between the two groups. Another important limitation of the study is that we have not correlated EEG findings with any measure of development. Larger studies with long-term follow-up are needed to determine the role of spectral EEG changes in preterm infants undergoing massage therapy or other types of early intervention.

CONCLUSION

We propose that the relative increase of EEG spectral power observed in our massaged infants is the effect of the postnatal enrichment represented by the multisensorial stimulation, which might be mediated by an action on synaptic activity similar to that observed in enriched animals. It needs to be strongly emphasized that this conclusion cannot be generalized to high-risk preterm infants or to those with congenital brain damage, as they were not the objects of our observation. No conclusions can be drawn from the present study for those higher-risk populations. In low-risk preterm infants we suggest that massage therapy favours a process of maturation of brain electrical activity similar to that observed (*in utero*) in term infants, probably through an attenuation of the discrepancies between the extra- and intra-uterine environments.

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