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ORIGINAL ARTICLE

Parent-led massage and sleep EEG for term-born infants: A randomized controlled parallel-group study

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Abstract

Aim: To examine the impact of parent-led massage on the sleep electroencephalogram (EEG) features of typically developing term-born infants at 4 months.

Method: Infants recruited at birth were randomized to intervention (routine parent-led massage) and control groups. Infants had a daytime sleep EEG at 4 months and were assessed using the Griffiths Scales of Child Development, Third Edition at 4 and 18 months. Comparative analysis between groups and subgroup analysis between regularly massaged and never-massaged infants were performed. Groups were compared for sleep stage, sleep spindles, quantitative EEG (primary analysis), and Griffiths using the Mann–Whitney *U* test.

Results: In total, 179 out of 182 infants (intervention: 83 out of 84; control: 96 out of 98) had a normal sleep EEG. Median (interquartile range) sleep duration was 49.8 minutes (39.1–71.4) (n = 156). A complete first sleep cycle was seen in 67 out of 83 (81%) and 72 out of 96 (75%) in the intervention and control groups respectively. Groups did not differ in sleep stage durations, latencies to sleep and to rapid eye movement sleep. Sleep spindle spectral power was greater in the intervention group in main and subgroup analyses. The intervention group showed greater EEG magnitudes, and lower interhemispherical coherence on subgroup analyses. Griffiths assessments at 4 months (n = 179) and 18 months (n = 173) showed no group differences in the main and subgroup analyses.

Interpretation: Routine massage is associated with distinct functional brain changes at 4 months.

Early infancy is a period of intense learning and development including the processes of neural proliferation, differentiation, migration, myelination, and circuit formation.[1] During this crucial time, we may expect to see the most marked effects of environment-dependent enrichment. Environmental enrichment occurs when stimuli are introduced into the environment, within the appropriate timeframe, positively affecting development through epigenetics and neural plasticity.[2] Infant massage can be considered an environmental enrichment as it involves tactile stimulation and social bonding.[3] Studies suggest that infant massage may counterbalance some negative outcomes resulting from adverse events in early life,[4] and accelerate preterm neurodevelopment,[3,5,6] although some changes fade over the second half of infancy.[3] However, much remains unknown about the possible benefits of infant massage on the neurodevelopment of term-born, low-risk infants.

A considerable part of infant life is spent in sleep, with term-born infants sleeping more than two-thirds of the day. Important sleep transitions related to maturation occur

Abbreviations: NREM, non-rapid eye movement; REM, rapid eye movement.

during infancy. For most infants, by 4 months of age, sleep onset no longer starts in rapid eye movement (REM) but in non-rapid eye movement (NREM) and sleep stages become more mature, with three different NREM stages being readily identifiable. Sleep spindles are well established by 4 months of age as a result of thalamic and cortical interactions and their features reflect processes of ageing, memory consolidation, and cognitive skills.[7] In addition, other sleep electroencephalogram (EEG) features such as EEG power spectrum characteristics also evolve with ageing, particularly in early life, and these changes are partly associated with neurodevelopment.[8]

The primary aim of this study was to explore the impact of massage on infant neurodevelopment using EEG assessment of sleep parameters such as sleep macrostructure, sleep spindles, and quantitative EEG (qEEG).

What this paper adds

- Routine massage of infants is associated with differences in sleep electroencephalogram biomarkers at 4 months.
- Massaged infants had higher sleep spindle spectral power, greater sleep EEG magnitudes, and lower interhemispherical coherence.
- No differences between groups were observed in total nap duration or first cycle macrostructure.

METHOD

Participants

Neonates were recruited post-delivery at Cork University Maternity Hospital, Cork, Ireland, during 2017 to 2018 to the BabySMART study (Study of Massage Therapy, Sleep And neurodevelopMenT, registered identifier NCT03381027), a randomized controlled parallel-group trial to evaluate the impact of massage intervention on infant neurodevelopment. The study was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Cork, Ireland. Inclusion criteria were gestational age greater than or equal to 37 weeks and singleton birth; exclusion criteria included admission to a neonatal intensive care unit, and suspected congenital or metabolic anomalies. Written informed consent was obtained from all parents or guardians. Infants were randomly assigned (1:1) to the intervention (daily massage) group or the control (routine care) group. Block randomization (with varying block sizes of two, four, and six) was used to allocate infants to each group. The randomization list was generated by a biostatistician using the 'ralloc' procedure in Stata. Sequentially numbered, opaque, sealed envelopes ensured concealment. Owing to the nature of the intervention, the recruiting research personnel, clinical team, and families of the infants were aware of group allocation. EEG recordings, neurodevelopmental assessments, and statistical analysis were performed blinded to group allocation.

Massage

A massage training session of about 45 minutes at the 2-week appointment and optional review classes during the study were provided to parents in the intervention group by a physiotherapist, certified by the International Association of Infant Massage (massage instructions booklet in Appendix S1). From 2 weeks of age until the 4-month appointment, parents were asked to perform a massage routine three times daily for at least 15 minutes on at least two body areas and to keep a massage diary. The parents were given 'Johnson's® Head-to-Toe® extra moisturizing baby cream' and parents were encouraged to use it during the infant massage but could use other products if they preferred. The control group were requested to use standard care throughout the study.

Assessments

The EEG recording technique has been described in detail in Ventura et al.[9] Briefly, at 4 months, EEGs were recorded using the Lifelines EEG (Lifelines Neuro, UK) acquisition system. An EEG was recorded using disposable electrodes placed according to the 10–20 system at positions Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, Pz, P3, P4, T5, T6, O1, O2, A1 and A2, plus reference, and ground with impedances less than 10kΩ. Extra channels included chin electromyography, electrooculogram, electrocardiogram, and a movement sensor to monitor respiration. The recording started as soon as all the electrodes were applied and ended when the infant was fully awake. During acquisition, quality of the recording was monitored using 24 bipolar EEG channels in a modified double-banana montage and 5 extra polygraphy channels. The appointments coincided with their normal diurnal nap time to increase the likelihood of sleep and were performed in the INFANT Research Centre sleep laboratory to reduce the influence of external stimuli.

Post-acquisition, sleep staging was performed according to American Academy of Sleep Medicine 2.4 definitions and rules[10] using a sleep staging application (Nicolet, Natus, USA); sleep spindles were annotated over left and right fronto-central regions with StratusEEG (Kvikna, Iceland) software. Both sleep stages and sleep spindles were identified manually by SV. All analyses were restricted to the first sleep cycle to avoid potential effects of decreasing sleep pressure on sleep features in subsequent sleep cycles. Parameters in the analysis included sleep spindles, sleep macrostructure derived from the sleep staging data such as sleep stage duration and latencies, and qEEG features, a set of objective biomarkers that capture key characteristics of the background EEG pattern.

Infants who fell asleep during electrode placement were excluded from sleep spindle number and density calculations because of a potential for missing spindles. Analysis of macrostructure features, except total sleep time, and qEEG was only performed for infants who had a complete first sleep cycle recorded. Within infants with a complete sleep cycle, those who had REM sleep before reaching criteria for staging N2 were excluded from the latency to REM analysis.

Spindle number and duration were calculated for each infant. Spindle density was defined as the number of sleep spindles per minute of NREM sleep. Mean frequency, brain symmetry index,[11] synchrony, and spectral power of sleep spindles were calculated using MATLAB (version R2020a, The MathWorks Inc., Natick, MA, USA). Spindle brain symmetry index was determined per epoch of 30 seconds using a sliding window with 75% overlap and an additional 9 Hz to 16 Hz passband filter to reduce the background activity present during a sleep spindle event. Synchrony calculation was based on the percentage of coincidental contralateral sleep spindles.[9]

Owing to the complexity of the EEG it was not possible to fully represent all EEGs by a finite set of features.[12] Instead, we characterized salient attributes of this complex, time-varying, multi-dimensional signal by generating multiple features that captured different overarching characteristics of the EEG. These features, generated using an open-source MATLAB toolbox (NEURAL version 0.4.3),[13] were divided into four groups: EEG magnitude, spectral distribution, continuity, and connectivity. Each group contained multiple features, described as follows.

The EEG magnitude group included features of spectral power and range-EEG (rEEG). Spectral power quantified EEG power in different frequency bands and rEEG quantified peak-to-peak amplitude. Four features were extracted from the rEEG: standard deviation (SD), median, and the 5th and 95th centiles of the rEEG; these last two are known as the lower (5th) and upper (95th) margins. The spectral distribution group captures frequency characteristics of the EEG which are independent of amplitude and power. This group included fractal dimension, an estimate of the slope of the power spectrum; spectral flatness, a measure of disorder (entropy) of the spectra; and spectral difference, a measure of change of the spectra over time. The continuity group captured deviations from a continuous EEG activity pattern. Features in this group included the skewness and kurtosis of the EEG and the rEEG asymmetry measure. The last group included measures of interhemispherical connectivity: brain symmetry index, a measure to quantify differences in spectral power across the hemispheres; and interhemispherical coherence, a measure of coupling calculated across bilateral electrode pairs.

Where applicable, features were further subdivided into a standard set of frequency bands: delta 1, 0.5 Hz to 2 Hz; delta 2, 2 Hz to 4 Hz; theta, 4 Hz to 8 Hz; alpha, 8 Hz to 12 Hz; sigma, 12 Hz to 15 Hz; beta, 15 Hz to 30 Hz; and gamma, 30 Hz to 45 Hz. Fractal dimension was calculated across the full bandwidth (0.5–45 Hz) and rEEG was pre-filtered to the 1 Hz to 20 Hz bandwidth, as detailed elsewhere.[13] All features were calculated for the different sleep stages. qEEG and spindle features estimated on short-time segments were summarized by a median value over time.

Infant neurodevelopmental outcome was assessed by a trained psychologist at 4 months and 18 months of age respectively using the Griffiths Scales of Child Development, Third Edition. The Griffiths Scales of Child Development, Third Edition measures overall general development (GD) and five neurodevelopmental areas: foundations of learning (A), language and communication (B), eye and hand coordination (C), personal–social–emotional (D), and gross motor abilities (E), with lower scores indicating more severe developmental delay. Sociodemographic questionnaires were given to the parents to complete at 2-week, 4-month, and 18-month appointments (data of the 18-month questionnaire not shown). At 4 months mothers also completed the Maternal Postnatal Attachment Scale, a 19-item questionnaire with possible scores ranging from 19 to 95, the latter score indicating the greatest maternal attachment[14] and Edinburgh Postnatal Depression Scale, a 10-item questionnaire with possible scores ranging from 0 to 30, the latter score indicating greatest likelihood of depression.[15]

Statistical analysis

For statistical analysis we used IBM SPSS Statistics (version 26.0, IBM Corp., Armonk, NY, USA). Continuous variables were described using median and interquartile range (IQR), and categorical variables using frequency and percentage. For comparisons between groups, a Mann–Whitney *U* test was used for continuous variables and a χ^2 test (with continuity correction for 2×2 tables) or Fisher's exact test (in the case of small expected counts) for categorical variables. All tests were two-sided and $p < 0.05$ was considered statistically significant.

We included a subgroup analysis where regularly massaged infants in the intervention group were compared to never-massaged infants in the control group. Participants in the intervention group were considered to massage regularly if the infant received at least two massage sessions, that lasted at least 5 minutes, over at least 4 days within each week for at least 10 weeks from week 4 to the end of week 16. Never-massaged control infants were identified on the basis of questionnaire responses from the parents.

We did not adjust for multiple comparisons in the analysis owing to the exploratory nature of this study and because reducing the probability of type I error would increase the probability of type II error.[16,17]

An a priori sample size calculation indicated that a sample of 150 infants (75 per group) was necessary for an independent-samples *t*-test to detect a difference of 6% in mean active sleep between the intervention and control groups, assuming a mean of 52% in the control group, a standard deviation of 13%,[18] a power of 80%, a level of significance of 0.05, and a two-tailed test.

RESULTS

Demographics

A total of 408 newborn infants were consented to the study and randomized to intervention and control groups ($n = 204$ per group). At 4 months of age, 84 infants remained in the intervention group and 98 in the control group. Three infants were excluded from the analysis: two females, one from each group, who did not sleep during the EEG, and a male infant in the control group who had a grossly abnormal EEG and was referred for further clinical assessment. Hence, 179 infants were included in the main analysis (83 from the intervention and 96 from the control group) (Figure S1). Demographic variables were similar between groups (Table 1). To assess the risk of bias, we compared demographic characteristics provided at registration between (1) infants included ($n = 179$) and those excluded in our analysis ($n = 229$) and (2) within those excluded, infants allocated to intervention ($n = 121$) and control ($n = 108$) groups (Tables S1 and S2). Maternal age was significantly lower in the excluded group than in the included group (mean 32 years 4 months [SD 5 years 3 months] vs 34 years 11 months [4 years 0 months], $p < 0.001$). No other statistically significant differences were observed. For the subgroup analyses, 33 regularly massaged infants in the intervention group and 57 never-massaged control infants were included (Figure S2). By 18 months, six infants were lost to follow-up. Hence, for the comparison of neurodevelopmental outcome at 18 months, 173 infants were included in the main analysis (81 from the intervention and 92 from the control group) and 89 infants were included in the subgroup analysis (33 from the intervention and 56 from the control group).

Sleep analyses

For those who had sleep onset recorded ($n = 156$), median (IQR) total sleep time was 49.8 minutes (39.1–71.4) with no significant differences between groups; the intervention group slept 50.5 minutes (40.0–68.0), $n = 75$; the control group 49.0 minutes (37.8–72.5), $n = 81$ ($p = 0.76$). Similarly, in the subgroup analysis, there was no statistically significant difference ($p = 0.68$) between total sleep time of regularly massaged intervention (50.0 minutes [42.6–62.4], $n = 32$) and never-massaged control infants (50.0 minutes [37.0–72.0], $n = 47$).

There were no statistically significant differences in any of the sleep macrostructure parameters studied (Table 2). For sleep spindle parameters, the spectral power was significantly different between groups, being higher in the intervention group (intervention: 8.89μV^2 [6.46–12.70], $n = 83$; control: 7.82μV^2 [4.75–11.40], $n = 96$; $p = 0.04$) (Table 2). In the subgroup analysis, spectral power remained significantly higher in the intervention group with greater differences between groups (intervention: 10.09μV^2 [6.89–13.67], $n = 33$; control: 7.86μV^2 [5.01–10.77], $n = 57$; $p = 0.03$). Similar to the main analysis, sleep macrostructure and other sleep spindle features were not statistically different.

qEEG features that were significantly different between the two groups in either the main or the subgroup analyses are presented in Table 3. We found higher magnitudes (i.e. spectral power and rEEG measures) across multiple frequency bands and sleep stages in the intervention group compared with the never-massaged group. In the subgroup analysis, most magnitude differences remained (Figure 1). N1 amplitude kurtosis in alpha, N3 delta 2 spectral flatness, REM theta, and N3 gamma relative powers were no longer statistically significant in the subgroup analysis. Within the subgroup analysis, some other statistical differences did emerge, namely higher standard deviation of rEEG in REM and N3 beta spectral differences in the intervention group and lower interhemispherical coherence (Figure 2) in regularly massaged infants. All results are shown in Tables S3 and S4.

Griffiths Scales of Child Development, Third Edition analysis

In the main analysis, intervention and control groups scored a median (IQR) of 117 (112–127) and 122 (112–127) at 18 months on Griffiths general development respectively ($p = 0.36$). There were no significant differences in any of the Griffiths scores at 4 and 18 months between groups in the main and subgroup analyses (Table S5 and Table 4 respectively).

DISCUSSION

To date, there is still no clear evidence of a beneficial effect of massage on cognitive development in term-born infants.[19] This randomized controlled study investigated the associations between routine parent-led massage during the first 4 months of age and neurodevelopment in a typically developing term-born cohort. This study has identified a higher background EEG magnitude across a range of frequencies and sleep stages, higher sleep spindle power, and lower interhemispherical coherence in regularly massaged infants at 4 months of age. The results may be generalizable to similar populations. Socioeconomics, maternal attachment, and likelihood of depression are factors that condition cognitive outcomes; no statistical differences were observed between groups (Table 1).

Massage typically coexists with other forms of social interaction,[19] so both handling and social interactions are key elements. In animal models, neonatal handling promotes specific learning and memory formation, modulates stress responses, and conditions an array of behaviours.[20] Maternal care is responsible for epigenetic modulation[21] and influences synaptogenesis.[22] Children whose mothers show more positive demonstrations of affection score better on performance and verbal IQ at later ages.[23] Infant massage

TABLE 1 Demographic data.

Demographics	Intervention			Control			p[a]
	n	n (%)[b]		n	n (%)[b]		
Registration and 2-week questionnaire							
Gestational age (weeks), median (IQR)	83	39.9	(39.0–40.9)	96	39.9	(38.9–41.0)	0.68
Birthweight (kg), median (IQR)	83	3.5	(3.2–3.8)	96	3.6	(3.3–3.8)	0.40
Sex, male	83	45	(54)	96	56	(58)	0.69[c]
Maternal age (years:months), median (IQR)	83	35:6	(32:4–37:8)	96	35:1	(32:9–37:7)	0.88
Maternal level of education	83			96			0.13[d]
Secondary school		2	(2)		7	(7)	
Third level certificate or diploma		19	(23)		17	(18)	
Degree or higher/graduate diploma		41	(49)		37	(39)	
Postgraduate		21	(25)		35	(35)	
Parents' annual net income after taxes	83			96			0.76[e]
€30 000 or less		5	(6)		8	(8)	
€30 001–€60 000		20	(24)		19	(20)	
€60 001 or above		37	(45)		40	(42)	
Prefer not to say/do not know		21	(25)		29	(29)	
4-month appointment and 4-month questionnaire							
Timing of recording, morning[f]	83	45	(54)	96	45	(47)	0.41[c]
Chronological age (weeks), median (IQR)	83	19.3	(18.3–20.4)	96	19.4	(18.6–20.4)	0.79
Weight (kg), median (IQR)	83	6.9	(6.5–7.6)	96	7.1	(6.4–7.8)	0.50
Type of feeding	80			96			0.51[e]
Breast fed		29	(35)		29	(29)	
Infant formula		38	(48)		54	(56)	
Both		13	(16)		13	(14)	
Fed on a regular schedule	80			96			0.60[e]
Yes, always		11	(14)		13	(14)	
Yes, try to		26	(33)		38	(40)	
No, fed on demand		43	(54)		45	(47)	
Duration of dermatosis with pruritus, if present	9			18			1.00[d]
Less than 6 weeks		5	(56)		9	(50)	
Between 6 weeks and less than 3 months		4	(44)		8	(44)	
Between 3 and 4 months		0	(0)		1	(6)	
Maternal EPDS, likelihood of depression	80			96			0.88[d]
Low (scored 0–9)		70	(88)		85	(89)	
Average (scored 10–12)		6	(8)		8	(8)	
High (scored >12)		4	(5)		3	(5)	
Maternal attachment score, median (IQR)	80	86.9	(83.0–90.5)	96	86.9	(82.7–90.5)	0.90

Descriptive statistics using median and interquartile range (IQR) or n (%).

Abbreviation: EPDS, Edinburgh Postnatal Depression Scale scores.

[a]From Mann–Whitney U test unless otherwise stated.

[b]Unless otherwise stated.

[c]From χ^2 test with continuity correction.

[d]From Fisher's exact test.

[e]From Pearson's χ^2 test.

[f]Recording performed in morning or afternoon.

TABLE 2 Sleep macrostructure and sleep spindle measures during the first sleep cycle, main and subgroup analysis.

	Intervention			Control			
Sleep parameters	***n***	**Median (IQR)**		***n***	**Median (IQR)**		***p*** [a]
Main analysis							
Sleep macrostructure							
1st sleep cycle duration (minutes)	67	43.00	(38.50–50.50)	72	43.25	(37.00–51.88)	0.78
N1 (minutes)	67	8.00	(5.00–11.50)	72	7.75	(4.50–13.38)	0.66
N2 (minutes)	67	5.00	(3.00–8.00)	72	4.50	(2.50–6.50)	0.48
N3 (minutes)	67	21.00	(15.00–25.00)	72	21.50	(16.63–25.38)	0.47
NREM total (minutes)	67	33.50	(28.00–39.00)	72	35.50	(30.13–40.50)	0.29
REM (minutes)	67	9.00	(5.00–12.50)	72	6.50	(3.63–11.50)	0.24
REM (%)	67	21.18	(13.16–28.57)	72	17.44	(9.49–27.70)	0.15
Latency to sleep (minutes)	67	9.00	(5.00–15.00)	72	8.50	(4.00–14.00)	0.85
Latency to REM[b] (minutes)	62	34.75	(28.00–41.00)	70	36.00	(30.50–41.63)	0.36
Sleep spindles							
Frequency (Hz)	83	12.99	(12.80–13.24)	96	13.02	(12.79–13.27)	0.78
Duration (s)	83	3.17	(2.68–3.54)	96	2.92	(2.60–3.58)	0.27
Spectral power (μV^2)	83	8.89	(6.46–12.70)	96	7.82	(4.75–11.40)	0.04*
Brain symmetry index	83	0.20	(0.17–0.25)	96	0.20	(0.16–0.29)	0.70
Synchrony (%)	83	59.44	(53.80–63.82)	96	59.21	(53.19–63.80)	0.52
Number[c]	75	242.0	(185.0–282.0)	81	244.0	(194.0–286.5)	0.59
Density[c] (spindles/minute)	75	6.67	(5.53–8.05)	81	6.72	(5.79–8.03)	0.73
Subgroup analysis							
Sleep macrostructure							
1st sleep cycle duration (minutes)	29	44.00	(39.50–50.50)	41	45.00	(37.50–53.25)	0.80
N1 (minutes)	29	8.00	(5.25–12.25)	41	8.50	(5.50–15.50)	0.47
N2 (minutes)	29	5.50	(2.75–8.75)	41	5.00	(2.75–6.50)	0.38
N3 (minutes)	29	22.50	(14.00–26.25)	41	22.00	(16.50–25.00)	0.87
NREM total (minutes)	29	37.00	(30.50–42.75)	41	36.00	(30.50–45.75)	0.97
REM (minutes)	29	7.50	(4.75–12.25)	41	7.50	(4.50–12.25)	0.89
REM (%)	29	18.27	(12.52–26.07)	41	17.74	(10.71–26.96)	1.00
Latency to sleep (minutes)	29	9.50	(5.50–18.00)	41	9.00	(3.75–16.75)	0.59
Latency to REM[b] (minutes)	26	37.00	(31.13–44.50)	41	37.00	(31.50–44.00)	0.86
Sleep spindles							
Frequency (Hz)	33	13.00	(12.68–13.15)	57	13.02	(12.81–13.27)	0.21
Duration (s)	33	3.07	(2.67–3.50)	57	2.84	(2.55–3.56)	0.70
Spectral power (μV^2)	33	10.09	(6.89–13.67)	57	7.86	(5.01–10.77)	0.03*
Brain symmetry index	33	0.21	(0.18–0.28)	57	0.19	(0.16–0.26)	0.09
Synchrony (%)	33	59.14	(53.44–62.93)	57	59.27	(54.69–64.02)	0.59
Number[c]	32	249.5	(187.3–297.0)	47	253.0	(192.0–295.0)	0.83
Density[c] (spindles/minute)	32	6.54	(5.42–7.94)	47	6.78	(5.35–8.72)	0.57

Abbreviations: EEG, electroencephalogram; IQR, interquartile range; NREM, non-rapid eye movement; REM, rapid eye movement.

[a]From Mann–Whitney *U* test; statistically significant differences ($p < 0.05$) marked with an asterisk.

[b]Infants who met criteria for staging REM before N2 were excluded.

[c]Infants who fell asleep before EEG were excluded.

TABLE 3 qEEG features with statistically significant differences between the two groups in either main or subgroup analyses during the first sleep cycle.

			Intervention		Control		
qEEG type	**SS**	**FB**	**Median (IQR)**		**Median (IQR)**		***p*[a]**
Main analysis[b]							
Amplitude kurtosis	N1	α	3.49	(3.41–3.70)	3.43	(3.36–3.56)	0.04*
rEEG: lower margin (μV)	N1		63.33	(54.37–73.86)	57.22	(50.72–68.68)	0.02*
rEEG: median margin (μV)	N1		94.28	(81.97–110.07)	85.59	(75.11–100.30)	0.02*
rEEG: upper margin (μV)	N1		138.57	(119.52–164.36)	127.13	(112.28–147.95)	0.04*
Spectral power (μV^2)	N1	δ1	342.09	(269.90–458.32)	298.50	(215.89–408.80)	0.05
Spectral power (μV^2)	N1	δ2	216.52	(162.77–293.43)	178.46	(132.67–256.30)	0.04*
Spectral power (μV^2)	N1	θ	79.71	(66.27–127.88)	72.36	(49.37–96.39)	0.02*
Spectral power (μV^2)	N1	α	7.40	(5.95–10.67)	6.23	(5.00–8.31)	0.01*
Spectral power (μV^2)	N1	σ	2.30	(1.64–2.97)	1.80	(1.44–2.53)	0.02*
Coherence	N2	δ1	0.26	(0.19–0.29)	0.26	(0.21–0.31)	0.79
Coherence	N2	δ2	0.14	(0.11–0.17)	0.14	(0.12–0.17)	0.84
Coherence	N2	α	0.06	(0.04–0.09)	0.06	(0.04–0.08)	1.00
Coherence	N2	σ	0.09	(0.07–0.13)	0.09	(0.07–0.12)	0.82
Spectral power (μV^2)	N2	δ1	445.74	(370.56–616.77)	376.30	(286.23–532.56)	0.008*
Spectral power (μV^2)	N2	θ	81.35	(64.63–106.66)	73.53	(55.33–89.08)	0.03*
Spectral power (μV^2)	N2	β	7.60	(5.55–8.91)	6.11	(5.02–7.86)	0.04*
Spectral power (μV^2)	N2	γ	2.66	(2.12–3.41)	2.13	(1.84–2.88)	0.01*
Coherence	N3	δ1	0.23	(0.20–0.29)	0.26	(0.22–0.28)	0.30
Coherence	N3	δ2	0.14	(0.10–0.16)	0.13	(0.12–0.16)	0.78
Coherence	N3	σ	0.09	(0.08–0.12)	0.10	(0.08–0.12)	0.37
Coherence	N3	β	0.07	(0.05–0.10)	0.07	(0.06–0.10)	0.25
Coherence	N3	γ	0.06	(0.04–0.10)	0.07	(0.05–0.10)	0.26
rEEG median margin (μV)	N3		122.51	(108.06–131.99)	114.50	(99.35–128.60)	0.12
Relative spectral power (%)	N3	γ	0.16	(0.13–0.19)	0.13	(0.11–0.18)	0.02*
Spectral difference	N3	β	0.003	(0.002–0.005)	0.003	(0.002–0.005)	0.58
Spectral flatness	N3	δ2	0.89	(0.86–0.90)	0.88	(0.86–0.90)	0.04*
Spectral power (μV^2)	N3	β	5.47	(4.67–6.72)	4.70	(3.97–5.94)	0.004*
Spectral power (μV^2)	N3	γ	2.02	(1.70–2.52)	1.61	(1.29–1.98)	<0.001*
Amplitude skew	R	θ	0.015	(0.013–0.017)	0.017	(0.014–0.019)	<0.001*
Coherence	R	γ	0.04	(0.04–0.07)	0.05	(0.04–0.06)	0.26
rEEG lower margin (μV)	R		51.09	(45.86–58.42)	46.67	(42.34–54.56)	0.006*
rEEG median margin (μV)	R		76.09	(66.54–84.93)	70.44	(62.02–80.59)	0.03*
rEEG upper margin (μV)	R		109.69	(94.74–123.51)	101.63	(91.45–117.31)	0.06
rEEG SD (μV)	R		17.24	(14.70–19.60)	16.24	(14.16–18.64)	0.12
Spectral flatness	R	δ2	0.90	(0.88–0.92)	0.89	(0.87–0.91)	0.004*
Relative spectral power (%)	R	θ	9.87	(8.57–11.58)	9.04	(7.86–10.77)	0.03*
Spectral power (μV^2)	R	δ2	128.81	(94.43–164.94)	106.94	(82.57–151.24)	0.08
Spectral power (μV^2)	R	θ	48.19	(39.05–69.23)	39.89	(32.09–51.98)	0.003*
Spectral power (μV^2)	R	α	5.22	(4.39–6.49)	4.78	(3.69–5.88)	0.04*
Spectral power (μV^2)	R	σ	1.51	(1.27–1.80)	1.25	(1.02–1.70)	0.02*
Spectral power (μV^2)	R	β	4.11	(3.30–5.07)	3.64	(3.06–4.52)	0.02*
Spectral power (μV^2)	R	γ	2.28	(1.68–2.74)	1.89	(1.55–2.49)	0.02*

(Continues)

TABLE 3 (Continued)

			Intervention		Control		
qEEG type	**SS**	**FB**	**Median (IQR)**		**Median (IQR)**		***p*[a]**
Subgroup analysis[c]							
Amplitude kurtosis	N1	α	3.47	(3.37–3.57)	3.43	(3.34–3.55)	0.20
rEEG lower margin (μV)	N1		63.60	(54.27–71.92)	56.22	(49.29–68.51)	0.07
rEEG median margin (μV)	N1		90.71	(83.17–106.61)	81.96	(71.57–104.79)	0.06
rEEG upper margin (μV)	N1		134.26	(123.25–158.84)	124.33	(105.98–149.89)	0.09
Spectral power (μV^2)	N1	δ1	336.24	(262.03–441.76)	274.61	(195.78–341.32)	0.04*
Spectral power (μV^2)	N1	δ2	200.34	(159.43–270.58)	169.37	(123.71–277.69)	0.10
Spectral power (μV^2)	N1	θ	87.73	(69.79–120.77)	71.11	(44.99–99.15)	0.02*
Spectral power (μV^2)	N1	α	7.94	(6.13–10.36)	5.88	(4.81–8.68)	0.05
Spectral power (μV^2)	N1	σ	2.53	(1.68–3.01)	1.70	(1.42–2.58)	0.03*
Coherence	N2	δ1	0.22	(0.16–0.29)	0.27	(0.21–0.30)	0.03*
Coherence	N2	δ2	0.13	(0.11–0.16)	0.15	(0.13–0.19)	0.03*
Coherence	N2	α	0.05	(0.03–0.06)	0.06	(0.04–0.08)	0.03*
Coherence	N2	σ	0.08	(0.06–0.10)	0.10	(0.07–0.13)	0.02*
Spectral power (μV^2)	N2	δ1	439.75	(368.76–596.72)	363.88	(275.66–502.29)	0.04*
Spectral power (μV^2)	N2	θ	86.18	(71.09–105.18)	71.48	(53.23–95.94)	0.04*
Spectral power (μV^2)	N2	β	7.33	(5.58–8.62)	6.81	(5.37–8.27)	0.48
Spectral power (μV^2)	N2	γ	2.78	(2.14–3.54)	2.30	(1.76–3.17)	0.07
Coherence	N3	δ1	0.20	(0.16–0.27)	0.26	(0.23–0.28)	0.003*
Coherence	N3	δ2	0.12	(0.10–0.15)	0.14	(0.12–0.16)	0.01*
Coherence	N3	σ	0.08	(0.06–0.11)	0.10	(0.08–0.12)	0.006*
Coherence	N3	β	0.06	(0.04–0.08)	0.07	(0.06–0.10)	0.04*
Coherence	N3	γ	0.05	(0.03–0.08)	0.06	(0.05–0.09)	0.03*
rEEG median margin (μV)	N3		125.36	(111.91–135.56)	112.31	(98.44–128.53)	0.05*
Relative spectral power (%)	N3	γ	0.16	(0.13–0.18)	0.14	(0.11–0.19)	0.47
Spectral difference	N3	β	0.004	(0.003–0.006)	0.003	(0.002–0.005)	0.04*
Spectral flatness	N3	δ2	0.90	(0.87–0.91)	0.88	(0.86–0.90)	0.10
Spectral power (μV^2)	N3	β	5.63	(4.96–6.65)	4.90	(4.04–6.25)	0.05
Spectral power (μV^2)	N3	γ	2.02	(1.78–2.62)	1.66	(1.30–2.11)	0.006*
Amplitude skew	R	θ	0.015	(0.013–0.017)	0.017	(0.015–0.019)	0.02*
Coherence	R	γ	0.04	(0.03–0.05)	0.05	(0.04–0.06)	0.03*
rEEG lower margin (μV)	R		52.97	(46.75–58.67)	45.72	(41.53–52.97)	0.007*
rEEG median margin (μV)	R		76.09	(67.05–87.24)	67.85	(61.64–78.15)	0.02*
rEEG upper margin (μV)	R		109.69	(97.32–125.32)	99.55	(88.16–118.56)	0.04*
rEEG SD (μV)	R		17.84	(14.84–19.71)	15.48	(13.62–19.29)	0.04*
Relative spectral power (%)	R	θ	10.29	(9.13–11.79)	9.38	(7.88–11.31)	0.17
Spectral flatness	R	δ2	0.91	(0.88–0.92)	0.88	(0.86–0.90)	0.01*
Spectral power (μV^2)	R	δ2	126.21	(95.81–165.02)	101.05	(72.07–145.70)	0.04*
Spectral power (μV^2)	R	θ	54.45	(41.47–69.48)	38.31	(31.71–54.07)	0.006*
Spectral power (μV^2)	R	α	5.76	(4.54–6.66)	4.95	(3.78–6.38)	0.10
Spectral power (μV^2)	R	σ	1.56	(1.31–1.82)	1.37	(1.07–1.77)	0.09
Spectral power (μV^2)	R	β	4.24	(3.62–5.14)	3.78	(3.01–4.84)	0.06
Spectral power (μV^2)	R	γ	2.41	(1.89–2.84)	1.94	(1.54–2.66)	0.02*

Abbreviations: EEG, electroencephalogram; FB, frequency bands: 0.5–2 Hz (δ1), 2–4 Hz (δ2), 4–8 Hz (θ), 8–12 Hz (α), 12–15 Hz (σ), 15–30 (β), 30–45 Hz (γ); IQR, interquartile range; qEEG, quantitative EEG; rEEG, range-EEG (frequency band 1–20 Hz); SS, sleep stage.

[a]From Mann–Whitney *U* test; statistically significant differences ($p < 0.05$) marked with an asterisk.

[b]Intervention: $n = 67$; control: $n = 72$.

[c]Regularly massaged intervention: $n = 29$; never-massaged control: $n = 41$.

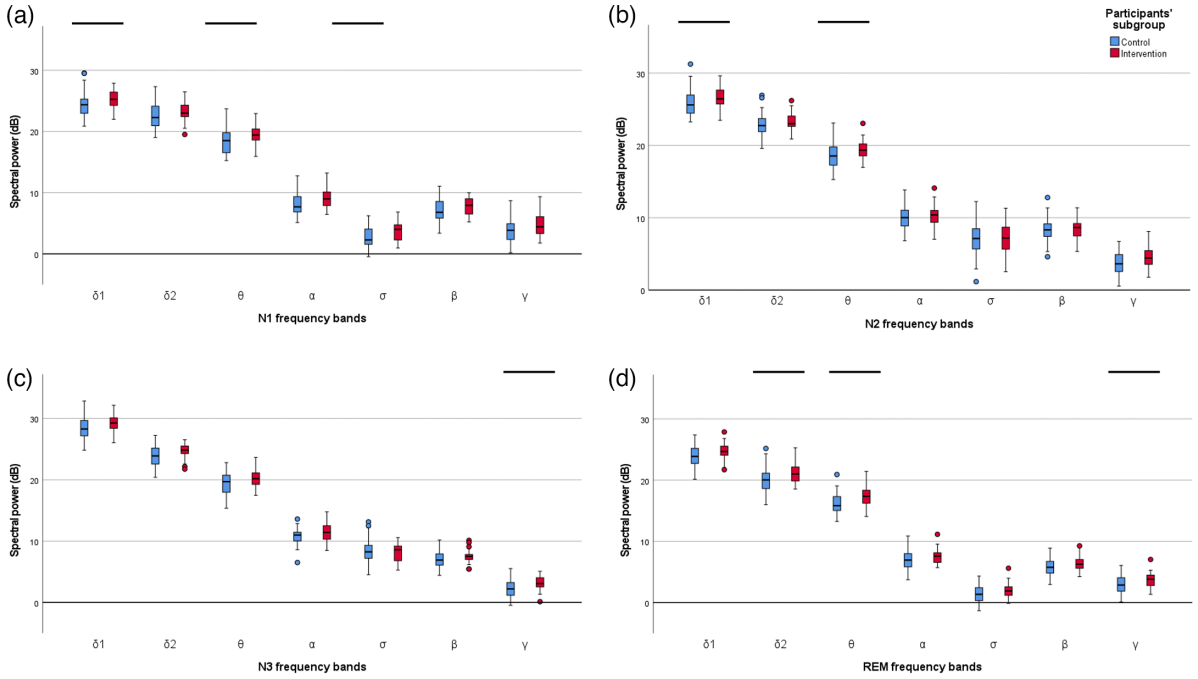

FIGURE 1 Spectral power across frequency bands and sleep stages during the 1st cycle on the basis of the subgroup analysis (i.e. the regularly massaged intervention group and never-massaged control infants). Horizontal lines indicate statistically significant differences between subgroups and circles indicate outliers. Units converted to decibels (dB; i.e. $10\log_{10}$[spectral power]) to compare magnitudes in different frequency bands. (a–d) Spectral power during N1, N2, N3, and rapid eye movement (REM) respectively.

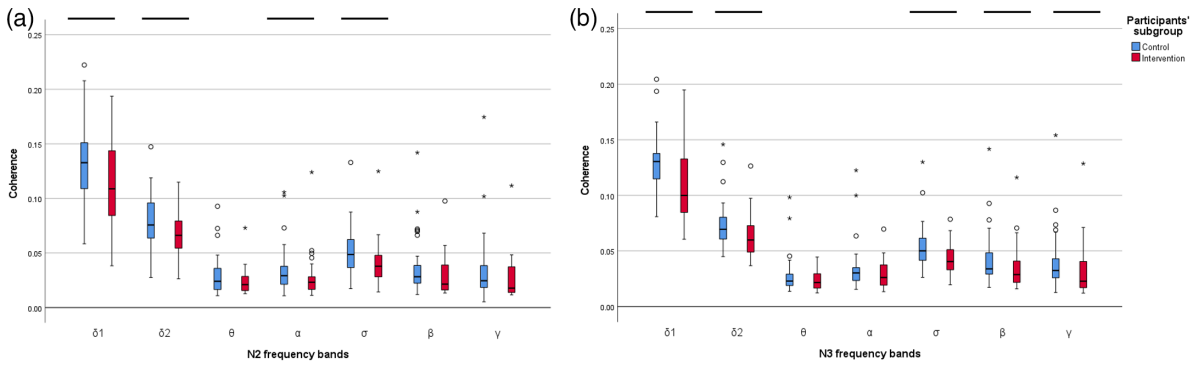

FIGURE 2 Interhemispherical coherence across frequency bands during the first cycle on the basis of the subgroup analysis (i.e. the regularly massaged intervention group and never-massaged control infants). Horizontal lines, indicate statistically significant differences between subgroups in the corresponding frequency ranges; circles and stars, outliers and extreme outliers respectively. (a, b) Coherence during N2 and N3 respectively.

may decrease stress-related hormones and increase serotonin.[4] This protective effect against stress may in itself influence neurodevelopment.[24]

Even though massage may help induce sleep,[4] evidence does not support its contribution to an overall daily increase of time spent asleep.[19] Similarly, in our study, routine massage had no effect on total time asleep during the nap, on first sleep cycle length, or duration of individual sleep stages (Table 2).

We found higher spectral power values for sleep spindles in the intervention group than in the control group, and these differences increased in the subgroup analysis (Table 2). These group differences were not observed in the sigma band spectral power during N2 and N3, indicating that spindle power increase was not simply due to a general increase in background magnitude in this band. Existing literature shows an increasing sleep spindle magnitude in infancy;[25] thus, these observations may be evidence of infant massage as an accelerator of brain maturation.[5] Sleep spindle power is positively associated with axial diffusivity in the forceps minor, anterior corpus callosum, and tracts in the temporal lobe and thalamus.[26] Axial diffusivity relates to the diffusion of water parallel to the axons. Although it is not entirely understood why increases in axial diffusivity can be present in early neurodevelopment, it is proposed to reflect decreased axonal tortuosity,[27] or increased extra-axonal

TABLE 4 Neurodevelopmental outcomes at 18 months.

	Intervention			Control			
Griffiths III results at 18 months	***n***	**Median (IQR)**		***n***	**Median (IQR)**		***p*** [a]
Main analysis							
General development[b]	81	117	(112–127)	92	122	(112–127)	0.36
Subscales							
A. Foundations of learning	81	114	(105–122)	92	114	(105–122)	0.67
B. Language and communication	81	109	(95–117)	92	109	(99–117)	0.53
C. Eye and hand coordination	81	114	(105–122)	92	118	(109–122)	0.23
D. Personal–social–emotional	81	118	(112–125)	92	122	(117–125)	0.28
E. Gross motor	81	130	(126–135)	92	135	(126–135)	0.15
Subgroup analysis							
General development[b]	33	122	(114.5–127)	56	122	(112–127)	0.33
Subscales							
A. Foundations of learning	33	114	(110–120)	56	114	(105–122)	0.59
B. Language and communication	33	109	(95–118.5)	56	104	(95–117)	0.44
C. Eye and hand coordination	33	118	(109–122)	56	116	(106–122)	0.66
D. Personal–social–emotional	33	122	(115–125)	56	118	(115–125)	0.26
E. Gross motor	33	130	(130–135)	56	135	(126–135)	0.90

Abbreviations: Griffiths III, Griffiths Scales of Child Development, Third Edition; IQR, interquartile range.

[a]From Mann–Whitney *U* test.

[b]A lower score indicates more severe neurodevelopmental delay.

space[28,29] due to pruning of superfluous connections.[30] Functionally, sigma power has been positively associated with full-scale and fluid IQ[31] scores, while spindle-related frequency was negatively associated with perceptual reasoning, comprehension, and working memory,[32] among others. Owing to the neuroplastic properties of spindles, they are thought to play a role in memory consolidation processes.[33]

Results of qEEG indicated two major differences in the intervention group: the signal magnitude-related features, which showed a higher magnitude of signals, measured by rEEG margins and spectral power across nearly all frequency bands studied, largely replicated in the subgroup analysis; and lower levels of interhemispherical coherence (Table 3). Some of the qEEG statistically significant features were not preserved after subgroup analysis; this was probably because of the reduced number of participants and consequent loss of statistical power.

Previous studies of massage in infants born preterm have found differences in spectral power during active sleep. A parent-led massage study showed a dose association up to term equivalent age on global relative power, and increased localized alpha in the massage group[6] and in a study with a massage-expert, significant local and global absolute spectral power interactions between massage and non-massage groups were found before and after a massage routine performed by an expert.[5] In line with previous observations, we also found effects of massage on spectral power in our group of term-born infants. Although changes in spectral power values of different frequency bands with maturation are regionally specific,[8] overall, there is a net increase of the spectral power during the first half-year of life.[34] In this context, our findings of increased EEG magnitude further support the notion of more advanced brain maturation in the routinely massaged group, extending observations to cohorts of infants born at term.[5,6]

Subgroup analysis revealed lower interhemispherical coherence, a marker of functional connectivity, in the intervention group in nearly all frequency bands studied, particularly during NREM sleep (Table 3). Advanced functional axonal pruning of the corpus callosum connecting the two hemispheres, which occurs during early infancy, may explain this finding. Although connectivity changes vary across maturation, reflecting cycles of synaptic establishment and elimination[35] occurring at different time points in different brain regions; our study revealed a net decrease in interhemispherical connectivity in those infants who had regular parent-led massage during their first 4 months of life. Previous studies have noted decrements of interhemispherical connectivity in specific points of infancy and childhood (see, for example, Xiao et al.[36]; Boersma et al.[37]). For example, from 5 to 7 years old, a general decrease of connectivity is accompanied by increased functional node clustering and path length and decreased heterogeneity of the synaptic weights; this indicates a possible transition from random to more organized network arrangement.[37] In infants and toddlers, interhemispherical decreases of connectivity between homologous

cortical areas may be expected as a result of neural segregation while integrating intrahemispherical areas of interest, accompanied by improvement of specific performances.[36,38] In our cohort, the changes were seen in a resting state after providing continued environmental enrichment in the form of parental massage. The changes provided by continued massage sessions may have caused plastic changes that contributed to the differences in patterns seen 'offline' in the sleeping state.

Our qEEG subgroup analysis also demonstrated differences in continuity (EEG skewness), and spectral distribution (spectral flatness and spectral differences) between groups. These results highlight that there are subtle changes in the EEG structure beyond the most evident sleep analysis that could only be observed through qEEG.[13]

There were no statistically significant differences on Griffiths assessments at 4 months and 18 months between the two groups (Table S5 and Table 4). We hypothesize that neurodevelopmental changes from routine massage are too subtle to be observable on Griffiths assessments at these early ages and that differences may only be evident at later time points, particularly school-age.

This study builds on knowledge about the effects of regular parent-led massage. So far, most studies of infant massage have focused on neurodevelopment in preterm cohorts. To our knowledge, this is the first study to report the effects of routine massage on the sleep EEG measures of typically developing term-born infants. With 179 infants included in this study up to 4 months, this is one of the largest and longest studies of infant massage. This study also included a diverse array of sleep measures that ranged from the duration of sleep stages, multiple sleep spindle features, and qEEG measurements. However, the approach in this exploratory study also implies that multiple analyses increase the probabilities of false-positive results. Because of this, we discuss general qEEG aspects instead of individual associations. The results were consistent, showing higher magnitude and lower coherence on intervention in several frequency ranges and sleep stages.

Before starting the massage routine, parents from the intervention group performed the massage on their children during the class with the International Association of Infant Massage-certified physiotherapist who corrected the technique if necessary. Parents were also invited to attend this class as a refresher if they had any further questions. However, we did not assess the quality of massage on a day-to-day basis, which can be considered a limitation of our study. A further limitation is that we did not perform a laboratory adaptation sleep session owing to logistics. First 'night' effects can alter some macrostructure and spindle features. However, as all participant EEGs were recorded under the same conditions in this randomized controlled study, this should not influence the results of the comparative analysis. Owing to the high dropout rate, we compared demographic characteristics measured at registration between participants included in our study and those excluded (Tables S1 and S2). However, the sociodemographic data obtained at registration were limited. Another limitation is the low compliance in the intervention group: only 33 out of 83 infants were regularly massaged, although all infants in the intervention group were massaged. One reason for non-compliance may have been a mismatch between expectations at recruitment and the actual reality of the considerable demands of being a new parent and accommodating additional regular massage into the daily routine. Although occasional phone calls of encouragement to parents may have helped retain some participants, future studies may achieve higher compliance if participants are enrolled after families are settled in their routines at home. Importantly, some group differences were still observed in the main analysis, indicating that less restrictive routine massage criteria may be acceptable to retain more participants and improve compliance. Further in-depth analysis should analyse the effects of massage by sex and relate infant massage to other neurodevelopmental assessments, including memory abilities, and examine the persistence of EEG changes observed in this study as participants age.

CONCLUSION

A parent-led massage routine during the first 4 months of age produced detectable changes in the sleep EEG. Those changes included higher spectral power in sleep spindles, higher magnitude of the EEG, and decreased interhemispherical coherence across most frequency bands and sleep stages. These findings indicate that environmental enrichment in the form of parental massage may be associated with a more mature neurodevelopmental profile observable in the infant sleep EEG at 4 months.

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DATA AVAILABILITY STATEMENT

It is not possible to share the datasets for the current study. The clinical data is collected under a written proxy consent from the participants' guardians/parents, which did not include permission for sharing or open data. To be allowed to share this data under Irish Health Research Regulations we are required to re-consent families or to obtain approval by the Health Regulation Consent Declaration Committee.

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REFERENCES

1. Stiles J, Jernigan TL. The basics of brain development. Neuropsychol Rev. 2010;20:327-48. https://doi.org/10.1007/s11065-010-9148-4.
2. Sale A. A Systematic Look at Environmental Modulation and Its Impact in Brain Development. Trends Neurosci. 2018;41:4-17. https://doi.org/10.1016/j.tins.2017.10.004.
3. Guzzetta A, Baldini S, Bancale A, Baroncelli L, Ciucci F, Ghirri P, et al. Massage accelerates brain development and the maturation of visual function. J Neurosci. 2009;29:6042-51. https://doi.org/10.1523/JNEUROSCI.5548-08.2009.
4. Field T, Grizzle N, Scafidi F, Abrams S, Richardson S, Kuhn C, et al. Massage therapy for infants of depressed mothers. Infant Behav Dev. 1996;19:107-12. https://doi.org/10.1016/S0163-6383(96)90048-X.
5. Guzzetta A, D'Acunto MG, Carotenuto M, Berardi N, Bancale A, Biagioni E, et al. The effects of preterm infant massage on brain electrical activity. Dev Med Child Neurol. 2011;53 Suppl 4:46-51. https://doi.org/10.1111/j.1469-8749.2011.04065.x.
6. Lai M, D'Acunto G, Guzzetta A, Finnigan S, Ngenda N, Ware RS, et al. Infant massage and brain maturation measured using EEG: A randomised controlled trial. Early Hum Dev. 2022;172:105632. https://doi.org/10.1016/j.earlhumdev.2022.105632.
7. Fernandez LMJ, Lüthi A. Sleep Spindles: Mechanisms and Functions. Physiol Rev. 2020;100:805-68. https://doi.org/10.1152/physrev.00042.2018.
8. Kurth S, Ringli M, Geiger A, LeBourgeois M, Jenni OG, Huber R. Mapping of cortical activity in the first two decades of life: a high-density sleep electroencephalogram study. J Neurosci. 2010;30:13211-9. https://doi.org/10.1523/JNEUROSCI.2532-10.2010.
9. Ventura S, Mathieson SR, O'Toole JM, Livingstone V, Ryan M-A, Boylan GB. Electroencephalographic sleep macrostructure and sleep spindles in early infancy. Sleep. 2021;45(1). https://doi.org/10.1093/sleep/zsab262.
10. Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, et al. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Version 2.4. Darien, IL: American Academy of Sleep and Associated Events; 2017.
11. van Putten MJ. The revised brain symmetry index. Clin Neurophysiol. 2007;118:2362-7. https://doi.org/10.1016/j.clinph.2007.07.019.
12. O'Toole JM, Boylan GB. Quantitative Preterm EEG Analysis: The Need for Caution in Using Modern Data Science Techniques. Front Pediatr. 2019;7:174. https://doi.org/10.3389/fped.2019.00174.
13. O'Toole JM, Boylan GB. NEURAL: quantitative features for newborn EEG using Matlab. 2017:[arXiv:1704.05694v1].
14. Condon JT, Corkindale CJ. The assessment of parent-to-infant attachment: Development of a self-report questionnaire instrument. J Reprod Infant Psychol. 1998;16(1):57-76. https://doi.org/10.1080/02646839808404558.
15. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987;150:782-6. https://doi.org/10.1192/bjp.150.6.782
16. Althouse AD. Adjust for Multiple Comparisons? It's Not That Simple. Ann Thorac Surg. 2016;101:1644-5. https://doi.org/10.1016/j.athoracsur.2015.11.024.
17. Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology. 1990;1:43-6.
18. Korotchikova I, Stevenson NJ, Livingstone V, Ryan CA, Boylan GB. Sleep–wake cycle of the healthy term newborn infant in the immediate postnatal period. Clin Neurophysiol. 2016;127:2095-101. https://doi.org/10.1016/j.clinph.2015.12.015.
19. Bennett C, Underdown A, Barlow J. Massage for promoting mental and physical health in typically developing infants under the age of six months. Cochrane Database Syst Rev. 2013;4:CD005038-CD. https://doi.org/10.1002/14651858.CD005038.pub3.
20. Raineki C, Lucion AB, Weinberg J. Neonatal handling: an overview of the positive and negative effects. Dev Psychobiol. 2014;56:1613-25. https://doi.org/10.1002/dev.21241.
21. Szyf M, Weaver I, Meaney M. Maternal care, the epigenome and phenotypic differences in behavior. Reprod Toxicol. 2007;24:9-19. https://doi.org/10.1016/j.reprotox.2007.05.001.
22. Liu D, Diorio J, Day JC, Francis DD, Meaney MJ. Maternal care, hippocampal synaptogenesis and cognitive development in rats. Nat Neurosci. 2000;3:799-806. https://doi.org/10.1038/77702.
23. Sheinkopf SJ, Tenenbaum EJ, Messinger DS, Miller-Loncar CL, Tronick E, Lagasse LL, et al. Maternal and infant affect at 4 months predicts performance and verbal IQ at 4 and 7 years in a diverse population. Dev Sci. 2017;20:e12479. https://doi.org/10.1111/desc.12479.
24. Gunnar M, Quevedo K. The neurobiology of stress and development. Annu Rev Psychol. 2007;58:145-73. https://doi.org/10.1146/annurev.psych.58.110405.085605.
25. Louis J, Zhang JX, Revol M, Debilly G, Challamel MJ. Ontogenesis of nocturnal organization of sleep spindles: a longitudinal study during the first 6 months of life. Electroencephalogr Clin Neurophysiol. 1992;83:289-96. https://doi.org/10.1016/0013-4694(92)90088-y.
26. Piantoni G, Poil S-S, Linkenkaer-Hansen K, Verweij IM, Ramautar JR, Van Someren EJ, et al. Individual differences in white matter diffusion affect sleep oscillations. J Neurosci. 2013;33:227-33. https://doi.org/10.1523/JNEUROSCI.2030-12.2013.
27. Lebel C, Treit S, Beaulieu C. A review of diffusion MRI of typical white matter development from early childhood to young adulthood. NMR Biomed. 2019;32:e3778. https://doi.org/10.1002/nbm.3778.
28. Rosas HD, Lee SY, Bender AC, Zaleta AK, Vangel M, Yu P, et al. Altered white matter microstructure in the corpus callosum in Huntington's disease: Implications for cortical "disconnection". Neuroimage. 2010;49:2995-3004. https://doi.org/10.1016/j.neuroimage.2009.10.015.
29. Della Nave R, Ginestroni A, Diciotti S, Salvatore E, Soricelli A, Mascalchi M. Axial diffusivity is increased in the degenerating superior cerebellar peduncles of Friedreich's ataxia. Neuroradiology. 2011;53:367-72. https://doi.org/10.1007/s00234-010-0807-1.
30. Luo L, O'Leary DD. Axon retraction and degeneration in development and disease. Annu Rev Neurosci. 2005;28:127-56. https://doi.org/10.1146/annurev.neuro.28.061604.135632.
31. Geiger A, Huber R, Kurth S, Ringli M, Jenni OG, Achermann P. The Sleep EEG as a Marker of Intellectual Ability in School Age Children. Sleep. 2011;34:181-9. https://doi.org/10.1093/sleep/34.2.181.
32. Gruber R, Wise MS, Frenette S, Knäauper B, Boom A, Fontil L, et al. The association between sleep spindles and IQ in healthy school-age children. Int J Psychophysiol. 2013;89:229-40. https://doi.org/10.1016/j.ijpsycho.2013.03.018.
33. Peyrache A, Seibt J. A mechanism for learning with sleep spindles. Philos Trans R Soc Lond B Biol Sci. 2020;375. https://doi.org/10.1098/rstb.2019.0230

34. Chu CJ, Leahy J, Pathmanathan J, Kramer MA, Cash SS. The maturation of cortical sleep rhythms and networks over early development. Clin Neurophysiol. 2014;125:1360-70. https://doi.org/10.1016/j.clinph.2013.11.028.
35. Thatcher RW, North DM, Biver CJ. Self-organized criticality and the development of EEG phase reset. Hum Brain Mapp. 2009;30:553-74. https://doi.org/10.1002/hbm.20524.
36. Xiao R, Shida-Tokeshi J, Vanderbilt DL, Smith BA. Electroencephalography power and coherence changes with age and motor skill development across the first half year of life. PLoS One. 2018;13. https://doi.org/10.1371/journal.pone.0190276.
37. Boersma M, Smit DJ, de Bie HM, Van Baal GCM, Boomsma DI, de Geus EJ, et al. Network analysis of resting state EEG in the developing young brain: structure comes with maturation. Hum Brain Mapp. 2011;32:413-25. https://doi.org/10.1002/hbm.21030.
38. Emerson RW, Gao W, Lin W. Longitudinal study of the emerging functional connectivity asymmetry of primary language regions during infancy. J Neurosci. 2016;36:10883-92. https://doi.org/10.1523/JNEUROSCI.3980-15.2016.

SUPPORTING INFORMATION

The following additional material may be found online:
Appendix S1 Massage booklet.
Table S1 Sociodemographic comparisons between excluded and included participants according to data provided at registration.
Table S2 Sociodemographic comparisons between excluded participants from intervention and control according to data provided at registration.
Table S3 qEEG features during the first sleep cycle.
Table S4 qEEG features during the first sleep cycle – subgroup analysis.
Table S5 Neurodevelopmental outcomes at 4 months.
Figure S1 Main analysis flow diagram.
Figure S2 Subgroup analysis flow diagram.

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