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Impact of Macrocephaly, as an Isolated Trait, on EEG Signal as Measured by Spectral Power and Multiscale Entropy during the First Year of Life

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Abstract
Macrocephaly has been associated with neurodevelopmental disorders; however, it has been mainly studied in the context of pathological or high-risk populations and little is known about its impact, as an isolated trait, on brain development in general population. Electroencephalographic (EEG) power spectral density (PSD) and signal complexity have shown to be sensitive to neurodevelopment and its alterations. We aimed to investigate the impact of macrocephaly, as an isolated trait, on EEG signal as measured by PSD and multiscale entropy during the first year of life. We recorded high-density EEG resting-state activity of 74 healthy full-term infants, 50 control (26 girls), and 24 macrocephalic (12 girls) aged between 3 and 11 months. We used linear regression models to assess group and age effects on EEG PSD and signal complexity. Sex and brain volume measures, obtained via a 3D transfontanellar ultrasound, were also included into the models to evaluate their contribution. Our results showed lower PSD of the low alpha (8–10 Hz) frequency band and lower complexity in the macrocephalic group compared to the control group. In addition, we found an increase in low alpha (8.5–10 Hz) PSD and in the complexity index with age. These findings suggest that macrocephaly as an isolated trait has a significant impact on brain activity during the first year of life.

Introduction

Brain development during the first year of life involves critical structural and functional changes that underlie the remarkable rapid sensorial, motor, and cognitive progresses observed in this period [1, 2]. Electroencephalography (EEG), a noninvasive technique, has shown to be an excellent tool to capture these developmental changes with high temporal resolution. Several metrics of the resting-state activity have been shown to be

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sensitive to both brain maturation and atypical trajectories. Power spectral density (PSD) is a common measure that can reflect the activity of groups of neurons firing in synchrony in a given frequency band. The frequency bands classically accepted are delta (1–3 Hz), theta (4–7), alpha (8–12 Hz), beta (13–30 Hz), and gamma (30–50 Hz) [3, 4]. The quantification of spectral power by frequency band has been relevant and has contributed to identify developmental trajectories in EEG signal, showing a decrease in slow activity (delta and theta) and an increase in faster activity (alpha, beta, gamma) associated with age in infants and children [3, 5, 6]. However, in recent years, a special emphasis has been placed on nonlinear methods that enable the quantification of EEG signal variability or complexity, given that EEG signal is not predictable (nonlinear) and reflects the activity of multiple cells at different timings during information transfer [7–10]. Thus, brain signal variability is thought to reflect the dynamic interplay between the local (segregation) and global (integration) interactions [11, 12]. In normal development, an increase in EEG signal variability with age has been shown [13–16], and it has been thought to reflect higher brain capacity to make the fluid and adaptive state transitions required to produce optimal cognitive and behavioral responses [10].

Macrocephaly is a relatively frequent condition found in about 2–5% of infant population [17, 18]. Some studies have associated this condition with neurodevelopmental disorders such as autism, given that a higher rate of macrocephaly is found in this population (20–30%) [19–21]. According to this literature, macrocephalic infants later diagnosed with autism may present structural brain alterations that emerge in the latter part of the first year of life. An overabundance of synaptic connexions and lack of pruning have been thought as possible mechanisms underlying an impaired communication between brain regions [19, 20, 22–24]. Although this hypothesis seems to be in line with studies showing a reduced degree of long-range connectivity and an enhanced local connectivity in autism [23, 25, 26], the strength of the association between macrocephaly and autism and the significance of macrocephaly as an indicator of neuropathology are still under investigation.

Further, macrocephaly has been mainly studied in the context of clinical populations and less is known about its impact on general neurodevelopment. To our knowledge, only one study has reported a significant relationship between greater head circumference (HC) in infancy and temperamental traits, such as lower effortful and lower surgency/extraversion, at the age of two in neurotypical boys [27]. These results suggest that macrocephaly during the first year of life needs further investigation in general population.

To better understand the effect of macrocephaly in a neurotypical population, we performed a spectral analysis. It has been suggested that in neurodevelopmental disorders, changes in PSD are observed [28, 29]. For example, an increase in resting PSD in the low (delta and theta) and high (beta and gamma) frequency bands and a decrease in the middle alpha frequency band have been reported in children with autism compared with a neurotypical group [28, 29]. For this reason, we hypothesized that if macrocephaly as an isolated trait is associated with altered brain activity, an increase in resting PSD in low (delta and theta) and high (beta and gamma) frequency bands along with a decrease in the middle alpha frequency band would be observed in macrocephalic infants.

We obtained the spectral power by means of the Fitting Oscillations and One-Over-F algorithm. This algorithm enables to extract and separate the periodic (rhythmic activity within a narrowband frequency band) and the aperiodic (no regular or rhythmic broadband activity) components of the EEG signal [30]. For this study, we focused our analysis on the periodic component. We obtained the PSD in the canonical frequency bands (delta, theta, beta, and gamma).

In the same way, EEG signal variability has been studied in autistic population, showing that infants at high risk for autism have lower brain complexity [31, 32]. However, whether macrocephaly, as an isolated trait, relates to alterations in brain signal variability in neurotypical infants is unknown. To address this issue, we aimed to investigate if EEG signal complexity can be affected by macrocephaly as an isolated trait in a general infant population during the first year of life. We used multiscale entropy (MSE) as a measure of brain complexity, which has been shown to be a reliable method to quantify EEG signal variability in infants [13, 14, 16, 31]. We hypothesized that if macrocephaly as an isolated trait is associated with altered brain development, less brain signal variability would be observed in macrocephalic infants.

We used HC measures to classify our participants as control or macrocephalic according to the World Health Organization (WHO) norms. Although HC constitutes the best noninvasive surrogate measurement of brain volume [33–35], we also included brain volume measures obtained via transfontanellar 3D ultrasound images. Transfontanellar ultrasound is a reliable, radiation-free, and low-cost technique that takes advantage of the different fontanelles or gaps between individual bones of the infant's skull [36, 37].

Materials and Methods

Participants' Characteristics

The sample consisted of 82 healthy infants aged between 3 and 11 months recruited from the Sainte-Justine Mother and Child University Hospital Center in Montreal. Families were first contacted in the postpartum department and in the radiology department (macrocephalic infants referred for screening by their family doctor) and recontacted later. Inclusion criterion was healthy full-term infants (>37 weeks of gestation). Exclusion criteria were the following: pregnancy or delivery complications, infants admitted to neonatal intensive care, infants born prematurely (<37 weeks of gestation), hydrocephaly, presence of any syndromic entity or other severe illness, family risk for autism. Parents signed an informed consent approved by the Ethics, Scientific, and Administrative Committee at the Sainte-Justine's Hospital Research Center. The background information, medical and developmental history were obtained via an in-house questionnaire completed by the parents.

Infants were classified into control (n = 54; 27 girls) and macrocephalic (n = 28; 14 girls) groups based on HC measures and WHO reference data. The HC was measured as the largest occipital-frontal circumference. HC and brain volume measures were obtained on the same visit for the EEG acquisition. Infants with an occipitofrontal HC exceeding the 97th percentile were included in the macrocephalic group.

Behavioral Measures

Adaptive Behavioral Assessment System

Adaptive skills were evaluated via the Adaptive Behavioral Assessment System-Second Edition (ABAS-II) [38], parent form (0–5 years old, French-Canadian version) in order to ensure infants had normal development at the moment of testing. Composite scores for three adaptive functioning domains (conceptual, social, and practical) can be obtained, and the General Adaptive Composite (GAC) score corresponds to a global score. Adaptive skills assess how the infant applies their developmental skills to daily living. Conceptual domain evaluates communication and self-direction skills; social domain includes social and leisure skills; practical domain explores self-care, health, and safety skills [39].

Brain Volume Measures

Two experienced radiologist physicians acquired 3D transfontanellar ultrasound images in the coronal plane and sagittal plane (voxel size: 1 × 1 × 1 mm) with a Philips EPIQ 7 system and the X6-1 matrix-array transducer. Brain volume was calculated with a geometric-based method using a 3D ellipsoid estimation technique implemented by Boucher and colleagues [34].

This segmentation technique optimizes the 3D model of an ellipse so that the Euclidean distance between the ellipse boundaries with the hyper-echoic contours of the skull is minimized. Then, the ellipsoid volume is calculated with the following formula: $V_{ellipsoid}=\frac{4}{3}abc\pi$ where a, b, and c are the ellipsoid semi-axes. The parameters a, b, and c are equivalent to half the size of the total width, length, and height of the brain, respectively. A detailed description of the implementation and validation of this method is provided by Boucher and colleagues [34].

Experimental Procedure

Continuous EEG was recorded while infants viewed a silent video (a fragment of Baby Mozart-Baby Einstein), typically for 2 min. Infants were seated on their parent's lap, 60 cm in front of the screen. The experiment was conducted in a dark, soundproof Faraday cage. The video was presented on a Tobii T120 Eye Tracking screen with 1,024 × 1,280-pixel resolution. A research assistant remained in the room to keep the infant comfortable and to encourage the infant to look at the screen when necessary.

EEG Acquisition

EEG was recorded continuously using a 128 electrode dense array system (Electrical Geodesics System Inc., Eugene, OR, USA). Signal was digitized and processed at a sampling rate of 1,000 Hz using the vertex electrode (standard midline central electrode also named "Cz") as an online reference. An online bandpass filter of 0.01–500 Hz was applied, respecting the Nyquist sampling theorem that posits that the sampling rate should be at least twice the maximum frequency component of the signal of interest (Nyquist frequency or 500 Hz in our study) to prevent the aliasing effect or the distortion introduced by sampling. Signals were acquired by a G4 Macintosh computer using NetStation EEG software (version 4.5.4). Impedances were kept below 40 kΩ [40].

EEG Artefact Elimination

Preprocessing was performed using MATLAB (R2017b) and the EEGLAB toolbox (version 14_1_1b). A high-pass band filter (0.5 Hz) and a "notch" filter (60 Hz) were applied offline. Twenty-eight electrodes containing muscular artefacts placed around the neck and face were excluded. The remaining noisy electrodes were removed using a semiautomatic procedure: electrodes with a total standard deviation higher than 200 μV and lower than 2 μV were automatically removed; electrodes with sporadic behavior were manually removed during subsequent visual inspection. Data were re-referenced to the average reference. A semiautomatic independent component analysis (runica algorithm) was used to remove blinks, saccades, and cardiac activity.

Continuous resting EEG signal was segmented into 2-s non-overlapping epochs. Visual inspection of the segmented data was performed to manually reject epochs with significant artefacts. After this procedure, the mean number of artefact-free segments available for analysis was 37.69 (SD = 15.65; range 15–86) for the control group and 49.3 (SD = 26.18; range 15–110) for the macrocephalic group. An independent samples t test showed no statistically significant difference between groups in the number of artefact-free segments (t (31.15) = 2.01, p = 0.053).

Spectral Analysis

Spectral analysis was performed in Python using the MNE package (v. 0.23.0) [41]. PSD (i.e., power estimation among frequency components) was estimated in the eight regions of interest (ROIs) previously described (central, frontocentral, left frontal, right frontal, left temporal, right temporal, parietal, and occipital) using the Welch method [42]. The Welch method splits the data into segments, computes a periodogram for each segment, and then averages all periodograms. It is a well-known method that allows reducing the estimation bias in the power spectrum. The Welch method was applied on 2-s sliding windows, smoothed by a Hamming weighting function, and half-overlapping across epochs (50%). PSD was also log-transformed for normalization and based on median averaging in order to correct for bias relative to the

Table 1. Characteristics of control and macrocephalic infants

Group	Macrocephalic	Control
Sex ratio (boys/girls), *N*	(12/12), 24	(24/26), 50
Age, mean (standard deviation)	6.78 (2.36)	6.1 (1.9)
Age range	3–11 months	3–11 months
HC, mean (standard deviation)	45.69 (2.04)	43.15 (1.85)
Brain volume, mean (standard deviation)	808.56 (89.1)	703.83 (81.7)
ABAS-II GAC score	105.18 (13.89)	101.98 (12.47)

Infants' demographic data including sex, age, and HC by group. Descriptive statistics (mean and standard deviation) by group for adaptive skills (ABAS-II).

mean and therefore get a more robust measure [41]. Frequency bands were defined as follows: delta (1–3 Hz), theta (3.5–8 Hz), low alpha (8.5–10 Hz), high alpha (10.5–13 Hz), low beta (13.5–22 Hz), high beta (22.5–30 Hz), and gamma (30.5–45 Hz). The initial fit of the aperiodic slope (1/f-like) was then estimated at each frequency using the Fitting Oscillations and One-Over-F algorithm (v. 1.0.0) and subtracted from the power spectrum, leaving the power in periodic components (https://fooof-tools.github.io/fooof/) [30].

Multiscale Entropy

MSE is a method to quantify the complexity of a time series developed by Costa et al. [43]. Theoretical basis and methodological details can be found in the study by Costa et al. [43, 44]. The algorithm is based on the sample entropy which assesses the regularity (predictability) of a time series by quantifying the appearance of repetitive patterns [45]. The MSE calculation involves two steps: first, multiple scale time series are derived from the original signal using a temporal coarse-graining procedure and second, sample entropy is computed on each coarse-grained time series. The scale 1 time series is the original time series. The scale 2 time series is calculated by averaging two successive values from the original series. This procedure is done n times, and sample entropy is recalculated at each time scale. In our study, the length of a single time series was 2,000 time points corresponding to 2,000 ms at 1,000 Hz sample rate. We computed coarse-grained series up to scale 40 for each channel. Entropy measures for scales >40 were not computed because the corresponding coarse-grained time series were too short (<50 time points) for reliable sample entropy estimation. Sample entropy represents the conditional probability that two consecutive data sequences of length (m) which are mutually similar within a prespecified amplitude range or tolerance (r) will remain similar at the next point (m + 1) across time in the EEG waveform [45–47]. Based on previous developmental studies, in the present study, we used $m = 2$ and $r = 0.5$ [8, 10, 11, 14, 48].

MSE was calculated for each channel on each 2-s segment and averaged across segments to produce individual subject MSE estimates. MSE estimates were then averaged by ROI. Eight ROIs, distributed across the scalp, were considered for analysis to investigate the effect of macrocephaly: central (5 channels: E7, E31, E55, E80, E106), frontocentral (5 channels: E5,E6, E12, E13, E112), left frontal (6 channels: E19, E20, E23, E24, E27, E28), right frontal (6 channels: E3,E4, E117, E118, E123, E124), left temporal (6 channels: E35, E40, E41, E46, E47, E51), right temporal (6 channels: E97, E98, E102, E103, E109, E110), parietal (channels: E58, E59, E65, E90, E91, E96), and occipital (7 channels: E70, E71, E74, E75, E76, E82, E83) (for an illustration of the exact location of ROIs on the Geodesics 128 electrode net, see online suppl. Fig. S1; for all online suppl. material, see www.karger.com/doi/10.1159/000529722).

Low values of MSE reflect high self-similarity, which means a greater number of pattern matches, a less random time series, and low complexity. In contrast, greater values of MSE reflect a smaller number of pattern matches, a more random time series, and high complexity [43].

We also computed the complexity index for each ROI by estimating the area under the curve of MSE as proposed by Costa and colleagues [43]. The complexity index has been considered a straightforward way to account for the complexity or general irregularity of EEG signals across a range of scale factors (SFs) [47, 49, 50]. Complex dynamics of EEG signal show a curve with sample entropy values that increase with scale, suggesting longer range interactions in time [31, 43].

Finally, given that it has been suggested that sample entropy values at finer SFs are associated with higher frequency signals, whereas coarser SFs seem to be associated with lower frequencies [47, 50, 51], we divided SFs into four levels (level 1: SF 1–10; level 2: SF 11–20, level 3: SF 21–30; level 4: SF 31–40) as a data reduction procedure. If the group effect was significant, we investigated if this effect was differentially observed in each of these levels across ROIs.

Statistical Analysis

First, to investigate if the variance in the PSD and in the complexity index can be significantly explained by the group (macrocephalic and control), age, brain volume, and sex, we performed hierarchical regression analyses for each ROI (central, frontocentral, left frontal, right frontal, left temporal, right temporal, parietal, and occipital). Group, age, brain volume, and sex were successively added to assess their contribution to the model. Adjusted R2 (explanation of variance), incremental explanation of variance, standardized beta values (β), and the p values of the change in variance between the models were computed. This procedure was repeated by ROI.

Second, in the case of the complexity index, to investigate if the group effect was differentially observed by SF level, we performed hierarchical regression analyses for each component in the ROIs where the group effect was significant. Group and age were successively added to assess their contribution to the model. Finally, we investigated the contribution of adaptive skills and of the number of free-artefact trials to the variance in the complexity index by SF level.

Third, with the aim to better understand the group effect and the relationship between behavior and brain signal, we investigated the contribution of adaptive skills to the variance in the PSD and in the complexity index only in the ROIs where the group effect was significant. Finally, we also investigated if the variance in the PSD

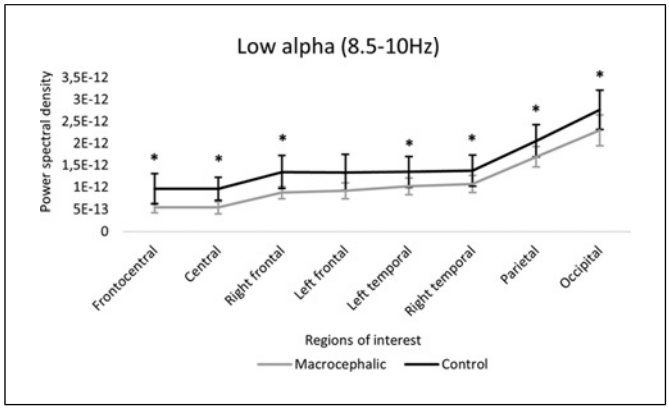

Fig. 1. PSD for the low alpha (8.5–10 Hz) frequency band by group and ROI. Plot demonstrating the group effect, showing the macrocephalic group to have lower PSD compared to the control group in all our ROIs, except the left frontal region. Error bars indicate 95% confidence intervals (corrected $p < 0.05$).

and in the complexity index was associated with the number of free-artefact trials by participant to prevent any potential confounding effect of this variable on our results.

For all our models, assumptions of linearity, homoscedasticity, normality, and collinearity were previously verified. None of the independent variables (age, brain volume) correlated higher with each other (>0.7). Tolerance values were higher than 0.3, while variance inflation factors were lower than 5 [52].

We used IBM SPSS Statistics (IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.) to carry out our analyses. We corrected for multiple hypotheses testing using the Holm-Bonferroni method by model [53, 54]. Only significantly adjusted *p* values are reported.

Results

Demographic Data

Independent samples *t* tests showed that there were no statistically significant differences between groups in terms

Table 2. Results of hierarchical regression analyses for PSD by ROI

ROI	Frequency band	*F*	*p* value	Square R	Beta coefficients		Corrected *p* value
Frontocentral	Low alpha (8.5–10 Hz)	$F(2,71) = 5.028$	0.009	0.124	β Group	0.261	**0.026***
					β Age	0.289	**0.026***
	Low beta (13.5–22 Hz)	$F(2,71) = 6.278$	0.003	0.150	β Group	0.302	**0.016***
					β Age	0.304	**0.016***
	High beta (22.5–30 Hz)	$F(2,71) = 6.040$	0.004	0.145	β Group	0.315	**0.012***
					β Age	0.279	**0.015***
	Gamma (30.5–45 Hz)	$F(1,72) = 8.653$	0.004	0.176	β Group	0.328	**0.004***
Central	Low alpha (8.5–10 Hz)	$F(2,71) = 9.18$	<0.0001	0.205	β Group	0.313	**0.002***
					β Age	0.389	**0.005***
Right frontal	Low alpha (8.5–10 Hz)	$F(2,71) = 7.578$	0.001	0.176	β Group	0.262	**0.020***
					β Age	0.379	**0.002***
Left frontal	Low alpha (8.5–10 Hz)	$F(2,71) = 4.465$	0.014	0.114	β Group	0.213	0.065
					β Age	0.304	**0.009***
Left temporal	Low alpha (8.5–10 Hz)	$F(2,71) = 8.242$	0.001	0.188	β Group	0.221	**0.046***
					β Age	0.416	**<0.0002***
	High alpha (10.5–13 Hz)	$F(2,71) = 5.447$	0.006	0.133	β Group	0.229	**0.045***
					β Age	0.328	**0.010***
Right temporal	Low alpha (8.5–10 Hz)	$F(2,71) = 11.734$	<0.0001	0.248	β Group	0.218	**0.041***
					β Age	0.490	**<0.0002***
	High alpha (10.5–13 Hz)	$F(2,71) = 10.151$	<0.0001	0.222	β Group	0.236	**0.030***
					β Age	0.454	**<0.0002***
	Low beta (13.5–22 Hz)	$F(2,71) = 6.954$	0.002	0.164	β Group	0.280	**0.013***
					β Age	0.348	**0.004***
	High beta (22.5–30 Hz)	$F(2,71) = 5.793$	0.005	0.140	β Group	0.302	**0.018***
					β Age	0.283	**0.018***
	Gamma (30.5–45 Hz)	$F(1,72) = 5.063$	0.028	0.115	β Group	0.256	**0.028***
Parietal	Low alpha (8.5–10 Hz)	$F(2,71) = 11.969$	<0.0001	0.252	β Group	0.236	**0.027***
					β Age	0.488	**<0.0002***
Occipital	Low alpha (8.5–10 Hz)	$F(2,71) = 16.36$	<0.0001	0.316	β Group	0.255	**0.013***
					β Age	0.549	**<0.0002***

Group and age as significant predictors. Holm-Bonferroni sequential correction. *$p < 0.05$.

Table 3. Results of hierarchical regression analyses for PSD by ROI

ROI	Frequency band	*F*	*p* value	Square R	Beta coefficients		Corrected *p* value
Frontocentral	Low alpha (8.5–10 Hz)	$F(3,64) = 5.097$	0.003	0.193	β Group	0.296	**0.036***
					β Age	0.266	**0.036***
					β GAC	0.283	**0.036***
	Low beta (13.5–22 Hz)	$F(3,64) = 5.601$	0.002	0.208	β Group	0.332	**0.015***
					β Age	0.279	**0.032***
					β GAC	0.267	**0.032***
Central	Low alpha (8.5–10 Hz)	$F(3,64) = 6.905$	<0.0001	0.245	β Group	0.342	**0.006***
					β Age	0.367	**0.003***
					β GAC	0.226	**0.044***
Right frontal	Low alpha (8.5–10 Hz)	$F(3,64) = 6.139$	0.001	0.223	β Group	0.291	**0.024***
					β Age	0.357	**0.006***
					β GAC	0.246	**0.031***

Group, age, and adaptive skills as significant predictors. Holm-Bonferroni sequential correction. *$p < 0.05$.

of age [$t(72) = 1.18$, $p = 0.121$]. A χ^2 test showed that there were no statistically significant differences between groups in terms of sex ratio ($X^2 = 0.026$, $p = 0.87$). However, there were significant differences in HC ($t(72) = 5.35$, $p < 0.0001$) and brain volume ($t(72) = 5.01$, $p < 0.0001$). Characteristics of control and macrocephalic infants are provided in Table 1.

Six missing values of the General Adaptive Composite (GAC) score (3 control and 3 macrocephalic) were registered (control group $n = 51$, macrocephalic group $n = 25$, total $N = 76$). All our participants, control and macrocephalic, obtained scores within the norms (mean = 100 [+/− 15]), and we did not find significant differences between groups in the GAC score ($t(66) = 1.22$, $p = 0.228$).

Regarding brain volume measures, seven missing values (4 control and 3 macrocephalic) were registered (control group $n = 50$, macrocephalic group $n = 25$, total $N = 75$). Finally, one macrocephalic infant was excluded from analyses because of extremely low complexity index values. Therefore, the final sample consisted of 74 infants (24 macrocephalic and 50 control) (age distribution by group is provided in online suppl. Table S1).

Fig. 2. Frontocentral region. Scatter plot illustrating group and age effects on complexity index. Macrocephalic and younger infants showed less complexity index.

Spectral Analysis

Power Spectral Density. Group as predictor. PSD in the low alpha frequency band (8.5–10 Hz) was better explained by a model including group and age as predictors. Macrocephalic infants showed lower PSD than control infants in all our ROIs, except the left frontal region (shown in Fig. 1). In addition, younger infants showed lower PSD than older infants in all our ROIs. These results are provided in Table 2.

Group and age were also significant predictors of PSD in the low beta (13.5–22 Hz), high beta (22.5–30 Hz), and gamma frequency (30.5–45 Hz) bands in the frontocentral and right frontal regions. Finally, PSD in the high alpha frequency band was better explained by a model including group and age as predictors only in the right and left temporal regions (descriptive statistics for PSD values by group, frequency band, and ROI are provided in online suppl. Table S2). Brain volume and sex were not significant predictors in our models.

Finally, we investigated the contribution of adaptive skills and the number of free-artefact trials to the variance in spectral power in the ROIs where the group effect was

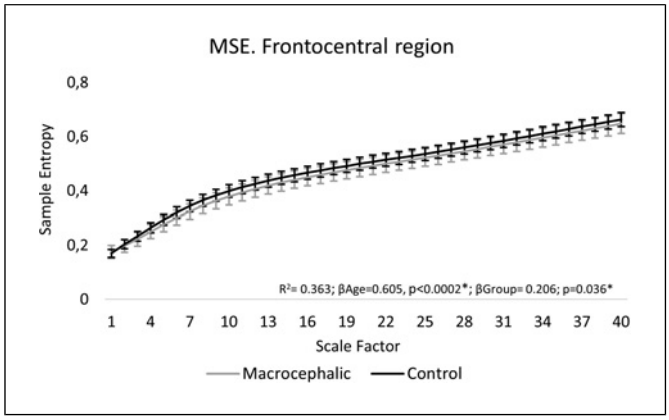

Fig. 3. Frontocentral region. MSE curve. Group was a significant predictor showing macrocephalic infants to have less sample entropy than normocephalic infants across SFs. Error bars indicate 95% confidence intervals.

Table 4. Descriptive statistics (mean and standard deviation) for complexity index values by group and ROI

Group	Macrocephalic		Control	
ROI	mean	SD	mean	SD
Frontocentral	18.19	2.81	18.78	2.99
Central	18.61	2.86	19.13	3.13
Left frontal	19.23	3.34	19.69	3.59
Right frontal	19.42	3.00	19.84	3.50
Left temporal	18.66	2.93	19.31	3.04
Right temporal	18.96	2.98	19.67	3.11
Parietal	18.67	2.77	19.25	2.90
Occipital	18.65	2.80	19.22	2.94

significant. The GAC score significantly contributed to explain the variance of the spectral power in the low alpha (8.5–10 Hz) frequency band in the frontocentral, central, and right frontal regions. In addition, the GAC score significantly contributed to explain the variance of the spectral power in the low beta (13.5–22 Hz) frequency band in the frontocentral region. However, the number of free-artefact trials did not improve our models. These results are provided in Table 3.

MSE Complexity Index

Group as Predictor

Complexity index was better explained by a model including group and age as predictors in the frontocentral, left temporal, right temporal, parietal, and occipital regions, showing macrocephalic infants have lower complexity index than control infants (shown in Fig. 2, 3; Table 4). Importantly, age was a significant predictor in all our ROIs, showing older infants have higher complexity index than younger infants. Results of hierarchical regression analyses for complexity index by ROI are provided in Table 5. Finally, brain volume, sex, adaptive skills, and the number of free-artefact trials were not significant predictors in our models.

Group as a Significant Predictor by SF Level

Group was a significant predictor in the last three SF levels (2–4 SF levels) in all our ROIs, showing control infants have higher complexity index than macrocephalic infants (topographical maps of mean complexity index by SF levels are provided in online suppl. Fig. S2). Descriptive statistics (mean and standard deviation) of complexity index by SF component, (ROI, and group are provided in Table 6. Results of hierarchical regression analyses for SF levels by ROI are provided in Table 7. Importantly, age was also a significant predictor in all our models, showing older infants have greater complexity index than younger infants. In addition, in the first SF level, only age was a significant predictor in the right temporal, parietal, and occipital regions. Finally, brain volume and sex were not significant predictors.

When we tested the contribution of adaptive skills and the number of free-artefact trials to the variance in the complexity index by SF levels, the GAC score was not a significant predictor, while the number of free-artefact trials improved our models in SF level 4 in five ROIs: frontocentral, right temporal, left temporal, parietal, and occipital. However, the group effect was not affected by the introduction of the number of free-artefact trials in our models. These results are provided in Table 8.

Discussion

The current study assessed if EEG PSD and signal complexity can be affected by macrocephaly as an isolated trait in a general infant population during the first year of life. With respect to the spectral analysis, we hypothesized an increase in resting PSD in low (delta and theta) and high (beta and gamma) frequency bands along with a decrease in alpha frequency band in macrocephalic infants. However, our hypothesis was only confirmed in the low alpha (8.5–10 Hz) frequency band, showing that macrocephalic infants have a lower PSD in all our ROIs except the left frontal region. In addition, adaptive skills contributed to explain the

Table 5. Results of hierarchical regression analyses for complexity index by ROI

ROI	*F*	*p* value	Square R	Beta coefficients		Corrected *p* value
Frontocentral	$F(2,71) = 20.27$	<0.0001	0.363	β Group	0.206	**0.036***
				β Age	0.605	<**0.0002***
Central	$F(2,71) = 19.05$	<0.0001	0.349	β Group	0.189	0.056
				β Age	0.595	<**0.0001***
Left frontal	$F(2,71) = 10.79$	<0.0001	0.233	β Group	0.151	0.158
				β Age	0.487	<**0.0001***
Right frontal	$F(2,71) = 14.89$	<0.0001	0.295	β Group	0.159	0.120
				β Age	0.549	<**0.0001***
Left temporal	$F(2,71) = 19.31$	<0.0001	0.352	β Group	0.209	**0.03**5*
				β Age	0.595	<**0.0002***
Right temporal	$F(2,71) = 20.85$	<0.0001	0.370	β Group	0.219	**0.025***
				β Age	0.609	<**0.0002***
Parietal	$F(2,71) = 21.54$	<0.0001	0.378	β Group	0.209	**0.031***
				β Age	0.617	<**0.0002***
Occipital	$F(2,71) = 22.25$	<0.0001	0.385	β Group	0.208	**0.031***
				β Age	0.624	<**0.0002***

Group was a significant predictor in five ROIs (in bold). Age was a significant predictor in all our ROIs. Holm-Bonferroni sequential correction. *$p < 0.05$.

Table 6. Descriptive statistics (mean and standard deviation) of complexity index by SF component, ROI, and group

	Group	Macrocephalic		Control	
ROI	SF level	mean	SD	mean	SD
Frontocentral	1 (SF 1–10)	2.55	0.58	2.69	0.59
	2 (SF 11–20)	4.37	0.79	4.54	0.86
	3 (SF 21–30)	5.22	0.80	5.36	0.87
	4 (SF 31–40)	6.04	0.87	6.19	0.91
Left temporal	1 (SF 1–10)	2.68	0.62	2.82	0.59
	2 (SF 11–20)	4.52	0.82	4.71	0.87
	3 (SF 21–30)	5.34	0.83	5.49	0.88
	4 (SF 31–40)	6.14	0.90	6.28	0.92
Right temporal	1 (SF 1–10)	2.71	0.62	2.90	0.61
	2 (SF 11–20)	4.60	0.84	4.83	0.90
	3 (SF 21–30)	5.42	0.84	5.58	0.90
	4 (SF 31–40)	6.23	0.90	6.36	0.93
Parietal	1 (SF 1–10)	2.68	0.58	2.86	0.60
	2 (SF 11–20)	4.50	0.77	4.70	0.84
	3 (SF 21–30)	5.34	0.76	5.46	0.82
	4 (SF 31–40)	6.15	0.82	6.23	0.85
Occipital	1 (SF 1–10)	2.65	0.57	2.81	0.58
	2 (SF 11–20)	4.49	0.78	4.68	0.84
	3 (SF 21–30)	5.34	0.78	5.47	0.84
	4 (SF 31–40)	6.16	0.84	6.27	0.88

variance of PSD in the low alpha frequency band in the frontocentral, central, and right frontal regions, showing infants with higher GAC score, to have a greater low alpha PSD. This finding is in line with the literature that suggests an association between alpha activity and cognitive development [55, 56]. Finally, the number of free-artefacts trials did not contribute to explain the variance of low alpha PSD, meaning that our results were not affected by this variable.

Table 7. Results of hierarchical regression analyses for SF levels by ROI

ROI	Level	*F*	*p* value	Square R	Beta coefficients		Corrected *p* value
Frontocentral	2 (SF 11–20)	$F(2,71) = 17.32$	<0.0001	0.328	β Group	0.202	**0.045***
					β Age	0.574	<**0.0002***
	3 (SF 21–30)	$F(2,71) = 26.12$	<0.0001	0.424	β Group	0.199	**0.033***
					β Age	0.657	<**0.0002***
	4 (SF 31–40)	$F(2,71) = 28.02$	<0.0001	0.441	β Group	0.200	**0.030***
					β Age	0.671	<**0.0002***
Right temporal	1 (SF 1–10)	$F(2,71) = 3.16$	0.048	0.082	β Group	0.192	0.102
					β Age	0.250	**0.034***
	2 (SF 11–20)	$F(2,71) = 17.93$	<0.0001	0.336	β Group	0.226	**0.025***
					β Age	0.576	<**0.0002***
	3 (SF 21–30)	$F(2,71) = 26.77$	<0.0001	0.430	β Group	0.205	**0.028***
					β Age	0.661	<**0.0002***
	4 (SF 31–40)	$F(2,71) = 29.54$	<0.0001	0.454	β Group	0.191	**0.035***
					β Age	0.682	<**0.0002***
Left temporal	2 (SF 11–20)	$F(2,71) = 16.55$	<0.0001	0.318	β Group	0.211	**0.038***
					β Age	0.563	<**0.0002***
	3 (SF 21–30)	$F(2,71) = 24.94$	<0.0001	0.413	β Group	0.202	**0.033***
					β Age	0.648	<**0.0002***
	4 (SF 31–40)	$F(2,71) = 27.45$	<0.0001	0.436	β Group	0.196	**0.034***
					β Age	0.667	<**0.0002***
Parietal	1 (SF 1–10)	$F(2,71) = 3.29$	0.043	0.085	β Group	0.184	0.115
					β Age	0.262	**0.026***
	2 (SF 11–20)	$F(2,71) = 18.27$	<0.0001	0.340	β Group	0.221	**0.027***
					β Age	0.581	<**0.0002***
	3 (SF 21–30)	$F(2,71) = 28.27$	<0.0001	0.443	β Group	0.195	**0.034***
					β Age	0.673	<**0.0002***
	4 (SF 31–40)	$F(2,71) = 32.23$	<0.0001	0.476	β Group	0.177	**0.046***
					β Age	0.700	<**0.0002***
Occipital	1 (SF 1–10)	$F(2,71) = 3.38$	0.039	0.087	β Group	0.175	0.133
					β Age	0.271	**0.021***
	2 (SF 11–20)	$F(2,71) = 19.30$	<0.0001	0.352	β Group	0.215	**0.030***
					β Age	0.594	<**0.0002***
	3 (SF 21–30)	$F(2,71) = 28.41$	<0.0001	0.445	β Group	0.189	**0.032***
					β Age	0.631	<**0.0002***
	4 (SF 31–40)	$F(2,71) = 31.66$	<0.0001	0.471	β Group	0.173	**0.039***
					β Age	0.651	<**0.0002***

Group was a significant predictor in three SF levels only in the right temporal region, whereas in the frontocentral, left frontal, and occipital regions, group was a significant predictor in the last two SF levels. Holm-Bonferroni sequential correction. *$p < 0.05$.

We also found a group effect in faster activity (beta and gamma), but only in the frontocentral and right temporal regions, showing that macrocephalic infants have a lower PSD. Even though these results were not as expected, they also suggest differences in brain activity in macrocephalic infants. In addition, adaptive skills contributed to explain the variance of PSD in the low beta frequency band only in the frontocentral region, suggesting that this brain activity is also associated with cognitive and behavioral development during the first year of life. Finally, the number of free-artefact trials did not improve our model.

Further, we used MSE and the complexity index as a measure of brain complexity. We hypothesized that if macrocephaly is associated with altered brain development, less brain signal variability would be observed in macrocephalic infants compared to control infants. In general, our results showed less complexity index in macrocephalic infants in the frontocentral, left temporal, right temporal,

Table 8. Contribution of adaptive skills and the number of free-artefact trials

ROI	Level	*F*	*p* value	Square R	Beta coefficients		Corrected *p* value
Frontocentral	4 (SF 31–40)	$F(4,63) = 13.60$	<0.0001	0.463	β Group	0.202	**0.028***
					β Age	0.574	<**0.0003***
					β GAC	0.017	0.856
					β Trials	0.215	**0.031***
Right temporal	4 (SF 31–40)	$F(4,63) = 14.53$	<0.0001	0.480	β Group	0.236	**0.036***
					β Age	0.649	<**0.0003***
					β GAC	0.011	0.904
					β Trials	0.209	**0.036***
Left temporal	4 (SF 31–40)	$F(4,63) = 13.30$	<0.0001	0.458	β Group	0.237	**0.038***
					β Age	0.633	<**0.0003***
					β GAC	0.019	0.843
					β Trials	0.206	**0.040***
Parietal	4 (SF 31–40)	$F(4,63) = 15.66$	<0.0001	0.499	β Group	0.220	**0.048***
					β Age	0.270	<**0.0003***
					β GAC	−0.002	0.981
					β Trials	0.206	**0.048***
Occipital	4 (SF 31–40)	$F(4,63) = 15.38$	<0.0001	0.494	β Group	0.230	**0.038***
					β Age	0.663	<**0.0003***
					β GAC	0.006	0.943
					β Trials	0.205	**0.038***

Results of hierarchical regression analyses for SF levels by ROI. The group effect was not affected by the introduction of the number of free-artefact trials in our models. The General Adaptive Composite (GAC) score was not a significant predictor, while the number of free-artefact trials improved our models in SF level 4 in five ROIs. Holm-Bonferroni sequential correction. *$p < 0.05$.

parietal, and occipital regions, suggesting a significant effect of macrocephaly, as an isolated trait, on brain development during the first year of life. Given that an association between complexity and brain connectivity has been shown [57, 58], the lower complexity index found in macrocephalic infants may suggest differences in brain connectivity. Further investigation is needed to verify this hypothesis. However, it is interesting to note that when we divided SF into levels, we found a significant effect of group in the last three SF levels in the frontocentral, left temporal, right temporal, parietal, and occipital regions, suggesting that coarse time scales are mainly affected by macrocephaly. It has been proposed that coarse time scales are associated with lower temporal frequencies and that may reflect long-range interactions across distributed neuronal populations [47, 51, 58, 59]. In accordance with this theory, a likely explanation of our results is that lower complexity at coarse time scales reflects differences in information processing among distributed connexions in macrocephalic infants. Considering that our macrocephalic cohort shows a typical cognitive and behavioral development, it is possible that the lower complexity found contributes only to explain individual differences in brain functioning that have low behavioral significance in neurotypical macrocephalic population; however, when combined with additional risk factors, it may also contribute to exacerbate altered brain connectivity under pathological conditions. In line with this result, adaptive skills did not contribute to explain the variance in EEG complexity. Future research must include additional developmental and connectivity measures to better understand the impact of the lower signal complexity observed in macrocephalic infants.

We also investigated the effect of the number of free-artefact trials as a potential confounding variable and although we found that a larger number of trials were associated with higher complexity in SF level 4, the group effect was still statistically significant, meaning that this effect was independent of the number of trials. In addition, it should be noted that even if there are not significant differences between groups, the number of free-artefact trials was slightly higher in the macrocephalic group; however, the complexity index was lower in this group, which emphasizes the effect of macrocephaly on EEG signal complexity.

In summary, the macrocephalic effect was observed independently of the metric used (PSD and complexity index), which suggests a differential brain dynamic in macrocephalic infants that can be captured by both linear (PSD) and nonlinear (complexity) brain signal analyses. These findings are significant because they could shed light on the mechanisms underlying macrocephaly that may interact with other risk factors involved in the manifestation of neurodevelopmental disorders. A better understanding of how brain overgrowth interacts with other risk factors during development will contribute to provide more sensitive screening tools that take into consideration the multifactorial etiology and complex interactions underlying neurodevelopmental disorders. Hence, it would be essential to consider brain size in future neurodevelopmental research to prevent confounding effects.

Regarding age effect, in accordance with previous literature, we found an increase in low alpha PSD [6] and in complexity [13, 14, 16] with age in all our ROIs. These findings may reflect the active brain network reorganization accompanying the remarkable growth of the brain structure that takes place during the first year of life and that underlies the sensorial, cognitive, and behavioral progresses observed in this period [2, 60, 61].

Finally, although most of our models showed large effect size to detect group and age effects [62], a larger macrocephalic sample may be required to detect brain volume and sex effects. Future studies should further investigate these effects.

Conclusion

In summary, our findings provide first evidence that macrocephaly as an isolated trait is associated with lower PSD in the low alpha (8.5–10 Hz) frequency band and lower EEG signal complexity during the first year of life. Although EEG signal complexity is thought to reflect brain connectivity, future research should investigate the correlation between brain complexity and connectivity measures in otherwise healthy macrocephalic infants to better understand the impact of macrocephaly as an isolated trait in the general population. Furthermore, the fact that both metrics (PSD and complexity index) showed a group effect highlights the need for further investigation of macrocephaly in neurotypical population. Finally, the longitudinal follow-up of this population to assess the potential long-term effects that macrocephaly may have on neurodevelopment is warranted.

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Statement of Ethics

Parents signed an informed consent approved by the Ethics, Scientific, and Administrative Committee at the Sainte-Justine's Hospital Research Center prior to the start of the study. The Sainte-Justine Hospital Committees (protocol No. 2016-1129) approved all the procedures.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

G.L.A. designed the study; acquired, analyzed, and interpreted the data; and drafted the initial manuscript; F.D. contributed in data collection and analysis; K.A., E.A.-D., and M.A.B. contributed analytic tools; I.S.K. conceptualized and implemented the study and participated in data collection and analysis; E.-J.R. contributed in data collection; D.A. designed the study and contributed in recruitment and data collection; K.S. designed the study and contributed analytic tools; and S.L. conceptualized and designed the study and interpreted the data. All the authors critically revised the manuscript and approved the submitted version.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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