

# Short-Term Changes in Hypsarrhythmia Assessed by Spectral Analysis: Group and Individual Assessments

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## Abstract

**Objectives:** To perform spectral analysis on previously recorded electroencephalograms (EEGs) containing hypsarrhythmia in an initial recording and to assess changes in spectral power ( $\mu\text{V}^2$ ) in a follow-up recording after a period of 10–25 days. **Methods:** Fifty participants, aged 2–39 months, with hypsarrhythmia in an initial recording (R1), were compared with regard to their spectral findings in a later recording (R2). Typically, anticonvulsant therapy was initiated or modified after R1. Average delta, theta, alpha, and beta power was derived from approximately 3 min of artifact-free EEG data recorded from 19 electrode derivations. Group and individual changes in delta power between R1 and R2 formed the main analyses. **Results:** Delta accounted for 84% of the total power. In group comparisons, median delta power decreased statistically significantly between R1 and R2 in all 19 derivations, for example, from  $3940 \mu\text{V}^2$  in R1 to  $1722 \mu\text{V}^2$  in R2, Cz derivation. When assessing individual participants, delta power decreases in R2 were >50% in 60% of the participants, but <25% in 24% of the participants. **Conclusion:** Spectral analysis may be used as an additional tool for providing a potential biomarker in the assessment of short-term changes in hypsarrhythmia, including the effects of treatment.

## Keywords

hypsarrhythmia, quantitative EEG, spectral analysis, delta power

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## Introduction

The essential features of hypsarrhythmia include a strikingly disorganized diffuse pattern comprising very high amplitude (>300  $\mu\text{V}$ ) slow waves and multifocal epileptiform discharges.<sup>1</sup> While these characteristics have remained largely unchanged for many years, their application in clinical practice seems to be burdened by poor inter-rater reliability.<sup>2</sup>

Since the original description of hypsarrhythmia by Gibbs and Gibbs in 1952<sup>3</sup> there has been a steady increase in the number of scientific publications involving this pattern. This trend is most apparent in the past decade.<sup>4</sup> Nonetheless, very little attention has been paid to the quantitative analysis of hypsarrhythmia.

In a landmark study, electroencephalogram (EEG) amplitude and power spectra were obtained in 21 infants with hypsarrhythmia and epileptic spasms and in a group of healthy controls. After an interquartile range of 19–45 days, when treatment had been instituted, repeat recordings were obtained. Statistically significantly higher amplitude was found in the hypsarrhythmia group. However, changes between the two recordings were not specifically analyzed.<sup>5</sup>

In a follow-up study, Smith et al<sup>6</sup> successfully distinguished patients from healthy controls using five categories of

quantitative EEG techniques, including power spectra. However, only 8 of 40 participants had pre-treatment hypsarrhythmia.

Jha et al<sup>7</sup> presented spectral power findings in older children with hypsarrhythmia, than are typically encountered. Delta power in these 3–10-year-olds far exceeded the spectral power of the faster frequency bands.

In the present study, emphasis was placed on short-term quantitative EEG changes in hypsarrhythmia, closely related to the initiation or modification of anticonvulsive therapy. A relatively large group of participants was assessed.

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Furthermore, emphasis was placed on inter-individual changes. The inter-recording interval included the 2-week period when both clinical and hypersarhythmic resolution can occur in response to therapy.<sup>8</sup>

## Methods

### Study Population

Fifty participants aged 2–39 months were included. Each had hypersarhythmia, identified in an initial standard clinical EEG recording using visual analysis. A second EEG recording was performed 10–25 days later. To fulfil this criterion, EEG recordings performed at the Steve Biko Academic Hospital in Pretoria, South Africa, were scrutinized from 2009–2019. Visual analysis of the clinical EEG was performed by an electroencephalographer with over 20 years' experience in pediatric EEGs. EEG recordings were requested by the Department of Pediatric Neurology. After the first recording (R1), anticonvulsant treatment was modified or commenced before the follow-up recording (R2). At R2, 29 participants were receiving vigabatrin plus a steroid, while 19 participants were being treated with either one of these drugs. Treatment in the remaining 2 participants consisted of other anticonvulsants.

### Study Design

Ethical approval was obtained from appropriate university and academic hospital committees. The clinical EEG recordings were performed in the Neurophysiology Unit of Steve Biko Academic Hospital using a Nihon Kohden EEG acquisition system (Nihon Kohden, Tokyo, Japan). The EEG recordings involved the placement of the international 10–20 electrode system. The duration of the recordings varied from 20–60 min. Visual analysis typically used a standard longitudinal bipolar 20-channel montage.

Spectral analysis was accomplished by using MultiView Version 2.2 software (MEGIS Software GmbH, Munich, Germany). Each recording was marked in epochs of a minimum of 3 s, excluding artifacts. Spectral analysis was performed on approximately 3 min of EEG per recording. As far as possible, both the R1 and R2 recordings of each pair contained epochs of the same level of alertness, which was determined by the annotation of eyes open/eyes closed during the EEG recording. When the participant's eyes were open, wakefulness was assumed, and when the participant's eyes were closed, drowsiness/sleep was assumed.

A common reference ipsilateral ear montage, containing 19 derivations, was used for all recordings, to facilitate interhemispheric comparisons (data not presented in this report). Midline electrodes were referred to the right ear. A low cut-off filter of 0.5 Hz was set with a roll-off slope of 6 dB/octave. The high cut-off filter was set at 30 Hz with a roll-off slope of 12 dB/octave. A notch filter of 50 Hz with a width of 5 Hz was also

utilized. The sampling rate was 200 Hz with an epoch length of 2.56 s. The frequency spectrum of 0.5–30 Hz was divided into four frequency bands: Delta (0.5–3.8 Hz), theta (4.0–7.8 Hz), alpha (8.0–12.8 Hz), and beta (13.0–30.0 Hz). Output was expressed as frequency band power ( $\mu V^2$ ).

Statistical analysis started with a comparison of delta power ( $\mu V^2$ ) in five longitudinal chains of electrodes to gauge topographical (anterior to posterior) distribution. A mixed effects maximum likelihood regression analysis using ranks was performed due to the large standard deviations and discrepancies between the mean and median values.

For each participant, spectral power in R2 was expressed as a percentage of the equivalent value in R1 (the lower the percentage value, the greater the change between the two recordings). The relative percentage change from R1 to R2 was classified in one of four categories: (1) <25%, (2) 25%–<50%, (3) 50%–<75%, and (4)  $\geq 75\%$ .

Fisher's exact test was used to compare differences in the level of alertness between those participants with hypersarhythmia still present in R2, and those participants without hypersarhythmia in R2.

## Results

In Figure 1, the spectral composition of hypersarhythmia in R1 is shown, using median spectral power at a selection of anterior and posterior electrode positions. The predominance of delta power relative to the other three frequency bands is apparent.

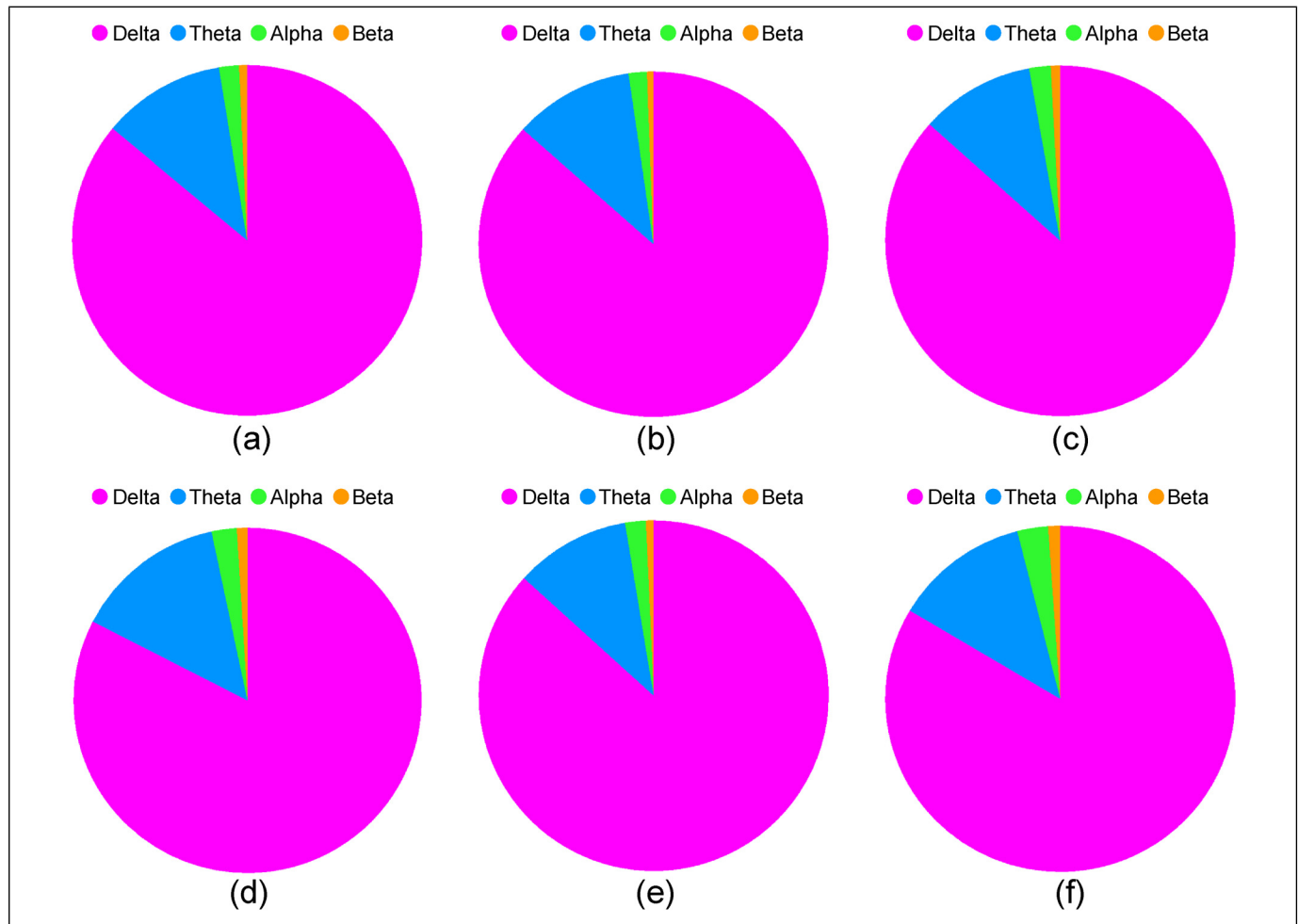
Wilcoxon's matched pairs signed rank tests were performed to compare group spectral delta power between R1 and R2 in 19 EEG derivations. Statistically significant differences in delta power were found for all 19 electrodes as shown in Table 1.

The relative (percentage) change in spectral power between R2 and R1 is shown in Table 2.

The pairs of recordings were divided into two groups based on the state of alertness during the EEG recordings. In 29 of 50 participants, R1 and R2 were both analyzed during the same state, either awake or asleep. For the remaining 21 participants, the state of alertness varied between R1 and R2. Fisher's exact test was applied to compare these two subgroups with respect to the percentage change in delta power between R1 and R2. The differences were not statistically significant ( $P = .308$ ).

A further analysis of spectral findings was related to the retention of hypersarhythmia (RH) in R2 or the shedding of hypersarhythmia (SH) in R2, as determined by previous visual analysis of the EEG. Median delta power was statistically significantly higher ( $P < .05$ ) for each of the 19 derivations in the RH subgroup compared to the SH subgroup.

In the RH subgroup, paired t-tests revealed significantly reduced delta power ( $P < .05$ ) for 12 of 19 derivations in R2 compared to R1. Median delta power was reduced in R2 for the remaining seven derivations, but the R1 and R2 comparisons did not reach statistical significance. In the case of the SH subgroup, median delta values were highly statistically significantly ( $P < .0001$ ) lower for each of the 19 derivations. The



**Figure 1.** The proportion of median spectral power in the delta, theta, alpha, and beta bands at (a) F4, (b) Fz, (c) F3, (d) T6, (e) Pz, and (f) T5. These derivations represent the more anterior and posterior electrode placements. Abbreviations: F4, right frontal electrode; Fz, frontal midline electrode; F3, left frontal electrode; T6, right posterior-temporal electrode; Pz, parietal midline electrode; T5, left posterior-temporal electrode.

differences between the SH and RH subgroups are further depicted in Figure 2.

Overall, the median percentage change values of delta power for all 19 derivations in the SH subgroup showed a greater reduction in delta power than those of the RH subgroup. All data points for the SH subgroup are well below all the data points for the RH subgroup in Figure 2.

## Discussion

Our median delta power values for participants with hypsarrhythmia in R1 were comparable to those of Jha et al.<sup>7</sup> Other compatible findings included a clear predominance of delta power relative to the other frequency bands. Delta power was highest in the frontal and central regions in our study, as reported by Smith et al.<sup>5</sup>

Group power median values for the midline derivations (Fz, Cz, Pz), for example, showed a marked decrease from R1 to R2.

The R2 medians decreased by 59%–66% across these derivations. Not apparent in our group findings were individual changes that spanned a broad spectrum from a greater than 75% decrease in delta power in R2 to an increase in delta power in R2. Further research is needed to explore the clinical relevance of these findings.

A novel finding is that when hypsarrhythmia was retained in R2, spectral analysis revealed statistically significant decreases in delta power, a change not easily recognized by visual analysis. For example, in this subgroup of participants, delta power in the three midline derivations unexpectedly decreased by 38%–46% despite a previous EEG report indicating the presence of hypsarrhythmia. The comparable changes in patients where hypsarrhythmia was no longer present by virtue of visual analysis had substantially higher decreases of delta power in the range of 71%–76%.

A limitation of our study was that the EEG recordings could not be consistently coordinated with the initiation of

**Table 1.** Comparison by Wilcoxon Matched-Pairs Signed-Rank Test of Initial Recordings (Recording 1) and Follow-Up Recordings (Recording 2) in Respect of Delta Power ( $\mu V^2$ ) in 19 EEG Derivations.

Electrode position	Recording 1						Recording 2						P value
	$\bar{X}$	SD	M	95% CI	Min	Max	$\bar{X}$	SD	M	95% CI	Min	Max	
Fp2	3374	2976	2665	2528–4220	204.9	15 108	1410	1332	948	1032–1789	85.2	5015	<.0001
F4	4337	3950	3564	3214–5460	268.5	26 626	1702	1776	1109	1197–2206	139.7	9033	<.0001
C4	3467	2177	3219	2848–4085	377.4	12 163	1426	1309	1022	1054–1798	98.0	5037	<.0001
P4	4351	3510	3537	3353–5348	493.8	19 669	1509	1293	1047	1141–1877	124.1	5117	<.0001
O2	3794	2578	2982	3062–4527	401.0	10 223	1577	1396	1115	1180–1973	98.7	6453	<.0001
Fp1	3427	2755	2582	2644–4210	324.2	14 145	1489	1344	887	1107–1871	79.6	4913	<.0001
F3	4832	4496	3358	3554–6110	544.7	26 491	1749	1816	1023	1233–2265	106.2	9420	<.0001
C3	3666	2668	2884	2908–4424	692.4	12 734	1461	1484	1161	1039–1883	112.9	8199	<.0001
P3	4069	3028	3330	3208–4930	560.6	15 282	1539	1277	1340	1176–1902	119.9	5795	<.0001
O1	4067	3103	2782	3185–4949	417.0	13 127	1611	1302	1438	1241–1981	96.3	4707	<.0001
Fz	5017	4428	3751	3759–6276	386.9	22 048	1722	1667	1296	1249–2196	128.0	8393	<.0001
Cz	4223	2533	3940	3504–4943	597.8	13 979	1722	1560	1183	1279–2165	119.6	6308	<.0001
Pz	4523	3440	3754	3546–5501	537.6	20 058	1662	1402	1058	1264–2061	129.7	5191	<.0001
F8	1801	1465	1474	1384–2217	133.3	8046	712	685	480	518–907	70.8	3214	<.0001
T4	1579	1375	1179	1188–1970	148.1	6054	647	635	345	466–827	49.0	2470	<.0001
T6	2998	2165	2479	2383–3614	388.8	10 532	1249	1155	921	921–1578	111.6	4586	<.0001
F7	2200	2010	1760	1629–2771	215.5	10 447	840	825	462	606–1075	52.6	3883	<.0001
T3	1531	1357	1301	1145–1916	141.0	6139	726	856	379	483–970	72.5	4274	.0001
T5	3383	2891	2616	2562–4205	440.7	14 693	1247	1235	842	896–1598	82.0	4662	<.0001

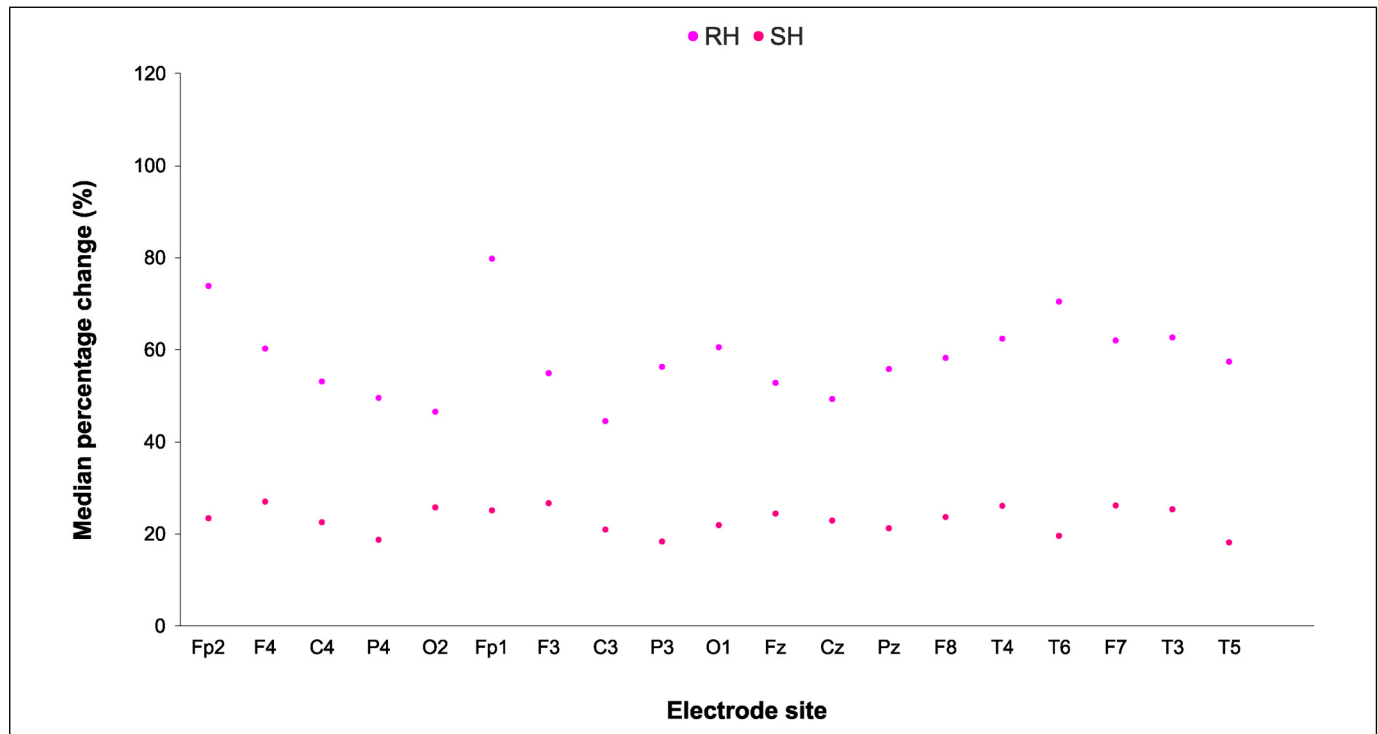
Abbreviations:  $\bar{X}$ , mean; SD, standard deviation; M, median; 95% CI, 95% confidence interval; Min, minimum; Max, maximum; EEG, electroencephalogram.

**Table 2.** Percentage Changes in Spectral Delta Power ( $\mu V^2$ ) for All 19 Derivations Across 50 Participants.<sup>a</sup>

Electrode position	Percentage change			Participants per percentage change category			
	$\bar{X}$	SD	M	<25%	25%–<50%	50%–<75%	≥75%
Fp2	59	61	38	19 (38%)	9 (18%)	7 (14%)	15 (30%)
F4	52	49	36	16 (32%)	13 (26%)	9 (18%)	12 (24%)
C4	51	47	37	20 (40%)	8 (16%)	9 (18%)	13 (26%)
P4	51	60	33	19 (38%)	14 (28%)	5 (10%)	12 (24%)
O2	62	84	38	17 (34%)	16 (32%)	3 (6%)	14 (28%)
Fp1	61	63	38	19 (38%)	9 (18%)	6 (12%)	16 (32%)
F3	53	55	33	19 (38%)	11 (22%)	7 (14%)	13 (26%)
C3	52	53	32	20 (40%)	13 (26%)	4 (8%)	13 (26%)
P3	58	70	31	22 (44%)	7 (14%)	8 (16%)	13 (26%)
O1	61	70	35	22 (44%)	8 (16%)	6 (12%)	14 (28%)
Fz	48	45	40	22 (44%)	7 (14%)	11 (22%)	10 (20%)
Cz	51	47	41	21 (42%)	10 (20%)	5 (10%)	14 (28%)
Pz	55	65	32	21 (42%)	10 (20%)	7 (14%)	12 (24%)
F8	65	75	36	20 (40%)	9 (18%)	7 (14%)	14 (28%)
T4	61	67	36	19 (38%)	10 (20%)	7 (14%)	14 (28%)
T6	66	99	39	20 (40%)	10 (20%)	5 (10%)	15 (30%)
F7	66	83	40	19 (38%)	11 (22%)	8 (16%)	12 (24%)
T3	80	110	31	17 (34%)	13 (26%)	4 (8%)	16 (32%)
T5	61	80	25	26 (52%)	6 (12%)	6 (12%)	12 (24%)
<b>Total:</b>				378 (40%)	194 (20%)	124 (13%)	254 (27%)

Abbreviations:  $\bar{X}$ , mean; SD, standard deviation; M, median.

<sup>a</sup>Recording 2 values were expressed as a percentage of recording 1. The number and proportion of participants falling in the four change categories is shown. The lower the percentage value, the greater the change in absolute delta power between R1 and R2. For example, <25% means that the delta power in R2 was less than 25% of what the power was in R1 (in other words the category of greatest change). The least change in delta power is in the 75% category meaning that the reduction between R2 and R1 was less than 25%.



**Figure 2.** Scatterplot comparing the median percentage change values of delta power per electrode site for all 50 participants, between the RH and SH subgroups.

Abbreviations: RH, retained hypsarrhythmia: those with hypsarrhythmia still present in the follow-up recording; SH, shed hypsarrhythmia: absent hypsarrhythmia after treatment.

specific anticonvulsive therapy relative to R1. However, in 31 of 50 participants, treatment with vigabatrin and/or ACTH or a steroid commenced after R1. The spontaneous remission of hypsarrhythmia between the R1 and R2 recordings is deemed unlikely in the light of the findings of Hrachovy et al<sup>9</sup> of a spontaneous remission rate of only 2% in a one-month period. Therefore, the effects of treatment were considered the most likely factor to explain the changes in spectral power in our study.

We were not able to consistently achieve the same levels of alertness in the R1 and R2 recordings. It is known that the expression of hypsarrhythmia can vary during sleep and wakefulness.<sup>9</sup> It was not possible to achieve both of these states in our R1 and R2 recordings due to time constraints. In 29 of 50 pairs of recordings the same level of alertness applied in R1 and R2, but was discordant in 21 pairs of recordings. We compared these two subgroups in terms of changes in delta power between R1 and R2. There were no statistically significant differences. Therefore, in the context of our study, differences in the state of alertness were not a major factor in short-term changes in delta power. Smith et al<sup>6</sup> reported globally higher spectral power in ES patients during both wakefulness and sleep when compared to a control group.

A limitation of spectral analysis is that it does not include the assessment of epileptiform abnormalities, which may persist

after the resolution of irregular high amplitude delta activity in patients with epileptic spasms.<sup>10</sup>

## Conclusion

While video-EEG is likely to remain the foundation for the diagnosis and therapeutic responses of epileptic spasms,<sup>10</sup> quantitative EEG analysis could contribute to the assessment of hypsarrhythmia. This should include the rapid short-term changes that may occur with the initiation of anticonvulsive therapy.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author, [JMF], upon reasonable request.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical Approval


This study was approved by Tshwane University of Technology Department of Biomedical Science Committee for Post Graduate Studies, the Faculty of Health Sciences Research Ethics Committee at the University of Pretoria, and Steve Biko Academic Hospital

Ethics Committee through the National Health Research Database where the study was carried out.

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