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# Hypsarrhythmia is associated with widespread, asymmetric cerebral hypermetabolism

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ABSTRACT

*Purpose:* Hypsarrhythmia is the interictal EEG pattern most often associated with infantile spasms. We set out to evaluate the metabolic impact of hypsarrhythmia among patients with infantile spasms by contrasting regional cerebral metabolic activity among children with and without hypsarrhythmia.
*Methods:* Patients with video-EEG confirmed infantile spasms who underwent simultaneous interictal EEG and FDG-PET as part of a surgical evaluation were retrospectively identified. Pons-normalized relative cerebral metabolic activity (RCA) was ascertained in 18 cortical and 6 subcortical pre-specified regions of interest (ROIs).
*Results:* We identified 63 patients with infantile spasms who underwent simultaneous EEG/PET, including children with hypsarrhythmia (n = 9), high-voltage EEG background (n = 20), and multifocal independent spike discharges (MISD) (n = 34). Among them, a putative epileptogenic zone was identified within the left-hemisphere only (n = 27), right-hemisphere only (n = 20), or assumed to be bilateral (n = 16). After adjustment for age at PET, the presence of hypsarrhythmia was associated with hypermetabolism in 11 of 18 cortical ROI's. After adjustment for lateralized epileptogenic zones, the association between hypsarrhythmia and hypermetabolism was generally stronger within the left hemisphere.
*Conclusion:* Hypsarrhythmia is associated with widespread—and curiously left more than right—elevations in pons-normalized RCA, which is not evident on routine clinical review of individual PET studies. This study suggests that hypsarrhythmia may be a quasi-ictal phenomenon based on widespread and usually bilateral cortical hypermetabolism.

## 1. Introduction

Infantile spasms is the most common epilepsy syndrome with onset in the first year of life, characterized by clusters of epileptic spasms, and often accompanied by a chaotic EEG pattern known as hypsarrhythmia [1]. Prompt and effective treatment is essential in preventing the severe neurodevelopmental sequela that frequently accompany infantile spasms [2]. There is broad consensus that successful response to any therapy in the treatment of infantile spasms requires resolution of both spasms and hypsarrhythmia [3]. However, the identification of hypsarrhythmia—or resolution thereof—has disconcertingly poor inter-rater reliability, and the influence of hypsarrhythmia on outcome independent of ongoing spasms is unknown [4]. Furthermore, many children with epileptic spasms never develop hypsarrhythmia, but are nevertheless at risk for severe neurodevelopmental impairment in the absence of effective treatment [5–7].

Given the challenge of identifying hypsarrhythmia and uncertainty as to the precise significance of hypsarrhythmia, there is a need for new methods to characterize disease burden in children with infantile spasms. One promising candidate is relative cerebral metabolic activity (RCA) as quantified by interictal 18-fluorodeoxyglucose positron emission tomography (FDG-PET). The utility of FDG-PET in identifying candidates for surgical resection is well established, even in the absence of structural lesions [8]. Previous studies using FDG-PET have implicated the the brainstem, lentiform nuclei, and temporal cortices in the pathogenesis of infantile spasms [8–10]. Several studies have linked normalization of RCA with cessation of spasms as well as favorable neurodevelopmental outcomes [11–15]. Conversely, the persistence of bitemporal hypometabolism is associated with particularly poor development, severe language impairment, and autism 10].

*Abbreviations:* BOLD, Blood oxygenation level-dependent; EEG-fMRI, EEG functional MRI; FDG-PET, 18fluorodeoxyglucose positron emission tomography; FMEP, Frequent multifocal epileptiform discharges; RCA, Relative cerebral metabolic activity; ROI, Region of interest; MISD, Multifocal independent spike discharges

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The impact of hypsarrhythmia and its component EEG features (i.e. high voltage and abundant multifocal epileptiform discharges) on RCA is unknown. As hypsarrhythmia is thought to signify profound global cerebral dysfunction, we suspected that the presence of hypsarrhythmia (or its component features) might be associated with RCA disturbances detectable by FDG-PET. In this study, we set out to identify a cerebral metabolic signature of hypsarrhythmia using a large cohort of patients with infantile spasms who underwent FDG-PET.

## 2. Methods

### 2.1. Standard protocol approvals

This use of human subjects and the analyses presented here were approved by the Institutional Review Board at UCLA.

### 2.2. Data ascertainment

Patients with video-EEG confirmed infantile spasms who underwent simultaneous EEG and FDG-PET as part of a surgical evaluation between August 2007 and March 2012 were retrospectively identified. Although patients with other coexisting seizure-types were included in this analysis, patients whose predominant seizure-type was not epileptic spasms were excluded. Patients meeting criteria for Lennox-Gastaut syndrome were specifically excluded. For each patient, we used video-EEG reports to tabulate the presence or absence of hypsarrhythmia (including 'atypical' or 'modified' hypsarrhythmia), high voltage (defined as non-epileptiform slow-waves consistently greater than 200 μV), multifocal independent spike discharges (MISD), and frequent multifocal epileptiform discharges (FMEP). MISD was defined as the presence of spikes, sharp-waves, poly-spikes, sharp-waves, or spike-, sharp-, or polyspike-and-wave discharges of any frequency, localized to at least three non-neighboring electrodes, with at least one locus in each hemisphere. FMEP was defined as multifocal (as defined for MISD) and specifically frequent (at least 1/min) epileptiform discharges (including spikes, sharps, polyspikes, or paroxysmal fast activity, with or without an associated slow-wave). Relative cerebral metabolism was ascertained using NeuroQ™ (Syntermed Inc, Atlanta, GA, USA), an FDA-approved software application used to carry out automated quantitative analysis of cerebral PET data. Pons-normalized RCA was determined in 18 cortical and 6 subcortical pre-specified regions of interest (ROIs) defined by established neuroanatomical or functional boundaries. We selected the pons as a reference to calculate normalized RCA because (1) we were primarily interested in cortical RCA, (2) none of the patients in this series exhibited a structural pontine lesion, and (3) we sought to avoid subcortical structures which have been previously implicated in the pathogenesis of infantile spasms, namely the caudate nuclei. Similarly, the thalami and cerebellum were avoided as a reference given their extensive reciprocal connections with the cortex. As a primary outcome, RCA in each ROI was compared between patients with and without hypsarrhythmia. In exploratory analyses, we evaluated the lateralized effect of hypsarrhythmia by evaluating right and left ROIs separately, and subsequently compared patients with and without (1) high-voltage background, (2) MISD, and (3) FMEP.

### 2.3. Statistical methods

Continuous summary data are presented as mean (standard deviation) or median (interquartile range), as appropriate, unless otherwise noted. Unpaired comparisons of proportions were accomplished using the Fisher exact test and the Fisher-Freeman-Halton test. Unpaired comparisons of medians were accomplished using the Wilcoxon rank-sum test. Ninety-five percent confidence intervals (95% CI) for percentages were calculated using the modified Wald method. ROI-specific comparisons of metabolic activity were conducted with sequential multiple linear regression. To specifically evaluate regional cerebral activity (RCA) as a function of hypsarrhythmia, with adjustment for age at PET (given that age is associated with RCA), we conducted multiple linear regression in which RCA was the dependent variable and both hypsarrhythmia and age were simultaneous predictor variables. We also conducted exploratory (underpowered) stratified analyses in which we plotted RCA as a function of age, among subgroups defined by laterality (left, right, or bilateral) of the epileptogenic zone. Statistical calculations were accomplished with STATA statistical software (StataCorp LP, Version 14, College Station, Texas, USA). Adjustment for multiple comparisons was not undertaken as sequential ROI-specific comparisons were not independent (i.e. there was considerable intercorrelation of RCA among the prespecified ROIs).

## 3. Results

### 3.1. Patients

We identified 63 patients with infantile spasms who underwent interictal FDG-PET with simultaneous video-EEG between August 2007 and March 2012. The patients were 19 (11.0–43.1) months old at the time of PET-EEG (Table 1). On routine clinical review of the video-EEGs, nine EEGs exhibited hypsarrhythmia, 20 exhibited high-voltage (not necessarily sufficient to meet criteria for hypsarrhythmia), 34 exhibited multifocal independent spike discharges, and 28 exhibited frequent multifocal epileptiform discharges. Based on a consensus review of all available studies including video-EEG monitoring, structural MRI, PET, MRI-PET co-registration, and magnetoencephalography in select cases, an exclusively left-sided epileptogenic zone was identified in 27 cases, and an exclusively right-sided epileptogenic zone was identified in 20 cases. In the remaining cases, an epileptogenic zone was assumed to be bilateral.

### 3.2. Hypsarrhythmia

In comparison to the 54 patients without hypsarrhythmia, RCA was significantly higher among the nine children with hypsarrhythmia in 11 of 18 bilaterally-represented ROIs, after adjustment for age at PET-EEG (Table 2, Fig. 1). Hypsarrhythmia did not impact RCA in any of the six subcortical ROIs (all $p > 0.05$, Table 2). Neither sex nor the number of concurrent medications at the time of PET confounded any of the above associations for any ROI.

**Table 1**
Characteristics of the study population.

| Clinical | Hypsarrhythmia (n = 9) | Hypsarrhythmia Absent (n = 54) | p-Value |
|---|---|---|---|
| Female sex, n (%) | 1 (11%) | 25 (46%) | 0.069[b] |
| Age at PET, months[a] | 14.8 (7.7-17.4) | 23.2 (13.2-49.3) | 0.062[c] |
| AEDs at PET, n[a] | 2 (1-2) | 2 (2-3) | 0.027[c] |
| Resection post-PET, n (%) | 3 (33%) | 26 (48%) | NS[b, d] |
| EEG Features | | | |
| High Voltage, n (%) | 9 (100%) | 11 (20%) | 0.001[b] |
| MISD, n (%) | 9 (100%) | 25 (46%) | 0.003[b] |
| FMEP, n (%) | 7 (78%) | 21 (39%) | 0.065[b] |
| Suspected EZ[e] | | | |
| Left, n (%) | 4 | 23 | NS[f, d] |
| Right, n (%) | 2 | 18 | |
| Bilateral, n (%) | 3 | 13 | |

[a] Median (interquartile range).
[b] Comparison by Fisher exact test.
[c] Comparison by Wilcoxon rank-sum test.
[d] Not significant (p-Value > 0.10).
[e] Epileptogenic zone.
[f] Comparison by Fisher-Freeman-Halton tes.

**Table 2**
Association between regional cerebral activity and hypsarrhythmia.

| Regions of Interest | Bilateral | | | Left Hemisphere | | | Right Hemisphere | | |
|---|---|---|---|---|---|---|---|---|---|
| Cortical | Coefficient | 95%CI | p-Value | Coefficient | 95%CI | p-Value | Coefficient | 95%CI | p-Value |
| Superior frontal | 0.156 | 0.003-0.309 | 0.045* | 0.171 | 0.021-0.321 | 0.026* | 0.142 | −0.029–0.313 | NS |
| Medial frontal | 0.211 | 0.040-0.383 | 0.016* | 0.228 | 0.045-0.41 | 0.015* | 0.195 | 0.022–0.368 | 0.027* |
| Sensorimotor | 0.140 | −0.017-0.296 | 0.079† | 0.185 | 0.025-0.346 | 0.025* | 0.094 | −0.094–0.282 | NS |
| Superior parietal | 0.109 | −0.050-0.269 | NS | 0.099 | −0.063-0.261 | NS | 0.120 | −0.054-0.294 | NS |
| Middle frontal | 0.205 | 0.026-0.384 | 0.025* | 0.218 | 0.038-0.397 | 0.018* | 0.192 | −0.009-0.394 | 0.061† |
| Inferior parietal | 0.194 | 0.021-0.368 | 0.029* | 0.221 | 0.042-0.400 | 0.016* | 0.168 | −0.032–0.368 | 0.098† |
| Anterior cingulate | 0.252* | 0.090-0.414 | 0.003* | 0.297 | 0.122-0.471 | 0.001* | 0.208 | 0.050-0.366 | 0.011* |
| Associative visual | 0.179 | 0.012-0.347 | 0.036* | 0.172 | 0.001-0.342 | 0.049* | 0.187 | 0.000-0.375 | 0.051† |
| Broca's region | 0.161 | −0.035-0.357 | NS | 0.215 | 0.002-0.427 | 0.048* | 0.107 | −0.125–0.340 | NS |
| Posterior cingulate | 0.190 | 0.003-0.378 | 0.047* | 0.217 | 0.028-0.406 | 0.025* | 0.164 | −0.025-0.352 | 0.088† |
| Parietotemporal | 0.200 | 0.033-0.368 | 0.020* | 0.198 | 0.027-0.370 | 0.024* | 0.203 | −0.008–0.413 | 0.059† |
| Superior lateral temporal | 0.184 | 0.000-0.368 | 0.050† | 0.274 | 0.093-0.455 | 0.004* | 0.095 | −0.144–0.333 | NS |
| Inferior frontal | 0.178† | −0.020-0.375 | 0.077† | 0.213 | 0.008-0.418 | 0.042* | 0.143 | −0.073–0.358 | NS |
| Primary visual | 0.065 | −0.142-0.272 | NS | 0.069 | −0.153-0.292 | NS | 0.061 | −0.147–0.268 | NS |
| Inferior lateral anterior temporal | 0.203* | 0.046-0.359 | 0.012* | 0.221 | 0.053-0.389 | 0.011* | 0.185 | 0.016–0.353 | 0.033* |
| Anterior medial temporal | 0.091 | 0.005-0.177 | 0.038* | 0.055 | −0.040-0.151 | NS | 0.127 | 0.034–0.220 | 0.008* |
| Inferior lateral posterior temporal | 0.170 | 0.011-0.330 | 0.036* | 0.175 | 0.019-0.331 | 0.028* | 0.166 | −0.018–0.350 | 0.077† |
| Posterior medial temporal | 0.071 | −0.040-0.182 | NS | 0.052 | −0.057-0.161 | NS | 0.090 | −0.031–0.212 | NS |
| Subcortical | | | | | | | | | |
| Caudate nucleus | 0.040 | −0.122-0.203 | NS | 0.030 | −0.156-0.217 | NS | 0.050 | −0.123–0.223 | NS |
| Thalamus | 0.134 | −0.017-0.284 | 0.081† | 0.191 | 0.042-0.340 | 0.013* | 0.076 | −0.100–0.253 | NS |
| Lentiform nucleus | 0.117 | −0.116-0.349 | NS | 0.125 | −0.114-0.363 | NS | 0.109 | −0.132-0.350 | NS |
| Cerebellum | 0.076 | −0.070-0.222 | NS | 0.084 | −0.076-0.244 | NS | 0.068 | −0.070–0.206 | NS |
| Midbrain | 0.011 | −0.042-0.065 | NS | Excluded | | | Excluded | | |
| Vermis | 0.107 | −0.036-0.250 | NS | Excluded | | | Excluded | | |
| Pons | Excluded | | | Excluded | | | Excluded | | |

Each reported coefficient reflects the independent impact of hypsarrhythmia on regional cerebral activity (RCA) and is derived from multiple linear regression in which RCA is the dependent variable, hypsarrhythmia is the predictor variable, and age at PET is a covariate. Positive coefficients represent increased metabolism associated with hypsarrhythmia.

* p-value < 0.05.

† p-value < 0.10.

### 3.3. Lateralized analysis

In an exploratory analysis to evaluate whether the impact of hypsarrhythmia on RCA might be asymmetric, we evaluated left and right cortical ROIs separately. We found that the association between hypsarrhythmia and hypermetabolism was stronger within the left hemisphere in 10 of the aforementioned 11 cortical ROIs (Table 2, Fig. 2). The only ROI in which an association between hypsarrhythmia and RCA was observed on the right, but not the left, was in anterior medial temporal cortex (p = 0.008). In addition, when evaluating the left-sided ROI's independently, we found that hypsarrhythmia was associated with hypermetabolism in 4 of the 7 cortical ROIs for which a significant association was not observed with "bilateral" analysis: left sensorimotor (p = 0.025), Broca's area (p = 0.048), left inferior frontal (p = 0.042), and left superior lateral temporal cortex (p = 0.004). In considering subcortical ROIs, we found that hypsarrhythmia was associated with left thalamic hypermetabolism (p = 0.013), but no significant association was observed in the right thalamus (p = 0.390). There were no other lateralized associations between hypsarrhythmia with RCA in other subcortical ROIs. Of note, neither the left nor the right caudate nuclei exhibited an association between hypsarrhythmia and RCA.

To ascertain whether this widespread and asymmetric (left > right) association between cortical RCA and hypsarrhythmia might be due to the presence of lateralized structural lesions, we further adjusted for the presence of the identified epileptogenic zone on the left side or right side with sequential multiple linear regression in which RCA was the dependent variable, hypsarrhythmia was the predictor variable, and age at PET-EEG and presence/absence of a left (or right) epileptogenic zone were covariates. The presence of an ipsilateral or contralateral epileptogenic zone did not confound any of the above associations for any ROI (Table 2). Likewise, stratified multiple linear regression with exclusion of patients with (1) left only or (2) right only epileptogenic zones did not significantly alter the observed RCA associations. Similarly, we undertook stratified analyses to explore whether associations between RCA and hypsarrhythmia were affected by laterality of the epileptogenic zone (Fig. 3). Using anterior cingulate cortex (the ROI with the strongest association with hypsarrhythmia) as an example, we present a series of scatterplots which illustrate that (1) pons-normalized RCA increases with age (panels A, E, I) in both the left and right anterior cingulate cortex, (2) among patients < 20 months old at the time of PET (including all but one patient with hypsarrhythmia), RCA

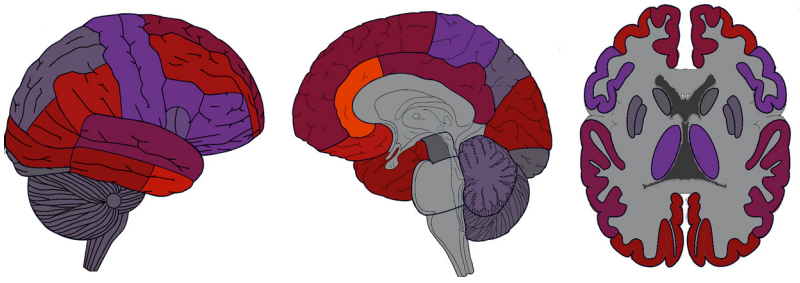


**Fig. 1.** Association between hypsarrhythmia and pons-normalized regional cerebral activity.
Visualization of bilateral analysis. Regional metabolic activity by hypsarrhythmia, adjusted for age at PET. Color gradient in logarithmic *P*-value scale. 46 of 47 pre-specified regions of interest are demarcated (exception posterior medial temporal cortex).

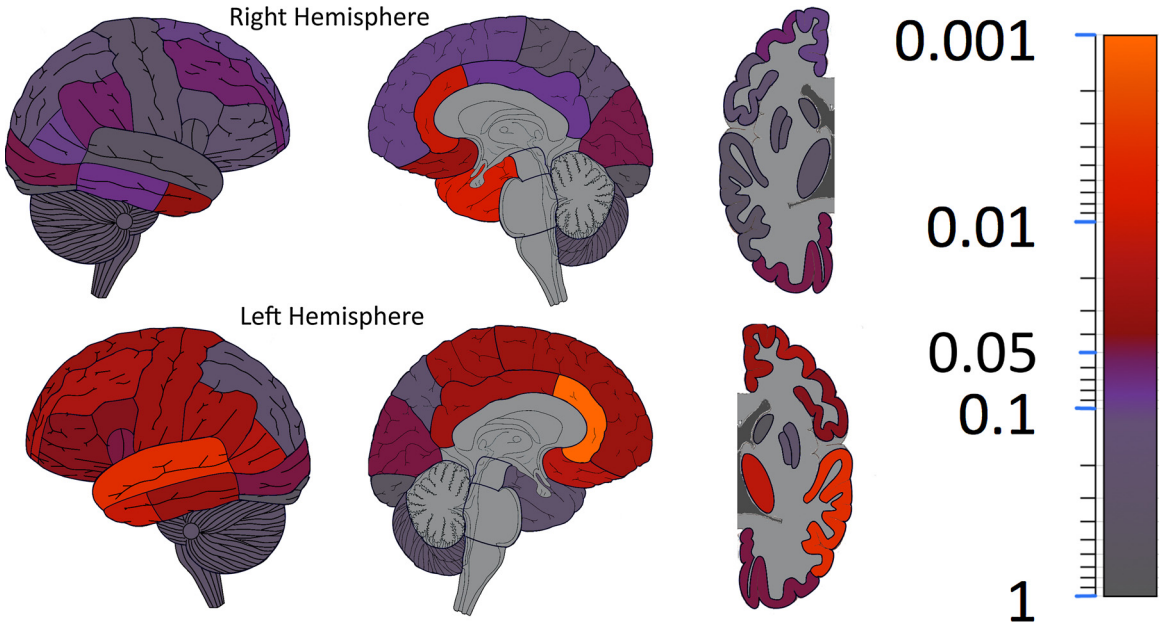


**Fig. 2.** Association between hypsarrhythmia and pons-normalized regional cerebral activity: Lateralized Analysis.
Visualization of lateralized analysis. Regional metabolic activity by hypsarrhythmia, adjusted for age at PET. Color gradient in logarithmic *P*-value scale. 46 of 47 pre-specified regions of interest are demarcated (exception posterior medial temporal cortex).

tends to be higher among those with hypsarrhythmia, and (3) both of these trends are preserved despite further stratification according to the side of the epileptogenic zone. This pattern in which stratification by epileptic zone laterality does not affect the association between RCA and hypsarrthymia was recapitulated throughout the cortex.

### 3.4. Components of hypsarrhythmia

With our observation that hypsarrhythmia is associated with widespread hypermetabolism, we sought to determine whether such changes in RCA are linked to any specific component of hypsarrhythmia, i.e. high voltage or FMEP. Therefore, on an exploratory basis, we determined whether RCA in each ROI was associated with high voltage and FMEP, and further screened for an interaction between high voltage and FMEP. Using sequential multivariate linear regression in which ROI-specific RCA was the dependent variable and predictor variables included age at PET, high voltage, FMEP, and a multiplicative interaction term (high voltage x FMEP), we found an association of the multiplicative interaction term with increased RCA in only three ROIs: Medial frontal cortex ($P = 0.038$), left medial frontal cortex ($P = 0.025$), and left inferior lateral anterior temporal cortex ($P = 0.037$). We screened for an association between RCA in each ROI with high voltage, FMEP, again using sequential multivariate linear regression, and without adjustment for multiple comparisons. With the exception of higher RCA associated with the presence of MISD in left inferior parietal cortex ($P = 0.026$), we did not observe any associations between RCA and any component feature of hypsarrhythmia. With the hypothesis that the presence of high voltage might confound an association with MISD or FMEP, or vice versa, we then evaluated for the impact of FMEP and high voltage in sequential models in which RCA was the dependent variable, and high voltage, FMEP, and age at PET were all covariates. In this scenario, with adjustment for the potential impact of high voltage, we observed an association between FMEP and hypermetabolism in only one ROI: Anterior medial temporal cortex ($P = 0.049$). In unilateral analyses, we found that FMEP was linked to hypermetabolism in left sensorimotor cortex ($P = 0.008$) and left inferior parietal cortex ($P = 0.033$). Of note, high voltage was not linked to hypermetabolism in any ROI, with and without adjustment for FMEP.

## 4. Discussion

This study is significant as we have observed an association between hypsarrhythmia and widespread—though curiously left more than right—hypermetabolism among patients with infantile spasms. This effect was exclusively cortical, with the exception of left thalamic hypermetabolism observed in an exploratory analysis. Although we had anticipated a possible link between hypsarrhythmia and RCA in the caudate nuclei, as infantile spasms in general are associated with relative caudate hypermetabolism [9], hypsarrhythmia was not associated with metabolic changes in the basal ganglia or brainstem. Just as we had hypothesized that hypsarrhythmia would be associated with changes in RCA, our a priori suspicion was that such differences would be explained—at least in part—by the presence or absence of high-voltage or frequent epileptiform discharges. The lack of association of RCA with these traditional components of hypsarrhythmia—especially considering our lack of adjustment for multiple comparisons in these exploratory subanalyses—is perplexing. This finding suggests that hypsarrthyhmia represents more than the sum of its traditional parts.

Whereas serial pre- and post-treatment FDG-PET studies suggest that cortical RCA abnormalities associated with infantile spasms resolve following successful treatment [11,12], it is unclear whether this normalization represents relief of metabolic burden from epileptic spasms, hypsarrhythmia, or both. Our finding of hypsarrhythmia-associated cortical hypermetabolism suggests that hypsarrhythmia contributes to RCA changes above and beyond any metabolic impact from epileptic spasms alone. This study further corroborates the view that hypsarrhythmia is not simply an interictal pattern, but that it may represent a quasi-ictal state based on widespread bilateral cortical hypermetabolism, even in cases in which focal epileptogenic zones are identified [16]. This contrasts with the view that hypsarrhythmia represents a persistent post-ictal state and instead lends some support to the notion that hypsarrhythmia could be classified as a form of non-convulsive status-epilepticus [17].

Although the pathophysiology of hypsarrhythmia remains obscure, our limited understanding is critically informed by several observations using FDG-PET. In particular, FDG-PET studies support the hypothesis that a focal cortical lesion can generate “generalized” hypsarrhythmia via interaction with subcortical structures [9]. In addition, surgical

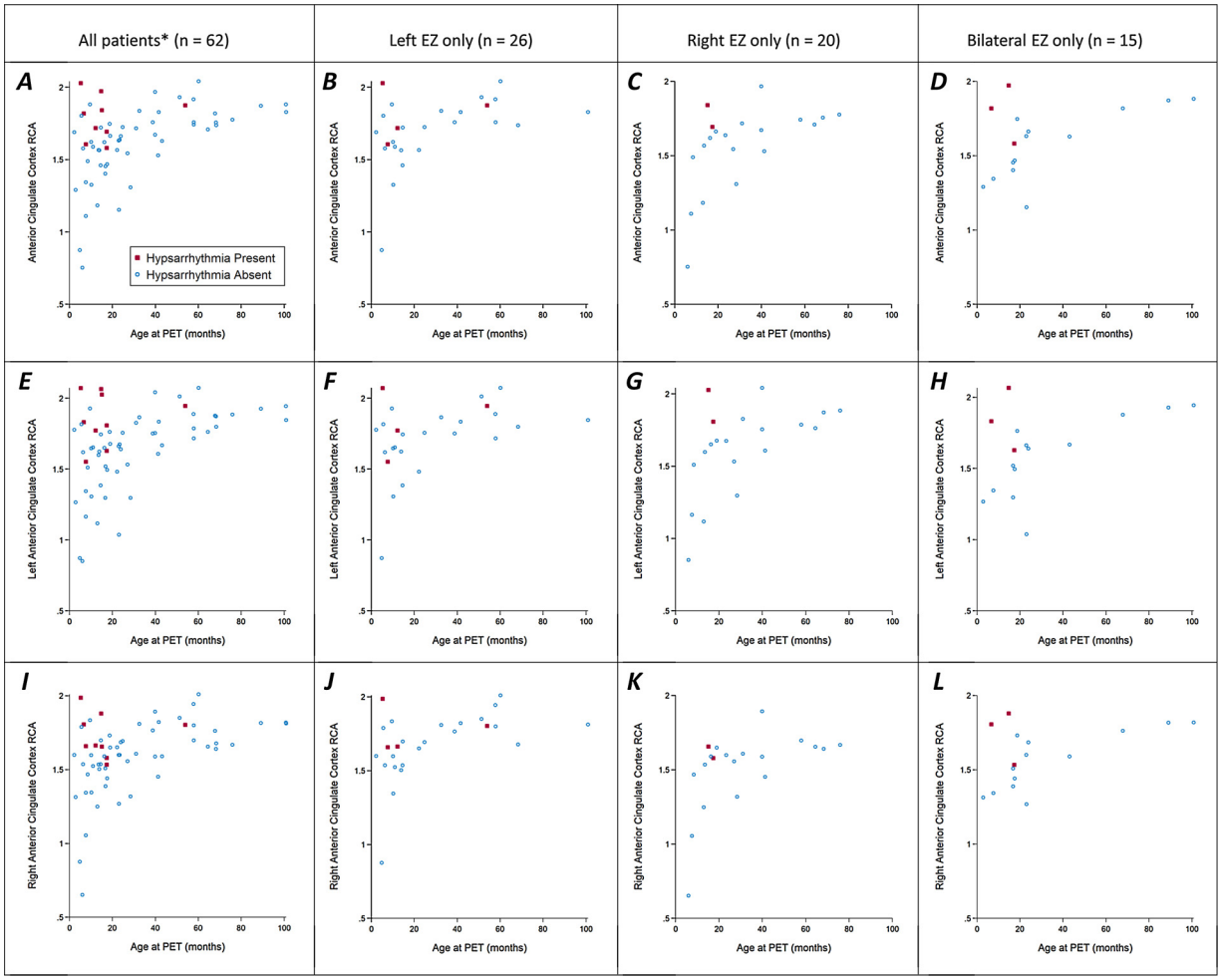


**Fig. 3.** Association between hypsarrhythmia and pons-normalized anterior cingulate cortex regional cerebral activity: Stratified analysis.
After adjustment for age, hypsarrhythmia is associated with higher RCA when considering all patients (Panel A). The same trend is seen with stratification according to the side of the epilepogenic zone (columns), and when considering left, right and bilateral anterior cingulate cortex RCA (rows). Bilateral (panels A – D), left (panels E – H), and right (panels I – J) anterior cingulate cortex RCA is plotted as a function of age at PET. Abbreviations: EZ, epileptogenic zone; RCA, regional cerebral activity.
*One patient with an anterior cingulate focal cortical dysplasia was excluded from these plots. None of the remaining patients (n = 62) exhibited an anterior cingulate cortical lesion.

resection of focal FDG-PET lesions, even in the absence of structural MRI abnormalities [8,18], ameliorates epileptic burden by presumably disrupting these pathologic cortical-subcortical interactions. Similarly, EEG functional MRI (EEG-fMRI) studies have bolstered this hypothesis with the demonstration that blood oxygenation level-dependent (BOLD) changes in both cortical and subcortical regions are associated with hypsarrhythmic epileptiform discharges and high-voltage slow waves [19]. Our findings of cortical hypermetabolism without changes in subcortical metabolism are compatible with these observations.

Though asymmetric—left greater than right—hypermetabolism has not been previously reported in FDG-PET studies, our finding may support prior speculation that left hemispheric excitatory synapses endure longer than their right hemisphere counterparts in infancy, and may thus be more vulnerable to epileptic activity [20,21]. Among patients with infantile spasms, structural imaging studies have demonstrated an asymmetric increase in left temporal grey matter volume [22], and functional studies using event-related potentials have identified impaired temporal maturation and network topology, which manifest as dysfunction of auditory processing [23,24]. The left greater than right hypermetabolism seen in our cohort may be a metabolic representation of these asymmetric structural and functional abnormalities. Together these data suggest that hypsarrhythmia may be an important factor in the disproportionate impairment of language development and relative sparing of motoric functioning among children with infantile spasms.

There are several major limitations of this study. Foremost, our analysis is predicated on the presence or absence of hypsarrhythmia as assessed by unblinded electroencephalographers, an assessment which we have previously demonstrated is imprecise [4]. As we relied on retrospective video-EEG reports in the medical record, EEG features such as burden of epileptiform discharges and slowing were determined by qualitative clinical assessment rather than an unbiased quantitative measurement.

Importantly, we are reporting changes in pons-normalized metabolic activity rather than absolute metabolic activity. To the extent that we have linked hypsarrhythmia to widespread cortical hypermetabolism, we must highlight the assumption that hypsarrhythmia is not associated with a change in pontine metabolism. A relatively simple alternative explanation for our findings is that hypsarrhythmia may be linked to pontine hypometabolism. Although we believe this alternative explanation is unlikely, we cannot exclude this possibility without determination of absolute (as opposed to relative) metabolic activity.

In addition, external validity is a significant concern. Our retrospective cohort represents a convenience sample, consisting of

medically refractory patients who underwent surgical evaluation and, as a result, were relatively older than typical infantile spasms patients. Although our analysis adjusted for age at time of PET, this may be an inadequate statistical control. In particular, there is concern that RCA may change over time as a function of myelination, duration of epilepsy, seizure frequency, or perhaps other time-varying factors. Although all patients in the cohort had ongoing epileptic spasms at the time of PET, we were unable to reliably quantify seizure frequency/burden with available medical records. Based on our clinical experience, we nevertheless suspect that the burden of epileptic spasms (number of spasms per cluster, and number of clusters per day) is higher among children with hypsarrhythmia. It is possible that the widespread hypermetabolism we attribute to hypsarrhythmia in this analysis is modified by, or confounded by, epileptic spasms burden.

Beyond age at PET, this cohort is not representative of patients with infantile spasms in general, and our conclusions may not generalize to younger patients with infantile spasms, and especially those without focal structural abnormalities, or those who respond to first-line therapies. In addition, our sample of patients exhibiting hypsarrhythmia during PET imaging was quite small from a statistical standpoint, which has limited our power to detect significant differences between those patients with and without hypsarrhythmia. The relative paucity of patients with hypsarrhythmia reflects the refractory character of the study cohort, with many patients having partially responded to prior therapies, with resolution of past hypsarrhythmia, but persistence of epileptic spasms. Furthermore, we lacked normal, age-matched controls which would have been useful in comparing our findings with prior FDG-PET studies. Similarly, our ability to control or adjust for the impact of focal structural abnormalities was imperfect and limited by the sample size. This study would be complemented by a similar analysis using a larger cohort of younger, less-refractory children with infantile spasms, who lack focal structural abnormalities.

Lastly, given that we have only obtained a single PET scan for each patient, we are limited in our metabolic sampling. There may be considerable within-patient variation over time, as suggested by the observations of Sakaguchi [25] and others, who have found that qualitative focal ("lesional") PET hypometabolism may attenuate or even disappear over time. Interestingly, our results may explain this phenomenon to some extent. We may speculate that as hypsarrhythmia resolves over time, the widespread cortical hypermetabolism identified in this study may similarly attenuate, thus reducing the "global vs lesional" contrast used to visually identify focal PET hypometabolism.

A means to enrich the identification and characterization of hypsarrhythmia would be valuable given the limitations of current clinical practice, and especially given the risk posed by enduring hypsarrhythmia. It is possible that successful response to treatment for infantile spasms should be defined by not only resolution of epileptic spasms and hypsarrhythmia, but by resolution of FDG-PET abnormalities as well. Further study is warranted to replicate the findings of this study and determine the utility of FDG-PET as a measure of disease burden and as a tool to predict long-term outcomes for children with infantile spasms.

The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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