Early Human Development 184 (2023) 105840

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Clinical value of cortical bursting in preterm infants with intraventricular haemorrhage

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ARTICLE INFO

Keywords:
IVH
Delta brushes
Spontaneous activity transients
Morphine
Developmental trajectory

ABSTRACT

Background: In healthy preterm infants, cortical burst rate and temporal dynamics predict important measures such as brain growth. We hypothesised that in preterm infants with germinal matrix-intraventricular haemorrhage (GM-IVH), cortical bursting could provide prognostic information.
Aims: We determined how cortical bursting was influenced by the injury, and whether this was related to developmental outcome.
Study design: Single-centre retrospective cohort study at University College London Hospitals, UK.
Subjects: 33 infants with GM-IVH $\geq$ grade II (median gestational age: 25 weeks).
Outcome measures: We identified 47 EEGs acquired between 24 and 40 weeks corrected gestational age as part of routine clinical care. In a subset of 33 EEGs from 25 infants with asymmetric injury, we used the least-affected hemisphere as an internal comparison. We tested whether cortical burst rate predicted survival without severe impairment (median 2 years follow-up).
Results: In asymmetric injury, cortical burst rate was lower over the worst- than least-affected hemisphere, and bursts over the worst-affected hemisphere were less likely to immediately follow bursts over the least-affected hemisphere than vice versa. Overall, burst rate was lower in cases of GM-IVH with parenchymal involvement, relative to milder structural injury grades. Higher burst rate modestly predicted survival without severe language (AUC 0.673) or motor impairment (AUC 0.667), which was partly mediated by structural injury grade.
Conclusions: Cortical bursting can index the functional injury after GM-IVH: perturbed burst initiation (rate) and propagation (inter-hemispheric dynamics) likely reflect associated grey matter and white matter damage. Higher cortical burst rate is reassuring for a positive outcome.

1. Introduction

In preterm infants, the largest burden of acquired brain injury is intraventricular haemorrhage arising from the germinal matrix (GM-IVH) [1–3]. This injury can occur spontaneously, or be triggered or exacerbated by acute illness such as sepsis or metabolic acidosis [4–6]. The injury is graded on a four-point ascending scale of severity, depending on the worst of serial cranial ultrasound scans. GM-IVH of grade II or higher is associated with worse outcomes relative to gestational age-matched comparisons, with ventricular dilatation and parenchymal involvement conferring additional risk of disability or death. However, structural injury grade only coarsely predicts outcome, e.g. up to half of surviving infants with parenchymal damage have entirely normal outcome at 5 years [7]. Complementary prognostic information would help to direct early therapeutic intervention.

At University College London Hospitals (UCLH), infants with GM-

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https://doi.org/10.1016/j.earlhumdev.2023.105840
Received 29 May 2023; Received in revised form 31 July 2023; Accepted 1 August 2023
Available online 2 August 2023

IVH are monitored with electroencephalography (EEG) when seizures are suspected, which are known to be associated with the injury [8,9]. Additionally, it is possible that the background EEG could contribute to neurological assessment and prognostication. This is customary following brain injury in full-term neonates [10], although its value in preterm infants has been interpreted more cautiously [11]. A dominant feature of the neonatal EEG is cortical bursting activity. Cortical bursts reflect excitatory input to pyramidal neurons in animal models [12]. Burst rate and dynamics in healthy preterm infants predict subsequent brain growth and microstructure, as well as cognitive development [13–17]. Cortical burst rate can be attenuated by GM-IVH [18–25]. Thus, we hypothesised that burst rate and temporal dynamics could index the functional injury and potentially be prognostic.

2. Material and methods

2.1. Infants

This project met the criteria of a retrospective service evaluation defined by the UK Health Research Authority, which we confirmed with the Research Quality and Safety Manager of the UCLH Research and Development Directorate, and therefore individual consent from parents was not required. All clinical data review was conducted by a UCLH-affiliated, state-registered Clinical Neurophysiologist (KW). We identified infants born between 2007 and 2022 who underwent EEG monitoring during the neonatal period (defined here as ≤40 weeks corrected gestational age (CGA)) which was available for review. Selection criteria comprised gestational age <35 weeks [1,19,21] and evidence of ≥grade II GM-IVH on routine cranial imaging. Infants were sub-categorised as having asymmetric GM-IVH if their cranial imaging was reported as asymmetric by a consultant neonatologist or neuroradiologist. Exclusion criteria included evidence of intrapartum hypoxic-ischemic insult, or acute severe metabolic disturbance at the time of EEG. This resulted in a total sample of 34 infants with median gestational age 25+5 weeks+days.

2.2. EEG monitoring for suspected seizures

A minimum of 4 Ag/AgCl recording electrodes were positioned at bilateral central and frontal sites (C4, C3, F4, F3), according to the international 10/20 electrode placement system. Eight/34 infants had more than one EEG. This resulted in a total of 52 recordings (Table 1), which were all reviewed for electrographic seizures [26].

2.3. EEG analysis of cortical bursting

2.3.1. Inclusion criteria

For the analysis of cortical bursting, we excluded 5 recordings with >20 % seizure burden [27] and/or during treatment with 3 anti-seizure drugs, which precluded appraisal of background EEG features [24,28,29]. One infant, who died on postnatal day 1, had no recording suitable for analysis of cortical bursting. All other infants had at least one recording suitable: 47 from 33 infants (Table 1). In these recordings, we selected segments with no or fewer seizures, including up to 2 days of data per recording: 41/47 segments included no seizures, and the remaining 6 segments had ≤0.5 % seizure burden.

2.3.2. Burst occurrence rate

Cortical bursts comprising fast oscillations, often nested into slower rhythms, are a dominant background pattern of the neonatal EEG [34–38]. To identify these bursts, we first removed artefactual sections by visual inspection. We then calculated root-mean-square (RMS) amplitude values between 8 and 30 Hz, using sliding 400-ms intervals [24]. We identified segments for each channel that were consecutively above a set threshold (1.5 times the standard deviation of its RMS signal over the whole recording [37,39]) for ≥0.5 s [35], using 'detectevent' in EEGLAB [40] (for illustration, see [41]). Please see Supplementary Information for further details about data acquisition and pre-processing.

Table 1
Infant demographics.

Sex (female:male)	12:22
Median (range) birth weight (g)	821 (533–1999)
Median (range) gestational age (weeks+days)	25^{+5} (23^{+4}–34^{+2})
Median (range) Apgar score at 1 min	4 (1–9)
Median (range) Apgar score at 5 min	8 (2–10)
No. of EEGs	52 EEGs from 34 infants
No. of EEGs suitable for analysis of cortical bursting[a]	47 EEGs from 33 infants
Grade II	7/33
Ventricular dilatation[b]	5/33
With parenchymal lesion(s)/periventricular haemorrhagic venous infarction (PHVI)	21/33
Total asymmetric injury	24/33 (5 grade II, 2 ventricular dilatation[c], 17 PHVI)
Median (range) postnatal age (days)	20 (2–104)
Median (range) corrected gestational age (weeks+days)[d]	30^{+1} (24^{+0}–40^{+1})
Morphine exposure	27/47
Anti-seizure drug exposure[e]	16/47
Median (range) corrected gestational age (weeks+days) at discharge home from hospital (in survivors)	42^{+6} (36^{+5}–56^{+3})

[a] In cases of >1 EEG being analysed from the same infant, the mean inter-recording interval was 10 days, which does not underestimate the variance of EEG-level analyses (see the supplemental information in [30]).
[b] Defined here as dilatation ≥97th centile and/or anterior horn width >6 mm [31–33].
[c] The ventricular dilatation was not markedly asymmetric, but one infant had unilateral intraventricular haemorrhage prior to both ventricles dilating, and the other infant had asymmetric bilateral intraventricular haemorrhages prior to both ventricles dilating.
[d] At which analysed EEG ended. Corrected gestational age = Gestational age + postnatal age.
[e] 15 phenobarbital, 3 benzodiazepine, 2 phenytoin, 1 levetiracetam, 1 paraldehyde. (Total adds up to >16 because 6 EEGs included in the analysis of cortical bursting were acquired during exposure to 2 anti-seizure drugs.)

2.3.3. Burst temporal dynamics

The relative timing of cortical bursts overlying different brain regions offers insight into functional connections [42,43]. To examine whether GM-IVH influenced the temporal relationship between burst onsets at recording channels overlying different regions, we represented their latencies with a gaussian window of 3 standard deviations around each value, using 'gauss' in EEGLAB. We then calculated cross-correlations for 6 positive and 6 negative lag values between −1500 and +1500 ms [44,45], normalised to the autocorrelation between identical burst latencies (i.e. correlation of 1.00 at lag 0 ms) [46].

2.3.4. Burst magnitude

The magnitude of bursts can be indexed by their power (μV^2). To characterise power changes of detected bursts relative to baseline, we convoluted the EEG signal with a Morlet wavelet between 0.1 and 45 Hz using an increasing range of cycles (3–270), employing 'newtimef' in EEGLAB. For bursts detected at each channel, we extracted the 8-30 Hz power at that channel over the course of the burst, and then normalised this value by dividing by its duration in seconds [46].

2.3.5. Cortical bursting and outcome

We assessed whether there was an association between cortical bursting and survival without severe language, motor, or cognitive impairment (defined here as Bayley Scales of Infant Development 3rd edition composite score ≤70/100, or unable to be assessed using Bayley Scales because of severe global delay and cerebral visual impairment; median 2 years follow-up, range 1–2 years corrected).

2.4. Statistical analysis

To assess differences between matched intra-subject variables or unpaired variables we used paired and unpaired *t*-tests respectively. To test for associations between two continuous variables we used Pearson correlations.

To investigate multiple factors potentially underlying variance in cortical bursting, we conducted a hierarchical linear regression in which CGA was entered as the first explanatory variable given its known large effect [38]. After that, we examined whether adding further EEG-level variables of morphine or anti-seizure drug(s) exposure, or electrographic seizure(s) during the analysed segment (all yes/no) improved model fit. Finally, we tested whether adding the infant-level variable of parenchymal lesion(s)/periventricular haemorrhagic venous infarction (hereafter: PHVI) optimised model fit. We reasoned that higher burst rate after accounting for these factors could reflect functional recovery, and predict positive outcome. To test this, we calculated standardised residuals (z-scores) after model fitting: a z-score above 0 indicates that burst rate was higher than predicted by the model, a z-score below 0 indicates that burst rate was lower than predicted by the model. To examine whether higher standardised residuals of burst rate predicted survival without impairment, we conducted a receiver operating characteristic (ROC) analysis and i) calculated the area under the curve (AUC) which is a combined measure of sensitivity and specificity: an AUC of 0.5 indicates prediction no better than chance and serves as the null hypothesis, while 1.0 would reflect a perfect predictor, and then ii) examined ROC curve coordinates to identify cut-off thresholds which were optimally predictive. Statistical analysis was performed using IBM SPSS v. 26 and significance was set at $p < .05$.

3. Results

3.1. Seizures

At the EEG-level, 17/52 (33 %) EEGs included electrographic seizures. At the infant-level, 15/34 (44 %) infants had electrographic seizures recorded during at least one EEG. These seizures were recorded at median postnatal day 6 (interquartile range 4–27) and 29+2 weeks CGA (interquartile range 26+6–34+6). Please see Supplementary Fig. 1 for a seizure example.

3.2. Characterisation of cortical bursts

47/52 EEGs were suitable for analysis of cortical bursting. These were of median duration 8 h (minimum 0.5 h in 45/47 recordings). Cortical bursts had mean duration 1.6 s. These bursts comprised an increase in power which peaked between 8 and 30 Hz as expected, coupled to a less pronounced but longer-duration increase in slower frequencies (Fig. 1). For bursts identified at each channel, the largest changes in 8-30 Hz power were at that channel as anticipated, although bursts involved other channels also, especially for slower frequencies (Fig. 1).

3.3. In asymmetric injury, cortical burst rate was lower over the worst- than least-affected hemisphere

To examine whether injury altered cortical burst rate, we first took advantage of a subgroup of 33 EEGs from 25 infants with asymmetric injury (Table 1), for whom we could use the least-affected hemisphere as an internal comparison. There were fewer central (but not frontal) bursts per minute over the worst-affected hemisphere (central: mean 7.9 vs. 9.3 [95 % CI of difference −2.10 −0.62], $p = .001$, Fig. 2b; frontal: $p = .648$). This inter-hemispheric difference in central burst rate did not significantly narrow with postnatal age ($p = .415$) or CGA ($p = .169$, Fig. 2c). In comparison and as expected, there was no inter-hemispheric difference in central burst rate in symmetric injury ($p = .204$, Fig. 2a), when inter-hemispheric bursting ratio was more equal than in asymmetric injury (mean ratio 1.04 vs. 0.85 [95 % CI of ratio difference 0.09 0.28], $p < .001$).

Central bursts over the worst-affected hemisphere were less likely to follow bursts over the least-affected hemisphere than vice versa (negative lags had lower cross-correlations than their paired positive lag between 250 and 1000 ms (e.g. −500 vs. +500 ms) ($p \leq .014$, Fig. 3). In comparison and as expected, in symmetric injury inter-hemispheric central burst onsets were balanced (no significant differences between the cross-correlations of paired lags: $p \geq .374$, Fig. 3).

3.4. Cortical burst rate was inversely associated with burst power

In asymmetric injury, the ratio of central burst rate over the worst- to least-affected hemisphere predicted higher mean central burst power at the worst-affected hemisphere ($r = -0.608$, $p < .001$), but not the least-affected hemisphere ($p = .350$). Pooling EEGs from all infants together, with either asymmetric or symmetric injury, also showed an association between lower burst rate and higher mean burst power at that same region ($r = -0.390$ to -0.569, $p \leq .007$).

3.5. Higher cortical burst rate predicted positive outcome

Of 33 infants with bursting analysed, 28 infants - who had 42 EEGs in total - had outcome information available: six infants died after redirection of care, and outcome was available for 22 surviving infants. Severe impairment in language, motor, or cognitive domains was present in 5/22, 9/22, and 7/22 surviving infants respectively. Ten/22 infants were severely impaired in at least one domain.

Central burst rate over the worst- or equally-affected hemisphere increased with CGA, and was slightly reduced by morphine exposure (but not by anti-seizure drug exposure, or proximal electrographic seizures) (Table 2). After controlling for CGA and morphine, higher central burst rate modestly predicted survival without severe language or motor impairment (language: AUC 0.673, sensitivity and specificity 86 % and 40 %, and motor: AUC 0.667, sensitivity and specificity 93 % and 37 %, both using a cut-off threshold of −0.77, Fig. 4a–b; cognitive: AUC 0.532).

After adding presence (yes/no) of PHVI to the CGA + morphine model explaining burst rate, model fit was improved because PHVI attenuated burst rate (Table 2; visualised in Fig. 4c), and the residuals weakly predicted survival without severe language impairment (AUC 0.600), and scarcely predicted survival without severe motor impairment: AUC 0.553). This suggests that the relationship between burst rate and outcome was partly mediated by whether GM-IVH was associated with PHVI, especially for the motor domain. However, Fig. 4a–b show that burst rate could also provide unique information: in several instances of PHVI but burst rate above the cut-off threshold, it was correctly predicted that the infant survived without severe impairment.

4. Discussion

Our intra- and inter-subject results indicate that GM-IVH, especially with associated PHVI, depresses burst rate over the sensitive period equivalent to the third trimester of gestation when cortical bursting refines neural circuits in animal models [24]. This is also when activity-dependent emergence of bilateral cortical networks occurs, which could be disrupted by skewed inter-hemispheric cortical burst dynamics when one hemisphere is injured relative to the other [43,47]. These abnormalities of burst initiation (rate) and propagation (inter-hemispheric dynamics) are likely to reflect the grey matter and white matter damage associated with GM-IVH grade II or higher [48].

Burst rate was modestly associated with outcome, which to our knowledge is the only recent report that the background EEG is prognostic in a large sample of infants with GM-IVH, since two much earlier papers published 35 and 22 years ago when neonatal intensive care was very different [9,19]. Although the association we observed was partly

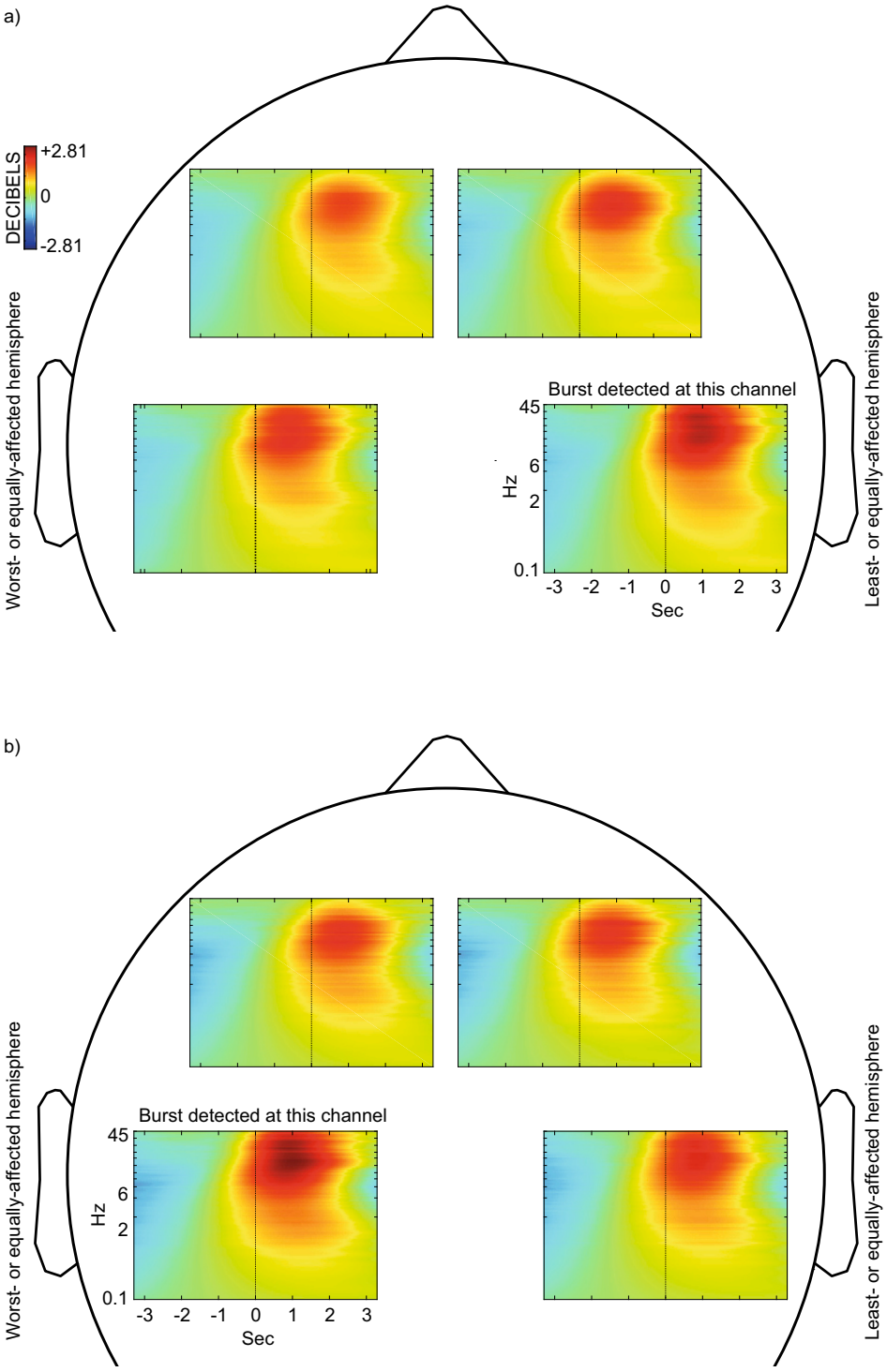

Fig. 1. Grand average time-frequency changes associated with cortical bursts. Bursts identified at the central channel overlying the least-affected hemisphere (or right hemisphere in the case of symmetric injury) (a) and worst-affected hemisphere (or left hemisphere in the case of symmetric injury) (b). Power changes between 0.1 and 45 Hz (logarithmic scale) are shown in decibels, relative to the mean power preceding burst onset (black vertical line), where increased power is red and decreased power is blue.

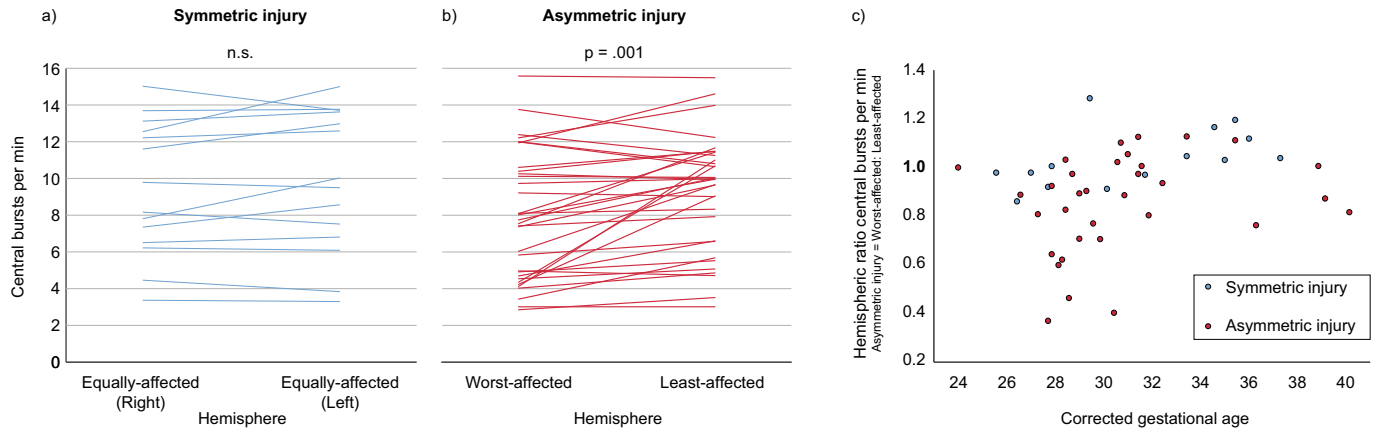

Fig. 2. In asymmetric GM-IVH, cortical burst rate was lower over the worst- than least-affected hemisphere. Left: Central burst rate over the two hemispheres when injury is symmetric (a: n = 14 EEGs) or asymmetric (b: n = 33 EEGs). Each EEG is represented by one line. c: Scatter plot of inter-hemispheric burst rate ratio against corrected gestational age at EEG. For infants with symmetric injury, the hemispheric ratio is left: right hemisphere. Each EEG is represented by one dot.

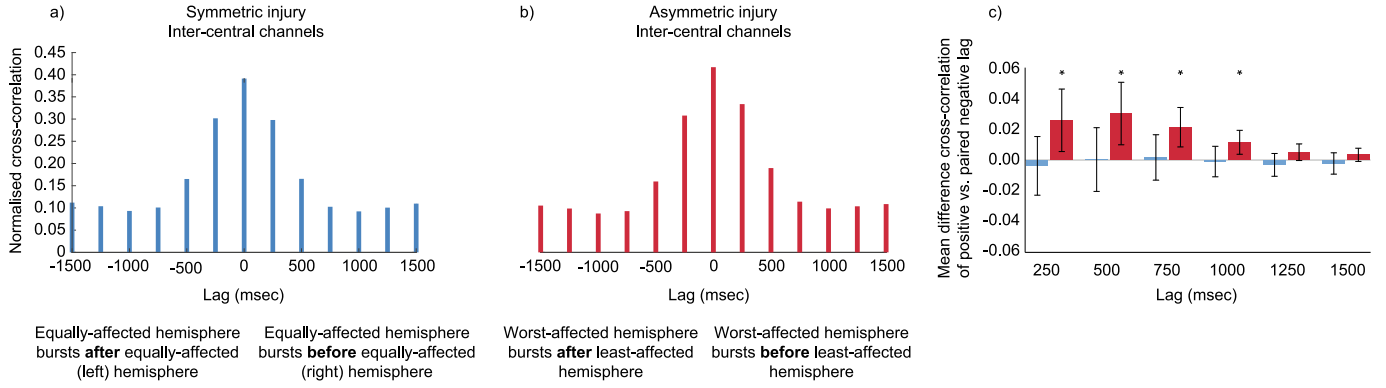

Fig. 3. Inter-hemispheric cortical burst dynamics were altered by asymmetric GM-IVH. Left: The relative timing of central burst occurrence over the two hemispheres when injury is symmetric (a: n = 14 EEGs) or asymmetric (b: n = 33 EEGs). c: Central bursts over the worst-affected hemisphere were less likely to immediately follow bursts over the least-affected hemisphere than vice versa. * = p < .05. 95 % confidence intervals are denoted by error bars.

Table 2
Hierarchical linear models of variables influencing central burst rate over the worst- or equally-affected hemisphere.

	B [95 % CI]	s.e.	p	R^2
Model 1: CGA				
CGA	0.637 [0.412 0.861]	0.111	<.001	0.421
Model 2: CGA + morphine[a]				
CGA	0.596 [0.382 0.810]	0.106	<.001	0.495
Morphine	−2.046 [−0.427–0.3.664]	0.803	.014	
Model 3: CGA + morphine + PHVI				
CGA	0.639 [0.433 0.845]	0.102	<.001	0.557
Morphine	−2.114 [−0.578–3.650]	0.762	.008	
PHVI	−2.007 [−0.351–3.664]	0.822	.019	

[a] Anti-seizure drug exposure and Electrographic seizures were both excluded from the model: p = .168 and .301 respectively.

mediated by structural injury grade, burst rate provided distinct information in some instances. This concurs with other recent work showing that neonatal EEG activity can independently predict outcome [41,49]. A great advantage of EEG is that it could be used to track prognostic information over time. This has the potential to provide real time monitoring of the effect of clinical interventions delivered on the neonatal unit after the injury, e.g. to support sleep cycling as it emerges from approximately 28–31 weeks CGA (Supplementary Fig. 2) [50,51].

Overall, our results indicate that the background EEG could contribute to neurological assessment and prognostication after brain injury in preterm infants, as is customary in full-term infants. Indeed, in both cohorts injury is associated with sparser, higher power cortical bursts, suggesting some similarity in how the insult impacts brain function [41,52,53] (also see [54]).

This work has some limitations. The sample was varied, but this is a true reflection of our clinical population and much of the inter-subject heterogeneity was controlled for by use of intra-subject analyses. We successfully used this intra-subject approach to show that burst rate was lower over the worst- vs. least-affected hemisphere, but a cleaner comparison would have been a matched group with no GM-IVH. Furthermore, the sample underwent EEG recordings because seizures were suspected; proximal seizures could contribute to the depression of interictal cortical bursting and therefore the sample may not be representative of the total population of infants with GM-IVH. In the future, a multi-centre study could be conducted to model predictors of outcome across this wider population, e.g. 52 infants from four centres allowed to create a four-variable model of outcome after GM-IVH in [55].

In summary, clinical EEG recordings can index the functional injury after GM-IVH, with higher cortical burst rate reassuring for a positive motor outcome over the first 2 years. This analysis has the potential to provide complementary prognostic information, but also to be used as a cotside non-invasive monitor of cortical health and development, particularly during therapeutic interventions.

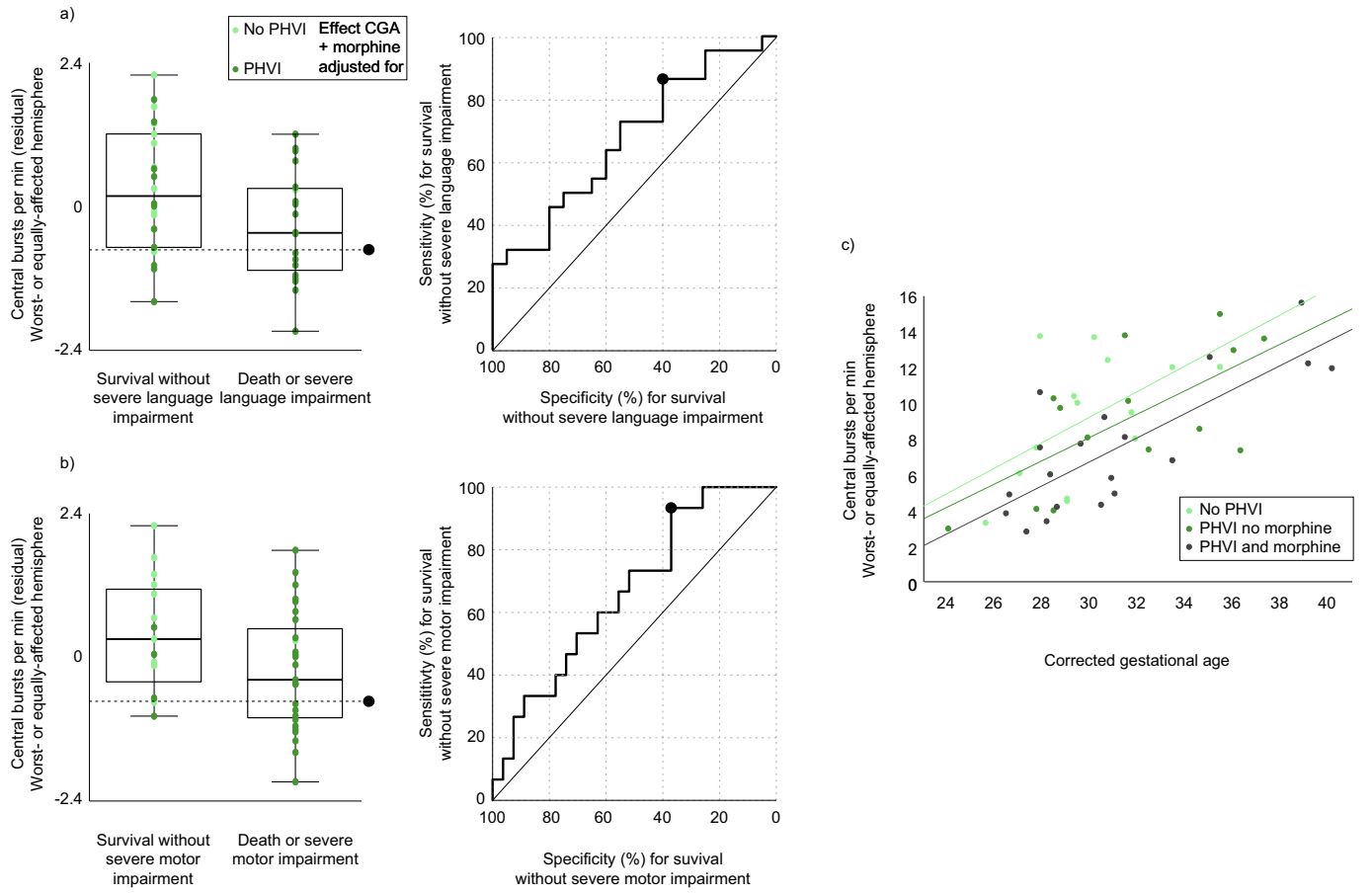

Fig. 4. Burst occurrence rate and survival without severe language or motor impairment. Left: Distribution of standardised residual of burst occurrence rate after corrected gestational age and morphine exposure controlled for in infants who did or did not survive without severe language (a) or motor (b) impairment. Each EEG is represented by a dot (n = 42). The cut-off threshold used to predict survival without severe impairment is represented by a black dashed line, and the adjacent ROC curve illustrates how this threshold was derived. Data are colour-coded by whether the infant had PHVI, to demonstrate the degree to which this co-varied with burst rate and outcome. c: For illustrative purposes, the cross-sectional developmental trajectory of burst rate is fitted separately for three subgroups to demonstrate how PHVI and morphine exposure reduced burst rate.

CRediT authorship contribution statement

Tuomas Koskela: Software
Judith Meek: Writing-Reviewing and editing
Angela Huertas-Ceballos: Data curation
Giles S Kendall: Data curation
Kimberley Whitehead: Conceptualisation, Funding acquisition, Investigation, Formal analysis, Writing-Original draft preparation.

Declaration of competing interest

None.

Acknowledgements

This work was supported by Brain Research UK, which had no role in the study design; collection, analysis and interpretation of data; writing of the report; or the decision to submit the article for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2023.105840.

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