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Functional brain maturation and sleep organisation in neonates with congenital heart disease

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ABSTRACT

Objective: Neonates with Congenital Heart Disease (CHD) have structural delays in brain development. To evaluate whether functional brain maturation and sleep-wake physiology is also disturbed, the Functional Brain Age (FBA) and sleep organisation on EEG during the neonatal period is investigated.
Methods: We compared 15 neonates with CHD who underwent multichannel EEG with healthy term newborns of the same postmenstrual age, including subgroup analysis for d-Transposition of the Great Arteries (d-TGA) (n = 8). To estimate FBA, a prediction tool using quantitative EEG features as input, was applied. Second, the EEG was automatically classified into the 4 neonatal sleep stages. Neonates with CHD underwent neurodevelopmental testing using the Bayley Scale of Infant Development-III at 24 months.
Results: Preoperatively, the FBA was delayed in CHD infants and more so in d-TGA infants. The FBA was positively correlated with motor scores. Sleep organisation was significantly altered in neonates with CHD. The duration of the sleep cycle and the proportion of Active Sleep Stage 1 was decreased, again more marked in the d-TGA infants. Neonates with d-TGA spent less time in High Voltage Slow Wave Sleep and more in Tracé Alternant compared to healthy terms. Both FBA and sleep organisation normalised postoperatively. The duration of High Voltage Slow Wave Sleep remained positively correlated with motor scores in d-TGA infants.
Interpretation: Altered early brain function and sleep is present in neonates with CHD. These results are intriguing, as inefficient neonatal sleep has been linked with adverse long-term outcome. Identifying how these rapid alterations in brain function are mitigated through improvements in cerebral oxygenation, surgery, drugs and nutrition may have relevance for clinical practice and outcome.

1. Introduction

Overall improvements in survival of neonates with complex congenital heart disease (CHD) have shifted the focus of attention to modify risk factors for associated neurological impairments [1]. The combination of innate patient and perioperative factors will consequently have impact on future neurodevelopmental outcome (NDO) [2], and there is a critical need for early markers of long-term neurological well-being.

Mounting evidence from neuroimaging studies have demonstrated delays in (micro)structural brain development, mainly in cortical folding and myelination and associated acquired brain injury in CHD [3–5]. The role of these findings in predicting NDO is however still not completely disentangled. Beca et al. showed that brain immaturity on MRI but not brain injury was associated with

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List of abbreviations

aEEG	amplitude Electroencephalography
AS	Active Sleep
AS1	Active Sleep 1
AS2	Active Sleep 2
BSID-III	Bayley Scale of Infant Development-III
CHD	Congenital Heart Disease
CNN	Convolutional Neural Network
CUS:	Cranial Ultrasound
d-TGA	d-Transposition of the Great Arteries
FBA	Functional Brain Age
HLHS	Hypoplastic Left Heart Syndrome
GA	Gestational Age
MRI	Magnetic Resonance Imaging
NIRS	Near Infrared Spectroscopy
NDO	Neurodevelopmental Outcome
NQS	NonQuiet Sleep
PGE1	Prostaglandins
PMA	Postmenstrual Age
PNA	Postnatal Age
qEEG	quantitative EEG
QS	Quiet Sleep
QS-HVS	Quiet Sleep- High Voltage Slow Wave Sleep
QS-TA	Quiet Sleep- Tracé Alternant
RF	Random Forest
rScO2 (%)	regional Cerebral Oxygen Saturation %
SWC	Sleep Wake Cycle

impaired NDO at 2 years of age [6].

Newborns with d-Transposition of the Great Arteries (d-TGA) are a homogeneous patient population, usually without a syndromal or underlying genetic entity, in general needing only one neonatal corrective intervention. In this cardiopathy, as well as in hypoplastic left heart syndrome (HLHS), the normal fetal circulation with preferential streaming of higher oxygen content blood to the brain is not present. The altered fetal blood flow pattern and decreased oxygenation in these fetuses have been linked with abnormal brain development [7–10]. Although high survival rates are reported in newborns with d-TGA after neonatal switch operation, long lasting effects of this abnormal fetal and neonatal cardial physiology result in impaired brain growth and early delays in motor milestones and long-term deficits in cognitive and behavioral domains [11–13]. Recently, Lim et al. [14] described the association between surgery beyond 2 weeks of age in neonates with d-TGA and impaired brain growth and slower language development. Because of the corrective nature of the surgery in d-TGA patients, there is no progression of the brain injury after surgery, in contrast to HLHS, which makes d-TGA patients optimal candidates to study [15–17].

Different groups have used amplitude-integrated electroencephalography (aEEG) as routine neuromonitoring in the preoperative and postoperative setting in neonates with CHD and investigated the relationship of abnormal background pattern, electrocortical seizure activity and presence of sleep-wake cycles (SWC) with neurological impairments or MRI [18–20]. Mulkey et al. [20]. reported abnormal aEEG and absent SWC in newborns with CHD and findings of brain atrophy and/or brain injury on preoperative MRI. Delayed recovery (>48h) of the aEEG in the postoperative setting have been related with worse NDO [21,22]. Birca et al. [23] provided new evidences of early functional consequences of this perturbed structural brain development and presence of brain injury manifested by altered network connectivity as seen on preoperative multichannel EEG.

Functional brain maturation in preterm and term neonates can be quantified in an automatic way on multichannel EEG, linking biomarkers of maturation and NDO [24]. Machine learning tools predicting Functional Brain Age (FBA) use different maturational quantitative EEG (qEEG) features as input [24,25]. Around term equivalent age, the prediction of a "normal" FBA is usually estimated within 1 week of the actual postmenstrual age (PMA) both visual and with analytic algorithms [24–26]. Moreover, quantitative FBA estimates provide the most accurate assessment of brain maturation compared to visual scoring [27]. Neurological dysfunction which presents as dysmature EEG, with a delayed FBA, has become a potential and objective predictor of early neurodevelopmental outcome in premature infants [24,25,28–30]. Neonatal sleep organisation is another marker of cerebral function and a potential predictor of short and long-term NDO [31,32].

Tracking FBA in patients with CHD gives the opportunity to document functional consequences of altered perinatal cerebrovascular physiology on early brain development. We examine the hypothesis that FBA is delayed in patients with CHD, particularly in neonates with impaired fetal brain growth such as infants with d-TGA. We further hypothesise that sleep organisation differs compared to healthy controls and investigate whether pre- or postoperative neonatal brain activity is associated with early NDO assessment. Since neuromonitoring with aEEG is easily applicable and more widely available in many cardiac and neonatal units, we also tested whether the FBA could also be predicted with reduced, 2-channel montage.

2. Methods

2.1. Patients

Between May 2013 and March 2016, we prospectively enrolled term neonates with CHD for pre-operative and postoperative NIRS and EEG. Neonates were excluded if born less than 36 weeks of gestational age (GA) or if a genetic malformation syndrome was diagnosed.

The ethics review board of our institution University Hospitals Leuven (UZL) approved the study protocol and participating neonates were enrolled after their parents had provided written informed consent. Clinical data were prospectively collected and summarized in Table 1.

2.2. Continuous EEG and NIRS monitoring

Continuous video-EEG lasting 4 h were acquired preo- and postoperatively, using portable BRAIN RT monitors, with a sampling rate of 256 Hz and a 0.1–70 Hz band-pass filter. Electrodes were applied according to the International 10–20 system of electrode placement modified for neonates (Fp1, C3, T3, O1, CZ, Fp2, C4, T4, O2 with reference to Cz and ground electrode). Physiological parameters were simultaneously recorded, including electrocardiogram, respiration, saturation, invasive blood pressure.

Measurement of cerebral oxygenation by regional cerebral oxygen saturation % (rScO2) (%) with Near Infrared Spectroscopy (NIRS) was applied upon admission on the neonatal ward for at least the first 96h or until surgery was performed. rScO2 (%) was measured using the FORE-SIGHT Cerebral Oximeter with the Small Sensor (CAS Medical Systems, Branford, CT)). rScO2 (%) was used to

Table 1
Clinical characteristics of the patient and control groups. GA = gestational age, PMA = postmenstrual age, paO2 = arterial partial pressure of oxygen, rScO2 = regional cerebral oxygen saturation, BSID-III= Bayley Scales of Infant Development-III. * Signficant p-values (p<0.05).

	d-TGA n = 8	non-TGA n = 7	Control n = 24	P value
Preoperative EEG	8	5	8	
Postoperative EEG	6	4	16	
Sex male	7/8	5/7	3/8 pre 7/16 post	ns
GA, weeks	38.8 (0.3)	39.1 (1.4)	38.6 (1.5)	ns
PMA at preoperative recording, weeks	39.1 (0.3)	39.1 (1.7)	39.3 (0.4)	ns
PMA at postoperative	40.5 (0.5)	40.7 (2.3)	40.7 (0.4)	ns
Recording, weeks				
Prostaglandins	8	4		ns
Balloon Atrial Septostomy	3	1	/	
Caffeine	7	2		0.04*
Tramadol	2	1		1
Mean paO2, mmHg	48.2	62.9		ns
rScO2 d1, %	66.9 (3.2)	75.9 (3.6)		0.001*
rScO2 d2, %	66.1 (3.3)	76.4 (3.3)		0.001*
rScO2 d3, %	67.0 (4.5)	77.2(6.4)		0.009*
rScO2 overall, %	66.6 (3.0)	76.7 (4.6)		0.000*
BSID-III motor	102.6 (14.2) 82–124	109.00 (5.8) 97–112		ns
BSID-III cognitive	96.9 (22.0) 70–140	100.00 (9.1) 90–115		ns
BSID-III language	92.00 (24.1) 62–129	103.8 (13.7) 94–124		ns
Hospital stay, days	17.9 (8.5)	18 (9.7)		ns
Apgar score 1	6.5 [3–9]	8 [7–9]		ns
Apgar score 5	8 (8–10)	8 [8–10]		ns

estimate changes in regional cerebral oxygenation in neonates with CHD.

Continuous EEG data of (near)-term newborns who underwent EEG-polysomnography monitoring upon parents request and with no signs of perinatal illness, intra-uterine growth restriction or congenital malformation, were used as normal control data. EEG data of cardiac and healthy controls were matched for the same postmenstrual age (PMA) (<3 days difference in PMA), permitting direct comparison of brain function related to the expected brain age. The median postnatal age (PNA) at recording was 7.5 days (range day 1–21, with 10 neonates recorded before d6.)

2.3. EEG computational analyses

2.3.1. Functional brain age

Computational EEG analysis was performed with a Random Forest (RF) model as described in Ref. [24]. First, the EEG was segmented in epochs of quiet sleep (QS) and non-quiet sleep (NQS) with a deep learning 2-Class Convolutional Neural Network (CNN) algorithm [33]. Next, the RF model takes as input a set of qEEG QS and NQS features that characterize the entire EEG recording and outputs a prediction of the neonate's FBA at the moment of the recording and thus the level of brain maturation (for an overwiew of quantitative features see Ref. [24]).

For each patient and each pre- or postoperative recording, the FBA is predicted and the difference between the estimated brain age and the actual PMA is computed, i.e. functional brain age delay: FBA − PMA. The FBA delay can be interpreted as a measure of brain dysmaturity.

2.3.2. Sleep staging

Second, an automated 4 class CNN model was applied to classify the EEG into the 4 sleep stages: Active Sleep 1 (AS1), Quiet Sleep High Voltage Slow Wave Sleep (QS-HVS), Quiet Sleep Tracé Alternant (QS-TA) and Active Sleep 2 or (AS2) [34]. For each of the 4 sleep stages, the median duration of the sleep epochs, the proportion of time spent in the sleep stage and the median duration of the SWC were computed.

2.3.3. Reduced channel montage

As proof of principle, the RF model was applied on different reduced channel montages, to represent electrographic activity derived from 2-channel aEEG. Different montages (fronto-central, fronto-occipital and central-occipital) were tested and correlations between the full FBA and 2-channel derived FBA were calculated. If the FBA proofs to be properly predicted using only 2-channels of an EEG, this reduce dramatically EEG data requirements.

2.3.4. Neurodevelopmental outcome

Neonates with CHD were followed until 24 months of age and invited for the Bayley Scales of Infants Development Version III (BSID-III) for NDO testing.

2.4. Statistical analysis

For statistical analysis of clinical variables in newborns with non-TGA compared to d-TGA and control data, IBM SPSS Statistics V26 was used. One Way ANOVA or independent sample *t*-test and Mann-Whitney *U* test/Kruskal Wallis was used for continuous data, respectively depending on normality of the data. Fisher's exact test was used for categorical variables. Pearson or Spearman correlation or nonparametric counterpart Kendall rank correlation coefficient was used to evaluate the relationship between clinical, EEG and outcome variables.

3. Results

3.1. Clinical data

Of the 21 eligible newborns with CHD, 15 neonates were finally included in the analysis.

D-TGA was the main cardiac diagnosis in 8 newborns (53%), Arch Obstruction in 3, Tetralogy of Fallot in 1, Double Inlet Left Ventricle-Ventricular Septum Defect in 1, congenital Double Discordance with Pulmonary Atresia in 1 and Total Anomalous Pulmonary Venous Return in 1. One neonate with Truncus Arteriosus was diagnosed with a 16p11.2 deletion with corresponding

clinical phenotype and therefore omitted from the further analysis. Five neonates were excluded since EEG could not be obtained, the cardiac diagnoses were Hypoplastic Left Heart Syndrome [2], Double Outlet Right Ventricle [2] and Pulmonary Valve Stenosis [1].

Most of the neonates were diagnosed prenatally and required stabilisation with prostaglandins (PGE1) before surgery. None of the neonates were mechanically ventilated nor received sedative medication during the EEG recordings. All d-TGA patients underwent cardiac surgery (arterial switch operation) in the first week of life (mean = day 3, range day 2–6). Neonates in the non-TGA group received either surgery or heart catheterisation. An EEG was performed 'pre' and 'post' this 'intervention'. No electrographical seizures were documented. Preoperative recordings were performed between day 1–6, postoperative recordings were obtained between day 7–16 postnatally. These postoperative recordings were performed after the intensive care period, on re-addmission on the pediatric cardiac ward. All neonates received a pre- and postoperative cranial ultrasound (CUS) which showed no overt abnormalities. Three non-TGA patients needed extracorporeal circulation in the subsequent months, however this was after the initial neonatal period with functional brain monitoring. All 15 CHD patients underwent BSID-III testing for cognition, language and motor development at 24 months. A list of demographic data is provided in Table 1.

3.2. Preoperative EEG recordings

3.2.1. Functional brain age

Functional brain maturation, measured as FBA, was significantly delayed in neonates with CHD compared to healthy controls on the preoperative EEG recordings ($p = 0.003$). Mean estimated FBA in d-TGA patients was 37.2 weeks for PMA of 39.1 weeks. In the non-TGA group, mean FBA was 38.2 weeks for a PMA of 39.1 weeks. The mean PMA of the control neonates was 39.3 weeks with FBA of 39.6 weeks. Fig. 1 depicts the group differences in FBA (negative: delay in brain age, positive: accelerated brain age, in weeks) between neonates with CHD and healthy controls.

All d-TGA infants received PGE1 during the preoperative recording and 7 out of 8 received caffeine, compared to 4 out of 7 neonates in the non-TGA group who received prostaglandin infusions (ns) and 2 out of 7 daily intravenous caffeine ($p = 0.04$). Two patients in the d-TGA group and 1 in the non-TGA group received tramadol (maximum dose of 6 mg/kg/day for 72h) for comfort measures. Significantly lower rScO2 values, a measure of cerebral oxygenation, were observed in the d-TGA group compared to non-TGA in the preoperative period ($p < 0.001$). We found a nonsignificant positive trend between lower rScO2 values and FBA delay ($r = 0.24$, ns). FBA delay was not related to GA.

FBA delay on the preoperative recordings was associated with lower motor BSID-III scores in neonates with CHD ($R = 0.84$, $p < 0.001$) (Fig. 2) and even more specifically for d-TGA ($R = 0.93$, $p < 0.001$). FBA delay was not significantly correlated with BSID-III language nor cognitive score at two years of age.

3.2.2. EEG sleep organisation

Sleep organisation was altered during the first postnatal days in neonates with CHD (Figs. 3–4). The proportion of AS1 in both d-TGA and non-TGA patients was significantly lower compared to healthy term neonates. Neonates with d-TGA spent less time in QS-HVS and more in QS-TA (proportion) compared to healthy term neonates ($p = 0.002$) and non-TGA (trend, ns). Importantly, there was no significant correlation with the FBA and sleep state. The total proportion of AS and the duration of the sleep cycle was significantly shorter in neonates with CHD compared to healthy controls ($p = 0.048$).We found no significant association between sleep state organisation during the first postnatal days and drugs (caffeine or PGE1s), rScO2 values and any of the neurodevelopmental scores. Additional clinical variables, such as highest lactate, mean pO2, Apgar scores at 1 and 5 min, rScO2 values and total days in hospital were not associated with any of the EEG or outcome variables and were omitted for brevity.

3.3. Postoperative EEG recordings

3.3.1. Functional brain age

Postoperatively, the delayed FBA was no longer seen, mean FBA was 40.1 weeks in neonates with d-TGA for a PMA of 40.5 weeks, 40.4 weeks FBA for a PMA of 40.7 weeks in non-TGA and 40.3 weeks FBA for a mean PMA of 40.7 weeks in healthy controls.

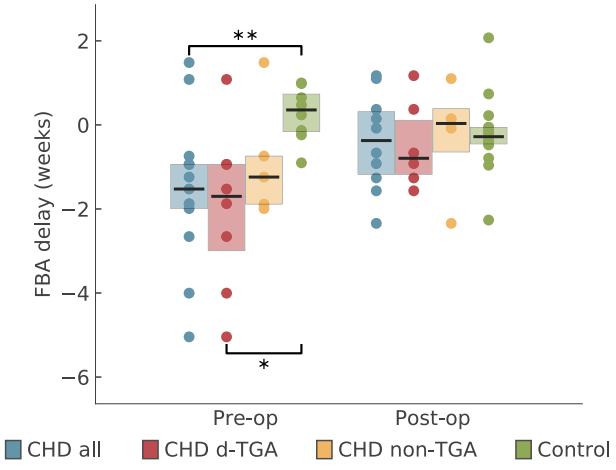

Fig. 1. Functional brain age delay in neonates with CHD on pre – and postoperative EEG recording.

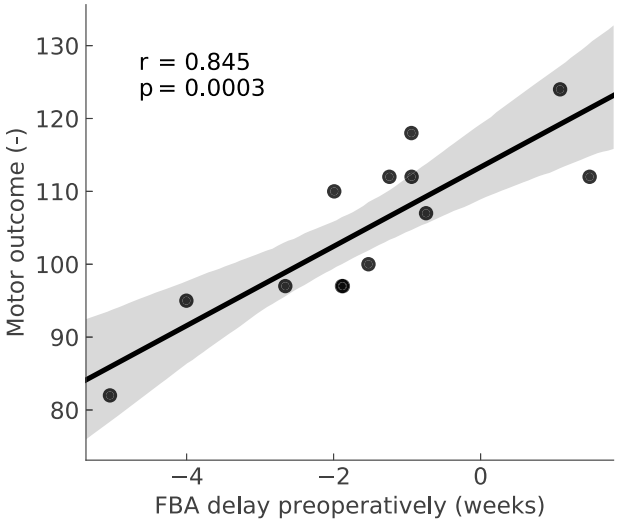

Fig. 2. Functional Brain Age delay (expressed in weeks) preoperatively and correlations with BSID-III motor scores at two years for neonates with CHD (n = 13, two neonates with overlapping data).

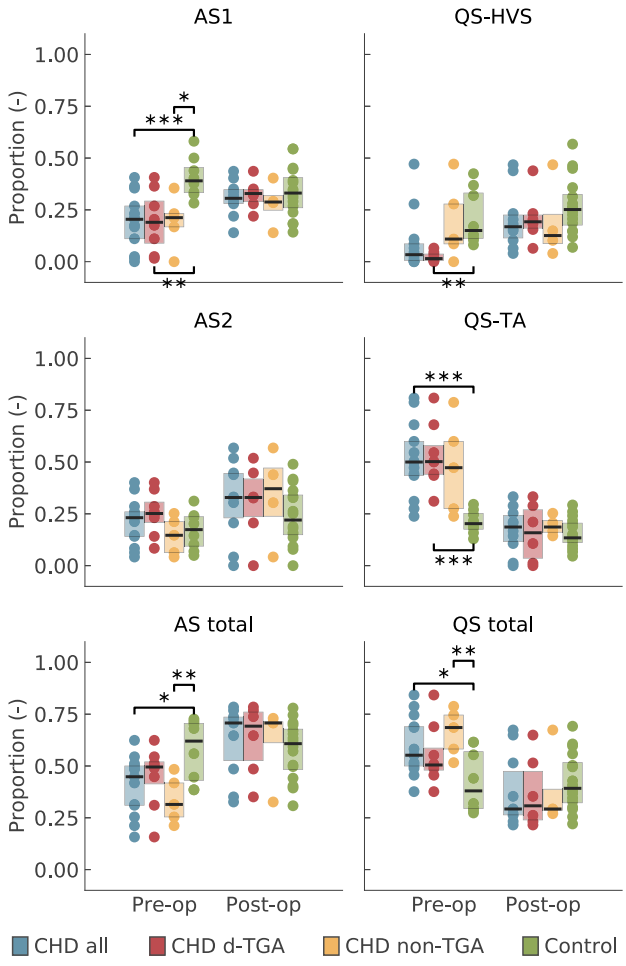

Fig. 3. Comparison of pre −and postoperative sleep organisation in neonates with CHD and healthy term newborns.AS1: Active Sleep 1, AS2, Active Sleep 2. AS total = proportion of AS1+ AS2. TA: Quiet Sleep-Tracé Alternant, HVS: Quiet Sleep- High Voltage Slow Wave Sleep. QS total: QS-TA + QS-HVS proportion.

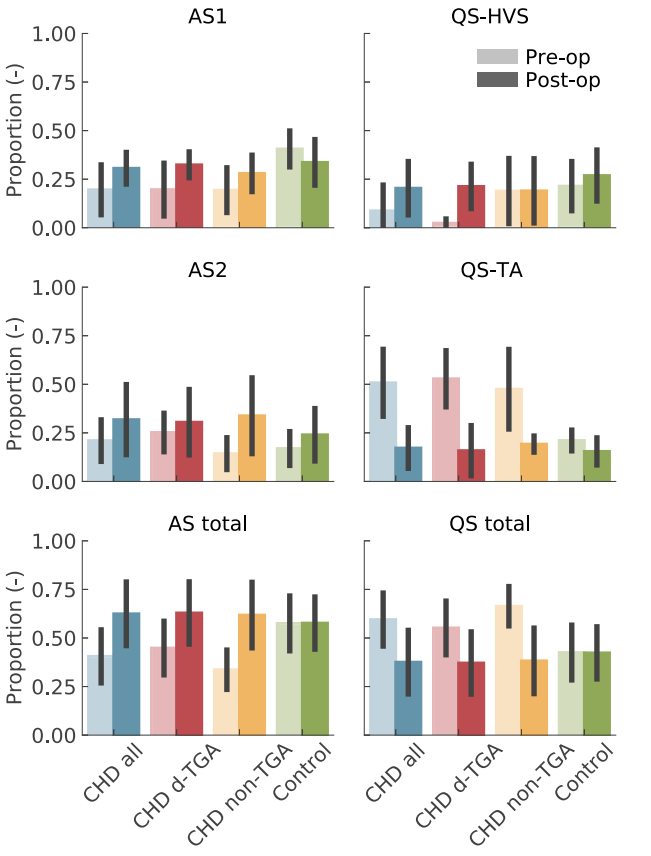

Fig. 4. Evolution of sleep organisation in neonates with CHD and healthy term newborns over time. Pre-op (preoperative), Post-op (postoperative).
AS1: Active Sleep 1, AS2, Active Sleep 2. AS total = proportion of AS1+ AS2. TA: Quiet Sleep-Tracé Alternant, HVS: Quiet Sleep- High Voltage Slow Wave Sleep. QS total: QS-TA + QS-HVS proportion.

3.3.2. *EEG sleep organisation*

Sleep state organisation in neonates with CHD did no longer differ from healthy controls in the postoperative phase. However, sleep organisation did change significantly over the pre- and postoperative time period in CHD. The proportion of QS-HVS significantly increased and QS-TA significantly decreased for d-TGA and all CHD, whereas the proportion of AS increased post-operatively for all CHD neonates (see Fig. 4). The median duration of QS-HVS in d-TGA patients was positively correlated with BSID−III motor scores ($R = 0.87$, $p = 0.025$). For the normal control data, no significant difference in sleep organisation was found for this one week difference in PMA (Fig. 4).

3.4. *Reduced channel montage*

Correlation between FBA on the full EEG and FBA on the reduced 2-channel EEG was good ($R = 0.8$, $p < 0.001$ for Fp-C and Fp-O, and $R = 0.79 < p = 0.001$ for C−O). For all of these derivations, the FBA and FBA delay remained significantly different in the preoperative EEG recordings in the CHD patients and d-TGA subgroup compared to healthy controls ($p < 0.01$).

4. Discussion

Among neonates with d-TGA and other complex CHD, we demonstrate objective differences in neonatal brain function, with delay in the FBA and alterations in sleep organisation. The FBA which is approximately two weeks younger compared to the actual PMA in patients with d-TGA, suggests functional reflections of previously observed anatomic immaturity and alterations in brain metabolism in newborns with d-TGA before they undergo arterial switch operation. Preoperative, neonates with CHD have an increased fraction of QS (through an increased proportion of QS-TA). Furthermore, larger preoperative FBA delay and shorter post-operative duration of QS-HVS are correlated with lower BSID-III motor scores, although overall developmental scores fall within normative norms [18].

Compelling evidence shows that early brain activity on EEG in the preterm infant is related with structural brain growth [35–37]. Different individual qEEG features such as the occurrence of burst and complexity measures are related with cerebellar growth, whereas the periods of brain inactivity (e.g. interburst intervals) and spectral measures are respectively negatively and positively correlated with the volume of the cortical grey matter and total brain volume [37]. Multiple of these qEEG features are used by the FBA algorithm. Direct correlations of the FBA with structural MRI brain volume/growth indices have not yet been performed. It is certainly of interest to investigate wheter the most important qEEG

features which drive the FBA have a relationship with regional developmental brain metrics in CHD.

In contrast to the results of an MRI study, which observed impaired *peri*operative brain growth in d-TGA, we found no longer significant differences in FBA compared to healthy controls after surgery [14]. However, the most important clinical predictor of impaired anatomical brain growth in this study was older age at arterial switch operation (>13 days postnatally), with a significant inverse relationship with postoperative brain weight z-score. In comparison, all our d-TGA patients had a prenatal diagnosis, early surgery (<6 days) and early optimal nutrition by the timing of the second EEG, which are suggested to be modifiable factors in favor of better perioperative anatomical brain growth [14,38,39]. Nevertheless, despite resolving of the FBA delay, it is still correlated with lower motor score. Taken together, these results support the idea of Mebius et al. [40] that prenatal and postnatal preoperative abnormal cerebral findings in neonates with CHD may play a role in long-term neurodevelopmental impairments. Preoperative EEG may help clarify the effects of injury which already present prenatally [40]. Further research is needed to clarify wheter early interventions which restore cerebral oxygen and nutrient delivery can alter developmental outcome in CHD.

Endogeneous brain activity during neonatal AS is crucial for early brain development, and experimental deprivation exerts short-term and long-term effects [41,42]. This state of high brain activity during AS results in a higher metabolic oxygen demand compared to QS, without the compensatory higher cerebral blood flow as seen in adults [43]. This leads to increased oxygen extraction to sustain cerebral oxygen consumption, which results in a decreased rScO2% during AS relative to QS [44]. We found significantly less AS (mainly AS1) in neonates with CHD, the sleep state of highest metabolic demand and more of the QS-TA pattern in d-TGA patients, a synchronized mode of thalamocortical networks with low and high amplitude bursts, which entails a low metabolic cost [43,45]. An explanation of our observation might be that AS is decreased because the brain of CHD neonates cannot compensate for the higher metabolic (oxygen) demand in AS due to the altered blood flow and lower arterial saturation (parallel circuits, mixing or single ventricle physiology) and consequently a globally lower oxygen content of blood supplied to the brain compared to healthy newborns. This is also reflected by the significantly lower rScO2 values in the d-TGA group during the first 3 preoperative days. Unfortunately, our concomittant NIRS/sleep data are too limited for separate QS/AS analysis to support this hypothesis.

We have corrected for postmenstrual age but not for postnatal adapation, as patients in the control group were slightly older (e.g. postnatal days) at the moment of EEG. Theoretically, this could influence sleep wake organisation. However, when we compare normative sleep data of full-term neonates available in literature, the predominance of AS over QS should be clear in healthy full-term neonates from early life [46,47]. The percentages of AS and QS in our healthy newborn group are similar to the reported sleep percentages by Korotchikova et al. [46] recorded in the first 36h after birth. Scher et al. [48] found no effect of postnatal adaptation on quantitative EEG sleep measures.

Moreover, different reports in literature identified an increased proportion of QS and decreased AS, similar to what we found in neonates with CHD, as an unfavorable prognostic sign [31,47,49,50]. Neonates with asphyxia, but without overt clinical or electrography evidence of hypoxic-ischemic encephalopathy, presented with altered sleep organisation with an increased percentage of QS at the expense of decreased AS [47]. Altered brain function, with more QS-TA, has also been documented in healthy preterms at corrected full-term age, associated with lower neurodevelopment at 1 and 2 years [28]. We found a positive correlation between motor outcome and the duration of QS-HVS in d-TGA patients. QS-HVS is the last sleep state to mature and an important developmental feature of the term EEG, with a gradual increase at the expense of QS-TA. These mature, polymorphous, 1–3Hz delta waves coincides with the maturation of long and short cortico-cortical connections [51,52]. In near-term newborns at risk for cerebral dysfunction, diminished low frequency EEG power during neonatal QS, which may stand for mature QS-HVS in our data, was predictive of worse 18- month language and motor outcome [31]. The link between this altered sleep physiology and the higher incidence of long-term behavioral and neurocognitive deficits in d-TGA patients, needs further attention [12,13,53].

All d-TGA patients in our cohort were diagnosed prenatally, which might have positively influenced hemodynamic state [39]. Overall, the neonates in this study were clinically stable without hemodynamic instability around the EEG. This might explain why we did not observe seizure activity nor suppressed background patterns. We documented clear SWC and transition of the different states, reflecting a continuous normal voltage on aEEG. Nevertheless, it remains hard to untangle whether the observed changes in EEG features are reflective of acute (e.g. drugs) or more chronic influences (effects as discussed above e.g. by chronic hypoxia and oxygen conformance, see Refs. [24,30,54]). None of the neonates required intubation nor sedative medication during the EEG, so we speculate that a potential acute depressive effect of drugs on brain function which can influence maturity features is negligible [19,55,56]. Data assessing the effect of caffeine on EEG in preterm yield heterogeneous and conflicting results [57,58], although caffeine, an Adenosine 2A antagonist, inhibits sleep [59]. Endogenous Prostaglandins (D2 and E2) regulate sleep/wake state transitions, by an alternating mechanism, where PGD2 promotes sleep through Adenosine System [59] and conversely, PGE2 promotes wakefulness [60]. The effect of Prostaglandin E1 (PGE1), used to maintain patency of the ductus arteriosus, on sleep physiology has not been shown. PGE1 can cause concomitant dose-dependent depression of respiration by inducing central apnea, suggesting an effect on brainstem respiratory control regions [61,62]. This suppressive effect might be further potentiated by concomitant use of opioids [63]. Possible direct or indirect effects of PGE1 on higher brain function and sleep organisation in humans remain highly hypothetical [62,64,65]. Olson et al. [66] did not report significant differences in sleep states on EEG between infants receiving PGE1 and those not in a group of 16 HLHS. However, this study is underpowered to analyse these complex pharmacodynamic interactions.

Our study has a number of important limitations. First, our study remains small with multiple confounding factors, although the measured effects are objective and clearly relevant for further investigation in larger samples. Second, the non-TGA group is a heterogeneous group and cerebral hemodynamics might be influenced by the underlying cardiac diagnosis. Third, we lack pre- and postoperative brain MRI, as impaired structural brain growth is most likely a complex interplay between developmental and destructive abnormalities [67]. Focal acquired brain injury is common [68,69] and easily overlooked with CUS [70]. However, since we clearly observed improvements between pre- and postoperative FBA and sleep, we believe that our results are not biased by clinically relevant, acquired brain lesions. Despite NIRS/EEG data were obtained in this study, concomitant measurements of EEG and NIRS data were scarce. The EEG recording might not be representative for the whole neonatal period.

For further work, we definitely aim to perform more in-depth analysis of the neurovascular coupling in CHD. However, the value of objective quantitative analysis of brain function, even feasible with reduced channel aEEG monitoring, displays the

potential clinical utility for cot-side monitoring and allows widespread use in multicentre studies.

In conclusion, we demonstrate preoperative FBA delay and altered sleep physiology in neonates with CHD, which might be reflective of the prenatal period. Postoperatively, rapid improvements in FBA and sleep organisation are observed. Identifying the long-term clinical signficance of these findings and how these rapid alterations of brain function and sleep organisation in neonates with CHD are mitigated through improvements in postnatal cerebral oxygen delivery and early surgery, drugs and nutrition are questions in pressing need.

Author contributions

KJ, LT, MG, BC and GN acquired the data. TH and AD analyzed the data. TH, AD, MDV, SVH and KP were involved in algorithm development. AD prepared the first draft of the manuscript. AD, KJ, LT, MG and GN were involved in the conception and design of the study and approved the manuscript. All authors critically reviewed, edited and approved the manuscript.

Declaration of competing interest

None.

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