REVIEW

Electroencephalography studies of hypoxic ischemia in fetal and neonatal animal models

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Abstract

Alongside clinical achievements, experiments conducted on animal models (including primate or non-primate) have been effective in the understanding of various pathophysiological aspects of perinatal hypoxic/ischemic encephalopathy (HIE). Due to the reasonably fair degree of flexibility with experiments, most of the research around HIE in the literature has been largely concerned with the neurodevelopmental outcome or how the frequency and duration of HI seizures could relate to the severity of perinatal brain injury, following HI insult. This survey concentrates on how EEG experimental studies using asphyxiated animal models (in rodents, piglets, sheep and non-human primate monkeys) provide a unique opportunity to examine from the exact time of HI event to help gain insights into HIE where human studies become difficult.

Key Words: *animal models; automatic detection; clinical; EEG; fetal; HIE; hypoxic-ischemic encephalopathy; neonatal; non-human primates; review; seizure*

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Introduction

Significant reduction in cerebral oxygen levels (hypoxia) and reduced perfusion (ischemia) due to various undesirable events at or around the time of birth (i.e., obstruction of the umbilical cord) is known to lead to sever hypoxic/ischemic encephalopathy (HIE) (Low, 2004; Mwaniki et al., 2012; Jonsson et al., 2014). Neonatal HIE is reported to be caused by a hypoxic insult that occurs before or during labor (Takenouchi et al., 2012; Ahearne et al., 2016). Despite the recent advances in the survival rates of at risk babies, neonatal HIE (asphyxia) remains a morbidity rate of 23% in neonates globally (World Health Organization, 2005). Evaluations by the World Health Organization highlighted that the number of HIE related neonatal deaths between 2000 and 2003 was much higher in Southeast Asia and Africa (~310,000 and ~240,000, respectively) as compared to be lower in Western pacific and Eastern Mediterranean regions (~125,000 and ~105,000, respectively), and even much lower in Americas and Europe (~32,000 and ~15,000, respectively) (World Health Organization, 2005). Clinical studies have demonstrated that most neuronal cells die after a hypoxic event and not during the event (Merchant and Azzopardi, 2015; Drury et al., 2014b). In surviving newborns, loss of neuronal axons in the white matter, post-HI insult, is shown to contribute in neurodevelopmental impairments (Back et al., 2007). Lack of oxygen in the blood disrupts neuronal cells' functionality and interrupts energy supply into the cells. This is shown to happen through progressive cellular depolarization that pushes calcium, sodium and water into the cells and reversely allows potassium out of cells (Kalogeris et al., 2012). The excessive progress of cellular depolarization will cause a severe drop in the cell activity and finally leads to extracellular accumulation of excitatory amino acids (EAAs) that causes neuronal damage (Burd et al., 2016; Hartings et al., 2017). It has been reported that the irreversibility of cell damage is highly dependent on the severity and duration of a HI insult with the most vulnerable brain areas are known as CA1, CA3, and CA4 hippocampal regions, cerebellum, some striatal parts such as caudate nucleus and 3rd, 5th, and 6th layers of the neocortex (Longo and Packianathan, 1997).

Research conducted on animal models have significantly contributed to our understanding about the progress of HIE (Wassink et al., 2014). In comparison to the restrictions around clinical studies, experiments conducted on animal models clearly allow much wider flexibility for studying of hypoxia/ischemia, from many hours before, during and days after HI insult. This can include monitoring of the desired signals under certain circumstances such as inducing the HI or any type of drug treatments. Neuronal activity in brain can be directly collected from cerebral cortex over scalp through electroencephalography (EEG). Guidelines for neonatal EEG monitoring are comprehensively described in (Tsuchida et al., 2013). Clinical studies conducted on both preterm and full-term infants have also indicated that abnormal spikes and sharp wave EEG transients significantly correlate with adverse neurological outcome and white matter injury (Biagioni et al., 1996, 2000; Okumura et al., 2003).

Current experimental investigation around hypoxia/ischemia have been mainly concerned with the clinical understanding of the evolution of hypoxia/ischemia as well as the possible drug or hypothermic treatment strategies. Animal species such as the sheep, piglet, rabbit, monkey and rodent have been used to mimic the pathophysiology of HIE and its outcomes (Yager and Ashwal, 2009).

Post-HI experiments conducted on animal models, indicate that asphyxia is followed by a temporary restoration of cerebral oxidative metabolism in reperfusion phase (10–30 minutes) that causes a transient limited increase in EEG power (Kalogeris et al., 2012). The reperfusion is followed by an early-latent (30 minutes–2 hours), then mid-latent (2–4 hours), and finally late-latent phases (4–6 hours), post-HI insult, while EEG power gradually rises until brain propagates high amplitude epileptiform seizures in the secondary phase (Bennet et al., 2006; Dean et al., 2006). Current experiments have been mainly focused on the post-ischemic brain development, diagnosis and treatment aspects of the HI brain injury at birth; suggesting that the damage is optimally treatable only if the neuroprotective protocols such as cerebral hypothermia (brain cooling) are administered within a

very critically short time period of less than a few hours (in the latent phase), after HI insult, and prolonged for 48–72 hours (Bennet et al., 2007; Gunn and Groenendaal, 2016). Hypothermia is shown to no longer be effective if delayed until after the latent phase (Gunn and Drury, 2013). Such findings are consistent with the reported results in clinical studies confirming that an early administration of cooling protocols before 3 hours of birth significantly improves outcomes (Thoresen et al., 2013).

We searched Google scholar, Scopus and other platforms using the related keywords. The article will start with a review of the cerebral physiology similarities that exists between human and different types of animal models used in HI EEG studies. This will be followed by a detailed review of studies performed in HIE using neonatal and fetal animal models since early 2000 to 2018.

Physiological Comparisons between Human and Animals in Hypoxic/Ischemic Insult

An ideal viable animal model should aim to optimally cover as many human physiological features as possible. Clearly, the comparison of equivalent gestational and cerebral phases across animal species to the human brain counterpart is a difficult task due to their brain vulnerability, different developmental stages, neuronal metabolism and/or regional plasticity (Roohey et al., 1997; Sengupta, 2011; Huang et al., 2017). Assessing both preterm and term animal models of HIE, a survey in 2015 has investigated how the signatures of inflammatory injury are affected by the brain's maturational stage at the time of a hypoxic-ischemic insult and concludes that no particular animal model can fully outline the complications of human conditions (Mallard and Vexler, 2015). They emphasized that neurodevelopmental process, at perinatal and early postnatal stage, can be significantly affected by HIE causing life-long functional abnormalities.

Despite the highlighted challenges above, cerebral maturation stages in animals can be explained relative to human neonates and an appropriate equivalent developmental period can be chosen for a specific study. Myelination is known to play a key role in the formation of connectivity across the nervous system in a growing brain, which is pivotal for higher-order cognitive functions (Radlowski et al., 2014). Unlike the fully postnatal process of myelination in rodents (Koehler et al., 2018), myelination starts prenatally in both primates (i.e., human and monkeys) and non-primates (i.e., sheep and piglets) (Back et al., 2012; Leyshon et al., 2016).

In general, unlike smaller laboratory mammals with lissencephalic (smooth) brains (i.e., mice, rat and rodents), the similar gyrencephalic structure of the larger animals' brain (i.e., sheep, piglet and monkeys) to human brain allows the opportunity to explore highly controlled structural experiments for studying of perinatal and neonatal brain function and structure (Hagberg et al., 2002; Silbereis et al., 2010; Back et al., 2012). Despite the differences in the *in utero* fetal environment to the neonatal-environment, which is an important factor to consider, fetal laboratory animals with gyrencephalic brain structure have been observed to display EEG activity such as delta, theta, alpha and beta brain rhythms similar to the ones observed in human newborns (Schmidt et al., 2000; Inder et al., 2004; Keogh et al., 2012b; Abbasi, 2017; Abbasi et al., 2019a).

We now describe the physiological similarities that exist between the various animal models and human neonates; starting with the simplest species (i.e., rodents) and progressing to the most complex species (i.e., *Macaca nemestrina* monkeys).

Rodent models

The equivalent period of development from pre-term to near-term in neonatal human takes place rapidly in neonatal rat models within the first five to seven days of birth (Back et al., 2012a). It has been reported that a rat's brain growth at around 5–7 days of age is equal to a human neonate's brain growth at the time of birth (Dobbing and Sands, 1979). As a limiting factor, the smaller brain size in rodents is a major restriction for performing a variety of invasive physiological experiments. In contrast, the bigger brain size in sheep, piglets and monkeys provides suitable framework for chronic instrumentations that will help for long-time continues monitoring of the vital signals (i.e., EEG, electrocardiogram (ECG), etc) and allows repeated blood sample examinations. Furthermore, due to the significant cortical and subcortical morphology and developmental differences, experimental results from rodent models are generally discussed to face difficulties when translated into human infants (Radlowski et al., 2014). In fact, the structure and physiology of a rodent's white matter cerebrovascular supply has been also reported to be very different to sheep and humans (Back et al., 2012a).

Sheep models

Cerebral development of white matter in the fetal sheep brain is known to be anatomically and physiologically similar to human brain (Back et al., 2012a). Histopathological features of fetal sheep brain has been shown to be sensitive to acute and chronic white matter injury, similar to human brain (Riddle et al., 2006, 2011). The anatomical similarities and the excess of cerebral white matter in fetal sheep brain makes them ideal models for mimicking human neuropathological studies, as opposed to the insufficient cerebral white matter in rodents' brain which is markedly different from humans (Back et al., 2012a). A sheep brain development at birth is also known to be more advanced compare to human neonates with a growth spurt peak that occurs well before birth (Dobbing and Sands, 1979). They reported that a fetal sheep's cerebral growth at around 12 days prior to birth is almost equal to a human's neonate of brain growth around the time of birth. In fact, neurodevelopmental characteristics of a preterm fetal sheep brain at gestational age of 0.65 to 0.75 (~95 to 108 days, term = 145) is equal to a human preterm between 27 to 32 weeks. A fetal sheep brain around 0.85 gestational age is approximately equivalent-enough to study near- and full-term neonatal human (Koehler et al., 2018). While, similar to the term human, a fetal sheep brain at around 0.9 gestation (~130–135 days) has been shown to display oligodendrocyte development (Back et al., 2012a).

Piglet models

Similar to human neonates, the majority of a pig's brain growth spurt, occurs during the late prenatal period to the postnatal age (Dobbing and Sands, 1979), with a growth spurt peak that occurs around the time of birth (Koehler et al., 2018). A piglet at around ~97 days of gestational age (term = 115 days) is shown to be physically similar to early premature stages of gestation, requiring cardiovascular and respiratory care (Eiby et al., 2013). A piglet at around ~97 days of gestational age (term = 115 days) is shown to be physically similar to early premature stages of human babies at 28–30 weeks gestation, requiring cardiovascular and respiratory care (Eiby et al., 2013).

It has also been reported that a neonatal piglet's brain anatomical features such as distribution of white and gray matter and EEG features are similar to what has been reported in human neonates (Radlowski et al., 2014). It has been shown that the perinatal brain growth, level of maturity at birth as well as myelination and patterns of cellular development are similar between human neonates and piglets (Eiby et al., 2013; Radlowski et al., 2014). Similar to sheep models, the larger physiological size of piglet models provides better opportunity for repeated blood sampling and extensive monitoring of the vital signals such as EEG, arterial blood pressure, respiration, heart rate and electrocardiogram. It has been reported that the relative level of maturation in many organs such as brain, lungs, and cardiovascular system in piglet models closely resembles the slower development in human neonates, as opposed to sheep models where the organs have been reported to develop faster than in the human (Eiby et al., 2013). A piglet's brain weight at birth has been specified to be around 25% of its adult weight which demonstrates the most weight percentage similarity to the human neonates with 27% of adult weight, compared to 76%, 53%, 15% and 12% for monkeys, sheep, rabbit and rats, respectively (Dobbing and Sands, 1979; Conrad and Johnson, 2015). Also, multiple similarities in terms of the gene, order, methylation, and DNA have been reported in the genomes of a piglet compared to human (Koehler et al., 2018).

Non-human primate models

Studies have reported much closer similarities in the brain developmental stages of non-human primates (i.e., monkeys) and human neonates (Pérez-Torres et al., 2000). Non-human primates such as *Macaca nemestrina* monkeys, similar to sheep, have been reported to possess a faster cerebral developments in brain maturation compared to human neonates with brain growth spurt peak that occurs in prenatal period prior to birth (Dobbing and Sands, 1979). The full gestational period in *Macaca nemestrina* monkeys is around ~174 days (full term). According to (Dobbing and Sands, 1979; Jacobson Misbe et al., 2011), a *Macaca nemestrina* monkey's cerebral maturation around 8 days prior to birth is equal to a human neonates at birth, therefore, similar to sheep models, *in utero* brain studies have used fetal monkey models to mimic the optimal brain growth of a human neonate. In 1959, a primary non-human primate study was conducted on five fetal near-term asphyxiated *Macaca mulatta* Rhesus monkeys at 157–164 days gestational age (term = 166 days), reporting close similarities in the type and distribution of neuronal cells variations post-asphyxia compared to human infants (Ranck and Windle, 1959).

The MRI-detectable basal ganglia thalamus brain stem injury caused by the obstruction of the umbilical cord in *Macaca nemestrina* monkeys, has been reported to be consistent with the deep nuclear brain stem injury patterns reported in human babies, post-severe HI-insult (McAdams et al., 2017b). A very early study in 1968 conducted on fetal Rhesus term monkeys reported pathological-induced patterns in the brain of those animals subjected to prolonged partial asphyxia; similar to the commonly addressed pathological patterns in human brain after perinatal HIE (Myers, 1968). Myers (1968) addressed that the neuronal system as well as their reproduction mechanism in Rhesus monkeys comply with the human. Similar to sheep and piglet models, *Macaca nemestrina* monkeys are referred as suitable HIE models due to their inherent similarities to human neonates such as complex neurological characteristics, white/gray matter proportion and their cortical folding features (Jacobson Misbe et al., 2011). Non-human primates are generally reported to be the most suitable HIE models, although, the ethical restrictions around these species has significantly reduced the practicality of conducting experiments on these type of animals (Foster et al., 2001). Studies have reported minor neuronal loss in dentate gyrus and normal hippocampus histological results in monkeys as opposed to the vulnerable hippocampal neuronal cells in human neonates; and thus, cerebellar cortical and cerebral pathology in monkey HIE models have been reported to be less severe compared to subcortical neuronal damage in human neonates (Koehler et al., 2018). However, the pathology of white matter and the pattern of injury in HIE monkeys, post-asphyxia, are reported to be relevant and closely resemble to human infants (Koehler et al., 2018).

Electroencephalography Studies in Hypoxic/Ischemic Animal Models

Rodents

Despite their lissencephalic (smooth) brain structure, but due to simplicity and availability, rodents models of HIE have been widely used as one of the main species in HI research.

In 2015, histological investigations using a cohort of HI asphyxiated C57 black mice at the age of 7 days old (n = 54) suggested that such species demonstrate low tendency in developing recurrent epileptiform seizures later on in adult ages (Peng et al., 2015). They injected a combination of diazepam and phenytoin within 45 minutes post-HI episodes as clinically suggested to help for suppressing seizures and reduce mortality, post HI-insult. Peng et al. (2015) indicated that their mouse models demonstrated low neonatal seizure tendency after HI insult in the recorded in the EEG (collected using twisted bipolar electrodes in a frequency band of 0.1–5000 Hz); however, they declare that the lower post-HI seizure activity in their models might have been underestimated due to the experimental limitations of shorter experiments of 10 days only.

Using asphyxiated adult rat models (n = 16), White et al. (2006) compared the performance of four different seizure detection strategies on 3 channel EEG recordings (sampled at 250 Hz), including EEG power (amplitude square), total distance of consecutive EEG data point, spike duration and frequency, as well as the combination of autocorrelation with spike frequency. White et al. (2006) demonstrated that, among their studied techniques, the autocorrelation strategy for seizure detection resulted in much better performance measures of positive predictive value (PPV), sensitivity and specificity of 95%, 100% and 99.98%, respectively.

Cuaycong et al. (2011) investigated the feasibility of an automated EEG seizure detector based on a nonlinear filtering approach that uses a 60-second moving window to capture seizure activity with different morphologies in the two channel EEG (sampled at 400 Hz) of immature rat models (n = 12) after 90 minutes of HI insult. Seizure detector algorithm was reported to result in 70–80% agreement with manual expert annotations, and the total amount of seizures and time to first post-ischemic seizure correlate with the spreading of brain damage and outcomes (Cuaycong et al., 2011).

A research has reported the existence of epileptiform seizure-like discharges as well as spikes and sharp waves in the 1000 Hz sampled two lead EEG of 12 7-days-old male neonatal rats, after 2 hours of HI induced hypoxia (Sampath

et al., 2014). They also analyzed the power spectra of the EEG data for 72 hours post-HI insult and reported that the integrated background EEG power from the right cortex demonstrated a reduction in all frequency bands of 1–50 Hz in the asphyxiated animals (n = 12) compared to the sham control group (n = 4).

Ranasinghe et al. (2015) reported abnormal cortical activity including diminished background activity and disrupted EEG patterns (i.e., spindle-like bursts) with a delayed morphological development from a cohort of neonatal immature rats (n = 27), subjected to 2.5–3 hours of asphyxia, similar to what they have observed in a group of premature human babies (n = 36). They recorded the EEGs through a PAL-8200 data acquisition system from Pinnacle Technology at the sampling frequency of 400 Hz.

Another study in 2015 has analyzed power spectral density and the frequency of seziures' profiles in the EEG, acquired through two integrated wire electrodes at the sampling rate of 120 Hz, to compare the effects of hypoxia/ischemia with hypoxia-alone using 7-days-old perinatal rat models (Zayachkivsky et al., 2015). They indicated that, unlike hypoxia in the absence of ischemia or injury, HIE attenuates hypoxia/ischemia-induced electrographic seizures and causes prolonged progressive suppression in the EEG background, during the first 2 hours of hypoxia/ischemia.

Sun et al. (2016) reviewed the methodology of hypoxia/ischemia-induced seizures along three channels EEG signals sampled at 1000 Hz as well as histology and pathology of the HIE in the immature brain of rat models. Later, Sun et al. (2016) studied the hypoxia/ischemia-induced seizures in the EEG recordings (acquired through two subdermal platinum electrodes) in developing immature brain of rat and mice HIE models (n = 33), after global hypoxia. Similar to immature neonatal human brain, neonatal rat brain represent more sensitivity to the hypoxia-induced seizures which could worsen long-term neuronal function and outcomes (Sanchez and Jensen, 2005).

Sampath et al. (2017) demonstrated that the total number and duration of neonatal EEG seizures (recorded through two lead at 1000 Hz sampling rate) are attenuated in Flupirtine-treated (a potassium channel opener) rat models, when the treatment is initiated at equivalent clinical time points of either 2 hours post-HIE or 5 minutes after the first seizure. Fupirtine is a more efficient treatment against electroclinical seizures in neonatal rat models compared to phenobarbital that is currently being clinically used as a common drug for neonatal seizure (Sampath et al., 2017).

Hu et al. (2017) using other type of treatments such as bumetanide has shown success in the rat models of HIE. They demonstrate that the application of bumetanide in a group of 124 neonatal Sprague-Dawley rats at age of 7 days is significantly effective to suppress the seizures in the 1000 Hz sampled two lead EEG and helps to restore neuronal network in dentate gyrus and improve cognitive function.

Using immature female rabbits at age of 2 weeks (n = 12), Takei et al. (2004) suggested that a 33°C hypothermia can attenuate the production of nitric oxide during kainic acid-induced seizures in the EEG (acquired through bipolar needle electrodes) and reduces hippocampal damage in the brain of immature rabbits. A reduction in the production of nitric oxide is known to reduce blood flow to the brain, hence, attenuation of nitric oxide production through a hypothermic protocol could help to justify the neuro-protectivity of the cooling process.

Piglet

Gavilanes et al. (2001) demonstrated that the degree of suppression in the EEG amplitude and the variation in delta frequency band of EEG recordings, obtained from neonatal piglets at age of 1 week (n = 6) using the cerebral function analysing monitor, alongside with the near infrared spectroscopy measures can be used to determine the severity of changes in cerebral perfusion.

A study conducted on newborn piglets (n = 44, median age of less than 24 hours) demonstrated that a 24 hours of mild hypothermia without sedation did not lead to neuroprotective results or reduced the number of seizures in two channels EEG recordings as opposed to the majority of the similar research (Thoresen et al., 2001).

Histological experiment conducted on 1-day-old neonatal piglets (n = 18), in 2001, has reported subcortical damage in five subcortical brain regions, including hippocampus, thalamus and cerebellum following a 30-minute severe insult group, as opposed to no observed damage in the mild insult group (20 minutes of insult) or control group (Foster et al., 2001). They reported that the EEG amplitude, recorded through three needle electrodes using CFM machine 30 minutes post-HIE, drops down to under 5 μV until 40 to 60 minutes after the start of insult (5% O_2) when the EEG trace gradually increases until 1.5 and 3 hours post-insult where the EEG amplitude reaches above 5 and 25 μV, respectively.

Using a cohort of 1-day-old neonatal piglets (n = 39, asphyxia duration: 30–37 minutes), Björkman et al. (2006) demonstrated that minimum EEG amplitude at 1 hour post-HI-insult significantly correlates to outcome where a lower EEG amplitude results in worse outcomes. The aforementioned article does not provide detailed information on the EEG acquisition procedure.

A study conducted on asphyxiated neonatal piglets at age of 7 days (full-term, n = 6) reported the reliability of the amplitude integrated EEG (aEEG) technique for accurate monitoring of cerebral functions at different cerebral regional oxygen saturation (rSO_2) levels, applied through a mild, moderate and severe HI insult (Zhang et al., 2008). aEEG is a highly filtered and rectified version of the standard EEG that is plotted on a semi-logarithmic scale and only provides limited information on the overall changes of the cerebral activities in the EEG (Toet et al., 2002). To obtain the aEEG signals, Zhang et al. (2008) digitally processed recordings from the raw EEG data through a single channel recording from a three electrode system (2 leads and one ground electrode).

Research using term piglet models of perinatal HIE (n = 42) indicate that strong relation exist between post ischemic two-channel EEG seizures and severity of subcortical brain damage injury (Björkman et al., 2010).

Using neonatal pigs at age of 7 days (n = 33), Zhang et al. (2012) demonstrated that aEEG and near infrared spectroscopy (NIRS), simultaneously, are complementary tools which allow to characterize cerebral function following an HI event and help for early assessment of neonatal HIE (i.e., severity of the injury). They obtained EEG data through a single channel bipolar recording collected from two biparietal EEG electrodes system with a frontal ground electrode and digitally calculated aEEG signal off-line.

Using full-term piglets at age of 5 to 7 days, Wang et al. (2014) has investigated post-hypoxia/ischemia consequences between two groups of 1) normothermic and 2) mild hypothermic (35°C for 24 hours). Continues profound low amplitude aEEG and severe abnormal burst suppression at 20 minutes, post-hypoxia/ischemia, in both studied groups; while lower aEEG abnormality in the recordings from CFM

5022 was reported in the hypothermic group (Wang et al., 2014).

Miller et al. (2016) using 1-day-old neonatal piglets, subjected to 30 minutes of hypoxia/ischemia, has reported aEEG seizures in almost half of the studied neonatal piglet cohort (n = 47) along two-channel aEEG recordings, assessed at 1, 24, 48 and 72 hours post HI-insult (BrainZ Instruments, Auckland, NZ).

Post-ischemic insult, monitoring of magnetic resonance spectroscopy and six-lead multi-channel aEEG/EEG recordings has demonstrated that a combination of inhaled argon (45–50%) with hypothermia (33°C) can help to improve energy metabolism of the brain in asphyxiated piglet models of age < 40 hours (Broad et al., 2016).

A very recent aEEG study conducted on newborn piglets (n = 26) within 24 hours of birth demonstrates that a longer duration of low amplitude neonatal aEEG (below 5 μV), between 1–12 hours post HI-insult, is associated with a bigger decrease in the cerebral blood volume in an HI hypothermia group compared to a smaller decrease in the cerebral blood volume of an HI normothermia group (Jinnai et al., 2018). Jinnai et al. (2018) obtained the aEEG data through two gold-plated electrode discs from parietal areas and measured with Nicolet One device and reported no differences between these two groups in terms of the post-insult low-amplitude EEG duration and the score of aEEG background. However, they suggested a combined assessment of aEEG alongside with analysis of cerebral oxygen metabolism through near infrared time-resolved spectroscopy and cerebral hemodynamics are evidential to clinch whether additional treatment apart from hypothermia was needed or not (Jinnai et al., 2018).

Sheep

Recent HIE animal studies using *in utero* fetal sheep models have highlighted a very critical short latent phase period of 5–7 hours, post HI insult, in which the neuroprotectivity of hypothermia is proven to be optimal. Our laboratory at the University of Auckland has been actively investigating hypoxic-ischemic related research using fetal sheep models, since early 90's. Due to the simplicity of surgical installation on fetal brain, the following works in sheep models use two-lead standard EEG/ECoG technology (with a reference electrode) which provides efficient subcortical information associated with hypoxia/ischemia, unless stated otherwise.

In very early studies in 1990 and 1992, the prognostic value of two lead EEG recordings (sampled at 111 Hz) for HIE diagnosis using asphyxiated fetal sheep (1990: n = 14, 1992: n = 33) and highlighted a gradual increase in the EEG amplitude within the first 8 hours including delayed high amplitude seizures between 6–12 hours after a severe HI insult (Williams et al., 1990; Williams et al., 1992). Gunn et al. (1992) demonstrated that the amount of decrease in the EEG intensity during the insult is associated with outcome and that the prolonged EEG suppression as well as epileptiform activity during the first 12 hours of HI insult are critical measures to predict subcortical damage.

Bennet et al. (2006) demonstrated that a mixture of superimposed slow and fast epileptiform transients along a dramatically suppressed preterm fetal sheep EEG (n = 7, two lead electrodes, sampling frequency: 256 Hz) during the early hours of HI insult which later evolve to high amplitude seizures around ~8 hours, post reperfusion phase.

Study conducted on a cohort of asphyxiated preterm fetal sheep (n = 24, asphyxia = 25 minutes), demonstrated that a continuous dizocilpine treatment from 15 min to 4 hours post-HI insult dramatically suppresses evolving micro-scale EEG transients and average of EEG intensity (two lead EEG), post-insult (Dean et al., 2006).

Cerebral hypothermic studies conducted on fetal sheep have demonstrated that a moderate process of cooling significantly improves the subcortical striatal neuronal loss and contributes in lowering of the average amplitude and total number of HI epileptiform micro-scale EEG events within less than 6 hours of HI insult (Bennet et al., 2007; Gunn et al., 1997, 1998; Roelfsema et al., 2004). For instance, using a cohort of *in utero* fetal sheep models (n = 24) in 2007, Bennet et al have indicated that the average amplitude of the high amplitude epileptiform seizures in two lead EEG sampled at 64 Hz was significantly reduced to 67 ± 21 μV from 135 ± 59 μV after hypothermia (Bennet et al., 2007). Bennet et al. (2007) also demonstrated that the total number of HI micro-scale EEG transients dramatically decreased during the first 6 hours of post-HI insult in the hypothermic group compared to the normothermic group.

Bennet et al. (2010) highlighted the existence of potential high-frequency low-amplitude transient biomarkers with durations of less than 400 ms in the EEG of fetal sheep, suggesting that complementary parameters provided through combinations of EEG and NIRS biomarkers could be used for early identification of HIE.

Using a cohort of preterm fetal sheep (n = 15), Davidson et al. (2011) reported that maternal dexamethasone leads to significant transient rise in EEG power (sampled at 512 Hz through two channel electrodes) that peaks at 12 hours. They also reported that dexamethasone causes reduces alpha, beta and theta activity while relatively increases delta components, within the 24 hours of insult, resulting in longer but fewer transient waveforms.

Hypothermia-EEG studies in 2015 and 2017, using asphyxiated near-term fetal sheep at 0.85 gestation (n = 24), demonstrated that the two lead EEG power was significantly improved in the 3 and 5 days hypothermia groups, respectively, compared to normothermia group (Davidson et al., 2015, 2017).

Bennet (2017) reported the effect of 25 minutes of umbilical cord occlusion asphyxia on preterm and near-term fetal sheep EEG activity at 0.6, 0.7 and 0.8 of gestational ages; reporting more significant suppression of the EEG power for near-term fetuses at 0.8 gestation, that are more metabolically active, compared to less EEG power suppressions in the 0.7 and 0.6 gestational age groups.

To date, apart from our group at the University of Auckland, no other preclinical animal experiments have reported the micro-scale prognostic biomarkers in the EEG/ECoG of the models, post HI event. Findings of our team indicate that evolutionary micro-scale epilptiform events in the standard raw EEG during the first 5–7 hours of an HI event are the reliable signatures to diagnose an HI event and significantly correlate to neuronal loss in fetal sheep models (Bennet et al., 2007, 2010; Abbasi et al., 2018, 2019a, b). Using *in utero* fetal sheep models, these studies have demonstrated that early prognostic biomarkers of HIE, in the form of micro-scale epileptiform events (i.e., HI spike and sharp waves), emerge along the high resolution standard EEG recordings sampled at 1024 Hz, during the latent phase of recovery post HI-insult, before the irreversible high amplitude epileptiform seizures indicate the closure of the window of opportunity for treatment (Bennet et al., 2010; Abbasi et al., 2019a, b, c).

For this reason, it is clear that accurate automated algo-

rithms could be ideally helpful to identify the EEG signatures of HIE, for early administration of the potential treatments, before the injury progresses beyond the latent phase of recovery is missed. Unlike the current clinical automated strategies that are mainly concerned with the identification of neonatal seizures (256 Hz clinical recordings), since 2009, researchers have demonstrated success in developing signal processing methods for the real-time detection and quantification of the EEG biomarkers in 1024 Hz recordings (particularly micro-scale HI spikes in gamma frequency band, sharp waves and SEMS transients).

Animal experiments conducted on sheep models have emphasized that micro-scale HI EEG seizures in the latent phase are the early indicative biomarkers of the HI injury when the neuro-protectivity of therapeutic hypothermia is proven to optimally peak, before the high amplitude epileptiform seizures alert the beginning of the irreversible secondary phase of the HIE. The necessity of having automated EEG biomarker identifiers within the latent phase is clearly important due to the critically short optimal treatment window of opportunity post a HI event (Gunn and Drury, 2013; Thoresen et al., 2013). Current clinical epileptiform seizure detection algorithms are only focused on automatic identification of high amplitude epileptiform seizures.

In general, EEG transients in sheep models are known to be in the same range as human (Szeto et al., 1985; Szeto, 1992; Mellor et al., 2005). Common types of hypoxic-ischemic micro-scale epileptiform events in sheep animal models are introduced and characterized as: 1) high-frequency spike transients (namely above 40 Hz in gamma frequency band), 2) conventional spikes (20–70 ms, 14.3–50 Hz), 3) sharp waves (70–250 ms, 4–14.3 Hz) and 4) slow waves (250–400 ms, 2.5–4 Hz), all with pointed peaks of ≥ 20 μV and also shown to emerge as 5) complexes (Andréet al., 2010; Bennet et al., 2010; Davidson et al., 2011; Abbasi, 2017; Abbasi et al., 2017, 2018, 2019a, c). Studies performed on hypoxic-ischemic fetal sheep models suggest the existence of early micro-scale biomarkers of HIE in the EEG signal during the latent phase of injury well-before the signs of the secondary phase of HIE, in the form of high amplitude epileptiform seizures, emerge in the signal. High amplitude epileptiform seizures are EEG discharges with various durations of less than a minute to a few minutes, frequency band of 0.3–2 Hz and amplitudes of 25–700 μV (Greene et al., 2008; Davidson et al., 2011).

To date, few studies have investigated automatic strategies for the identification and quantification of the hypoxic-ischemic micro-scale EEG biomarker patterns within the latent phase which has not been performed in other animal studies (Bennet et al., 2010; Abbasi et al., 2016b, 2018, 2019a, b, c). The following sections discuss attempts for real-time automatic identification of HI micro-scale seizures that will ideally play an important role in early diagnostic and treatment of at risk infants before the HIE evolves beyond the window of opportunity for treatment.

Walbran et al. (2009) from the University of Auckland initially investigated the performance of a semi-automated time-frequency technique based on the short-time Fourier (STFT) for micro-scale spike transient detection in low resolution two lead EEG, sampled at 64 Hz, during the early hours of HI insult of an asphyxiated *in utero* preterm fetal sheep at 0.7 gestation. Later, Walbran et al. (2011) demonstrated initial success for the automatic identification of potential EEG biomarkers of HIE in the form of spike transients in the same data set using multi-resolution Haar wavelet transform with an evaluated overall performance of ~80% over three 10-minute intervals of the latent phase.

Keogh et al. (2012a) investigated the possibility of discrimination between mild and severe HIE through spectral analysis of EEG power (two lead EEG sampled at 256 Hz) from a group of preterm fetal sheep at 0.7 gestation (15 minutes of asphyxia: n = 13, 25 minutes of asphyxia: n = 13). They reported limited predictive changes in the EEG power within 3 hours of HI insult in both groups.

Studies using pre-mature fetal sheep demonstrated that a highly selective inhibition of neuronal nitric oxide synthase either during or post severe asphyxia (n = 24) significantly improves striatal neuronal survival which was shown to be associated with smaller EEG power (two lead EEG with sampling frequency of 256 Hz) (Drury et al., 2014a).

Abbasi et al. (2014b) demonstrated that a type-2 fuzzy classifier in conjunction with an adaptive thresholding strategy outperforms Walbran's time-frequency methods for the identification of hypoxic-ischemic micro-scale spikes in the same EEG dataset from an asphyxiated preterm fetal sheep. Abbasi et al. (2014a) indicated the capability of a fusion strategy based on wavelets and type 2 fuzzy classifiers for the identification of micro-scale HI sharp waves in high resolution two lead EEG datasets from an *in utero* preterm sheep, sampled at 1024 Hz compared to 64 Hz sampled signals. Later, Abbasi et al. (2017) demonstrated that a compact and robust 'footprint of uncertainty' can be built from the wavelet transformation of sharp waves from 1024 Hz sampled two lead EEG that can be fed into a type-2 fuzzy classifier for the identification of HI sharp waves (Abbasi et al., 2017). The method was validated by using preterm fetal sheep (n = 5) and addressed that a proper selection of wavelet and the corresponding scale plays an important role in obtaining much higher identification accuracy. Abbasi et al. (2018) validated the performance of their wavelet type-2-fuzzy classifier for quantification of HI sharp waves using a cohort of *in utero* preterm sheep (n = 6). They highlighted that results of the developed sharp wave classifier comply manual quantifications indicating that the number of automatically quantified sharp waves in the first 2 hours after HI insult is associated to considerable neuronal survival in caudate while the number of quantifications in 2–4 hours post-hypoxia/ischemia is correlated with less striatal neuronal survival (Abbasi et al., 2018, 2019b). In 2019, they introduced a novel deep Convolutional Neural Network strategy in conjunction with Wavelet Scalograms for online identification and classification of sharp waves in 1024 Hz EEG/ECoG recordings of *in utero* preterm sheep (Abbasi et al., 2019c).

A preliminary study, in 2015, initially introduced an advanced fusion technique based on the reverse bi-orthogonal wavelets and fuzzy classifiers that resulted in promising performance metrics for the identification of high-frequency micro-scale spike transients in the 1024 Hz two lead EEG from an *in utero* preterm sheep model (Abbasi et al., 2015). The study also detailed how the application of reverse biorthogonal mother wavelet is superiorly efficient for the identification and quantification of high frequency transients as compared to the conventional mother wavelets such as haar, daubechies and mexican hat wavelets. In a very recent study, using a cohort of *in utero* preterm sheep (n = 7), the performance of the reverse-biorthogonal wavelets-fuzzy classifier was validated for the automatic identification and quantification of high-frequency HI spike transients in the latent phase of 1024 Hz sampled two lead EEG/ECoG (Abbasi et al., 2019a). Abbasi et al. (2019a) suggested that

the time-localization of automatically quantified spike transients could provide precursory information on the timing of evolutionary HIE, with higher number of spikes emerged during the first 2 hours post-hypoxia/ischemia, even in the experiments with shorter occlusion periods.

A study introduced a wavelet-fuzzy-based classifier for the identification of a new potential HIE EEG biomarker in the form of stereotypic evolving micro-scale seizures in the 1024 Hz sampled two lead HI EEG of an *in utero* preterm sheep (Abbasi et al., 2016a). Complementary information about the discussed automated studies above is supplied in **Table 1**.

Researchers from the Netherlands have also performed research on preterm sheep models of HIE. In 2015, researchers from the Maastricht University in the Netherlands evaluated the performance of a SVM-based seizure detection algorithm, developed by the researchers in Ireland (Temko et al., 2011), which was fed with EEG features and trend template information of seizures extracted from 1000 Hz sampled two lead bipolar EEG recordings of asphyxiated preterm sheep at 0.7 gestation (n = 17). Zwanenburg et al. (2013) suggest that application of trend templates in Temko's SVM-based seizure detector could be helpful in NICU monitoring devices for a better identification of shorter seizures of less than a minute long. Researchers from the Netherlands have also demonstrated profound cerebral inflammation causes marked neuronal and brain functional loss in asphyxiated preterm fetal sheep of 0.7 age subjected to 25 minutes of umbilical cord induced global HI (Jellema et al., 2013).

Monkey

As discussed earlier, preterm and term in non-human primates such as rhesus monkeys have been addressed as one of the most suitable animal models with remarkably higher similar pathological HIE distribution to the human brain (Painter, 1995; Inder et al., 2004). Unfortunately, the number of EEG leads used and sampling frequency has not been specified in the following HI EEG studies in monkeys. Although, these studies have used CFM or Brainz monitor devices which are by default configured to obtain recordings through two lead standard configuration at 256 Hz clinical sampling frequency rate.

In 2007, an experiment using a cohort of term fetal *Macaca nemestrina* monkeys (n = 50) demonstrated that a 15 minute umbilical cord obstruction prior to delivery, as opposed to 12 and 14 minute occlusions, can lead to a non-lethal reproducible HI brain injury in neonatal animal models of perinatal asphyxia (Juul et al., 2007). They reported severe attenuated cortical activity in the conventional multi-channel EEG at 90 minutes of birth in the 14 minutes asphyxiated animals. Jull et al. (2007) demonstrated that the background EEG activity was improved and contained sharp discharges at 6.5 hours after birth which later improved to more normal amplitudes at 24 hours of life. Using the aEEG from single channel CFM monitor (CFM 6000), Jull et al. (2007) also reported that the EEG power was gradually increasing from the time of birth up to 24 hours with ongoing burst suppressions.

In 2010, a perinatal MRI study conducted on term *in utero* fetal *Macaca nemestrina* monkeys (n = 12) demonstrated that a 15 or 18 minute obstruction of the umbilical cord in monkeys can lead to severe asphyxia at birth causing impaired neuronal developments and growth (Jacobson Misbe et al., 2011). They also reported abnormal postnatal aEEG recordings, obtained from BrainZ monitor (BRM3), between the very first 3 and 6 hours after birth.

McAdams et al. (2017a) using a cohort of near-term *in utero* fetal *Macaca nemestrina* monkeys (n = 4) reported 4–5 hours burst suppression in the post-asphyxia aEEG recordings with seizures observed between 9 to 26 hours, post 18 minutes of *in utero* occlusion, causing focal brain injury. The recordings were obtained through subdermal scalp electrodes fed into the Brainz BRM3 Monitor aEEG device. McAdams et al. (2017b) also assessed term fetal *Macaca nemestrina* macaques (n = 34) asphyxiated through 15–18 minutes of umbilical cord occlusion to analyze neuropathological variations associated with subcortical and cerebral palsy, post-HIE, suggesting that a combined hypothermia and erythropoietin treatment leads to less brain pathology. They demonstrated that aEEG recordings using BrainZ monitor (BRM3) are indication depressed voltages in the signal during the first 24 hours.

Conclusion

Examining the literature since late 90's, this article highlighted the recent preclinical advances around HIE using both non-primate and primate animal models such as rodents, piglets, monkeys and sheep. It was discussed how the different physiological brain growth around the time of birth in the studied animals adds complexity to the HIE models compared to human neonates. It was noted that, among all animals, prenatal and postnatal cerebral maturation of piglets are the most similar to human neonates where sheep and monkeys have shown faster prenatal developments and rodents are very slow with a fully postnatal cerebral maturation. Also, monkeys and sheep possess the highest percentage of adult birth weights closer to human neonates as opposed to rodents and piglets, respectively (Dobbing and Sands, 1979). To mimic the optimal cerebral physiological and maturational similarities to human neonates at birth, animal studies using monkeys and sheep models have been largely conducted at prenatal fetal stages in the *in utero* environment; whereas studies using piglet and rodent models have been performed at the neonatal and postnatal stages either at or up to 7 days of birth.

The review highlights how the smaller physiological brain structure in rodents becomes a limiting factor compared to piglets, sheep and monkeys where chronic instrumentation using larger brain sizes permits for better framework allowing repeated experiments and extensive monitoring of the vital signals. In addition, the larger brain size in monkeys, sheep and piglets, as opposed to rodents, provides the opportunity to mount more than two EEG leads if required and acquire more detailed spatial cerebral information. However, this would be technically easier in piglets as piglet studies have been performed post birth whereas sheep and monkey studies are performed *in utero*. The survey also addressed the significant cortical and subcortical morphology and developmental differences of rodent models that limits the experimental achievements when translated into human neonates, compared to other HI animals. The article also discussed that the neural system and mechanism, neurological characteristics, white/gray matter proportion and their cortical folding features in the monkey models demonstrate very close similarity to the human neonates. This was discussed to be less similar in the piglet and sheep and totally different in rodents. For the reasons above, non-human primates are generally suggested to be the most suitable models for HIE studies, however, the ethical restrictions and complications around these species has recently limited experiments using these type of animals.

The majority of animal studies using piglets or monkeys

have either used aEEG or reported EEG recordings at or around the clinical sampling frequency of 256 Hz; whereas standard EEG signals recorded at the higher sampling frequencies of ~1000 Hz in the recent rodents and sheep models have demonstrated superiority in providing beneficial timing-related information at higher frequency bands associated with deeper brain structures. The application of highly-filtered aEEG recordings and/or EEG signals at the current clinical sampling frequency of 256 Hz could be seen as a limiting factor in the monitoring and detection of subtle clinical EEG biomarkers that experimental data have shown to emerge with higher frequency components (Abbasi et al., 2015, 2017, 2019a, c). To date, pre-clinical fetal experiments on sheep and monkeys are reasonably comparable, however, to the knowledge of the authors, apart from fetal sheep studies, no HI EEG biomarkers have been reported in other animal models including the non-human primate monkeys. The article addressed that among all experimental species only a few fetal sheep studies have investigated the real-time automatic signal processing strategies for the identification and quantification of prognostic micro-seizure biomarkers of HIE in the post HI 1024 Hz EEG recordings during the latent phase of recovery (Bennet et al., 2010; Davidson et al., 2011; Abbasi et al., 2014, 2015, 2016, 2018, 2019a, b, c; Lakadia et al., 2016). Thus, increasing the current sampling frequencies to higher rates of ≥ 1024 Hz, in both clinical practice and other animal models, namely, monkeys, piglet and rodents, could permit the capture of early signs/markers of HI injury in the EEG as reportedly addressed in the sheep models.

Despite the limitations of animal models, studies have reported progressive improvements in the HIE experiments from all the different animal species (including non-human primates) concluding that future work must evaluate the influence of neuroprotective drugs more carefully (Lingam et al., 2016). They have also pointed out that optimal mixture and timing of the current therapeutic strategies are needed to be defined for smaller animals before shifting up to more larger animals such as sheep and piglets and prior to be tested on human. Lingam et al. (2016) have suggested that the three 'R's of refining the methodology, replacing animal use and reducing the number of animals should be taken into account according to the animal welfare in further preclini-

Table 1 Automated strategies on the detection of epileptiform seizures post a hypoxic-ischemic event

Reference	Subjects	Number of subjects	Epileptiform events	Number of events	Length of recordings (hours)	Number of experts	EEG acquisition	Sampling frequency (Hz)
White et al. (2006)	Adult rats	8	Spike seizures	75	312	1?	Bipolar electrode	250
Walbran et al. (2009)	Preterm fetal sheep (0.7 gestation)	1	Spike	374	0.5	1	2 channel ECoG	64
Walbran et al. (2011)	Preterm fetal sheep (0.7 gestation)	1	Spike	374	0.5	1	2 channel ECoG	64
Cuaycong et al. (2011)	Neonatal rats	12	Seizure	154	1080	1	Two channels EEG	400
Abbasi et al. (2014)	Preterm fetal sheep (0.7 gestation)	1	Spike	374	0.5	1	2 channel ECoG	64
Abbasi et al. (2014)	Preterm fetal sheep (0.7 gestation)	1	Sharp	73	0.5	1	2 channel ECoG	1024/256
Abbasi et al. (2015)	Preterm fetal sheep (0.7 gestation)	1	High frequency spike	334	0.5	1	2 channel ECoG	1024
Zwanenburg et al. (2015)	Preterm fetal lambs (0.7 gestation)	17	Short seizures	3159	1976	3	2 channel EEG	1000 down-sampled to 250
Abbasi et al. (2016a)	Preterm fetal sheep (0.7 gestation)	1	Stereotypic Evolving Micro-scale Seizures		13.5	1	2 channel ECoG	1024
Tieng et al. (2016)	Neonatal mouse model of epilepsy (7–8 week old)	4	High frequency spike	2014	8	1	2 channel ECoG	256
Abbasi et al. (2017)	Preterm fetal sheep (0.7 gestation)	5	Sharp	5186	30	1	2 channel ECoG	1024/256
Abbasi et al. (2018)	Preterm fetal sheep (0.7 gestation)	12	Sharp	3984	48	1	2 channel ECoG	1024
Abbasi et al. (2019a)	Preterm fetal sheep (0.7 gestation)	7	High frequency spike	3291	42	1	2 channel ECoG	1024
Abbasi et al. (2019c)	Preterm fetal sheep (0.7 gestation)	2	Sharp	690	3	1	2 channel ECoG	1024/256

Reference	Feature extraction	Algorithm	Sensitivity (%)	Specificity (%)	Selectivity (%)	GDR (%)	ROC (%)	Accuracy (%)	FDR (h^{-1})
White et al. (2006)		Autocorrelation method	100	99.98	95				
Walbran et al. (2009)		Time-frequency analysis with power thresholding	77.8		83.77				
Walbran et al. (2011)		Thresholded Haar Wavelet transform	78.7		77.7				
Cuaycong et al. (2011)			70–80						
Abbasi et al. (2014)	A set of features	Fuzzy classifier	89.06		90.3				
Abbasi et al. (2014)		Wavelet-Type 2 Fuzzy classifier	95.96		79.49				
Abbasi et al. (2015)	A set of spectral and time domain features from raw EEG	Thresholded reverse biorthogonal Wavelet transform and Fuzzy classifier	99.1		99.4				
Zwanenburg et al., (2015)	Non-linear energy operator & wavelet decomposition	Support Vector Machine				59.5			0.033
Abbasi et al. (2016a)		Wavelet-Type 2 Fuzzy classifier	73.59		86.92				
Tieng et al. (2016)	Five EEG features	Adapted CWT-based classifier	96.72	94.69					
Abbasi et al. (2017)	A set of time & freq. domain features	Wavelet-Type 2 Fuzzy classifier						97.4	
Abbasi et al. (2018)		Wavelet-Type 2 Fuzzy classifier	97.76		90.21			93.99	
Abbasi et al. (2019a)	A set of spectral and time domain features from raw EEG	Thresholded reverse biorthogonal Wavelet transform and Type-1 Fuzzy classifier	100		99.56			99.78	
Abbasi et al. (2019c)	2D Wavelet scalograms	Deep Convolutional Neural Network	100	93.57	93.66			95.34	

AUC: Area under the curve; ECoG: electrocorticography; EEG: electroencephalogram; FDR: false detection rate; GDR: good detection rate; ROC: receiver operating characteristic.

cal research. Thus, for ethical reasons, because higher numbers of smaller animals are permitted for HI experiments (such as rats, rabbits and mice) and are better suited to the investigation of the physiological mechanisms of perinatal HIE (Huang et al., 2017). Whereas, larger HIE animal models (such as sheep, piglets and monkeys) are more suited for translational and treatment research due to the lower number of animals permitted ethically for experiment.

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