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TOPICAL REVIEW

Waking up too early – the consequences of preterm birth on sleep development

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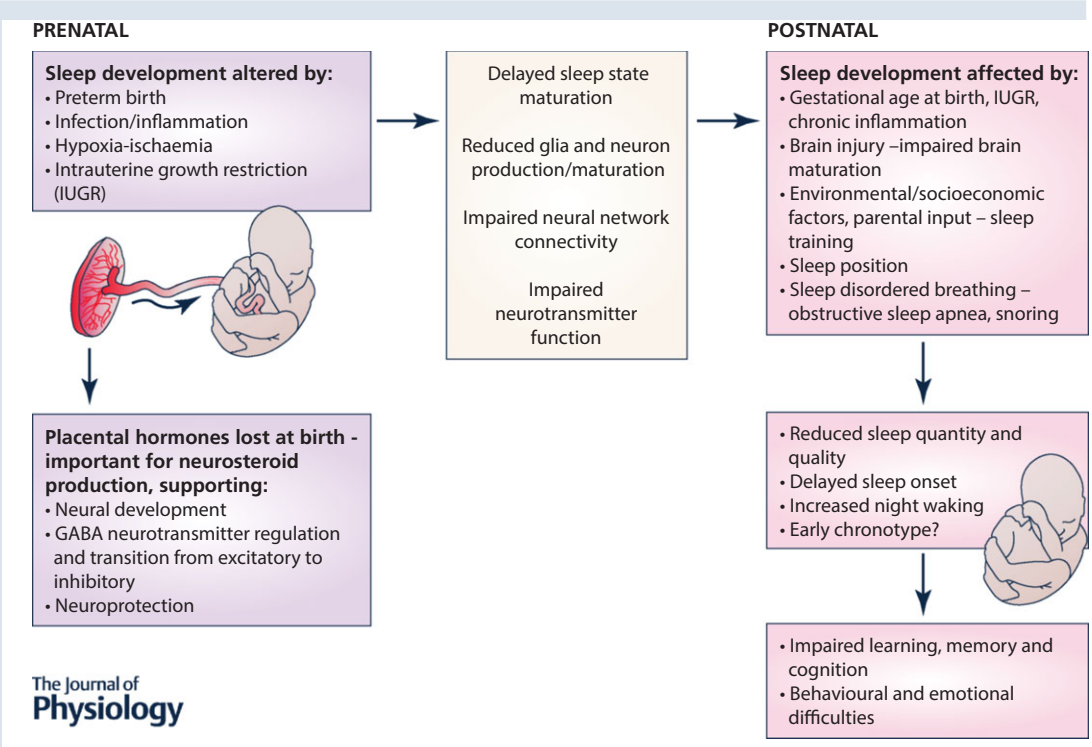

Abstract Good quality sleep of sufficient duration is vital for optimal physiological function and our health. Sleep deprivation is associated with impaired neurocognitive function and emotional

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control, and increases the risk for cardiometabolic diseases, obesity and cancer. Sleep develops during fetal life with the emergence of a recognisable pattern of sleep states in the preterm fetus associated with the development, maturation and connectivity within neural networks in the brain. Despite the physiological importance of sleep, surprisingly little is known about how sleep develops in individuals born preterm. Globally, an estimated 15 million babies are born preterm (<37 weeks gestation) each year, and these babies are at significant risk of neural injury and impaired brain development. This review discusses how sleep develops during fetal and neonatal life, how preterm birth impacts on sleep development to adulthood, and the factors which may contribute to impaired brain and sleep development, leading to altered neurocognitive, behavioural and motor capabilities in the infant and child. Going forward, the challenge is to identify specific risk factors for impaired sleep development in preterm babies to allow for the design of interventions that will improve the quality and quantity of sleep throughout life.

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Abstract figure legend Schematic illustration of how adverse events before and during birth, including the loss of critical placental factors, can impair brain maturation and alter sleep development.

Introduction

As children we fight it, as adults we crave it – that mysterious period of relative unconsciousness we experience each day called sleep. After we are born, sleep is defined as a "reversible behavioural state of perceptual disengagement from and unresponsiveness to the environment" (Carskadon & Dement, 2011). Our brain is driven to go to sleep through two integrated processes; an increase in hypnogenic substances throughout the day which drive the homeostatic need for sleep (Process S) interacting with our internal biological circadian clock (Process C) (Schwartz & Kilduff, 2015). The purpose of sleep is multifactorial, but primarily it facilitates the encoding and consolidation of information (memory retention and forgetting) (Feld & Born, 2017), as well as the emotion we experience during the day and over time (Altena *et al.* 2016). Additionally, sleep appears essential for maintenance of the neural network, facilitating neuronal and glial connectivity and synaptic plasticity (Cirelli & Tononi, 2017; Feld & Born, 2017; Lowe *et al.* 2017).

Sleep is vital for our health and wellbeing. Short- and long-term sleep deprivation, for example, negatively impacts on our neurocognitive capacities such as executive functioning, sustained attention, memory retention and retrieval of long-term memory (Krause *et al.* 2017; Lowe *et al.* 2017). Impaired or inadequate sleep is also associated with an increased risk for cardio-metabolic diseases, immune compromise, cancer and premature death, as well as fertility and pregnancy problems (Sen & Sellix, 2016; Cappuccio & Miller, 2017; Hatori *et al.* 2017). Indeed, active disruption of sleep and loss of the circadian drive for sleep through such factors as increased activity at night, and exposure to light-emitting electronic devices and shift-work, is now recognised as a significant public health risk (Hatori *et al.* 2017).

As this review will demonstrate, the foundational architecture of our sleep is laid down before we are born, and continues to evolve throughout our lives as the brain grows and changes its internal connectivity. This raises the question of what happens when we interrupt the normal ontogeny of sleep development through being born too early. Each year around 15 million babies are born preterm (<37 weeks of gestation), and preterm birth has an adverse impact on neurodevelopment (Kidokoro *et al.* 2014; Brumbaugh *et al.* 2016; Back, 2017), which persists into adult life (Allotey *et al.* 2018). A recent meta-analysis of 74 studies (64,061 children) showed that prematurity *at any age* was associated with lower academic, cognitive and motor skills, and increased behavioural problems such as attention deficit hyperactivity disorder, with younger babies more at risk (Allotey *et al.* 2018). Structural brain abnormalities and altered functional connectivity of the neural network underpin these cognitive, motor and behavioural deficits (Kidokoro *et al.* 2014; Brumbaugh *et al.* 2016; Scheinost *et al.* 2016; Back, 2017). Thus, how does sleep develop in a brain that itself does not develop normally? The purpose of this review is to discuss the development of sleep before birth, the impact of preterm birth on sleep from infant to adult life, and the factors which may contribute to the development of sleep dysfunction.

The ontogeny of sleep from fetus to newborn

Development of the neural network. Sleep-like activity evolves as the brain matures and the neural network becomes more coherent (Kostovic & Judas, 2010), and

evaluation of sleep can be considered "a complex phenotype of developmental neural plasticity" (Scher & Loparo, 2009). By the time that embryonic neurulation is complete, the brain is producing cells at a rate of around 250,000 per minute (Stiles & Jernigan, 2010). By the end of the embryonic phase at the 12th week of gestational age (GA), the basic structures of the central and peripheral nervous systems are in place (Stiles & Jernigan, 2010). In humans, neuron production starts around embryonic day 42 and this process is largely complete by mid-gestation, and neural migration effectively completed by 26–29 weeks GA (Bystron *et al.* 2008; Tymofiyeva *et al.* 2012). The earliest oligodendrocyte progenitors migrate from the ventricular and sub-ventricular zones around 20–22 weeks GA (Rivkin *et al.* 1995), with peak production for these future myelin producing cells occurring between 23 and 32 weeks GA (van Tilborg *et al.* 2017). Thus, this preterm period of life is critical for white matter and subsequent cortical neuronal development, the latter itself requiring appropriate maturation of white matter (Back, 2017; van Tilborg *et al.* 2017). As discussed below, it is also a critical time for establishing functional connectivity of the neural network which is important for sleep regulation.

The ontogeny of the major neural networks is harder to determine, but some evidence suggests that circuit formation begins around 16–21 weeks GA in human development, with first synapses evident around 16 weeks GA (de Graaf-Peters & Hadders-Algra, 2006; Tymofiyeva *et al.* 2012). Functional magnetic resonance imaging (fMRI) studies have been used to examine the development of neural networks in both fetuses (Jakab *et al.* 2014; Thomason *et al.* 2015; Friedrichs-Maeder *et al.* 2017), and infants (Smyser *et al.* 2010; Fransson *et al.* 2011; Ball *et al.* 2012, 2014). The ability of the brain to functionally process complex signals requires the development of a structural, hierarchically connected network that allows for fast, short-range (adjacent areas) and local processing of information within specific network modules (regional intra-clusters and connector inter-clusters), combined with global integration between modules or hubs through long-range connections (e.g. thalamocortical), and so called 'rich-club' hubs (densely connected network hub regions) (Ouyang *et al.* 2017).

fMRI studies have demonstrated the existence of primitive neural networks in human fetuses as young as 21–24 weeks GA (Jakab *et al.* 2014; Thomason *et al.* 2015). Networks expand in a region-specific manner starting with the occipital region followed by network activity in temporal, frontal and then parietal regions, i.e. from primary sensory to association and higher order processing areas (Jakab *et al.* 2014; Thomason *et al.* 2015). There is increasing coherence between networks with age (Jakab *et al.* 2014; Thomason *et al.* 2015), and the expansion of the overall connectivity network, short-range, and interhemispheric connections peaks at around 26–29 weeks GA (Jakab *et al.* 2014). These data suggest that the architectural foundation of local network hubs is established in the second and third trimester at the time of peak expansion of white matter (Jakab *et al.* 2014). Notably, short-range structural connectivity plays a key role in how the brain develops and in mediating our neurocognitive function after we are born (Ouyang *et al.* 2017). In contrast, there is a linear development of long-range connections throughout gestation (Jakab *et al.* 2014), and long-range connectivity is greater at 30 weeks GA, consistent with white matter tract maturation. Magnetic resonance imaging (MRI) studies have also shown that the advancement of grey and white matter in the fetus is inter-related, and highly dependent on the integrity and complexity of the underlying axonal circuitry within the white matter tracts (Friedrichs-Maeder *et al.* 2017). As discussed below, preterm birth disrupts the establishment of the neural connectivity framework, and this impacts on the development and efficiency of sleep.

Fetal sleep. Sleep during fetal life is, by definition, difficult to determine given that the human fetus cannot be directly assessed. Animal studies allow more direct access, as discussed below, but in human studies the fetus is assessed by indirect measures such as ultrasound to evaluate behaviour (e.g. eye, body and breathing movements) and fetal heart rate recordings. In clinical obstetrics, fetal ultrasound studies show that preterm fetal behaviour consists of random movements, but from mid-gestation defined rest and activity periods start to develop, with increasing prolongation of periods of quiescence (reduced body movements) with advancing gestational age (Ten Hof *et al.* 2002). These patterns are also seen in preterm infants after birth, and thus are not a consequence of reduced intrauterine space, but rather reflective of maturation of basic neuro-inhibitory processes (Ten Hof *et al.* 2002). From at least 32 weeks GA, fetal behaviour can be categorised into four states based on fetal heart rate, and body and eye movements, viz. 1F, quiet sleep (F denotes fetus, and 1F consists of slow regular heart rate, infrequent body movements, mostly startles and no eye movements), 2F active sleep (regular heart rate, eye movements, frequently and periodic gross body movements, mostly stretches), 3F, quiet awake (fast regular heart rate, eye movements, no body movements), and 4F, active awake (fast irregular heart rate with prolonged periods of tachycardia, eye movements, continual body movements) (Nijhuis *et al.* 1982, 1999). While the terminology of awake is used as part of these definitions, there is limited if any evidence for actual wakefulness in fetal life, as discussed below.

In younger fetuses (<30 weeks GA), specific clusters of behaviour cannot be readily identified, and this is referred to as indeterminate sleep (Nijhuis *et al.* 1999; Mirmiran

et al. 2003). A gradual co-ordination between behaviours is seen from 25 to 30 weeks GA (Drogtrop *et al.* 1990; Nijhuis *et al.* 1999), with clear linkages seen after 32–34 weeks GA (Visser *et al.* 1987; Nijhuis *et al.* 1999), and accelerated maturation at 34–36 weeks GA (Nijhuis *et al.* 1999). With maturation, the fetus spends most time (∼90%) in 1F and 2F, with very little time spent in 3F and 4F (Pillai & James, 1990; Nijhuis *et al.* 1999).

In late gestation, fetuses switch between 1F and 2F in an ultradian cycle of 70–90 min (Visser *et al.* 1992), and the stability of concordant behaviours, along with organised short transition phases between states, are used as measures of normal neurodevelopment (Van den Bergh & Mulder, 2012). The maturation of fetal behaviour has been examined by determining the sequence of transitions with gestational age (Arduini *et al.* 1989; Nijhuis *et al.* 1999). Fetal heart rate is the first variable to change during transition between 1F to 2F between 28 and 39 weeks, and the last to change during 2F to 1F transitions between 32 and 39 weeks, but this is lost in growth retarded fetuses where there is no maturational order (Arduini *et al.* 1989; Nijhuis *et al.* 1999), presumably reflecting immature and/or impaired neural network development. More recently it has been shown in children at 8–9 and 14—15 years of age, independent of other socio-economic factors, that the duration of their fetal state transitions in late gestation was significantly associated with their degree of self-regulation or effortful control (defined as more effective emotional control and executive functioning) (Van den Bergh & Mulder, 2012). In particular, quick transitions from 1F to 2F were associated with higher levels of effortful control (Van den Bergh & Mulder, 2012). Thus, the association between quicker, synchronised sleep state switching and better behavioural control in postnatal life suggests better maturation of the brain in these individuals during fetal life. These data reinforce the concept that how sleep evolves before birth is important to postnatal neurocognitive outcomes in later life.

Behavioural patterns are influenced by a number of physiological and pathological factors, including fetal growth (Nijhuis *et al.* 2000), maternal glucocorticoid administration (Mulder *et al.* 2009), circadian rhythms (Patrick *et al.* 1982; Visser *et al.* 1982; de Vries *et al.* 1987), maternal alcohol consumption (Mulder *et al.* 1998), and medical conditions such as diabetes (Mulder *et al.* 1987). A recent study showed that maternal sleeping position can also alter the behavioural sleep states of late gestation fetuses, as determined by fetal heart rate variability (Stone *et al.* 2017). This study demonstrated that, compared to 2F, 4F activity was seen almost exclusively when the mother was in a left or right lateral position, while 1F was more common when the mother was supine (Stone *et al.* 2017). Further, 4F was more common between 21.00 and 01.00 h than between 01.00 and 07.00 h (Stone *et al.* 2017). These data are consistent with previous circadian studies showing increased fetal activity in the late evening in humans and animals (Dalton *et al.* 1977; Patrick *et al.* 1982; Visser *et al.* 1982; de Vries *et al.* 1987; Seron-Ferre *et al.* 2012). The quality of maternal sleep itself is also important, because pregnant women suffering obstructive sleep apnoea (OSA) show evidence of established placental hypoxia (Ravishankar *et al.* 2015), and an increased incidence of preterm birth, low birth weight, poor Apgar scores and stillbirth (Pien *et al.* 2014; Bourjeily *et al.* 2017). It has been suggested that the incidence of OSA in pregnancy is dramatically under-reported (Pien *et al.* 2014), and in industrialised countries OSA during pregnancy is increasing due to the obesity epidemic, particularly in younger women, and is associated with a number of pregnancy complications (Bourjeily *et al.* 2017).

The neonatal surrogate for fetal sleep. Supporting these *in utero* studies are observations made in infants born preterm, where direct measurements of electroencephalographic (EEG), electromyographic, and electrooculographic activity are added to behavioural and heart rate measures. However, the authors note the caveat that the *in utero* environment (including the placenta) plays a key regulatory role in fetal brain activity and behaviour, as discussed below. Fetal neural control is different, not only as a function of maturation, but also because of the *in utero* environment. For example, while the fetus does not breathe for oxygenation, it does make breathing movements to mature the lungs and respiratory musculature (Walker *et al.* 2000). In late gestation, fetal breathing movements (FBMs) are episodic in nature, with the apnoeic periods unique to the fetus regulated by nuclei in the lateral pons (Walker *et al.* 2000). Similarly, there is no respiratory chemoreflex in response to hypoxia, and the fetal response is characterised by apnoea and a switch to 1F, rather than the arousal and an increase in respiratory activity seen postnatally (Walker *et al.* 2000).

Sleep states after birth are generally defined as quiet sleep (QS, equivalent to 1F) and active sleep (AS, equivalent to 2F), and these states are the precursors to rapid eye movement (REM) and non-rapid eye movement (NREM) sleep in adults. QS is characterised by high voltage low amplitude EEG activity, the absence of eye movements, higher muscle tone, and regular heart rate and respiration, while AS is characterised by low amplitude high frequency EEG activity, eye movements, reduced muscle tone and irregular heart rate and respiration (Curzi-Dascalova *et al.* 1988). However, the distinction between sleep states in very premature infants is acknowledged as being difficult to objectively assess before 30 weeks GA, and prior to this sleep is largely characterised as indeterminate sleep (Curzi-Dascalova,

2001; Mirmiran *et al.* 2003). EEG activity is characterised as being discontinuous in nature with bursts of variable amplitudes and frequencies, and quiescent/suppressed periods (interburst intervals) (Vanhatalo & Kaila, 2006; Tolonen *et al.* 2007; Andre *et al.* 2010; Omidvarnia *et al.* 2013; Koolen *et al.* 2017).

However, some studies suggest that a rudimentary sleep–wake cycle can be seen between 24 and 30 weeks GA. This is based on alternating periods with and without eye movements related to EEG discontinuity (Vecchierini *et al.* 2003; Scher *et al.* 2005). With maturity, the percentage of indeterminate sleep falls to <20% at term as AS and QS become established (Curzi-Dascalova *et al.* 1988; Mirmiran *et al.* 2003). The preterm newborn spends proportionally more time in AS up to term equivalent age (Peirano *et al.* 2003), and AS is important for brain growth and development of complexity of the neural networks (Marks *et al.* 1995; Mirmiran *et al.* 2003; Cirelli & Tononi, 2017). QS is harder to determine in preterm infants as chin submental hypotonia is difficult to evaluate (Curzi-Dascalova *et al.* 1988). QS becomes clearly identifiable around about 36 weeks GA, consistent with maturation of the thalamocortical and intracortical pathways and increased synaptogenesis (Peirano *et al.* 2003; Kostovic & Judas, 2010).

The proportion of time spent in QS and wakefulness increases with maturational age from term equivalent age (Holditch-Davis & Edwards, 1998; Peirano *et al.* 2003). QS is also important for brain development and some preterm infants have been reported to experience longer sleep cycles and QS periods (Roffwarg *et al.* 1966; Scher *et al.* 1992, 2011; Peirano *et al.* 2003). This may be an adaptive response to the altered physiological and hormonal environment of extra-uterine life, or accelerated maturation (Scher *et al.* 1992, 2011; Holditch-Davis *et al.* 2004; Graven, 2006). QS may play a role in brain development by promoting synaptic remodelling through reactivation and processing of neural information encoded during wakefulness (Peirano *et al.* 2003). Quantitative analysis of neonatal EEG during sleep has demonstrated that even late preterm infants (34 0/7 and 36 6/7 weeks GA) have structurally different sleep, with differences observed in several indices such as arousals during QS, spectral beta/alpha power ratios during AS and QS, sleep cycle length, and spectral correlations between homologous centro-temporal regions during QS (Scher *et al.* 2011). These changes demonstrate that being born too soon, at any age impacts on the development of the neural network that regulates sleep architecture (Scher *et al.* 2011). These data are consistent with the finding that moderate to late-preterm and near-term infants also have a higher risk of neurodevelopmental disability compared to their full-term counterparts (Ortinau & Neil, 2015; Brumbaugh *et al.* 2016)

A key feature of the immature EEG that supports development of the neural network neural network/sleep-like activity, is the occurrence of spontaneous activity transient (SAT) activity, which derives from brainstem or deep brain structures, and which occurs when long neural pathways are actively developing as discussed above (Ben-Ari, 2001; Vanhatalo & Kaila, 2006; Omidvarnia *et al.* 2013). These intermittent events appear important for guiding activity-dependent structural development of the neural network (Vanhatalo & Kaila, 2006; Omidvarnia *et al.* 2013). In preterm infants, total brain volume, and in particular subcortical grey matter volume, grew faster in infants with more SAT activity and with greater cortical activity (Benders *et al.* 2015). Dysregulation of preterm SAT activity leads to impaired cortico-thalamic connectivity (Catalano & Shatz, 1998). The general fall in EEG amplitude with maturation in part reflects a reduction in SAT activity (Vanhatalo & Kaila, 2006), which may be mediated by a gradual shift from an excitatory role for the neurotransmitter gamma-aminobutyric acid (GABA), when chloride efflux promotes depolarisation (Ben-Ari, 2001), to the inhibitory, hyperpolarising activity of GABA seen in late gestation and after birth (Ben-Ari, 2001; Vanhatalo *et al.* 2005).

Sleep ontogeny in pre-clinical animal studies

The chronically instrumented fetal sheep is the primary experimental model for studying fetal physiology and behaviour, where the fetus can be studied growing and developing *in utero* over long periods without the confounding effects of anaesthesia (van den Heuij *et al.* 2016). The authors note the caveat that the precocial development of the fetal sheep brain is such that the brain may be considered equivalent to the human brain at around 125–130 days GA (term in the sheep is 145–150 days) (Barlow, 1969; McIntosh *et al.* 1979), and thus studies after this time reflect a post-mature brain.

In preterm fetal sheep at 0.6–0.7 gestation (85–105 days sheep gestation, which is equivalent to human brain development around 25–32 weeks GA), electrocorticogram (ECOG) activity is discontinuous and comprises mixed amplitude and frequency, interburst intervals, and high amplitude transients (Clewlow *et al.* 1983; Bennet *et al.* 1999; Mellor *et al.* 2005; Davidson *et al.* 2011). Fetal behaviour (FBMs, eye and body movements) is not closely related to brain ECOG activity, but is rather continuous and appears to be coincidental (Clewlow *et al.* 1983; Mellor *et al.* 2005). The regular alternation between REM and NREM sleep-state like cycling starts to emerge in ECOG recordings after 110–115 days, with clear evidence by 120 days (Dawes *et al.* 1972; Ruckebusch *et al.* 1977; Clewlow *et al.* 1983; Szeto & Hinman, 1985; Walker *et al.*

1990; Richardson *et al.* 1994; Keen *et al.* 2011). There is a clear diurnal rhythm in some fetal behaviours and endocrinology (Dalton *et al.* 1977; Zemdegs *et al.* 1988; McMillen *et al.* 1990; Houghton *et al.* 1993), with maternal entrainment of the fetal circadian clocks evident from many animal studies (for review, see Seron-Ferre *et al.* 2012).

As fetal sleep state cycles develop, fetal behaviour becomes episodic in nature. REM-like brain activity is associated with rapid eye movements and relative body muscle atonia; characteristic features of REM sleep after birth. Associated with fetal REM sleep is the periodic presence of FBMs and other behaviours such as licking and swallowing, but reduced or absent body movements (Dawes *et al.* 1972; Walker *et al.* 1990; Richardson *et al.* 1994), and blood pressure, cerebral blood flow and metabolism increase, while heart rate is lower (Clapp *et al.* 1980; Richardson *et al.* 1994; Akay & Szeto, 1995; Czikk *et al.* 2001). In contrast, NREM sleep-like activity is associated with a reduction or cessation in FBMs and the presence of body movements (Dawes *et al.* 1972; Walker *et al.* 1990; Richardson *et al.* 1994), and blood pressure, cerebral blood flow and metabolism decrease, while heart rate is higher (Richardson *et al.* 1994; Akay & Szeto, 1995; Czikk *et al.* 2001). This compartmentalisation of behaviour may reflect the development of the cortico-spinal pathways that are fundamentally involved in the regulation of sleep (Walker *et al.* 2000), and may have the important function of managing fetal energy expenditure to balance the demands of growth with the necessity of preparing the body (e.g. lungs, respiratory musculature) for the demands of postnatal life. Temporary paralysis of fetal lambs with anaesthesia or a neuromuscular blocking agent results in a fall of total fetal oxygen consumption of 15–20% (Rurak & Gruber, 1983; Rurak, 2017), indicating the energy expense of fetal activity, and suggesting that fetal sleep is a mechanism to reduce this 'non-purposeful' use of energy. On the other hand, an abnormal reduction in FBMs is associated with lung hypoplasia (Harding & Hooper, 1996).

In the maturing sheep fetus, REM state predominates initially, occurring 40–60% of the time, but this percentage gradually falls with maturation, as is seen in the human fetus and neonate (Akay & Szeto, 1995; Rao *et al.* 2009; Keen *et al.* 2011). The duration of NREM is positively correlated with the duration of the previous REM phase (Rao *et al.* 2009), and the authors of this study suggested that this positive REM/NREM linkage supports the homeostatic model for sleep (Rao *et al.* 2009). Both REM and NREM support brain growth, as is observed postnatally (Cirelli & Tononi, 2017). Evidence from fetal sheep, for example, demonstrates that there is protein turnover and degradation during NREM (Czikk *et al.* 2003), suggesting that NREM activity may support new protein synthesis as part of supporting brain maturation. In addition to REM and NREM activity, a third behavioural state is observed, the incidence of which increases with maturation. This state consists of mixed ECOG frequency, with coincidental expression of FBMs, eye and body movements, and variable blood pressure and heart rate responses. These periods of fetal arousal are similar to newborn wakefulness, and thus it has been postulated that this state represents fetal wakefulness (for review, see Mellor *et al.* 2005). However, in reality, is the fetus ever truly awake?

Fetal sleep – if I sleep, do I wake? How different is *in utero* life?

Philosophically it is interesting to consider what benefits the fetus would gain in waking in such an enclosed environment; deprived as it is of the capacity to interact with its environment and care-givers. Perhaps fleeting moments of drowsy wakefulness towards term are useful for practising for the moment of birth where being awake is part of our daily life cycles, just as FBMs prepare the fetus for the mechanics of breathing. Certainly it is easy to be convinced that the fetus must be awake when looking at a three dimensional ultrasound picture of a fetus displaying complex behaviours, some of which look like wakefulness in infants (e.g. eyes open and sucking thumbs). Further, in late-gestation we know that the fetus can process auditory stimuli (i.e. the fetus can hear; Walker *et al.* 1971; Hepper, 1997), and data show that the fetus and newborn are physiologically responsive to the sound of their mother's voice (e.g. heart rate and respiration change when they hear her but not others; Hepper, 1997). This suggests that fetuses can form memories, which are retained by the neonate, albeit briefly as this recognition pattern is lost shortly after birth. Is this evidence of conscious awareness? Further, numerous studies show that the fetus physically responds to noise (such as vibroacoustic stimulation) and to touch (such as inadvertent contact with a needle during obstetric sampling procedures) with jerking, limb withdrawals and increased heart rate (Mellor *et al.* 2005), just as we would act if startled. Such stimuli generally cause us to wake up and if we wake then it may be reasoned that these fetal responses provide evidence that the fetus also wakes up. Supporting this perception is the widespread use in clinical and pre-clinical studies of the terminologies of awake or wakefulness when describing fetal behaviour, as discussed in the previous sections.

It is critical, however, to put these potentially perceptual biases into a physiological framework of understanding. The clinical descriptions of fetal behaviour are derived from clusters of behaviour such as heart rate, eye and body movements observed in *infants* during sleep and wake periods (Nijhuis *et al.* 1982; Visser *et al.* 1987),

not evidence of a fetal awake state or activation of the neurophysiological processes which ensure transition to an awake state (Mellor *et al.* 2005). Similarly, in fetal sheep studies, reference is also made to these clinical definitions. For example, nuchal muscle tone is used as a surrogate measure of wakefulness (high tone) and sleep (low tone), based on neonatal observations (Karlsson *et al.* 2011). Fetuses can indeed process auditory stimuli, but we know that wakefulness or consciousness is not necessary to entrain memory, as sleep is important for memory processing and we can create memories while asleep (e.g. dreams remembered when we wake). Further, surprisingly complex behaviours can be displayed when fully asleep, including opening of eyes and sucking of thumbs; witness the behaviour of adults and children who sleep and those who sleepwalk. Finally, fetal arousal to noise or touch could be considered as evidence of brainstem and subcortical reflex actions rather than *prima facie* evidence of activation of the cortical arousal to wakefulness.

Importantly, it should be appreciated that the fetus lives in a very different environment to that experienced after birth, an environment which includes the placenta (Mellor *et al.* 2005). Evidence strongly suggests that the fetal brain is actively inhibited from initiating cortical arousal to an awake state, even in late gestation, through significant release of inhibitory neurotransmitters and modulators from the placenta as well as the fetal brain itself, such as steroids, adenosine and prostaglandin D2 (Lee *et al.* 2002; Hunter *et al.* 2003; Nguyen *et al.* 2004). These inhibitors are further increased during hypoxia and other noxious stimuli such as hypercapnia and pain that would cause arousal to wakefulness after birth. In the fetus these stimuli induce transition to 1F or NREM activity, or even greater suppression of brain activity along with cessation of FBMs and body movements in term and preterm fetuses (Walker *et al.* 2000; Mellor *et al.* 2005; Bennet, 2017).

Further proof that the fetus may not be truly awake *in utero* comes from an intriguing study in fetal sheep by Rigatto and colleagues that allowed investigators to physically observe the developing fetus during different behavioural states (Rigatto *et al.* 1986). Despite many thousands of hours of observations, during all types of fetal behavioural states, the researchers did not find any evidence of wakefulness in terms of conscious awareness and interaction with the environment or the observers; the hallmarks of the awake state (Rigatto *et al.* 1986). Collectively, the evidence suggests that periods of fetal arousal represent another form of sleep, albeit brief, similar to subcortical sleep arousal in infants which promotes (IPWGA, 2005) cardiorespiratory and neural development, and which is mediated by subcortical and brainstem activity, not arousal to consciousness (McNamara *et al.* 2002).

This section provided a general overview of the ontogeny of sleep and how sleep reflects the maturing neural network. It emphasises the importance of the preterm period as a critical phase in the development of sleep state cycling. In the following section we examine the known impact of preterm birth on the ontogeny of sleep from infant to adult life. We then discuss the perinatal factors which may mediate altered sleep development.

The neural network and preterm birth

Sleep is vital to the development and function of an optimal neural network, and impaired sleep may disturb myelination of the maturing brain (Kurth *et al.* 2016). Individuals born preterm are at a significant risk for impaired neurodevelopment, this includes moderate to late-preterm and near-term infants who also have a higher risk of neurodevelopmental disability compared to their full-term counterparts (Back, 2015; Brumbaugh *et al.* 2016; Allotey *et al.* 2018). Underpinning impaired neurodevelopment is an altered cerebral architecture characterised by reduced grey and white matter volumes, diffuse non-cystic white matter loss, and reduced cortical folding and gyral complexity (Back, 2017). Reduced brain growth is associated with impaired cortical arborisation and synapse formation, synaptic pruning, and white matter dysmaturation, leading to compromised neuronal integrity and functional capacity (Back, 2017). In turn this leads to an altered development of the neural network and connectivity, characterised by fewer connections and disruption to local and short-path connections and cortical to subcortical relays, i.e. to less complexity of the neural network and an altered connectome (Hagmann *et al.* 2010; Ball *et al.* 2015; Meng *et al.* 2016; Scheinost *et al.* 2016). Evidence suggests that the rich-club hub network, which is established before birth as discussed earlier, is maintained at the expense of peripheral connections after preterm birth (Ball *et al.* 2014; Fischi-Gomez *et al.* 2016).

A less complex, less well connected neural network, for example, reduces the efficiency of information processing, requiring more connections to achieve the same response, often with a loss of those vital short-term and local connections we discussed earlier (Hagmann *et al.* 2010; Rathbone *et al.* 2011; Thompson *et al.* 2016; Cao *et al.* 2017). Reduced brain volumes and the aberrant intrinsic network connectivity seen in neonates persists into adult life (Meng *et al.* 2016), and is associated with adult neurocognitive dysfunction (Meng *et al.* 2016). Thomason and colleagues showed that impaired functional connectivity can also be observed in fetuses who go onto be born preterm (Thomason *et al.* 2017), and this is associated with both acute and chronic chorioamnionitis and funisitis, demonstrating a strong association between perinatal inflammation and impaired neurodevelopment, as discussed below (Thomason *et al.* 2017). These researchers also demonstrated disturbed

brain connectivity, complexity and network structures in 7-year-olds who were born <30 weeks GA, and observed a strong correlation between perinatal infection and a lower density of white matter connections, and that bronchopulmonary dysplasia was associated with reduced connection strength within some sub-networks (Thompson *et al.* 2016). We discuss the impact of such respiratory conditions on sleep further below.

The causes of impaired neurodevelopment and functional connectivity are multifactorial and for younger preterm infants are seldom isolated events, but rather the preterm brain can be subjected to multiple insults, combined and intermittently, and that combination insults can both sensitise the brain to greater injury or create tolerance to subsequent insults (Dammann & Leviton, 2014; Hagberg *et al.* 2015; Back, 2017). Challenges include exposure of both the fetus and newborn to acute and chronic infection and inflammation and perinatal hypoxia–ischaemia (HI), the adaptation of immature organs to the physiological demands of the *ex utero* environment and all the clinical interventions (e.g. cardio-respiratory support, as well as pain and seizure medication) necessary to ensure survival (Bennet *et al.* 2013; Back, 2017; Yawno *et al.* 2017).

Effects of preterm birth on the development of sleep after term equivalent age

Sleep disruptions can occur from the first hours of life. The quality of sleep can be impaired by clinical treatments including the light and noise of neonatal intensive care units (NICU) (van den Hoogen *et al.* 2017) and respiratory support (Collins *et al.* 2015). Further, the development of sleep may be compromised by the many morbidities experienced by preterm infants.

The maturation of sleep is one of the most important physiological processes occurring during the first year of life and is particularly rapid during the first 6 months after birth, with term-born newborns spending 70% of each 24 h asleep and preterm-born newborns spending approximately 90% of their time asleep (Gaultier, 1995). As with the fetus, the natural emergence of coherent sleep states in the newborn is dependent on the maturation of the central nervous system and is a reliable indicator of the normal development of the brain (Curzi-Dascalova, 2000). Indeed, the quality of sleep between 27 and 28 weeks GA appears to be an important determinant of functional brain development (Holditch-Davis & Edwards, 1998).

Thus it is surprising how little research there is on the impact of preterm birth on the development of sleep. Such assessment is rarely included in the assessment of preterm newborns (Shellhaas *et al.* 2017). Polysomnography is the gold standard method for sleep analysis, and access polysomnography equipment or the degree of instrumentation required may be rate-limiting steps to uptake in the neonatal intensive care unit. In this regard, we have recently demonstrated the utility for 2 lead aEEG recordings, which are increasingly used in neonatal intensive care units, for the analysis of sleep activity (Bennet *et al.* 2016). Hoppenbrouwers and colleagues reported that beyond the neonatal period preterm birth does not seem to affect the maturation of sleep states and sleep architecture, with the percentage of time spent in QS, AS, indeterminate sleep or wake being similar to that in age-matched term infants between 38 and 55 weeks post-conceptional age (Hoppenbrouwers *et al.* 2005). No sleep duration, night-waking or sleep-onset difficulties were observed in children from birth to 10 years of age, assessed by parental report, who were born at a median age of 34.1 weeks GA (range 27.1–36.8 weeks GA) compared to term born controls (Iglowstein *et al.* 2006). Similarly, no differences were found in night waking, sleep onset or co-sleeping between preterm infants between 32 and 36 weeks GA and term infants at 20 months and 56 months of age, assessed by structure interview with parents (Wolke *et al.* 1998).

However, recent studies suggest that, for some infants, preterm birth affects sleep structure and efficiency, as discussed in detail below (Asaka & Takada, 2010; Perkinson-Gloor *et al.* 2015; Shellhaas *et al.* 2017; Stangenes *et al.* 2017; Yiallourou *et al.* 2017). In some studies, sleep is associated with apparent neural injury, although the authors note that neural assessment for injury is not routinely assessed in sleep studies in infants and children. Sleep disturbances in children with cerebral palsy (CP) are well known and include difficulties initiating sleep and morning awakening, repeated night waking, nightmares, insomnia, and sleep anxiety (Lelis *et al.* 2016). However, it must be appreciated that sleep disturbances can occur in the absence of injury. As discussed previously, impaired brain maturation associated with prematurity can occur independently of injury, and this is associated with impaired neurodevelopment and functional connectivity of the brain (Back, 2017).

In 11-year-old children born very preterm (<28 weeks completed GA, or weighing <1000 g), who had neurodevelopmental disabilities (assessed at 5 years of age), there was a higher percentage of sleep problems compared to term-matched control counterparts (Stangenes *et al.* 2017). The preterm-born infants went to bed earlier, had longer sleep-onset latency, increased night waking, and they slept longer. Sleep differences increased as a function of neurodevelopmental disabilities severity. Notably, however, preterm infants with no reported neurodevelopmental disabilities also had sleep difficulties, which were similar to those reported for their preterm counterparts with neurodevelopmental disabilities (Stangenes *et al.* 2017). Longer nocturnal sleep duration, more night

awakenings, and longer daytime sleep duration was also observed in 6-month-old infants born at an older age (31.5 ± 3.2 weeks GA, 1467 ± 588.6 g, mean±SD) compared to term control infants (Huang *et al.* 2014). The authors of this study did not evaluate neurodevelopmental disabilities, but did note that sleep disturbances were associated with respiratory problems (Huang *et al.* 2014).

We have shown that sleep is disturbed in infants who do not have neurodevelopmental disabilities. We demonstrated that both prematurity and growth restriction (see below for further discussion on growth) are associated with altered micro- and macro-sleep architecture changes indicative of reduced sleep quantity and quality in childhood (Yiallourou *et al.* 2017). Children were studied with overnight polysomnography and the children born preterm had less total sleep time (by 45 min), more wake after sleep onset and lower sleep efficiency, all indicating reduced and more fragmented sleep patterns. Furthermore, the preterm–born children had reduced amounts of NREM sleep (by 40–48 min), in particular N2 stage sleep was significantly shorter compared to children born at term and also those born preterm with fetal growth restriction and a higher proportion of N3 stage sleep. Consistent with these macro-architecture findings, reduced delta and sigma EEG power were recorded, indicting less deep sleep and fewer sleep spindles. Shorter sleep duration and a higher proportion of N3 stage sleep, may reflect compensatory sleep recovery to repay sleep debt that occurs due to poor quality sleep or excessive daytime sleepiness (Yiallourou *et al.* 2017).

In contrast to studies reporting longer sleep durations, several studies report shorter day and night time sleep durations. At 1 year after preterm birth, very low birthweight infants (27.4 ± 2.2 weeks GA, 937 ± 202 g, mean±SD), with no evident neurological injury, slept less during the night compared to full-term infants and had a greater number of night wakings compared to term infants (Asaka & Takada, 2010). In a subsequent study at 1 and 2 years of age that included older preterm infants (28.6 ± 4.0 weeks, 1042 ± 420, mean±SD) the authors only observed a reduction in total duration of sleep (Asaka & Takada, 2013), whether this reflects a greater degree of brain maturation is unclear. In a separate study, prematurely born children (31.1 ± 2.4 weeks GA, 1600.8 ± 501.2 g, mean±SD) studied at 2 years of age were shown to get to sleep more quickly and were earlier to rise, but had increased incidences of night waking and restlessness and breathing problems associated with poor attention, greater negative emotions, and hyperactivity (Caravale *et al.* 2017). In a similar cohort of children, a reduction in sleep duration and quality of sleep was associated with an increased risk of attention deficit hyperactivity disorder (Gossel-Symank *et al.* 2004).

In a combined Australian and Canadian study of older children (5–12 years of age) born preterm (∼27 weeks GA, 942–998 g), sleep measured by actigraphy and by parental assessment showed that these children also had a shorter sleep duration, sleeping on average around 8 h (Biggs *et al.* 2016), with earlier bed and wake times seen in the Australian children. This is in contrast to the recommended sleep durations of 10–13 h for 5-year-olds, 9–11 h for 6–13-year-olds (Biggs *et al.* 2016). Other studies have shown that preterm birth (29.7 ± 1.9 weeks GA, 1302 ± 408.7 g), is associated reduced sleep efficiency with more nocturnal awakenings, more stage 2 sleep, and less NREM sleep (less restorative sleep) in children between 6 and 10 years of age when compared to term-born children (Perkinson-Gloor *et al.* 2015).

In this study, sleep dysfunction was associated with behavioural and emotional problems and lower morning and evening cortisol. An associated study on this cohort of children demonstrated that sleep dysfunction related to impaired cognitive function (Hagmann-von Arx *et al.* 2014). Decreased verbal working memory performance was observed in children 6–9 years of age born preterm (median 28 (range 23–32) weeks GA, 915 (range 470–2360) g (McCann *et al.* 2018). This did not correlate with day time sleepiness, but rather the cognitive restraints of slower processing speed and reduced short-term memory storage capacity. The quality of night-time sleep was also associated with reduced executive function in preterm, but not term children who slept poorly (McCann *et al.* 2018).

Inefficient or shorter sleep is also seen in unwell near-term infants. In term infants (>35 weeks GA) assessed at 18 months of age, who had evidence of hypoxic–ischaemic encephalopathy at birth, sleep was characterised by increased QS with lower EEG delta power (Shellhaas *et al.* 2017). This study also demonstrated that children born preterm had attenuated changes in cerebral fractional tissue oxygen extraction between QS and wakefulness, as measured by near-infrared spectroscopy (Shellhaas *et al.* 2017). The study demonstrated that attenuated differences in fractional tissue oxygen extraction between wake and QS predicted worse cognitive, language, and motor scores at 18 months of age (Shellhaas *et al.* 2017).

It was notable that many studies (from infants to adults) report that individuals born preterm, have phase shifts in their sleep with significantly earlier bed and wake times (Bjorkqvist *et al.* 2014; Hibbs *et al.* 2014; Schwichtenberg *et al.* 2016; Stangenes *et al.* 2017). These studies suggest that chronotype (i.e. early *vs.* late rising) may be programmed early in life. Further, data suggest that preterm infants adopt their circadian 24 h cycle earlier than term counterparts (Guyer *et al.* 2015). These observations in young children are important, as they support the concept that chronotype, which typically manifests in adolescence, has

its origins much earlier in life (Kuula *et al.* 2017). In the longer term, chronotype resetting to become an 'early bird' may be beneficial, as it is associated with better health outcomes, but this can be offset by circadian disruption, for example, shifting sleeping patterns, e.g. normally early risers staying up later, which often occurs in adolescence (Vetter *et al.* 2015).

It should be noted, however, that many behavioural factors can impact on how sleep develops, including the role of parents (Biggs *et al.* 2010). Parents of preterm babies can be stressed by the many health challenges their infants face and are often sleep-deprived themselves (Blomqvist *et al.* 2017). Improved parental sleep and nutrition can improve sleep in their children (Nordheim *et al.* 2016), and their perception of the sleeping patterns of their infants (Blomqvist *et al.* 2017). Inadequate or inappropriate sleep training in infancy and childhood can increase sleep latency and prolonged night waking (sleep-onset association disorder) in children and adolescents (Biggs *et al.* 2016; Owens *et al.* 2016). Sleep-onset association disorder can occur, for example, if parents fail to be consistent with bed-times and if children depend on parental attention to get to sleep, leading to a failure to learn to 'self-soothe' and the requirement of parental attention to return to sleep (Biggs *et al.* 2016; Owens *et al.* 2016). Additionally, sleep impairment is also associated with parent–infant attachments, sleep location, socioeconomic status and cultural factors such as co-sleeping (for review, see Schwichtenberg & Goodlin-Jones, 2010), and with sleep position (as discussed further below in the section on postnatal hypoxia and cardiovascular instability).

In summary, for many infants being born too soon has significant effects on brain development, which is reflected in the development of sleep and in turn associated with neurocognition and behavioural difficulties. These differences persist throughout childhood and there is some evidence that they are still evident in adulthood. Why some preterm children go on to experience relatively normal sleep, while others have impaired sleep is unclear at this time. However, as discussed below, the development of sleep may be compromised by the many morbidities experienced by preterm infants.

Mediators of altered brain and sleep development

Fetal hypoxia. Many infants born preterm are at risk of exposure to general hypoxia, cerebral ischaemia or even both during the perinatal period. The incidence of hypoxic–ischaemic encephalopathy is significantly higher in preterm birth than in full-term infants: 5–9/1000 live births *versus* 1–3/1000 live births at term (Salhab & Perlman, 2005; Logitharajah *et al.* 2009; Chalak *et al.* 2012; Gopagondanahalli *et al.* 2016). In term infants, the acute adaptation (3 days post insult) to a mild-to-moderate HI insult is an increased percentage of QS and IS at the expense of AS (Scher *et al.* 2002).

Complicating our understanding about the role of HI insults in mediating neural injury or impaired neurodevelopment is the fact that, for many infants, significant hypoxia may occur well before birth. Such antenatal insults may contribute to many cases of CP that have their origins in the antenatal not the intrapartum period (Tan, 2014; see also Ellery *et al.* 2018, in this issue). Further, it is important to appreciate that the preterm fetuses of many species, including humans, have cardiac glycogen stores which peak in preterm life, significantly increasing the anaerobic tolerance to HI in terms of survival (for review, see Bennet, 2017). Thus many infants may experience antenatal HI well before birth but survive with injury or impaired brain development to go on to be born at term without further complications. Importantly, current evidence suggests that mild HI may cause greater injury to the immature brain than it does to the term brain. For example, a mild HI insult in postnatal (P) 3 neonatal rats (24–28 weeks GA human brain maturation equivalent) causes compromised cortical growth and selective alteration of cortical myelinated axons with persistent gliosis (Sizonenko *et al.* 2003), and at P7 (30—34 weeks GA human brain equivalent) mild HI leads to delayed cerebral atrophy and infarction many weeks after the insult (Geddes *et al.* 2001). In neonatal mice, intermittent but mild non-ischaemic hypoxia caused evolving non-cystic white matter injury, hypomyelination and sensorimotor deficits (Juliano *et al.* 2015).

In preterm fetal sheep at 0.65–0.7 gestation (28–30 weeks human brain maturation equivalent), transient hypoxia can significantly disrupt maturation of the fetal sub-plate neuron arborisation and activity, and the degree of compromise relates to the level of hypoxia (McClendon *et al.* 2017). Hypoxia and associated neuroinflammation may contribute to impaired brain and neural network development by impairing the maturation of white matter cells during preterm life (Back, 2017; Bennet *et al.* 2017). Consistent with this, acute lesions are not seen in many infants who develop CP, but there is delayed loss of white matter and hypo-myelination (Woodward *et al.* 2006). Currently we lack reliable biomarkers (Bennet *et al.* 2010) to determine whether an insult has occurred *before* birth, and the nature of that insult, and thus the relative contribution of antenatal events in mediating impaired neurodevelopment.

Intrauterine growth restriction and chronic hypoxia. Intrauterine growth restriction (IUGR) is characterised by varying degrees of hypoxia and malnutrition, which can occur at any stage in pregnancy, and is a common precursor of preterm birth (Korzeniewski *et al.* 2017). IUGR

is associated with poor brain growth (Korzeniewski *et al.* 2017) and a recent systematic review demonstrates that IUGR increases the risk of adverse neurodevelopmental outcomes and that this risk increased in children who had preferential redistribution of blood flow to central organs such as the brain (Murray *et al.* 2015). IUGR also impacts on the organisation of sleep states in both infants (Cohen *et al.* 2018) and children (Yiallourou *et al.* 2017). It is difficult to separate the contribution of preterm birth from the effects of impaired growth in this regard, but it is clear that IUGR fetuses have decreased amounts of AS and increased amounts of QS and indeterminate sleep compared to appropriately grown fetuses (Gazzolo *et al.* 1995). This may be an adaptive response by potentially reducing cerebral metabolic demand (Richardson & Bocking, 1998). In a growth restriction fetal sheep model, chronically hypoxic fetuses had a 30% reduction in REM ECOG activity (reflecting AS sleep) compared to age-matched and appropriately grown fetuses (Keen *et al.* 2011).

A decrease in the time spent in AS could potentially have a significant effect on brain maturation, as AS may play a key role in stimulating central nervous system development in the fetus and the neonate (Cirelli & Tononi, 2017). For instance, AS provides endogenous stimulation to sensory processing areas in the central nervous system via fetal movements, breathing movements, sucking, swallowing, yawns, stretches, and eye movements which all characteristically occur in AS (Peirano *et al.* 2003). A rat model of IUGR produced by maternal under-nutrition also found that the offspring, studied at P90–100 days, spent 20% more time in slow-wave sleep (equivalent to N3 in humans) and 61% less time in REM sleep compared to control rats (Datta *et al.* 2000).

The incidence and duration of sleep state transitions was also altered in chronically hypoxic fetuses (Arduini *et al.* 1989; Keen *et al.* 2011). Notably, transition between sleep states takes longer in human IUGR fetuses (Arduini *et al.* 1989). Sleep–wake transitions in preterm infants born small for gestational age (SGA) at ∼31 weeks GA, have some predictive power for neural development (Weisman *et al.* 2011). For example, those infants whose sleep shifted between QS and wakefulness had better neural development and behavioural and cognitive outcomes at 5 years of age, compared to those who cycled between AS and high arousal or between short episodes of AS and QS (Weisman *et al.* 2011).

Only a limited number of studies have investigated the long-term effects of preterm birth and IUGR on sleep in humans. In infants born IUGR, the development of sleep is altered during both the neonatal and post-neonatal periods. Preterm infants born with IUGR have higher amounts of AS compared with age matched preterm infants with appropriate birth weights (Hoppenbrouwers *et al.* 2005). A study of 26 IUGR children and 47 control children aged between 4 and 7 years, using actigraphy to determine sleep–wake patterns, showed that the IUGR children have poorer sleep, defined as lower sleep efficiency, shorter sleep and more awakenings (Leitner *et al.* 2002). In polysomnographic studies, IUGR preterm-born infants demonstrated altered EEG power spectrum maturation compared to age-matched appropriately grown preterm and term infants, with the IUGR preterm infants having less delta power and increased theta, alpha and beta power, reflecting less deep sleep at 1 month term corrected age (Cohen *et al.* 2018). Recent studies in children (aged 7–12 years), which separated the effects of IUGR and preterm birth, found that preterm birth with appropriate-for-gestational-age birth weight had reduced sleep quantity and quality, whereas children born preterm with IUGR had altered sleep micro-architecture as assessed by spectral analysis of EEG patterns, potentially reflecting sleep disruption (Yiallourou *et al.* 2017).

Several recent studies have evaluated the development of neural networks in children (1, 6 and 10 years) born preterm (28–35 weeks GA) with either normal birthweight or IUGR (Fischi-Gomez *et al.* 2016; Munoz-Moreno *et al.* 2016). These studies have shown that children from both preterm groups significantly differ in terms of neural network organisation (as discussed above) to children born at term, but both had a similar brain trajectory, in terms of connectivity, to each other. However, IUGR was associated with a greater reduction in structure and organisation of neural connections between brain regions, and lower neural myelination (Munoz-Moreno *et al.* 2016). This was associated with worse neurocognitive and behavioural outcomes compared to preterm birth alone (Fischi-Gomez *et al.* 2016; Munoz-Moreno *et al.* 2016).

The loss of the placenta and neurotrophic support. As discussed in the section on fetal sleep and wakefulness, the placenta plays a key role in modulating fetal behaviour, in particular by providing steroids that are further metabolised in the fetal brain to suppress activity and induce sleep (Crossley *et al.* 1997; Mellor *et al.* 2005; Brunton *et al.* 2014). By 7 weeks GA, the human placenta becomes the primary source of steroids during pregnancy, with progesterone-dependent immunomodulation important for maintenance of pregnancy (Brunton *et al.* 2014). Placental steroids and those synthesised in the fetal brain are essential for brain development, promoting white matter development and myelination (Brunton *et al.* 2014), and in guinea-pig studies, inhibition of neurosteroids in late gestation is associated with behavioural abnormalities in juveniles after birth (Brunton *et al.* 2014). Placental steroids play a key role in modulating fetal sleep-related behaviour,

both in normoxia (Nicol *et al.* 1997; Yawno *et al.* 2011) and hypoxia (Yawno *et al.* 2011). Neurosteroids are neuroprotective in a variety of species (Brunton *et al.* 2014). For example, in fetal sheep, suppression of the metabolite allopregnanolone, which is synthesised from progesterone, after an HI insult increased brain injury and seizures (Yawno *et al.* 2009). Allopregnanolone increases in the fetal sheep brain during the early phase of recovery from an HI insult which may facilitate endogenous neuroprotection by reducing neural excitation (Nguyen *et al.* 2004; Yawno *et al.* 2009).

Importantly, the expression of the key enzymes for allopregnanolone synthesis 5 α-reductase type 1 and 2, which transforms progesterone into 5α-dihydroprogesterone, increase in the human placenta during the third trimester, suggesting that placental neurosteroid production rises towards term (Brunton *et al.* 2014). This may, in part, help facilitate the gradual switch from an excitatory role for GABA, which promotes development of the neural network (Ben-Ari, 2001), to an inhibitory one, as allopregnanolone has greater affinity for $GABA_A$ receptors containing subunits which permit tonic inhibition of excitation (Brunton *et al.* 2014). Supporting this supposition, a magnetic resonance spectroscopy and fMRI study in human preterm and term infants reports regional neural changes in GABA concentrations after preterm birth that correlated to resting state connectivity and which are consistent with delayed maturation of GABA (Kwon *et al.* 2014).

Thus, preterm birth is associated with a sudden loss of the supply of progesterone needed for allopregnanolone synthesis, which cannot be compensated for after preterm birth in contrast to term birth (Shaw *et al.* 2015). 5 α-reductase type 2 expression is reduced in the brain of growth-restricted fetuses, suggesting that IUGR further limits the capacity for neurosteroid synthesis in the brain following birth (Kelleher *et al.* 2011; for recent review, see Tolcos *et al.* 2017). This potentially leaves the brain vulnerable to injury and impaired neurodevelopment, with consequences for the development of the neural network. The role of *in situ* neurosteroid synthesis in the neonatal brain in determining sleep after preterm birth, with or without growth restriction, deserves further attention.

Postnatal hypoxia and cardiovascular instability. While it is difficult to determine whether mild or intermittent hypoxia has occurred antenatally, it can be clearly observed postnatally. The mild hypoxia seen with conditions such as the apnoea of prematurity and periodic breathing in children born preterm is clearly associated with impaired neurodevelopment (Schmidt *et al.* 2017). This has been confirmed in a recent study in neonatal rats, where intermittent mild hypoxia between P2 and P12 (P12, approximate brain maturation equivalent to neonatal human) caused reduced deposition of myelin and elevated cytokines between P13 and P22 (P22, approximate brain maturation equivalent to an infant around 2 years of age) (Darnall *et al.* 2017). Some preterm infants are at risk of significant cerebral oxygen desaturations as measured by near-infrared spectroscopy, particularly during AS (Decima *et al.* 2015). A longitudinal study of ex-preterm infants showed that short apnoeas and periodic breathing persists, and that falls in cerebral oxygenation were more marked at 2–3 months and 5–6 months than at 2–4 weeks of age (Horne *et al.* 2017*a*). These data suggest that the preterm infant remains at risk of repeated exposure to mild hypoxic events, which may contribute to adverse neurocognitive outcomes (Horne *et al.* 2017*a*).

Adults with OSA have impaired sleep (D'Rozario *et al.* 2017), and this is associated with altered functional connectivity and impaired neural network organisation (Park *et al.* 2016). Sleep patterns are less disrupted by OSA in children than in adults (Yang *et al.* 2010). However, OSA is nevertheless associated with neurocognitive deficits and behavioural difficulties in both pre-school (Jackman *et al.* 2012) and school-aged children (Bourke *et al.* 2011*a*,*b*). Although neuroimaging studies in children with OSA are scarce, changes in brain metabolites, systemic inflammatory responses and reductions in grey matter have been reported (Halbower *et al.* 2006; Gozal *et al.* 2007; Philby *et al.* 2017). fMRI studies suggest that children with OSA had *greater* neuronal recruitment in brain regions associated with cognitive control, conflict monitoring, and attentional allocation (Kheirandish-Gozal *et al.* 2014). Children with severe OSA, who exhibited impaired attention and visual-fine motor coordination, showed reduced regional grey matter volumes (Chan *et al.* 2014; Philby *et al.* 2017). Diffusion tensor imaging studies have identified that both chronic and acute changes occur, indicating that both short-term and long-lasting processes are operating in children with OSA, probably resulting from a combination of ischaemic and hypoxic mechanisms associated with the syndrome (Horne *et al.* 2017*b*). Preterm-born children are 3–5 times more likely to be diagnosed with OSA than those children born at term (Rosen *et al.* 2003). However, it is yet to be elucidated if the repetitive hypoxia and sleep disruption associated with persistent apnoea and OSA in children born preterm is associated with behavioural and neurocognitive deficits that are prevalent in this population.

In addition to respiratory complications, infants born preterm are at risk of cardiovascular instability (Bennet *et al.* 2012), which during infancy is most marked during sleep (Gaultier, 1995). Altered haemodynamic control has implications for brain oxygenation and metabolism, with consequent effects on brain maturation. Preterm infants have impaired autonomic control compared with term infants studied at or before term equivalent age

(Reulecke *et al.* 2012; Thiriez *et al.* 2015; Yiallourou *et al.* 2017), which can be sustained in nature (Patural *et al.* 2008). Longitudinal studies after term equivalent age have identified that preterm infants exhibited lower blood pressure, delayed blood pressure recovery following head-up tilting and impaired baroreflex control of blood pressure and heart rate across the first 6 months corrected age, when compared with age-matched term infants (Witcombe *et al.* 2012; Yiallourou *et al.* 2013; Fyfe *et al.* 2015*a*,*b*). Further, preterm infants (<32 weeks GA) have reduced baroreflex control of blood pressure compared to term infants (Fyfe *et al.* 2015*c*).

Sleep position has a significant impact on sleep in infants. In term infants, sleeping on the tummy or in the prone position decreases arousability from both AS and QS at both 2–3 weeks and 2–3 months of age (Horne *et al.* 2001). Furthermore, the nature of the arousal response is altered by sleep position, with more cortical arousals and fewer subcortical arousals when term infants slept prone at 2–3 months of age. This age coincides with the peak incidence for sudden infant death syndrome (SIDS) and prone sleeping is the major risk factor for SIDS. The authors suggested that increased cortical arousals in healthy term infants was a protective response which may be reduced in those infants who died from SIDS (Richardson *et al.* 2008). Preterm infants are at increased risk for SIDS and when slept prone had increased cortical arousals across the first 6 months after term equivalents age in both AS and QS (Richardson & Horne, 2013). When arousal responses were compared between term and preterm infants, preterm infants had significantly fewer cortical arousals in QS when prone at 2–3 months of age and more cortical arousals when prone at 2–4 weeks in AS. There were no differences in either sleep state when infants slept supine (Richardson & Horne, 2013). Thus, in preterm infants increased cortical arousals maybe protective against the prone sleeping position.

Recently, studies have identified that cerebral oxygenation is also lower in preterm compared to term infants across the first 6 months corrected age when infants slept prone (Fyfe *et al.* 2014), and that cerebrovascular control after a head-up tilt was more variable (Fyfe *et al.* 2015*c*), indicating immature or impaired autonomic control. Thus, persistent immature cardiovascular and cerebrovascular control in infants born preterm may further compound the effects of any hypoxic insults that occur with the frequent respiratory disturbances in this population. This additive insult further contributes to impaired brain development and adverse neurodevelopmental outcomes.

Inflammation. Immune factors, such as interleukin-1 beta (IL1) and tumour necrosis factor alpha (TNFα), play a regulatory role in sleep homeostasis (Clinton *et al.* 2011). Both central and peripheral immune cells express circadian clock genes which regulate the circadian oscillations in the synthesis and release of pro- and anti-inflammatory factors (Curtis *et al.* 2014; Labrecque & Cermakian, 2015). The circadian sensitivity of our immune cells can be seen during exposure to the inflammatory mediator lipopolysaccharide, a component of the outer membrane of Gram-negative bacteria. Alamili *et al.* (2014) demonstrated, for example, that lipopolysaccharide given during the day stimulated release of anti-inflammatory cytokines, while night time exposure promoted release of pro-inflammatory cytokines. Chronodisruption, such as sleep deprivation or broken sleep can cause immune compromise (Curtis *et al.* 2014; Labrecque & Cermakian, 2015). Inflammation can independently shift the timing of the circadian clock, alter clock gene expression and increases suprachiasmatic nucleus cytokine release, (Curtis *et al.* 2014; Labrecque & Cermakian, 2015). In adults, chronic inflammatory conditions such as diabetes are associated with white matter lesions, altered neural network functional connectivity, and altered sleep patterns including an increased propensity for QS (Mullington *et al.* 2010; Hoogenboom *et al.* 2014; Ramos *et al.* 2014).

The preterm fetus and newborn is at significant risk of exposure to inflammation. The inflammatory condition of chorioamnionitis, for example, complicates nearly all preterm births before 24 weeks and a quarter to a third of births before 34 weeks GA (Hagberg *et al.* 2015; Bennet *et al.* 2017), and inflammation may persist well beyond birth (for recent review, see Bennet *et al.* 2017). The Extremely Low Gestational Age Newborns study has shown that circulating levels of pro-inflammatory cytokines can be elevated for the first month of life after preterm birth and this correlates with adverse neurological outcomes in children at 10 years of age (Kuban *et al.* 2017; Yanni *et al.* 2017). Inflammation, and hypersensitisation to inflammation, may persist for even longer as demonstrated by Lin and colleagues in preterm children with white matter-induced CP (Lin *et al.* 2010).

Markers for inflammation, such as C-reactive protein and cytokines, are elevated in children born preterm who have conditions such as OSA, particularly in children who go on to have neurocognitive disorders (Gozal *et al.* 2007). Similar to the cardiovascular and systemic inflammation seen in adults, a recent report in children studied at 9–10 years of age born full-term has shown that primary snoring and sleep disordered breathing is associated with higher ascending aorta peak systolic blood flow velocity (indicating altered vascular function) and systemic levels of cytotoxic T cell lymphocytes producing tumour necrosis factor alpha and T cell interferon gamma compared to that seen in non-snoring children (Kontos *et al.* 2017). Inflammation is likely to be a persistent occurrence in preterm children who have a greater risk

of sleep-disordered breathing, and potentially this is a significant contributor the increased risk for adverse neurodevelopmental outcomes.

Conclusions and perspectives

In summary, our review has demonstrated that many infants born preterm go on to have altered sleep patterns throughout life characterised by reduced sleep efficiency and quality of sleep. It is of note that there is variability between reports, for example, some studies suggest shorter sleep, while others have observed longer sleep durations. Further, not all studies found an effect of prematurity on the development or quality of sleep. What is clear is that considerable further work is needed in this area, with more consistent methodologies. We suggest that it would be of value for future studies to include assessment of the brain for injury, along with measures of neurodevelopmental disabilities. Standardised use of direct measures of sleep/behaviour in addition to parental reporting would help address potential issues related to the stress parents have when caring for preterm children that have been raised in some studies. For example, do preterm children go to sleep earlier (does prematurity set the chronotype of early rising?), or do parents who are sleep-deprived themselves institute earlier bedtimes? Do preterm children wake frequently at night, or do parents of preterm children check up on them more frequently given the increased health issues these children have (e.g. respiratory complications)? It would also be of value to more tightly define the preterm age range studied to address the question of the impact of specific stages of brain maturation has on subsequent sleep development. There is also a need to consider the age of term control subjects, given that data now to show that very late-preterms, i.e. those within a few weeks of normal GA birth, are also at risk of impaired neurodevelopment, which may affect sleep (Brumbaugh *et al.* 2016).

Our review has highlighted several mediators which may contribute to the variable findings on the effect of prematurity on sleep development, including the degree of prematurity, growth restriction, neural injury and/or impaired neural maturation, sleep disordered breathing, and systemic inflammation which may be chronic in nature. Many of these factors will occur in combination or be additive, and they will produce self-reinforcing feedback loops. For example, perinatal inflammation leading to impaired neural maturation may predispose to impaired sleep function and sleep disordered breathing, which in turn mediates further inflammation, which then in turn impacts upon ongoing neural maturation. We recognise that we have not addressed many other influential factors such as the role of sexual dimorphism in sleep regulation (Mong & Cusmano, 2016). However, an important consideration arising from the material reviewed above is that preterm babies may need to be cared for until term-equivalent age under conditions that reproduce, or at least endeavour to replace, the hormonal conditions present *in utero* (for reviews, see Brunton *et al.* 2014; Hirst *et al.* 2014).

As discussed at the start of this review, sleep is vital for optimal neurocognitive function, and impaired sleep is a risk factor for many diseases. Being born prematurely alters how the brain develops, and is associated with increased risks of significant health issues throughout life (Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007). Our review demonstrates that impaired sleep from infancy to adulthood may be contributory to these risks. Significant research is now needed to determine specific factors related to prematurity, and their timing, which influence sleep development in order to facilitate the development of timely interventions and treatment strategies that will promote better sleep throughout life.

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Additional information section

Competing interests

The authors declare no competing financial interests.

Author contributions

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