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When do Mammalian Young Become Sentient?

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Summary

Published literature and studies from our laboratory show that neurological development in mammalian young at birth ranged from being exceptionally immature (e.g. newborn marsupials), through moderately immature (e.g. newborn cats, dogs, mice, rabbits, rats) to mature (newborn cattle, deer, goats, sheep, horses, pigs, guinea-pigs). In all cases, brain electrical activity indicates that under normal circumstances none of these young exhibit consciousness before birth. This is the case with exceptionally and moderately immature young because their neurological development is not adequate to support consciousness until several months and several days, respectively, after birth. Neurologically mature newborns do have the neurological capacity for consciousness before birth, but this is usually prevented by the operation of a number of neuroinhibitory mechanisms that are unique to fetal life. After birth these newborns exhibit consciousness within minutes or hours. The evidence for this and the implications for safeguarding the welfare of fetuses and newborns of these different mammals in experimental settings are discussed.

Keywords: fetus, newborn, neurological development, unconsciousness

1 Introduction

Animals considered to be sentient have the ability to experience positive and negative affective states or feelings (Duncan, 2006). These feelings arise via the operation of sensory mechanisms that scan the internal functional state of the animal and its external environment. *Internally-focused* sensory activity contributes to the brain processing that gives rise to a number of experiences including thirst, hunger, breathlessness, pain, nausea, sickness and malaise, and informs the brain when the conditions underlying those feelings are absent; at the same time, *externally stimulated* neural inputs contribute to affective experiences mediated by the sensory modalities of sight, hearing, smell, taste, touch, thermal comfort and others (Dawkins, 2006; Kirkwood, 2006; Mellor et al., 2009a). Although it is philosophically and scientifically problematic to demonstrate unequivocally that higher-order non-human animals do in fact experience such feelings (Dawkins, 2006; Duncan, 2006), for most practical purposes we interact with them as if they do (Dawkins, 2006; Mellor et al., 2009a). Moreover, a presumption

of the existence of sentience among higher-order animals generates strong motivation to treat them humanely. This is especially so now that the welfare status of animals is widely understood to reflect the integrated balance between all sensory inputs to the animal's brain that are cognitively processed and emotionally experienced as feelings (Mellor et al., 2009a).

Sentience, therefore, requires the presence of a nervous system that is functionally sophisticated enough to enable the animal to cognitively and emotionally experience its status (its welfare) as good, neutral or bad. This capacity is cautiously attributed to most vertebrates and some invertebrates (Kirkwood and Hubrecht, 2001; Duncan, 2006; Kirkwood, 2006), but perhaps especially to mammals and birds. Allied to sentience, of course, is the requirement that the nervous system be in a state of consciousness, because unconscious animals cannot experience anything (Baars, 2001; Mellor and Diesch, 2006; Boveroux et al., 2008).

In addition to this linkage between the phylogenetic status vis-à-vis brain sophistication of a species and its capacity for sentience and consciousness, it is evident that within those spe-



cies that exhibit these attributes as adults, the first appearance of the capacity for sentience and consciousness also depends on the pattern of neurological development during the early stages of each animal's life cycle (Mellor and Diesch, 2006, 2007). The developmental stages when young of different species first exhibit this capacity are therefore of interest, especially when considering safeguards to be applied during their use in scientific and other procedures that would have negative welfare impacts were they conscious adults. Resolution of this question bears directly on when and how necessary, or safe, it is to employ *refinement strategies* such as the use of anaesthetics or analgesics in developing fetal, newborn and young mammals. We have drawn attention to these issues elsewhere (Diesch et al., 2008, 2009; Mellor et al., 2008). It also bears on the legal definition of an animal framed in animal welfare terms, as discussed elsewhere in these proceedings (Mellor et al., 2010).

The present paper updates understanding of the science underlying the conclusion that consciousness, and therefore the capacity to experience noxious sensations, does not appear until after birth in any mammal examined to date, and that the timing of the onset of consciousness after birth depends on the degree of neurological maturity of the newborn in each species (Mellor et al., 2009b). For the sake of brevity, review articles that fully reference the relevant scientific literature have been used here together with pertinent additional publications.

2 The developmental pattern of brain electrical activity is similar across species

Brain electrical activity, as reflected in the electroencephalogram (EEG), shows distinct patterns during waking consciousness and during the unconsciousness of sleep, general anaesthesia, coma and epileptic "states of absence" (Baars, 2001; Bovereau et al., 2008). On this basis the first appearance of spontaneous EEG activity and the different EEG patterns observed subsequently have been used cautiously to infer when the brain exhibits states of unconsciousness and when consciousness may first appear during neurological development (Mellor and Gregory, 2003; Lee et al., 2005; Mellor et al., 2005, 2009b).

The development of EEG activity appears to follow a similar pattern in all mammalian young examined to date (Ellingson and Rose, 1970; Walker and Berger, 1978; Snead and Stephens, 1983; Mellor et al., 2005; Brusseau and Mashour, 2007). For descriptive convenience this pattern can be divided into six stages categorised as follows:

- Stage 1: the EEG is absent, isoelectric or "silent";
- Stage 2: a predominance of electrical "silence" is punctuated by very short epochs of low voltage EEG activity;
- Stage 3: prolonged periods of electrical "silence" are punctuated by epochs of more sustained low voltage EEG activity that progressively increase in duration;
- Stage 4: continuous "mixed" EEG activity containing elements of both rapid-eye-movement (REM) and non-REM sleep-like patterns is present;

Stage 5: continuous EEG activity is differentiated into distinct REM and non-REM patterns with regular cycling between the two states;

Stage 6: sleep-wake cycles, where the EEG and behaviour indicate that periods of sleep alternate with periods of conscious wakefulness, are present.

Progression through these stages is presumed to reflect increasing degrees of functional and structural maturation of the brain (Mellor et al., 2005; Brusseau and Mashour, 2007; Diesch et al., 2009) and is paralleled by increasingly precise control and coordination of movements of the trunk, head, limbs and other body parts (Bolles and Woods, 1964; Tyndale-Biscoe and Janssens, 1988; Mellor and Gregory, 2003). Nevertheless, the characteristics of the EEG suggest that the brain remains in unconscious states throughout stages 1 to 5. Moreover, there is a temporal association between differentiation of REM-non-REM EEG patterns at stage 5 and the establishment of neural connections between the cerebral cortex and underlying brain structures including the thalamus (Ellingson and Rose, 1970; Lee et al., 2005; Mellor et al., 2005; Brusseau and Mashour, 2007). In light of the important functional roles attributed to cortico-thalamic connections in physiologically, pharmacologically and pathologically induced transitions between consciousness and different states of unconsciousness (Evans, 2003; Bovereau et al., 2008) and evidence for the absence of consciousness in prematurely born infants before the establishment of these neural connections (Lee et al., 2005; Mellor et al., 2005), their appearance during brain development is considered to be a prerequisite for the capacity of young animals to exhibit consciousness (Mellor et al., 2009b). According to this reasoning, therefore, unconscious states would persist until the end of the period of differentiated REM-non-REM patterns at stage 5.

3 Neurological maturity of young at birth varies widely between species

Although the general pattern of neurological development, judged in these terms, appears to be common to many mammals, the stage when birth occurs during this developmental path depends on the species and obviously determines the neurological maturity of the young at that time (Ellingson and Rose, 1970; Tyndale-Biscoe and Janssens, 1988; Mellor et al., 2005; Mellor and Diesch, 2006). This may be illustrated by comparing mammalian young that are neurologically exceptionally immature, moderately immature or mature at birth.

3.1 Neurologically exceptionally immature young

Newborn marsupial joeys fall into this category and, as indicated below, would have electrically "silent" EEGs (stage 1). On this basis, joeys would have no capacity to consciously experience any sensations before, during and for some period after birth.

The tamar wallaby joey (*Macropus eugenii*), which is born after a 28-day pregnancy, has a cerebral cortex that consists of only two layers of cells and resembles that of a 40-

day human or 26-day sheep embryo (Reynolds et al., 1985). After entering the pouch the individual joey remains continuously attached to a teat for about 100 days, and intermittently thereafter, leaving the pouch permanently after approximately 250 days (Tyndale-Biscoe and Janssens, 1988). The EEG of anaesthetised joeys remains isoelectric (stage 1) until about 120 days, after which it develops progressively (through stages 2 and 3) to become continuous by 150-160 days (stage 4) (Diesch et al., 2008, 2010). Anaesthesia precludes observation of differentiated REM-non-REM EEG patterns (stage 5) and also sleep-wake EEG cycles (stage 6). However, opening of the external ear canals at 125-130 days and eye-opening at about 140 days (Hill et al., 1998), and the presence of behavioural signs such as the joey standing unaided by about 160 days, beginning to look out of the pouch at about 180 days and first exiting the pouch at about 190 days (Tyndale-Biscoe and Janssens, 1988), together suggest that the capacity for conscious perception of auditory, visual, tactile, proprioceptive and other sensations would appear in tammar joeys at around 160-180 days. Finally, EEG responses of anaesthetised joeys to noxious stimulation (toe clamping) are consistent with this suggestion, as there was no response at 94-127 days, a minimal response at 142-181 days and a marked response at 187-261 days (Diesch et al., 2010).

Virginia opossum joeys (*Didelphis virginiana*), born after a 13-day pregnancy, enter the pouch where up to 13 of them attach to teats (McManus, 1974). They remain attached to a teat continuously for 55-65 days, then intermittently until 70-90 days, after which they leave the pouch and ride on the mother's back until weaned at 100-110 days (McManus, 1974; Krause and Saunders, 1994; Darlington et al., 1999). The EEG of non-anaesthetised opossum joeys remains mostly electrically "silent" (stage 1) before about 60 days, after which continuous low voltage activity begins to appear (progressing from stage 2 to 4), with early signs of non-REM activity evident by about 65 days and REM-non-REM differentiation (stage 5) by about 75 days (Walker and Berger, 1978). The behaviour of joeys suggests that sleep-wake EEG cycles (stage 6) would appear soon after this. Overall, these behavioural and EEG observations together suggest that opossum joeys would have a well developed capacity for conscious perception around 70-90 days after birth, presumably with the earliest evidence of consciousness occurring before this.

It follows that the earliest postnatal appearance of sentience and consciousness, estimated by reference to EEG patterns, behaviour and/or responses to noxious stimulation, is likely at about 4-5 months in tammar wallaby joeys and about 2 months in Virginia opossum joeys.

3.2 Neurologically moderately immature young

Newborn rat and mouse pups, rabbit kits, kittens and puppies fall into this category. Immediately after birth they exhibit isoelectric, intermittent or continuous but undifferentiated EEGs (stages 1-4), and thereafter it takes several days for REM-non-REM differentiation (stage 5) to occur and sleep-wake cycles (stage 6) to become established (Ellingson and Rose, 1970;

Jouvet-Monier et al., 1970; Snead and Stephens, 1983; Daszuta and Gambarelli, 1985).

In rat pups, for instance, EEG stages 2-4 are evident at 5-7 days after birth, the transitions to stage 5, and then to stage 6, begin around 10-12 days and are complete by about 18 days, and adult EEG patterns appear around 18-20 days after birth (Diesch et al., 2009). Pup behaviour develops over the same period (Bolles and Woods, 1964). Pups aged 5-7 days huddle with littermates, suck from their mother, crawl, stretch, yawn and show rudimentary grooming. At 9-10 days, walking, cage exploration and orientation away from the mother and nest appear, and by days 12-13 these activities become more vigorous or prolonged. Increased attention to objects follows eye opening at about 14 days, with the first obvious awareness of the investigator occurring at about 19 days. At 17-20 days, pups are often physically active with fighting between littermates common. Finally, when pups are weaned at 21 days by removal of the mother their physical activity decreases for about one day. These observations together suggest that conscious perception by rat pups is not likely before about 10-12 days of age. EEG responses of anaesthetised pups to noxious stimulation (tail clamping) are consistent with this suggestion, as there was no response at 5-7 days, a marginal response at 12-14 days and a marked response at 21-22 days (Diesch et al., 2009).

If it is conservatively assumed that conscious perception cannot occur any earlier than the postnatal age when stage 5 REM-non-REM differentiation *first* appears, bearing in mind that stage 5 EEGs indicate physiological states of unconsciousness (Baars, 2001; Bovereau et al., 2008), then the published evidence suggests that conscious experience of sensory inputs is likely to occur postnatally only after about 4 days in rabbit kits, 7 days in kittens, 10-12 days in rat and mouse pups, and, perhaps depending on the breed, 4-14 days in puppies (Ellingson and Rose, 1970; Jouvet-Monier et al., 1970; Snead and Stephens, 1983; Daszuta and Gambarelli, 1985).

3.3 Neurologically mature young

Newborn calves, fawns, kids, lambs, foals, piglets and guinea-pig pups, and indeed human infants, are included in this category on the basis of neuroanatomical, neurophysiological and behavioural evidence (Ellingson and Rose, 1970; Jouvet-Monier et al., 1970; Mellor and Gregory, 2003; Mellor and Stafford, 2004; Lee et al., 2005; Mellor et al., 2005; Mellor and Diesch, 2006; Brusseau and Mashour, 2007). They pass through the first five EEG stages before birth, reaching stage 5 (REM-non-REM pattern differentiation) about 75-80% of the way through pregnancy at around the time the critical corticothalamic connections are established. As noted above, human infants born prematurely after about 30 weeks of the 40-week pregnancy exhibit increasing behavioural and EEG evidence of conscious perception (Lee et al., 2005), yet in fetal lambs before or during labour, whether premature or not, there are no signs of stage 6 sleep-wake EEG cycles (Rigatto et al., 1986; Mellor et al., 2005; Mellor and Diesch, 2006). Moreover, noxious stimuli that arouse sleeping newborns to conscious wakefulness are not similarly effective in fetuses during stage 4 or 5



sleep-like states of unconsciousness (Mellor et al., 2005). Evidently, therefore, neurologically mature fetuses develop the capacity for sentience and consciousness during late pregnancy, but remain in unconscious states throughout. This is attributed to a unique set of neuroinhibitory factors, with demonstrated effects on the fetal EEG, that function *in utero* to maintain fetal unconsciousness (Mellor et al., 2005; Mellor and Diesch, 2006, 2007). These neuroinhibitors, whose actions have been described in detail elsewhere (Mellor et al., 2005), include adenosine (a potent promoter of sleep and/or unconsciousness), allopregnanolone and pregnanolone (neuroactive steroids with well-established anaesthetic, sedative/hypnotic and analgesic effects, synthesised by the fetal brain), prostaglandin D₂ (a potent sleep-inducing agent synthesised by the fetal brain) and a placental peptide neuroinhibitor, as well as warmth, cushioned tactile stimulation and buoyancy.

Maintaining the fetus in unconscious states may help to ensure an adequate supply of oxygen to its brain. The fetus has no control over the restricted supply of oxygen it receives across the placenta (Mellor and Diesch, 2007), yet its brain in particular is vulnerable to oxygen shortages (Hunter et al., 2003a). Limiting its cerebral oxygen consumption would therefore be beneficial. In adult humans, high cerebral oxygen consumption during consciousness is reduced during sleep, being about 40% and 10% lower during non-REM and REM sleep, respectively (Boveaux et al., 2008). It follows that the observed presence of sleep-like states in the fetus (Mellor et al., 2005) may reduce its brain requirements for oxygen. There is evidence from fetal sheep to support this: the mean cerebral oxygen consumption is about 80% lower in immature than in mature fetuses (Gleason et al., 1989), and in mature fetuses the mean value is about 40% lower than in the newborn and about 25% lower than in the adult (Rosenberg et al., 1982); also, the mean consumption is about 17% lower during non-REM than REM sleep-like states in mature fetuses (Richardson et al., 1985). Furthermore, oxygen-sparing changes occur in the fetus in apparent preparation for labour, during which oxygen supply may become compromised by uterine contractions. These changes include an increasing incidence of the non-REM EEG state and fetal motor systems becoming largely quiescent (see Mellor and Diesch, 2006). Finally, there is an emergency response mechanism. It ensures that complete occlusion of the umbilical cord during individual labour contractions would lead to an isoelectric EEG within 60-90 seconds (Mallard et al., 1992; Bennet et al., 1999; Hunter et al., 2003b) and to an associated reduction in cerebrocortical oxygen consumption by at least 95% (Hunter et al., 2003a). Although both the EEG and cerebral oxygen consumption would usually return to normal once the contraction-induced cord occlusion has passed, protracted marked oxygen shortages lead to brain damage (Hunter et al., 2003b).

It appears, therefore, that although neurologically mature young develop the capacity for sentience before birth, they remain unconscious while *in utero*, and consciousness first appears only after birth. This occurs through an immediate or progressive postnatal withdrawal of the *in utero* neuroinhibitors noted

above, combined with a progressive onset or marked surge in stimulation from a set of potent neuroactivators that includes 17 β -oestradiol, noradrenaline, cold exposure, contact with hard surfaces, and auditory, visual and other sensory inputs. Detailed descriptions of the proposed mechanisms have been provided elsewhere (Mellor and Gregory, 2003; Mellor and Diesch, 2006; Mellor et al., 2009b). Critical to the appearance of consciousness after birth, however, is the rapid and successful onset of breathing. This oxygenates brain tissue to well above the highest levels ever achieved before birth, and this, in its turn, is considered to remove an overriding adenosine-induced inhibition of cerebrocortical activity, thereby “permitting” the neuroactivators to act. The result, as assessed behaviourally, is the onset of consciousness over minutes or hours (Mellor and Stafford, 2004; Mellor et al., 2009b).

Interestingly, during the first few days after birth, a persistent, but reduced and decreasing brain synthesis of the previously mentioned “fetal” neuroactive steroids having anaesthetic, sedative/hypnotic and analgesic actions (Mellor and Diesch, 2006; T. J. Diesch, D. J. Mellor, C. B. Johnson and D. W. Walker, unpublished observations) may reduce the newborn’s experience of pain due to compression-induced or other birth injuries. Any such analgesic effects are likely to be highest immediately after birth and then wane as the circulating concentrations of these steroids decrease. Consistent with this are lower EEG responses to noxious stimulation (castration) in anaesthetised lambs during the first 1-3 days after birth compared to those of older lambs (Johnson et al., 2009).

4 Concluding remarks

The observations made above are fresh insights derived from recent integrative syntheses of well-demonstrated, yet not well-known, findings in the scientific literature. Although the literature provides a compelling case for persistent unconsciousness before birth, even in neurologically mature fetuses, this proposition is contrary to views held by some biomedical scientists working in the field of fetal pain management (e.g. Anand, 2006, 2007) and contradicts the speculation that brain stem processes are capable of supporting some forms of consciousness (Merker, 2007). Accordingly, a major purpose of presenting this alternative view, together with a summary of the supporting scientific evidence, is to stimulate others to challenge them experimentally. If the present conclusions survive such challenges, they may be adopted more widely. Regardless of the outcome, the evidence presented already exists in the scientific literature and needs to be assimilated into our understanding of developmental processes in mammalian young before and after birth.

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