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Biomechanical studies in an ovine model of non-accidental head injury

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ABSTRACT

This paper presents the head kinematics of a novel ovine model of non-accidental head injury (NAHI) that consists only of a naturalistic oscillating insult. Nine, 7-to-10-day-old anesthetized and ventilated lambs were subjected to manual shaking. Two six-axis motion sensors tracked the position of the head and torso, and a triaxial accelerometer measured head acceleration. Animals experienced 10 episodes of shaking over 30 min, and then remained under anesthesia for 6 h until killed by perfusion fixation of the brain. Each shaking episode lasted for 20 s resulting in about 40 cycles per episode. Each cycle typically consisted of three impulsive events that corresponded to specific phases of the head's motion; the most substantial of these were interactions typically with the lamb's own torso, and these generated accelerations of 30–70 g. Impulsive loading was not considered severe. Other kinematic parameters recorded included estimates of head power transfer, head–torso flexion, and rate of flexion. Several styles of shaking were also identified across episodes and subjects. Axonal injury, neuronal reaction and albumin extravasation were widely distributed in the hemispheric white matter, brainstem and at the craniocervical junction and to a much greater magnitude in lower body weight lambs that died. This is the first biomechanical description of a large animal model of NAHI in which repetitive naturalistic insults were applied, and that reproduced a spectrum of injury associated with NAHI.

1. Introduction

While non-accidental head injury (NAHI; or "shaken baby syndrome") is an important cause of death and severe neurological dysfunction in children under three years of age, the majority of cases occurring in the first 12 months of age, its pathogenesis and biomechanics are incompletely understood (Blumbergs et al., 2008). Early reports recognized subdural hemorrhage, retinal hemorrhages, and long bone fractures as being suggestive of inflicted head injury in infants and young children (Caffey, 1972, 1974). However, this concept has now evolved into a constellation of lesions (acute encephalopathy, and subdural and retinal hemorrhages) referred to as NAHI (Blumbergs et al., 2008; Krugman et al., 1993). In NAHI, death occurs in 10–40% of cases and many survivors are left with cognitive and behavioral disturbances, cerebral palsy, blindness and epilepsy (Blumbergs et al., 2008).

Many aspects of NAHI remain controversial and intermittently undergo revision (Donohoe, 2003) including whether shaking alone is sufficient to injure the brain or whether an additional head impact is required. This is due, in part, to varying mechanisms of brain injury between individual cases (Bandak, 2005) usually lack of a reliable history of the circumstances surrounding the suspected abuse (Leestma, 2005) and frequently denial of maltreatment by the perpetrator. Moreover, the absence of any external evidence of TBI does not necessarily preclude a diagnosis of NAHI and the lesions found in such cases are not pathognomonic (Blumbergs et al., 2008).

Very few animal models have been developed to study the biomechanics of NAHI and extrapolation of data from adult models to the pediatric population is frequently inaccurate (Gerber and Coffman, 2007; Margulies and Coats, 2010).

There have been several studies of NAHI in laboratory rodents (Bonnier et al., 2004; Smith et al., 1998), but the small, lissencephalic brain of these species does not satisfactorily replicate real-world human NAHI; the smooth lissencephalic brain surface may resist deformation after a traumatic insult more than brains possessing gyri, and since shearing forces and inertial loading are related to brain mass, small rodent brains can tolerate much greater angular acceleration forces than animals with larger gyrencephalic brains (Margulies and Coats, 2010).

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We recently developed an ovine model of NAHI (Finnie et al., 2010, 2012). This species was selected because lambs have a relatively large, gyrencephalic brain and weak neck muscles resembling that of human infants. This study proved that manual shaking of a younger, lighter body weight subset of lambs could result in death, without an additional head impact being required (Finnie et al., 2012). Neuropathological examination of these lambs revealed mild, focal macroscopic subdural hemorrhage in three of nine shaken animals (the dura was not examined histologically) and, sometimes, microscopic subarachnoid hemorrhage. Axonal injury, neuronal reaction, and albumin extravasation was widely distributed in the brain and cervical spinal cord and of much greater magnitude than higher body weight shaken lambs that did not die. The eyes of shaken lambs showed damage to retinal inner nuclear layer neurons, mild, patchy ganglion cell axonal injury, widespread Muller glial cell reaction, and uveal albumin extravasation. It was suggested that mechanical deformation of the brain, rostral spinal cord and eyes was probably largely responsible for the observed pathology (Finnie et al., 2012). Pathological data has been reported previously and is summarized in Table 1.

This paper describes the biomechanical events that produced the reported neuropathological findings in this ovine model (Finnie et al., 2010, 2012). The objective of this study is to characterize the kinematics of lamb heads during shaking episodes, together with some general characterization of the relative motion of the head to the body.

2. Materials and methods

2.1. Experimental protocol

Nine anesthetized and ventilated lambs were manually grasped under the axilla and vigorously shaken for 20 s with sufficient force to move the head rapidly back and forth, similar to head motions believed to occur in human NAHI. There was no intentional head impact and the head moved freely during each episode. Each lamb was shaken in this manner 10 times over a 30-min period and then placed quietly in the sphinx position for 6 h under anesthesia. Four control lambs were not shaken, but were otherwise subjected to the same experimental protocol. Lambs were maintained under anesthesia for the full duration of the experiment, without ever regaining consciousness, until killed by perfusion fixation of the brain (Finnie et al., 2010, 2012).

The experimental protocol complied with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (National Health and Medical Research Council, 2013) and was approved by Animal Ethics Committees of the University of Adelaide and SA Pathology.

2.2. Biomechanical analysis

The acceleration of the head was acquired at 20,000 Hz using an 8 g triaxial accelerometer (Endevco©). The position and orientation of the head and torso were registered using the FASTRAK© system (Polhemus©): two 9.1 g motion sensors were used. The triaxial accelerometer and one motion sensor were mounted on the skull using plastic supports mounted in epoxy putty. A second motion sensor was sutured under the axilla of the right forelimb in order to measure the motion of the torso. This sensor was held under the hand of the operator during each shaking episode.

The position of the accelerometer and the head motion sensor was registered in an anatomical coordinate frame using a three-dimensional coordinate measuring arm. Sensor data were transformed into this consistent anatomical coordinate frame.

2.3. Signal processing

Acceleration and FASTRAK were synchronized using cross-correlation between the sensor data. The acceleration data could therefore be located both in time and in space, in order to determine which phases of the shaking motion high accelerations were occurring. Acceleration data were filtered forward and in reverse using a 500 Hz 8th order Chebychev digital filter, post-acquisition.

Severity was characterized by peak levels of head acceleration and the power transfer to and from the head. The Head Injury Criterion used in impact testing is similar to a power calculation (Hutchinson et al., 1998), and more than one power criterion has been proposed in the past (Neal-Sturgess, 2002; Newman et al., 2000). Power was estimated by taking the scalar product of the head acceleration vector and the head velocity vector; the power was expressed in the units of W/kg.

2.4. Brain injury evaluation

Full details of neuropathological findings may be found in Finnie et al. (2010, 2012) and are briefly highlighted in Section 1 of this paper and Table 1. A particular focus was on the amount of axonal and neuronal damage revealed by immunohistochemistry.

3. Results

3.1. Head kinematics—displacement

Three individuals manually shook animals over the course of the experimental series. Each animal was shaken at a frequency of about 2 Hz resulting in approximately 40 cycles per episode and about 400 per animal. The shaking input occurred generally in the sagittal plane. The motion of the axilla position sensor (at the hand of the shaker) was generally anterior–posterior, although there was cranial–caudal (vertical) displacement in some episodes. In response, the center of gravity of the head typically moved within or about the anterior–posterior plane of the animal.

Trajectories are shown below and in supplementary animated figures that are available electronically. Fig. 1 shows the trajectory of the head motion sensor and the axilla sensor in the laboratory space in the fourth shaking episode of Subject 3. The motion of the axilla sensor was cranial–caudal and anterior–posterior. In response, the head was propelled away from the shaker until it reached the lowest point in the laboratory space, after which the head rose vertically, closer to the shaker. An animation of this trajectory is shown in three orthogonal views in Supplementary Fig. S1.

Supplementary material related to this article can be found online at http://dx.doi.org/10.1016/j.jbiomech.2014.06.002.

The position of the axilla sensor represents the position of the torso of the subject and can be used to locate the head relative to the body (Fig. 2). In most episodes, this relative motion of the head was “C”-shaped trajectory.

3.2. Head kinematics—acceleration

Each shake was characterized by local acceleration peaks at various phases of the shaking cycle. An example of a single cycle (beginning at α and ending at ω) is shown in Fig. 3; the labeled points indicate the incidence of acceleration peaks. The acceleration history of this episode and the acceleration levels over the cycle α to ω are shown in Fig. 4. There were three acceleration peaks during the cycle (A, B and C). The first occurred as the head passed the summit of its arc and was being accelerated downwards (A; c.f. Fig. 3). A larger pulse was measured at the nadir of the arc as the head/neck reached the limit of motion (B) and short, sharp acceleration was recorded as the head suddenly reversed direction relative to the torso (C). This location corresponded to a point where the head interacted with the posterior aspect (dorsum) of the torso of the subject.

Local peak acceleration levels and their associated locations in the head trajectory, across the entirety of Episode 4 of Subject 3 are shown in the top left panel of Fig. 5, and in a real-time animation on three orthogonal views in Supplementary Fig. S2. The peak acceleration level recorded in this episode was 67 g.

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3.3. Head kinematics—power

An example of the power calculation is shown in the top right panel of Fig. 5. Negative power was associated with decelerations of the head at the nadir of the shake cycle and also as the head interacted with the dorsum of the animal. Although the first of these events appears more important, there may have been equally numerous high magnitude power pulses related to the second event, but because of the lower sampling frequency of the FASTRAK system, many of these may not have been captured. Periods of high power transfer reflected periods of high acceleration or deceleration of the head.

3.4. Head kinematics—head extension and flexion

An indication of head extension and flexion was derived using the head and torso position sensors. Localized peak values of extension and flexion are shown in the lower left panel of Fig. 5 for Episode 4 of Subject 3. Note that zero on the scale is arbitrary and may not be indicating a truly neutral position of the head/neck. However, the values indicate that the head/neck was furthest in extension either at the bottom of the shake cycle or shortly afterwards on the head's upward trajectory. The head was placed in flexion near the top of the downward phase of the shake cycle.

The gradient of the sagittal flexion–extension angle is shown in the lower right panel of Fig. 5. The gradient of the sagittal angle indicates periods of high angular speed of the head relative to the torso; the highest angular speeds occurred as the head was in the a caudal–posterior position (increasing extension) and when the head was at the extremity of the cranial–anterior position at the highest point of the shake cycle (increasing flexion).

3.5. Variations in shaking kinematics

Shaking styles varied between individual shakers and also depended upon the weight of the animal. Smaller animals showed different biomechanical characteristics by virtue of their smaller size, and the shaking occurred within a smaller physical range. The regions of highest acceleration were often found when the head was at the most anterior position. For example, lamb 7 weighed only 5 kg. A typical episode of the shaking of this animal is shown in Fig. 6 (see also Fig. S3 for an animation in three orthogonal views).

Supplementary material related to this article can be found online at http://dx.doi.org/10.1016/j.jbiomech.2014.06.002.

3.6. Summary statistics

Summaries of parameters that define the shaking are shown in Table 1. Axonal damage in lambs that died (7, 8 and 9) was greater than in animals that survived to the planned experimental endpoint. However, in general there was no consistent correlation between mechanical input and the injury scores based on neuropathological examination. This is illustrated in Fig. 7, which shows, for each subject, the number of local peaks in acceleration that exceeded a given acceleration value. The accelerations of the heads of the animals that died before the endpoint of the experiment (lambs 7–9) showed no features that were not also present in lambs that survived shaking, despite their premature deaths and high axonal injury scores. Lamb 3 is a particular outlier in this figure, as it exhibited numerous high acceleration impulses, but produced the least axonal injury. Similarly, lambs 5 and 6 experienced higher acceleration inputs than lambs 2 and 4, but had similar levels of brain injury.

Instead the amount of axonal injury showed a strong negative correlation with subject weight ($R^2=0.84$), a multivariable regression suggested that weight, average pulse acceleration and peak acceleration could explain the majority of the variance in axonal injury across the series ($R^2=0.95$). Some caution is warranted over the interpretation of these correlations however, as they are greatly influenced by the results from subjects that died (7, 8 and 9) and there are well known pitfalls in interpretation of the results of stepwise multivariable regression in general.

Table 1
Injury levels and mechanical inputs in the lamb model of non-accidental head injury.

Subject	Weight (kg)	Time to death (h)	Axonal injury score	Neuronal injury score	Acceleration of impulses > 30 g		
					Peak (g)	Average peak (g)	*N*
1	12	6	10	49	39	38.5	1
2	11	6	13	56	53	37.9	14
3	10.5	6	6	37	67	39.9	120
4	10	6	12	74	40	34.1	15
5	10	6	15	61	73	44.9	225
6	8.5	6	15	71	80	40.4	98
7[a]	6	5	31	66	66	41.5	78
8[a]	5.5	2	30	75	58	35.9	20
9[a]	5	3	26	58	79	37.3	21
Average			18	61	62	41.6	66

[a] Intermittent signal failure on one acceleration channel may have caused an under estimation in average and peak values of acceleration and power.

4. Discussion

This study has presented the biomechanics of shaking in a naturalistic large animal model of NAHI. The main features of this model are that the insults closely resemble events thought to occur during episodes of abuse to human infants, and that it produced a spectrum of injuries that resembles those suffered by children who are victims of NAHI. Acceleration events were between 40 and 80 g and each subject generally experienced many such impulses.

The model was designed to closely resemble real-world human infant manual shaking episodes and, as such, is likely to be a more accurate replication of what occurs in pediatric NAHI than previous models. The disproportionately large lamb head containing a gyrencephalic brain is effectively a poorly controlled mass laxly supported by weak neck muscles and thus has the craniocerebral anatomical features of a human infant.

Raghupathi et al. (2004) concluded that the intensity and nature of the resulting axonal injury in their model were dependent upon both the number of insults and severity of the loading. It might have been expected that, in this study, the number and intensity of events occurring during shaking episodes would be related to the production of brain injury. While the present study was not designed to elicit any such correlations, their absence deserves comment. First, it appears that subject weight had a significant bearing on the amount of axonal injury observed. The effect of weight did not appear to be a consequence of some resulting variation in the intensity of the head accelerations experienced, although it should be noted that the characterization of the biomechanics in such a complex biomechanical model is not straightforward; impulsive and kinematic severity were characterized using several parameters, but there were some omissions; the kinematics of the craniocervical junction could not be measured and was only characterized indirectly, while angular acceleration was not measured. Nevertheless, we noted a substantial degree of

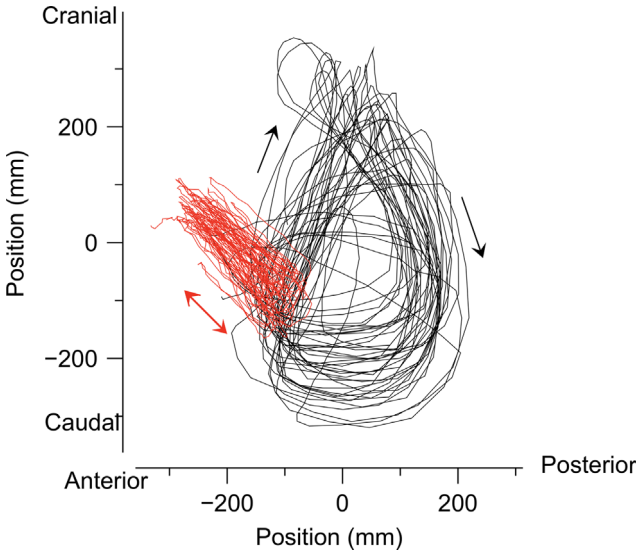

Fig. 1. Trajectory of the axilla (hand) sensor (red) and the head position sensor (black) in one episode (Subject 3; Episode 4). See also Supplementary Fig. S1.

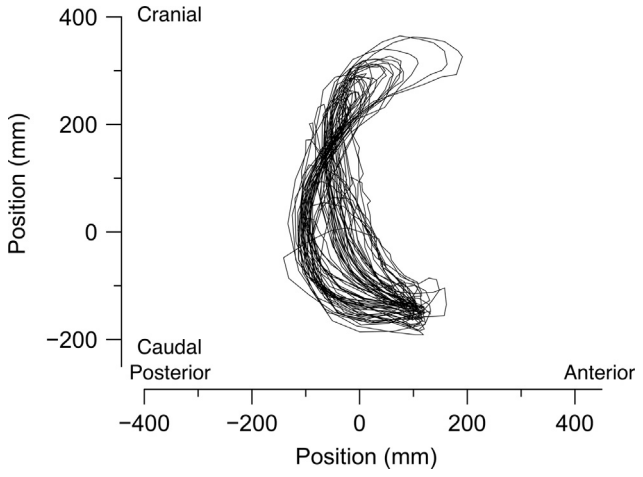

Fig. 2. Relative trajectory of the head position sensor to the axilla sensor in one episode (Subject 3; Episode 4).

concordance between the different measures of severity that we were able to characterize, and other measures that might have been recorded, we would expect, would reflect a similar order of severity between the nine animals. Nevertheless, it might be that there was some unmeasured biomechanical response to shaking, critical to the development of brain injury, that is greatly affected by developmental changes occurring over the first days and weeks of life.

4.1. *The immature ovine brain as a model for the infant human brain*

Ethical considerations meant that there was no option but to ensure each animal was under deep-plane anesthesia for the duration of the experiment. Unanesthetised lambs would be expected to have greater neck muscle tone and correspondingly less head acceleration after shaking. This is a relevant consideration insofar as it might affect the model as an analog of the human infant. It is arguable that the lower neck muscle tone of anesthetized lambs in the present study is more likely to resemble the very weak neck muscles of a human infant.

The development of a satisfactory animal model of non-accidental head injury (NAHI) in children is required, but selection of an appropriate species has proved to be difficult (Gerber and Coffman, 2007). Rodents have been used as experimental models, but they have smooth, lissencephalic brains with scant white matter, unlike the gyrencephalic brains of large mammalian species. Moreover, the presence of gyri affects the movement of the brain within the skull and, after a shaking episode or head impact, significantly more brain deformation occurs than in brains

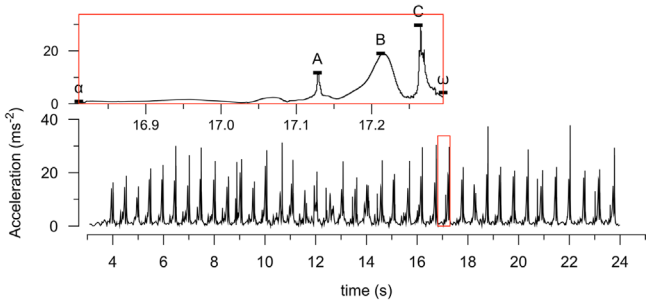

Fig. 4. Acceleration history in Subject 3, Episode 4. Detail shows acceleration events in one cycle (α–ω): Accelerations at positions A, B and C are indicated.

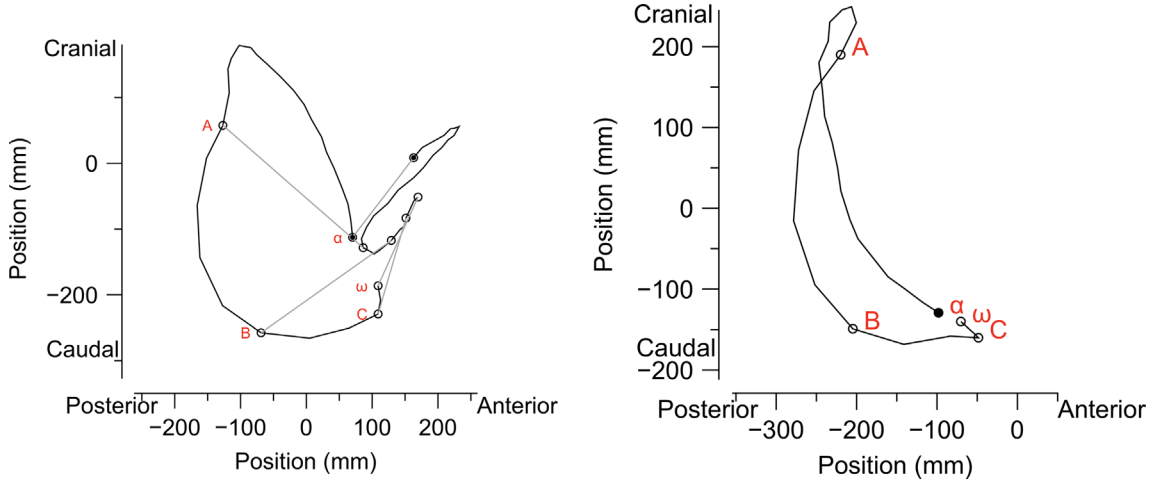

Fig. 3. Detail of a single cycle of motion (α–ω) in Subject 3, Episode 4. Labeled points refer to regions of interest and may be cross-referenced with Fig. 5. Trajectory of head and hand in laboratory space (left), and head relative to hand (right).

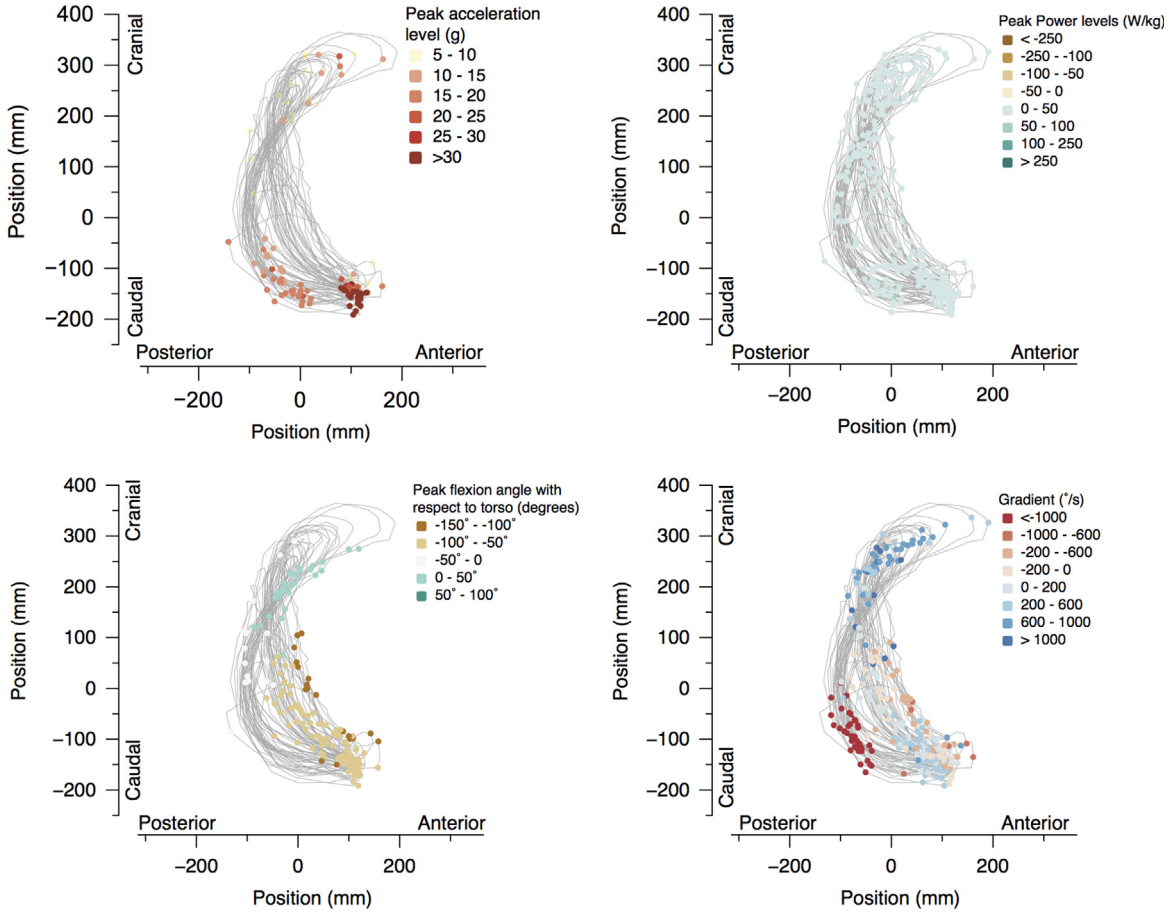

Fig. 5. Trajectory of the head position sensor relative to the axilla sensor in Episode 4 of Subject 3. The location and levels of local peaks in the acceleration (top left), power (top right), peak flexion (lower left) and flexion/extension gradient (lower right) are overlaid on the trajectory.

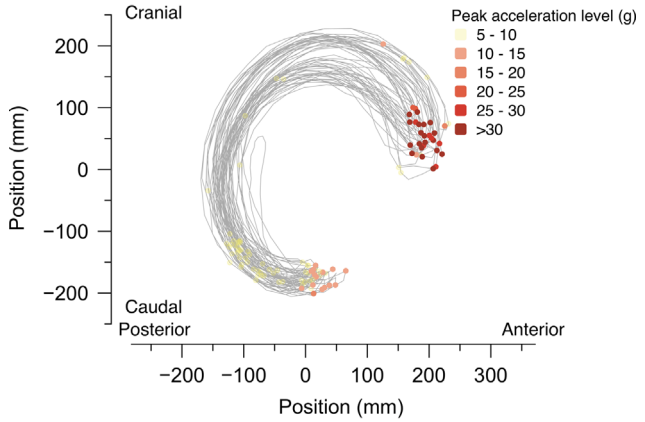

Fig. 6. Trajectory of the head position sensor relative to the axilla sensor in the sagittal plane of Episode 3 of Subject 7. The location and levels of local peaks in the acceleration are overlaid on the trajectory.

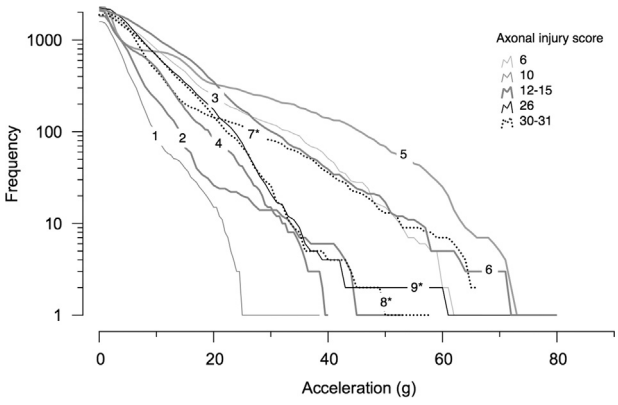

Fig. 7. Frequency of transient peaks in acceleration exceeding a certain value. Distributions are labeled with Subject numbers; asterisked numbers indicate subjects that died. The line legend indicates injury severity.

devoid of gyri. Since shearing forces and inertial loading are related to brain mass, small rodent brains can also tolerate much greater angular acceleration forces than animals with large gyrencephalic brains (Margulies and Coats, 2010).

Recognition of the contribution of neonatal craniocerebral anatomical features to the development of NAHI pathology is critical when selecting an animal model. Relative to its body size, the infant human head is significantly larger when compared to that of an adult, and the brain has a higher water content, is incompletely myelinated, and the subarachnoid space is relatively large. In addition, cervical paraspinal muscles are weak, so the infant has generally poor control of a disproportionately large head on a weak neck. Taken together, these factors may permit significant differential movement of the immature brain with respect to the skull during the rapid acceleration/deceleration produced by violent manual shaking. In view of the importance of

these anatomical characteristics of the human infant, we selected a lamb model of NAHI as this species also has a relatively large, gyrencephalic brain, a large head relative to body size, and weak neck muscles.

It might be argued that the immature ovine brain may not sufficiently represent the human infant in that the human infant has a relatively undeveloped brain compared to the ovine brain, which has more functional maturity at birth. Human neonates, if classified by their relatively immature development of the body and motor skills, might be considered to be relatively underdeveloped at birth compared to sheep; but, in fact, the relatively advanced development of the human brain and many aspects of perceptual systems at birth suggests that, in many respects, a great deal of its development occurs prenatally (Dobbing and Sands, 1979).

In sheep, the cerebral hemispheres develop earliest, followed by the brainstem and spinal cord, then the cerebellum. Although the two growth spurts of the cerebral hemispheres occur at 40–90 days of gestation (~150 days) and after 95 days, most of the growth in other brain regions occurs postnatally. At postnatal day 7, for example, the cerebellum and brainstem are only at 50% of their final weight and the spinal cord 30%. Myelination in this species is largely complete by the first week of postnatal life, but there is a second, postnatal phase of myelination at postnatal days 10–20, especially in the spinal cord (Finnie et al., 2012). Hence, in several important respects, the brain of the neonate sheep is still developing and there are good reasons to consider this model as being relevant to the human infant.

4.2. Reproducibility

While all animals showed pathology usually associated with NAHI, there was heterogeneity across subjects that appeared to be explained primarily by variation in subject weight. It might be noted that substantial changes in subject weight would appear to occur over a very short period; the first group of animals were 7–9 days old and 8.5–12 kg, whereas the lighter group were 5 days old and 5–6 kg. Hence a logical next step would be to restrict the weight of subjects, which implies restricting subjects to a small window of postnatal development, requiring careful programming of experiments so that they occur at a specific number of days postpartum. Graded injury might be attained by more tightly controlling the insult, and introducing controlled variation into the shaking. The results presented herein provide a basis for an improved protocol, and suggest the nature of the kinematics that is required to produce clinically relevant injuries.

To conclude, this study represents a novel animal model of NAHI that is characterized by repetitive and cyclical manual shaking that can produce repeated impulsive contacts with the body of the animal itself and lower-magnitude impulses that are induced throughout the shake cycle. The manual shaking of lambs in this series was associated with widely distributed axonal injury, neuronal reaction, and albumin extravasation, with death supervening in lower body weight animals before the designated end point of the experiment. The magnitude of the input in this model was sufficient to cause substantial neural damage, and even death, in shaken lambs.

Author disclosure statement

No competing financial interests exist.

Conflict of interest statement

On behalf of all the authors I declare that no competing financial interests exist.

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