

## **Influence of Planar Head Motions on the Production of Prolonged Traumatic Coma in the Miniature Pig**

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### **ABSTRACT**

*Diffuse axonal injury was produced in twenty-one miniature pigs as a result of accelerating their heads in a controlled rotational motion without impact. The experimental paradigm rotated the animal's head in either a coronal plane (n=15) or an axial plane (n=6) over a brief period (<40 milliseconds), thereby exposing the miniature pig brain to a significant inertial load. All fifteen animals that had their heads rotated in the coronal plane regained consciousness within five minutes after injury. These animals showed no functional effects of traumatic brain injury but exhibited widespread microscopic multi-focal axonal damage with gliosis primarily throughout the cerebral hemispheres. In comparison, the six animals that had their heads rotated in the axial plane exhibited either moderate (4 out of 6) or severe (2 out of 6) periods of traumatic coma instantaneously after injury, even though these animals experienced lower levels of inertial loading than the coronal plane group. The pathological features of experimental brain injury in this set of experiments also imitated the pathological features of a severe head injury in humans: widespread microscopic multi-focal axonal damage occurred throughout the brainstem and cerebral hemisphere, overlying hemorrhagic cortical contusions were observed along the frontal lobes, and small intracerebral hematoma lesions were noted in most animals injured using the axial plane rotation. Regression analysis of the neuropathological lesion patterns in the axial plane injury group showed that the severity of the contusions and axonal injury in the brain were related directly to the peak change in angular velocity, therefore providing a means to control directly the lesion pattern in future animal experiments. Taken together, this empirical evidence extends the hypothesis of cerebral concussion put forth previously (Ommaya and Gennarelli's (1974)), showing the evolution of brain injury does not always occur in a centripetal sequence, but rather is a complex result of the applied planar loading conditions, the given neuroanatomy, and the resulting spatial distribution of intracranial strains from these applied loads and geometrical constraints.*

## INTRODUCTION

Of all the forms of traumatic brain injury, diffuse axonal injury (DAI) is responsible for the most cases of poor neurological outcome in victims of head injury, and it is associated with a significant mortality rate (Gennarelli, Spielman et al. 1982; Graham, Adams et al. 1993). The clinical manifestation of DAI is a continuum of brain injuries that range from mild concussion to deep coma. It is common for DAI to be diagnosed either in the absence of any evidence of macroscopic injury (Cooper, Maravilla et al. 1979; Zimmerman and Bilaniuk 1979; Clifton, McCormick et al. 1981; Levin, Meyers et al. 1981; Adams, Graham et al. 1982; Blumbergs, Jones et al. 1989; Levi, Guilburd et al. 1990) or in the presence of other post traumatic lesions (Cooper, Maravilla et al. 1979; Sahuquillo-Barris, Lamarca-Ciuro et al. 1988; Katz, Alexander et al. 1989; Levi, Guilburd et al. 1990). Anatomically, its hallmark regions of microscopic damage include the corpus callosum, dorsolateral brainstem, subcortical white matter, basal ganglia, periventricular, and parahippocampal gyri. The multi-focal injury pattern in DAI is well documented; however, the exact relationship between these injury patterns and the neurological deficits observed in DAI is not well understood.

It is now well accepted that the mechanism responsible for DAI is the local deformation of the white matter tissue within the brain. As a head accelerates into motion, the applied inertial forces cause the intracranial material to experience a deformation gradient that is dependent upon many factors that include the applied inertial loading, the overall brain geometry, the local brain material properties, and the boundary conditions between the brain and skull. These factors all contribute to the deformation gradient applied locally to the tissue, and thus the control of one or more of these characteristics will offer a method to control the distribution and severity of the lesions within the brain white matter. In turn, the change in the distribution of lesions will lead to potentially different neurological deficits, thereby offering an opportunity to better examine the relationship between the pathological and clinical endpoints of diffuse brain injuries.

The objective of this paper was to demonstrate the importance of different plane head rotations in a model of experimental brain injury in the miniature pig. In particular, we examined the consequences of either coronal or axial plane head rotations on the distribution of axonal injury throughout the brain and brainstem, as well as the functional consequences of the injury patterns caused by these different head rotations. Due to neuroanatomical alignment, our overlying hypothesis was that head rotations in the miniature pig axial plane would produce prolonged traumatic coma preferentially. In addition, we used this new data to examine the centripetal theory for brain injury proposed for concussion and more severe injuries (Ommaya and Gennarelli, 1974), offering an extension of this theory that accounts for the results presented in this report.

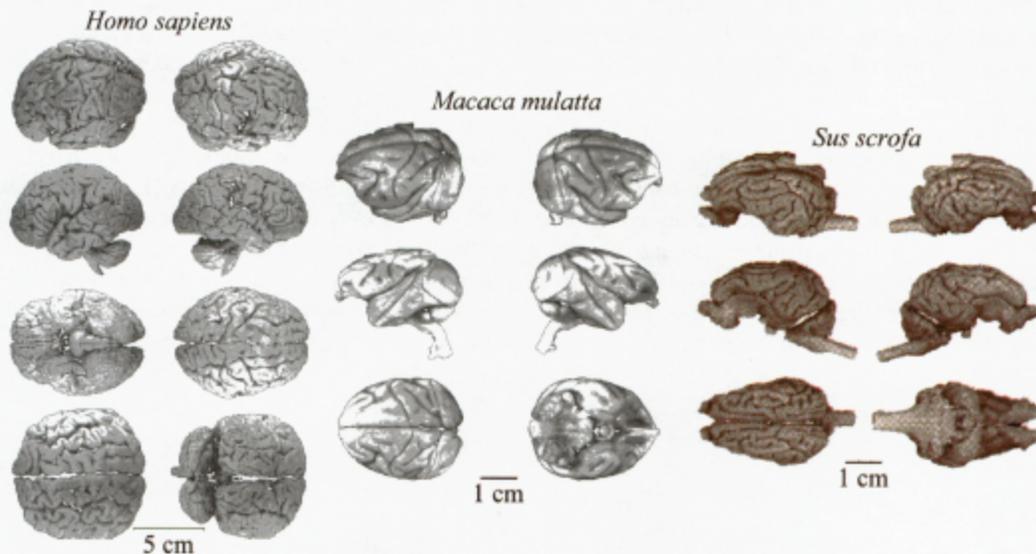
## EXPERIMENTAL DESIGN AND METHODS

### *Experimental Model of Traumatic Coma*

This experimental model contains many advantages for studying traumatic brain injury, including the ability to modulate the inertial loading parameters to the head to better assess the relationship between specific forms of brain injury and the different loading conditions. In a series of earlier experiments (PENN I and PENN II) using non-human primates, it was determined that coronal plane head rotations would cause the most severe form of diffuse axonal injury that included an immediate, prolonged traumatic coma (Gennarelli, Thibault et al. 1982; Gennarelli, Thibault et al. 1987; Thibault and Gennarelli 1990). In more recent studies (Ross, Meaney et al. 1994; Meaney, Smith et al. 1995; Miller, Smith et al. 1996; Smith, Chen et al. 1997), coronal plane head rotations

were used to examine the resulting brain injury in the miniature pig. Although these coronal plane head rotation experiments demonstrated some of the pathological features of diffuse axonal injury, they were not able to produce prolonged coma.

After reviewing the results of these previous experiments and noting, in particular, the miniature pig's central nervous system's axis alignment with respect to its cerebral hemisphere, it was hypothesized that by rotating the miniature pig's head in the axial direction would result in a more severe form of diffuse axonal injury. As illustrated in Figure 1, the miniature pig's brainstem and spinal axis are aligned, or parallel, with its cerebral hemisphere. In comparison, the brainstem axis is roughly perpendicular to the cerebral hemispheres in the non-human primate. Therefore, rotating the miniature pig's head in the axial direction would produce deformations in the brainstem analogous to the strains resulting from the rapid rotation of the non-human primate's head in the coronal plane. Although the miniature pig lacks a significant falx and is further differentiated in neurological development than a non-human primate, there are enough remaining similarities to suggest that axial plane rotations in the miniature pig would produce an injury pattern more closely resembling the severe DAI lesion pattern in man, including lesions in the upper brainstem and throughout the hemispheres.



**Figure 1.** Gross brain for a human, rhesus monkey, and miniature pig.  
(Source: University of Wisconsin-Madison Brain Collection)

Based on these neuroanatomical considerations, the experiments in this study were designed to test the relevancy of different plane head rotations in a model of experiential brain injury in the miniature pig. In particular, we studied the consequences of axial and coronal plane head rotations on the neurological deficits and neuropathological lesion patterns produced in the miniature pig.

#### *Animal preparation*

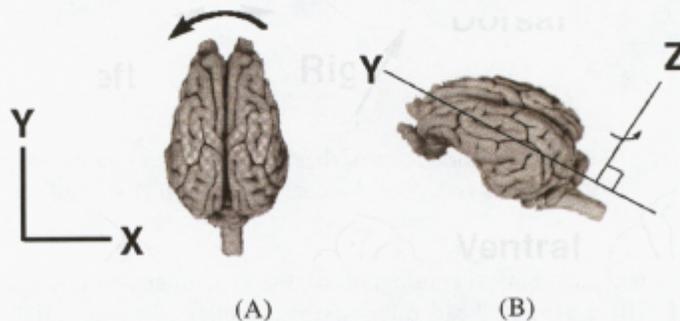
Fifteen young adult miniature pigs (*Sus scrofa*), 3-4 months in age, weighing 13-24 kg had their heads rotated in the coronal plane, while six pigs, 17-26 kg had their heads rotated in the axial plane (Charles River, MD and Sinclair Research Center, Inc., MO). All procedures used in the preparation, injury, and post-injury monitoring were approved by the University of Pennsylvania

Institutional Animal Care and Use Committee (IACUC). To reduce the possibility of unnecessary complications each animal was fasted for 12 hours and water intake restricted for 2 hours pre-injury. To prepare the animal for the experimental setup and post-injury monitoring, each animal was anesthetized with an initial intramuscular injection of midazolam (400-600 mg/kg), supplemented with atropine sulphate (0.05 mg/kg), endotracheally intubated, and catheterized with a venous catheter. For a selected series of coronal plane experiments and all of the axial plane experiments the necessary surgical preparations were made to monitor mean arterial pressure (MAP), intracranial pressure (ICP), electrocardiogram (EKG), electroencephalogram (EEG), and body temperature (TEMP). In addition, for each experiment end tidal carbon dioxide (CO<sub>2</sub>), respiration rate (RES), heart rate (HR), and oxygen saturation (O<sub>2</sub>) were continuously monitored. These physiological variables were recorded and stored on a personal computer every half-hour post injury. During the time the animal was secured to the injury apparatus, the animal was sedated with 2% isoflourane anesthesia with a flow rate of 500-600 ml of oxygen per minute.

At either one week (coronal plane experiments) or six to eight hours (axial plane experiments) after injury, each animal received an overdose of pentobarbital (150 mg/kg I.V.) and perfused with 4% paraformaldehyde to prepare the brain tissue for histological staining. After the brain was removed from the cranial vault, each brain was examined macroscopically, sectioned at the ventral roots of the first spinal nerve and weighed. The cervical vertebral bodies were inspected for fractures and a second tissue sample was taken at the first thoracic vertebra to check for spinal chord impingement.

#### *Injury Device*

The experimental model of diffuse axonal injury uses a pneumatic injury apparatus (Bendix, NY) that delivers a controlled, non-centroidal, rotational acceleration without impact to a miniature pig's head. This method of injuring an animal adds more control over the brain's mechanical response than free head impact, in turn reducing the variability of each experimental data set. As shown in Figure 1A, to rotate the animal's head in a controlled plane the animal's head is secured to the linkage assembly by inserting a padded metal bit plate into the animal's mouth and tightening down padded spring steel bands which encircle the snout to the metal plate.



**Figure 2.** Experimental injury model. Animals were injured using either a coronal plane angular acceleration/deceleration (B) or axial plane head angular acceleration/deceleration (A). Both rotational motions were accomplished using a pneumatic cylinder attached to a custom linkage, converting linear motion of the actuator to an angular motion over a prescribed range (92-104 degrees).

By securing the animal's mouth to the linkage assembly in this manner, the animal's head moved through either a coronal plane or axial plane arc. A pneumatic cylinder drives both rotational motions through the custom linkage assemblies attached to the apparatus, both of which convert the piston's translational motion into a rotational motion.

Control of the head's rotational acceleration profile allows one to examine the effect of a range of kinetic loading conditions, an important feature for developing a controlled range of brain injuries in the animal. Control of the acceleration profile was accomplished through two primary means - adjusting the hydraulic fluid level within the actuator cylinder, or adjusting the pneumatic pressure sent to the actuator. In combination, these adjustments will affect the magnitude and duration of both the angular acceleration and angular deceleration accelerations.

Coronal plane head rotations in the miniature pig were studied by scaling conditions from similar plane rotations causing prolonged coma in the non-human primate (Gennarelli, Thibault et al. 1982; Gennarelli, Thibault et al. 1987). To deliver a non-centroidal head rotation in the pig's axial plane, the coronal plane linkage assembly was modified extensively. The bite plate was rotated 90 degrees and attached to the inside of the cross bar that connects the two side arms. The animal was placed on its right side and secured to the bite plate with padded steel spring bands. As a result of securing the animal to the linkage in this manner, the animal's head moved through an arc with the center of rotation in its lower cervical spine. To add more control over the experiment, the injury device's reaction mass was redesigned to eliminate its rigid body motion during an experiment.

#### *Recording the Inertial Loading Parameters*

Three different transducers were used to determine the transient angular acceleration, angular velocity and angular displacement profiles. The data acquisition protocol for recording and calculating these transient inertial loading parameters has been described elsewhere in detail (Miller, Margulies et al. 1998). In brief, an uniaxial accelerometer was used to calculate the angular acceleration profile, an angular rate sensor was used to measure the angular velocity profile, and an absolute encoder was used to measure the angular displacement. Theoretically, any one of the three inertial profiles could be used to fully characterize the inertial load, however, filtering and/or either differentiating or integrating a signal may potentially introduce numerical errors into the estimated kinetic profile. Recognizing these shortcomings, however, all three inertial profiles were eventually recorded independently to verify both the accuracy of these transducers and the peak inertial loading parameters.

Previous coronal and axial plane experiments have limited the animal's head to rotate between 94 - 104 degrees in less than 35 milliseconds. Coronal plane experiments recorded peak angular decelerations between 180 - 260  $\text{krad/s}^2$  with peak angular velocities between 310 - 352  $\text{rad/s}$ . Anticipating that the orientation of the brainstem and the central nervous system's spinal axis play a critical role in the onset of traumatic coma, the axial plane experiments limited the peak angular decelerations to between 90 - 240  $\text{krad/s}^2$  with peak angular velocities of 213 - 287  $\text{rad/s}$ . To provide a normalizing scale for the inertial loading parameters, each experiment's brain mass and peak kinetic parameters were normalized according to Holbourn's scaling using an average miniature pig brain mass of 72 grams (Holbourn 1956).

#### *Scoring the Neurological Deficit from Inertial Loads*

The definition of unconsciousness used by Gennarelli and colleagues (1982) to grade the severity of experimental coma was used to evaluate the neurological deficit caused by the angular acceleration/deceleration insult. Unconsciousness was defined as a lack of behavioral contact with the environment, degree of pupil dilation, state of corneal reflex, and the ability to breath without

mechanical ventilation. Basically, the following four category scale was used to characterize the duration of unconsciousness.

Cerebral concussion: Coma lasting less than 15 minutes.

Mild prolonged traumatic coma: Coma lasting between 16 to 119 minutes.

Moderate prolonged traumatic coma: Coma lasting between 2 to 6 hours.

Severe prolonged traumatic coma: Coma lasting greater than 6 hours.

Animals were withdrawn from anesthesia immediately prior to injury and were monitored continuously after injury until they showed signs of emerging from the anesthesia. Once signs of emergence appeared, the anesthesia was resumed and the duration of coma was recorded.

#### *Grading the Pathological Effect from Inertial Loading*

After removing the perfused brain from the cranial vault, each brain was sectioned at the ventral root of the first spinal nerve and weighed. As the brain was removed, the cervical vertebral bodies were inspected for fractures and a second tissue sample was taken at the first thoracic vertebra to check for spinal cord impingement.

*Mean Total Contusion Index.* To grade the severity and extent of macroscopic hemorrhagic contusions, Adams and colleagues (1985) contusion index was used. This index grades the severity of injury by identifying the depth of the contusion in terms of being either localized, mildly extensive, moderately extensive, or extensive (Adams, Doyle et al. 1985). If it extends through the partial thickness of the cortex it is graded a 1 (localized). If it extends the full thickness of the cortex it is graded a 2 (mildly extensive). If it extends into the white matter it is graded a 3 (moderately extensive) and if it extends deep into the white matter it is graded a 4 (extensive). To grade the extent of a macroscopic hemorrhagic contusion, the number of surfaces that were affected by the contusion must be identified. If the contusion were restricted to the crest of one gyrus or two continuous gyri it was graded a 1. If the contusion extended over one surface it was graded a 2 and if the contusion extended over more than one surface it was graded a 3. The contusion index was then calculated by multiplying the depth grade by the extent grade. A mean total contusion index (MTCI) was then calculated by summing the individual contusion indices and standardizing it by a total contusion index of 120.

*Standardized Total Axonal Injury Index.* Once the brain was ready for histological staining, several sections of brain tissue were examined under a light microscope. The primary immunocytochemical markers for axonal injury neurofilament antibodies (NF-68, NF-200, SMI-31, SMI-32) and beta amyloid precursor protein ( $\beta$ -APP). These are traditional markers of axonal injury used in previous studies (Ross, Meaney et al. 1994; Smith, Chen et al. 1997).

Following a lesion pattern grading system used in humans, axonal damage was identified by the pattern of axonal labeling and swelling. Axons that have either substantial axonal swelling or terminal clubbing are considered injured axons in contrast to normal "uninjured" axons. The following three category axonal injury rating scheme was used to grade the severity of axonal damage:

- 1<sup>+</sup> = 1-5 axonal swellings or terminal clubs, under a 200 X objective
- 2<sup>+</sup> = 6-15 axonal swellings or terminal clubs, under a 200 X objective
- 3<sup>+</sup> = > 15 axonal swellings or terminal clubs, under a 200 X objective

After all of the sections were examined, two-dimensional injury patterns were created and assigned to either coronal or axial representative brain sections. These semi-quantitatively injury maps summarized the severity and extent of axonal injury.

In order to transform these semi-quantitative injury maps into quantitative scores the Axonal Injury Index (AII) was developed. This injury index is capable of grading the extent and severity of axonal injury of specific anatomical regions of the brain by combining the advantages of Adams's contusion index, Blumberg's axonal injury sector scoring method, and our two-dimensional injury grading method (Adams, Doyle et al. 1985; Blumberg, Scott et al. 1995; Miller, Smith et al. 1996). To determine AII's value, the brain is sectored according to anatomical region with the extent and severity of axonal injury in those regions given a score. The anatomical regions are subdivided according to the dorsal/ventral and left/right orientation. These regions include the four brain lobes (frontal, parietal, temporal, and occipital), the cerebellum, periventricular regions, the brainstem, deep internal nuclei (thalamus and basal ganglia) and the corpus callosum. These anatomical regions are then subdivided into either a lateral or medial region. The lateral region identifies axonal injury around the different gyrus and internal capsule, while the medial region identifies injury in the deeper white matter. As a result 58 sectors are defined. To grade the injury's extent the following three category injury rating scheme was used:

- 1<sup>+</sup> = 1 - 3 axonal swellings per field, under a 20 X objective
- 2<sup>+</sup> = 4 - 6 axonal swellings per field, under a 20 X objective
- 3<sup>+</sup> = > 6 axonal swellings per field, under a 20 X objective

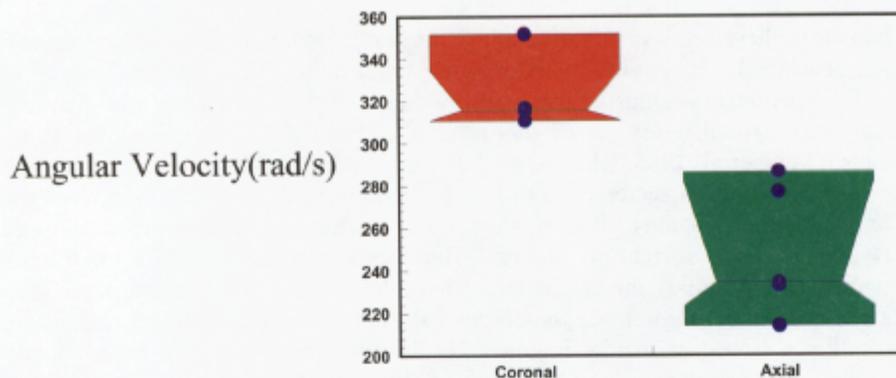
A standardized total axonal injury index (STAI) is then calculated by summing the individual axonal indices and standardizing it by a total axonal index of 522.

#### *Controlling the severity of MTCI and the Duration of Prolonged Traumatic Coma*

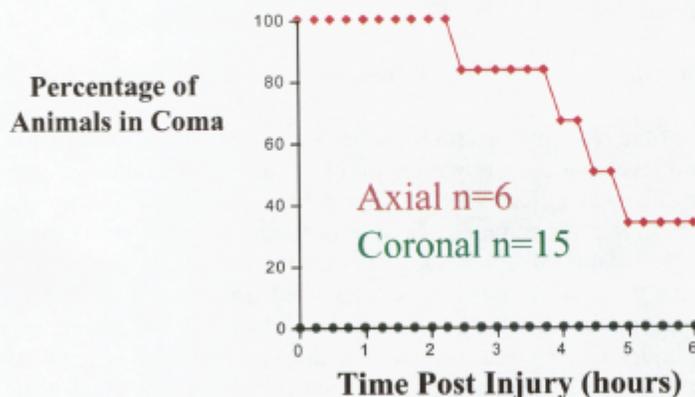
In order to control the severity of the resulting macroscopic hemorrhagic cortical contusion in the last axial plane experiment, the fluid level and operating pressure of the injury apparatus were set to a predetermined level. The operating characteristics of the actuator device were set as follows: the linear relationship between the severity of the prior animal's MTCI with their peak angular velocities (n=5) were examined and a 'target' MTCI value of 2 was identified on the regression curve. The predicted peak angular needed to achieve this MTCI value was extrapolated from the curve, and the operating characteristics of the device were set to achieve this angular velocity in an experiment. Following the animal experiment, the injury pattern was evaluated in the same manner as previous experiments to determine the feasibility of predicting or targeting lesion patterns in the axial plane rotation experiments.

## **RESULTS**

*Inertial Loading Conditions* - Repeated tests under the same conditions yields little variation of less than 1% for both peak values in an angular acceleration, angular deceleration, changes in angular velocity, and angular displacement (Miller, Smith et al. 1996). Peak changes in angular velocity were significantly less in the axial plane experiments (Figure 3), while there was no significant difference in the peak angular deceleration magnitude. The lack of a difference in peak angular deceleration between the coronal and axial plane injury groups is likely due to the redesigned reaction mass, which was available for all of the axial plane tests and only some of the coronal plane tests.



**Figure 3:** Comparison of kinetic loading parameters (peak angular velocity, rad/s) between axial and coronal plane experiments. All data is scaled using Holbourn's relationships (Holbourn 1956). Average peak change in angular velocity and average peak angular deceleration is significantly different between the two rotation groups.



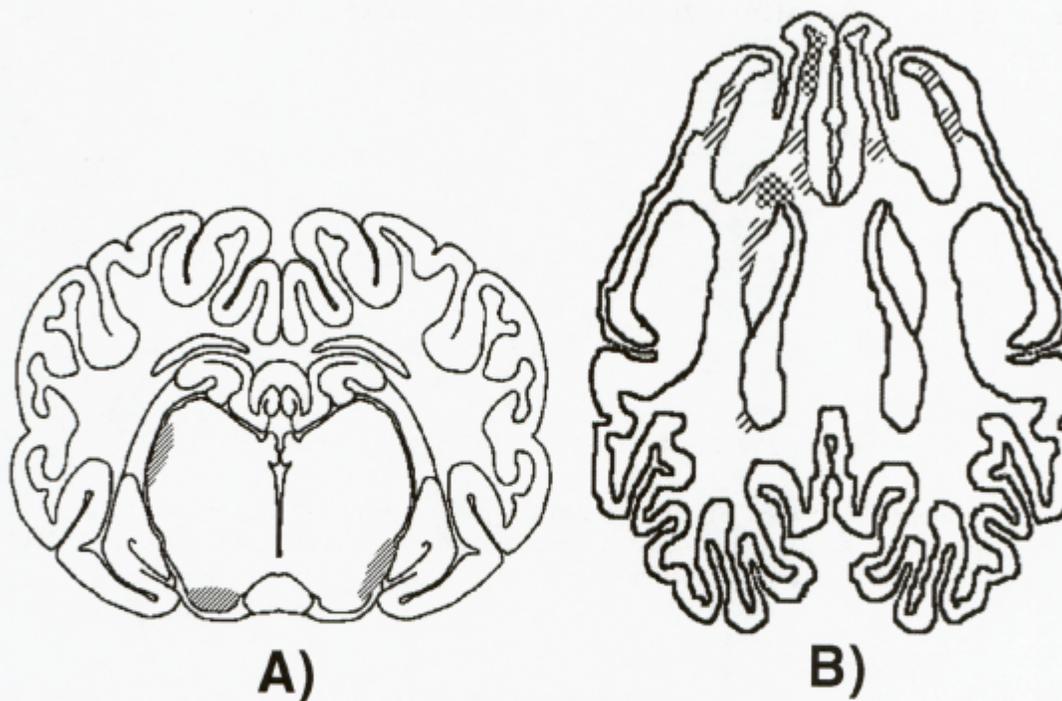
**Figure 4:** Comparisons of duration of coma between axial and coronal plane experiments. Axial plane rotations showed a significant increase in the average coma duration ( $P < .005$ ), despite the lower inertial loading levels used in these experiments.

*Significance of the Loading Direction.* As illustrated in Figure 4, six out of six animals that had their head rotated in the axial plane at considerably lower inertial loads than coronal plane experiments, were either moderately (4 out of 6) or severely impaired (2 out of 6) as defined by Gennerally's (1982) prolonged traumatic coma scale. On the other hand, all fifteen animals that had their head rotated in the coronal plane showed neither any functional effect nor macroscopic hemorrhagic cortical contusions, microscopic intracerebral hemorrhages, blood in the ventricles, or enlarged ventricles. The observations on average coma duration between the two groups is highly significant ( $p < 0.0005$ ).

*General Injury distribution.* Empirically, when an animal's head is subjected to a controlled inertial load, the resulting injury pattern is asymmetric. A series of coronal plane experiments were conducted in which the first group ( $n=5$ ) had their heads rotated from the left to right while the second group

(n=10) had their heads rotated from the right to left. As a result, coupling this change in loading direction with the different kinetic loading parameters the following general observations were made about the distribution of diffuse axonal injury:

The distribution of injury was asymmetric (both rotational motions). The leading hemisphere was always more vulnerable to injury than its trailing counterpart (both rotational motions). The dorsal, interior trailing region was injured consistently (coronal plane). In the majority of the cases, there was no difference in the severity of injury between the peripheral and interior regions, however in a few cases specific interior regions did suffer a greater injury than their peripheral counterpart.

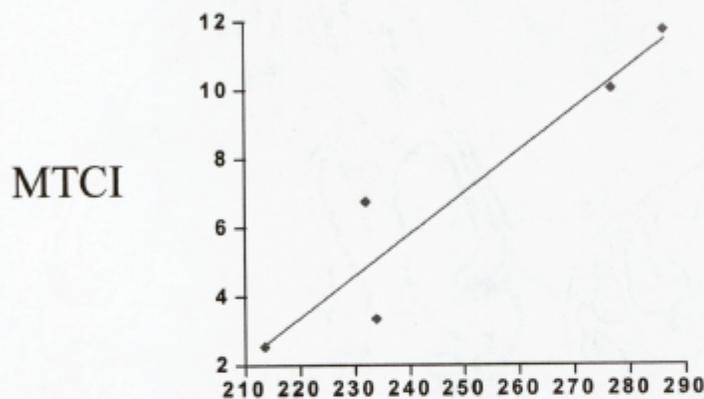


**Figure 5:** A) Caudal-hippocampal coronal plane injury map (#97-3, one week post injury). B) Mid-cortex axial plane injury map (#97-11, six hours post injury). Both animals had their head rotated to the right to left. Legend: shaded regions indicate areas of axonal injury (1+ = diagonal lines, 2+ = checkered box), while solid black lines indicate the areas of contusion observed along the brain surface.

*Axonal Injury Patterns.* As shown in Figure 5, the axonal injury map summarizes semi-quantitatively the extent and severity of axonal injury. In general, the injury patterns can be described as multi-focal through the brain, with damage appearing along the periphery of the white matter and areas bordering the ventricles. The multi-focal and asymmetric distribution of injury is similar to those observed in both similar non-human primate experiments and in human head injuries. Interestingly, the injury pattern in the axial plane does not occur in a centripetal manner – injury is localized in the upper brainstem region and not along the peripheral margins of the white matter in the cerebral hemispheres.

### *Controlling the Severity of MTCI and the Duration of Prolonged Traumatic Coma*

Using the loading conditions from five prior experiments, a regression of the MTCI in relation to the peak change in angular velocity yielded a reasonable linear relationship (Figure 6A), identifying a threshold value of 187 rad/s for contusions to appear in the brain. With a target MTCI value of 2 and an estimated brain mass of 72 grams, a target level of 200 rad/s was identified from this linear regression relationship. Recognizing that this target level was significantly lower than the previous axial plane angular velocities, a separate regression of the coma duration and applied peak angular velocity as performed. It was predicted from this second regression that the duration of coma in this targeted axial plane experiment would not exceed four hours (i.e. the shortest duration of coma before the last experiment). The applied angular velocity in the animal experiment was 204 rad/s. Evaluation of the injured brain yielded a MTCI of 2.5, and the measured duration of coma was 2.5 hrs.



**Figure 6:** Correlation between MTCI and applied peak angular velocity in the axial plane experiments. A linear regression of this data yielded loading conditions to produce an MTCI of 2.0 in the 97-12 animal experiment.

## DISCUSSION

This study has shown that the direction of planar angular acceleration/deceleration used in an experimental model of brain injury can affect both the distribution of lesions in the brain and the resulting neurological status of the animal post-injury. Although the relationships between lesion patterns and neurological function are only beginning to be understood, we propose that our findings are due to the interrelationship between the applied planar head motion, the neuroanatomical alignment of the miniature pig brain/brainstem, and the different deformation gradient patterns produced from these two rotational motions. For the miniature pig, the spinal axis is parallel to its cerebral hemisphere, unlike the perpendicular orientation that exists in the nonhuman primate. Therefore, to produce a deformation gradient in the brainstem similar to the gradient produced in earlier non-human primate experiments using lateral plane head rotations, an axial plane head rotation is required for the miniature pig. Interestingly, we determined that similar inertial loading levels in the axial plane produced more severe brain injuries than the coronal plane motions, including contusions, limited intracerebral hematomas, and tissue tears. We view this finding as important, showing that more focus needs to be placed on the interrelationship between planar motions and the severity of brain injuries when developing tolerance levels for diffuse brain injuries.

These findings can be placed in the context of previous free head impact studies using sheep (Lewis, Finnie et al. 1996) and nonhuman primates (Ono, Kikuchi et al. 1980). Free head impact represents a more realistic but complex inertial loading profile, and the loading conditions used in the previous studies were constrained to impact points at the temporal region (sheep), and either the occipital and frontal region (nonhuman primates). All impact directions produced lesions throughout the brain that included contusions frequently at the impact site, axonal damage in the brainstem and hemispheres (sheep), and a minority of skull fracture. Neither study produced the predominantly brainstem lesion patterns observed in our axial plane experiments, primarily because both species have similar neuroanatomical organization and the applied head motions would not preferentially increase the deformations in the upper brainstem area. Perhaps for this reason, duration of unconsciousness was less than the axial plane experiments reported herein, although we cannot discount the potential difference in the kinetic loading conditions used across these studies.

The patterns of injury observed in our animal experiments highlight an important point to consider in describing the relationship between the applied mechanical loading and the resulting neurological deficits observed in the animal. For example, cerebral concussion is defined as "a graded set of clinical syndromes following head injury where an increasing severity of disturbance in level and content of consciousness is caused by mechanically induced strains affecting the brain" (Ommaya and Gennarelli 1974). It is proposed that these mechanically induced strains appear in a centripetal manner, where the strains are highest along the periphery of the brain in mild mechanical insults and gradually penetrate into deeper brain structures as the applied mechanical energy level increases. In part due to the different neuroanatomical organization of the miniature pig, we have found that this overlying hypothesis for the evolution of brain injury needs to be further clarified. Specifically, mechanically induced strains do not universally begin at the surface of the brain, especially in studying animal models; indeed, the complex interaction between the anatomical factors (geometry, organization, intracranial membranes) and the inertial loading may lend internal structures more at risk in comparison to structures along the periphery. In our experiments, we found that it is possible to have multi-focal injury distributions in the brain's interior region - including the diencephalic-mesencephalic core - with much less evidence of injury in the peripheral regions of the brain. It is the magnitude and location of the particular deformation gradient coupled with the centripetal sequence of mechanically induced strains that determine whether there is mild or severe brain injury occurs in the animal model.

The ability to develop a preferential distribution of brainstem injury and associate this lesion pattern to prolonged coma raises one direction for further study. In developing tolerance levels for diffuse brain injuries, it is already recognized that lesion patterns in the brain are sensitive to the head planar motions (Thibault and Gennarelli 1990). However, the tolerance for injuries with long term impairment (e.g., cognitive deficits) may be distinct from those developed for immediate neurological deficits such as traumatic coma, since the anatomic substrate of injuries associated with impairment may be different from those associated with coma. The complex interaction of the injuries to different white matter tracts throughout the hemispheres may further highlight these differences, since this multifocal injury may present problems for long term recovery. Therefore, it appears that the injury specific tolerance level efforts that are developed for brain injury may also need to consider the temporal course of the injury - i.e. if the tolerance is targeted towards acute or long term impairment.

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