Effect of the Inhomogeneous Brain Mechanical Characteristic on Dynamic Responses of Head under Trauma

Lihai Ren, Daniel Baumgartner, Johan Davidsson, Jikuang Yang, Rémy Willinger

Abstract Finite element (FE) brain models have been used as an effective tool for the investigation of traumatic brain injuries. The biofidelity of these models has been improved constantly in recent years. However, the inhomogeneous mechanical characteristic of brain tissue has to a large extent been neglected in FE brain modeling. The objective of this study was to determine the effect of such inhomogeneous characteristic on brain responses under traumatic mechanical loadings. Based on region-specific experimental rat brain tissue responses, an inhomogeneous rat brain FE model was developed. Sagittal plane rotational impact tests were simulated and intracranial dynamic responses of the new inhomogeneous model were compared with those of a homogeneous model.

The stress responses changed distinctly from the homogeneous model to the inhomogeneous model while dramatic and significant differences of the peak values were observed in the hippocampus, brainstem and cerebellum. The strain responses of these two rat brain models were similar while the significant difference of the peak values was only observed in the hippocampus with a small relative error.

The study illustrated that the intracranial stress responses were more sensitive to such inhomogeneous characteristic than the intracranial strain responses when the head is subjected to rapid sagittal plane rotational acceleration trauma.

Keywords Animal experiment, finite element modeling, inhomogeneous brain model, traumatic brain injury

I. INTRODUCTION

Traumatic brain injury (TBI) is a serious public health problem in our modern society while severe TBI may result in permanent or long-term disability, or even death. In the United States, 1.7 million people sustained TBI annually, and 52,000 civilians died from TBI-related injuries every year on average between 1997 and 2007 [1]. A summary of 23 European reports showed that, for every 100,000 population in Europe, about 235 people suffered a TBI [2]. Meanwhile, TBI is also an economic problem because of the huge financial cost of TBI-related hospitalizations [3-4] and the valued years of potential life lost due to TBI-induced death and disability [5]. Thus, numerous studies have been conducted in the last decades to clarify the pathological and biomechanics of TBI.

In the last ten years, finite element (FE) brain models have been widely used as an effective tool to investigate the mechanism of TBI. Due to the visualized mechanical responses in FE simulations, the combination of FE brain model simulations and *in vivo* impact tests has gradually been one of the most essential strategies for the investigation of the mechanisms of TBI. Recently, via the reconstructions of *in vivo* impact tests on rat brain (using validated rat brain FE models), the thresholds of traumatic brain injuries resulting from rapid rotational accelerations were investigated [6-9]. Also by using a validated rat brain FE model, Mao and Yang [10] investigated the mechanism and corresponding thresholds of TBI resulting from controlled cortical impacts. A series of frontal and occipital impacts on macaques were reconstructed by using the macaque brain FE model to find suitable predictors for concussion [11-12]. Meanwhile, validated FE brain models have been widely used in real world accident reconstructions. For example, accident reconstructions related to football game injuries for 24 head-to-head collisions were studied by Zhang et al. [13], where the predicted shear stress in the upper brainstem region of the human brain FE model was proposed as an effective predictor for mild TBI.

Lihai Ren is a PhD student in Mechanical Engineering at Hunan University, China and a visiting student at the University of Strasbourg, France. D. Baumgartner is an Associate Prof in Biomechanics at the University of Strasbourg, France (tel: +33 3 68 85 29 42, daniel.baumgartner@unistra.fr). J. Davidsson is an Associate Prof at the Division of Vehicle Safety at Chalmers University of Technology, Sweden. R. Willinger is a Prof in Biomechanics at the University of Strasbourg, France, and J. Yang is an Associate Prof at the Division of Vehicle Safety at Chalmers University of Technology, Sweden and a Prof at Hunan University, China.

Via reconstructions of 58 football head impacts, the injury prediction performances of various predictors for mild TBI were evaluated by Kleiven [14]. Marjoux et al. [15] evaluated the TBI injury prediction capabilities of both kinematics-based predictors and FE brain model-based criteria via reconstruction studies of 61 real world accidents where patients included footballers, motorcyclists and pedestrians. In their study, the criteria based on intracranial mechanical response parameters of an FE brain model were revealed as more effective predictors for moderate and severe neurological injuries than the criteria based on the global accelerations.

For the increase of the reliability of FE simulations, the biofidelity of FE brain models should be improved. Inhomogeneity is one of the essential characteristics of mammalian brain where mechanical properties vary from region to region [16-21]. For example, as observed in the micro-indentation tests, the short-term shear moduli of rat brain tissue varied from 1.5 kPa of cerebellum gray matter to 5.5 kPa of hippocampus CA1 area with the effective indentation strains around 10% [18]. On the basis of the inhomogeneous characteristic, existing FE brain models could be classified into three groups: homogeneous brain models, semi-homogeneous brain models and inhomogeneous brain models. In homogeneous brain models, only one or two material properties were assigned for various regions of brain tissue, such as the human brain model developed by Kang et al. [22]. In semi-homogeneous brain models, the brain tissue was divided into several components to represent the principal anatomical features, especially in the cerebrum where brain tissue was modeled by gray matter and white matter roughly [14, 23-26]. In inhomogeneous brain models, more anatomical features were represented and assigned with corresponding material properties, especially in the cerebrum where the hippocampus, thalamus, corpus callosum and other regions were represented [27]. By using those inhomogeneous (semi-homogeneous or inhomogeneous) brain models, influences of the inhomogeneous mechanical characteristic on intracranial dynamic responses have been investigated. In the study of Zhou et al. [26], a significant different shear response was observed in the inhomogeneous brain compared with those corresponding responses in the homogeneous brain. Simulations conducted by Kleiven [14] demonstrated that the stress pattern was different from the strain pattern in an inhomogeneous brain model, while Von Mises stress showed high levels close to and at the stiffer brainstem and mid-brain areas. In the study of Mao et al. [27], by sustaining the controlled cortical impacts, the strain pattern of the rat brain FE model with an inhomogeneous hippocampus was similar to the strain pattern in the rat brain with a homogeneous hippocampus, while different peak strain responses were observed in a few regions of the hippocampus. Even with these findings, the influence of the inhomogeneous characteristic on intracranial mechanical responses under trauma is still not clearly understood.

Thus, the objective of this study was to investigate the intracranial dynamic responses in rotational trauma using two FE-rat brain models: one with the brain properties being modeled as inhomogeneous and one with the brain properties being modeled as homogeneous. This will be helpful to the further investigation of the injury mechanisms and tolerances of TBI related to rotational impacts, as well as to future human brain FE model developments.

II. METHODS

FE rat brain model

A new inhomogeneous and a homogeneous rat brain FE model were built based on a model developed by Baumgartner et al. [28] and previously refined and validated in [7]. The model was composed of 156,656 hexahedral elements and 12,881 shell elements with an average edge size of 0.25mm. In the current study, components of the brain model were reorganized according to a rat brain atlas [29]. The rat brain (Fig. 1) was reorganized into 23 parts, which represented all essential anatomical features of rat brain, including cerebellum, olfactory bulbs, brainstem, cingulate cortex, orbitofrontal region, parietal region, striatum, temporal region, occipital region, entorhinal cortex, corpus callosum, hippocampus, septum, superior colliculus, subiculum, inferior colliculus, thalamus, hypothalamus, ventral tegmental nuclei, mesencephalic, tegmentum, mesencephalic tegmentum and aqueduct. The skull-brain interface was modeled as a component which was comprised of two layers of hexahedral elements, and connected with skull inner surface and brain surface through common nodes. A linear viscous elastic material model with low shear stiffness (0.5 kPa for the short-term shear modulus, 0.1 kPa for the long-term shear modulus and 80 $.s^{-1}$ for the decay constant) was

assigned to the skull-brain interface to represent the relative motion between the brain and skull. The outermost shell layer with rigid property was modeled to represent the skull of the rat head.

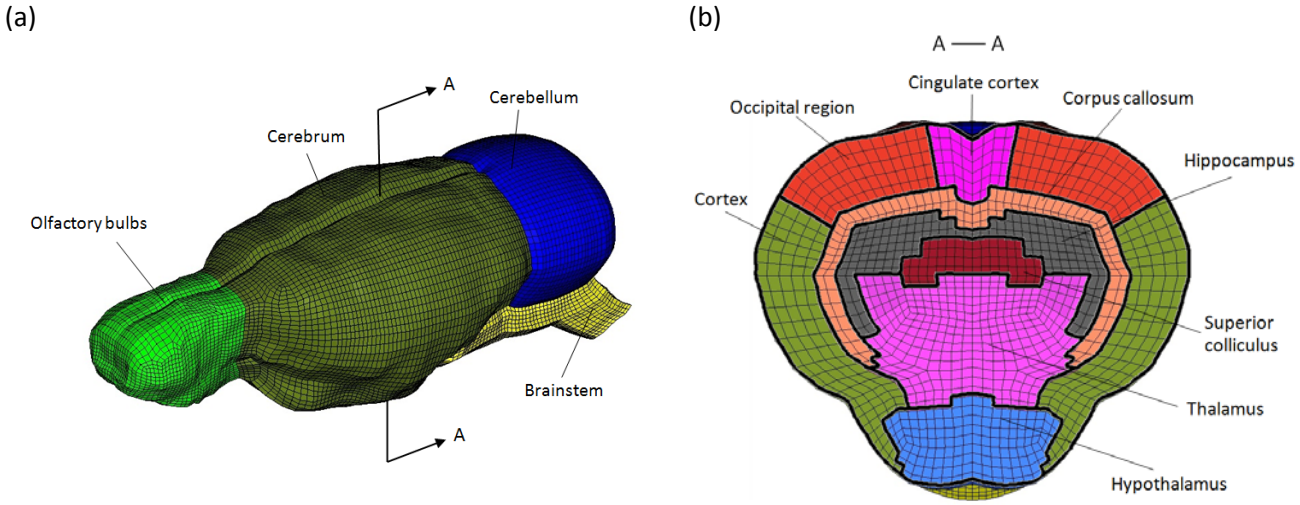

Fig. 1. The rat brain model with reorganized components. (a) Global view, (b) a coronal section view at the middle of the cerebrum.

In this study, region specific material properties measured from micro-level indentation-relaxation tests [18] were assigned to corresponding anatomical regions of the new inhomogeneous rat brain FE model. The regional relaxation functions for rat brain are illustrated in Fig. 2, and the Generalized Maxwell Kelvin model was used to represent the mechanical behavior of the rat brain tissue (as shown in Eq. 1).

$$G(t) = G_{\infty} + \sum_{1}^{3} G_i e^{-t/\tau_i} \tag{1}$$

where $G(t)$ are shear moduli and G_∞ are the long-term shear moduli in the indentation-relaxation tests. Prony series are used to describe the material behavior of brain tissue in the relaxations, where G_i are shear moduli and τ_i are the associated relaxation times. The detailed material constants for various brain regions and the solution for assigning the material properties into the current rat brain FE model are listed in Table 1. Additionally, a homogeneous rat brain model was developed to minimize the bias of brain stiffness, and one group of material properties with moderate stiffness (the relation function 3) was applied for all regions in the rat brain.

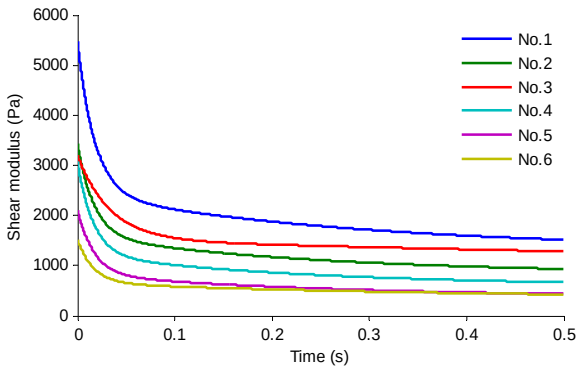

Fig. 2. Regional relaxation functions for rat brain. Note: The relaxation function 1 was measured from the CA1 area of the hippocampus; the relaxation function 2 was measured from the thalamus; the relaxation function 3 was measured from the middle layer of the cortex; the relaxation function 4 was measured from the corpus callosum; the relaxation function 5 was measured from the brainstem; the relaxation function 6 was measured from the grey matter of the cerebellum.

TABLE 1
MATERIAL PROPERTIES of INHOMOGENEOUS RAT BRAIN MODEL

No.	Anatomical regions	G_∞(Pa)	G_1(Pa)	τ_1(s)	G_2(Pa)	τ_2(s)	G_3(Pa)	τ_3(s)

1	Hippocampus, septum, superior colliculus, subiculum, inferior colliculus	667	1,026	0.265	3,042	0.0175	755	5.79
2	Thalamus, hypothalamus*, ventral tegmental nuclei, mesencephalic, tegmentum, mesencephalic tegmentum, aqueduct	398	1,825	0.0168	692	0.218	522	4.32
3	Cingulate cortex, orbitofrontal region, parietal region, striatum, temporal region, occipital region, entorhinal cortex, olfactory bulbs*	575	1,676	0.034	942	1.75		
4	Corpus callosum	199	1,843	0.0161	578	0.211	459	4.83
5	Brainstem	178	1,286	0.0168	424	0.239	230	4.33
6	Cerebellum	140	859	0.167	276	0.349	238	6.2

Note: The relaxation behaviors of the marked regions (*) were not measured in [18], thus material properties of corresponding neighboring regions were applied to these regions instead.

Simulation of sagittal plane rotational impacts

An *in vivo* animal model that produced diffuse axonal injury (DAI) in the rat brain has been developed by Davidsson et al. [30-31]. The model was designed to study head impacts resulting in sagittal plane rotational acceleration of the head that were found to produce DAI mainly in the corpus callosum and the brain stem.

The amount of DAI, as detected by the presence of Amyloid Precursor Protein (APP) in the injured axons, was classified into four grades according to the shape and the dimension of APP positive axons. For grade 1, observed APP positive axons were small but asymmetric. For grade 2, observed APP positive axons were large and asymmetric. For grade 3, observed APP positive axons were large and some extended along the axon which means severe axonal injury occurred. For grade 0, only slight APP stains were observed in the cell body.

In this study, three typical head impact tests were selected in order to represent low risk, moderate risk and high risk of DAI, respectively. The grades of axonal injury were 0 in all the sections of the rat brain when suffering the low rotational acceleration. Suffering the medium rotational acceleration, the grades of axonal injury could be grade 1 or above in most of the sections of the rat brain. The grade of axonal injury could be 2 or above in most of the sections of the rat brain following the impact with high rotational acceleration. The selected acceleration curves (as shown in Fig. 3) were imposed on the nodes of the skull layer in those simulations with the rotational center defined as the same as it was in the experiments: approximately 6.5 mm beneath the center of gravity of the rat brain (as shown in Fig. 4).

The intracranial mechanical responses (Von Mises stress and maximum principal strain) were calculated and compared between the homogeneous and inhomogeneous rat brain models. Especially, the time historical responses were extracted from the elements of eight anatomical regions of interest for a quantitative analysis, including the cingulate cortex, corpus callosum, hippocampus, thalamus, hypothalamus, olfactory bulbs, cerebellum and brainstem. Moreover, a one-way analysis of variance (ANOVA, anova1.m in MATLAB) was conducted on the mechanical responses to test for an effect of the mechanical inhomogeneity. The F-test was used to test for differences between the mechanical responses of those two rat brain FE models in each region of interest. A value of p greater than 0.05 was considered as not statistically significant.

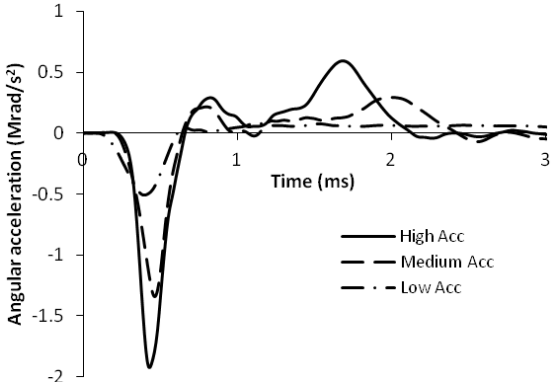

Fig. 3. Angular accelerations of three typical experiment cases.

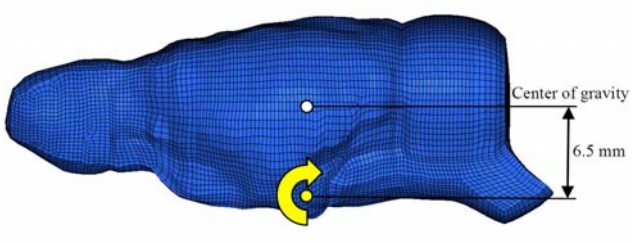

Fig. 4. Setup of the FE simulation. The yellow node represents the rotational center and the yellow arrow represents the rotational direction of rat brain.

Validation of the inhomogeneous rat brain FE model

The performance of the newly developed inhomogeneous rat brain FE model subjected to the current sagittal plane rotational impact was validated in this study. Three additional tests were conducted for the measurement of the kinematic responses of the brain tissue under the sagittal plane rotational acceleration by using the same *in vivo* animal model [9]. To record the kinematic responses of the brain tissue, a steel needle with a diameter of 0.5 mm was inserted into the rat brain and the rear part of the needle was firmly fixed with the skull cap which was glued to the skull. The trace of the inserted needle (presented as the scratch/blood clot) in the rat brain was measured at certain distances below the brain surface in the horizontal plane. The relative skull-brain displacements, which are equal to the corresponding scratch length minus the diameter of the inserted needle, were calculated at 0.5 mm below the brain surface (as listed in Table 2).

TABLE 2
EXPERIMENTAL DATA OF THE ROTATIONAL IMPACTS WITH A INSERTED NEEDLE

	Peak rotational acceleration (Mrad/s^2)	0.5 mm below the brain surface	
		Scratch length (mm)	Relative skull-brain displacement (mm)
Test RKI300	1.64	1.1	0.6
Test RKI301	1.73	1.3	0.8
Test RKI302	1.65	1.1	0.6
Average	1.67	1.17	0.67

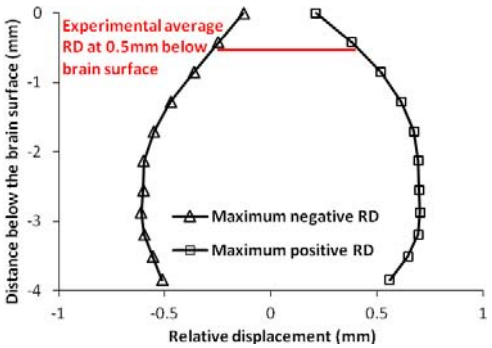

Fig. 5. Relative skull-brain displacements (RD) in the anterior-posterior direction of the rat brain. The triangular symbols indicate the maximum negative displacement relative to the skull of nodes at the location where the needle was inserted into the brain (approximately 3.5 mm to the rear and 2.2 mm to the right of the Bregma), while the rectangular symbols indicate the corresponding positive relative diplacements.

The average rotational acceleration curve was implemented on the inhomogeneous rat brain FE model for the

validation of the inhomogeneous rat brain FE model. The motions of the brain tissue relative to the skull in the anterior-posterior direction were extracted at the position where the needle was inserted. As illustrated in Fig. 5, the relative skull-brain displacement in the inhomogeneous rat brain FE model was close to the average experimental relative displacement (0.67 mm).

III. RESULTS

The inhomogeneous rat brain FE model and the new homogenous rat brain FE model were developed from the prior validated homogeneous rat brain FE model via the implementation of recently measured mechanical properties of brain tissue in various regions. In this study, three sagittal plane rotational impact tests were reconstructed by using the homogeneous and inhomogeneous rat brain models, respectively. Intracranial dynamic responses were calculated and are illustrated below. Especially, a quantitative analysis of the influence of inhomogeneity on the intracranial mechanical responses was conducted in eight regions of interest. For each of the eight anatomical regions, 64 elements in a cube area at the general position of maximal dynamic responses were selected for a calculation of the mean peak value of the stress/strain responses. Thus, the occurrence of isolated elements, presenting maximal but not meaningful values, was avoided. The one-way ANOVA method was conducted to test the difference in peak mechanical responses of these selected elements in each region of interest between the homogeneous and inhomogeneous models.

Von Mises Stress (VMS)

As illustrated in Fig. 6, the contours of VMS responses were quite different between the homogeneous rat brain model and the inhomogeneous rat brain model, especially in the central areas of the rat brain. In the homogeneous model, high VMS responses were observed in the cingulate cortex, hypothalamus region and center areas of the rat brain. Compared with VMS response of the homogeneous model, intensified stress concentrations were observed in the center areas of the inhomogeneous rat brain model.

The peak stresses of those eight regions of interest are illustrated in Fig. 7. In the homogeneous rat brain model, the highest peak stress was at the cingulate cortex, followed by the peak stress at the hippocampus, while the lowest peak stress was at the olfactory bulbs. Unlike the distributions of peak stresses in the homogeneous model, the highest peak stress was at the hippocampus in the inhomogeneous model, followed by the peak stress at the cingulate cortex. Dramatic differences of VMS responses were observed in the hippocampus, cerebellum and brainstem between the homogeneous model and the inhomogeneous model with significant differences ($p<0.01$). In the hippocampus, around 60 percent higher peak values of Von Mises stresses were produced by the inhomogeneous characteristic. On the contrary, around 40 percent and 50 percent lower peak values of Von Mises stress were produced by the inhomogeneous characteristic in the brainstem and the cerebellum, respectively.

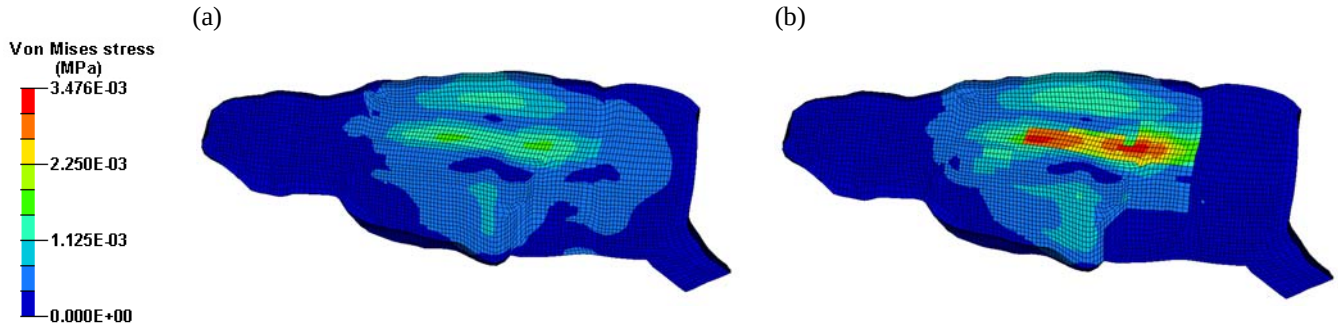

Fig. 6. Contours of VMS at the middle sagittal plane with the medium rotational acceleration (at the simulation time when maximum stress response was observed at the inhomogeneous model). (a) The homogeneous rat brain model, (b) the inhomogeneous rat brain model.

(a) (b)

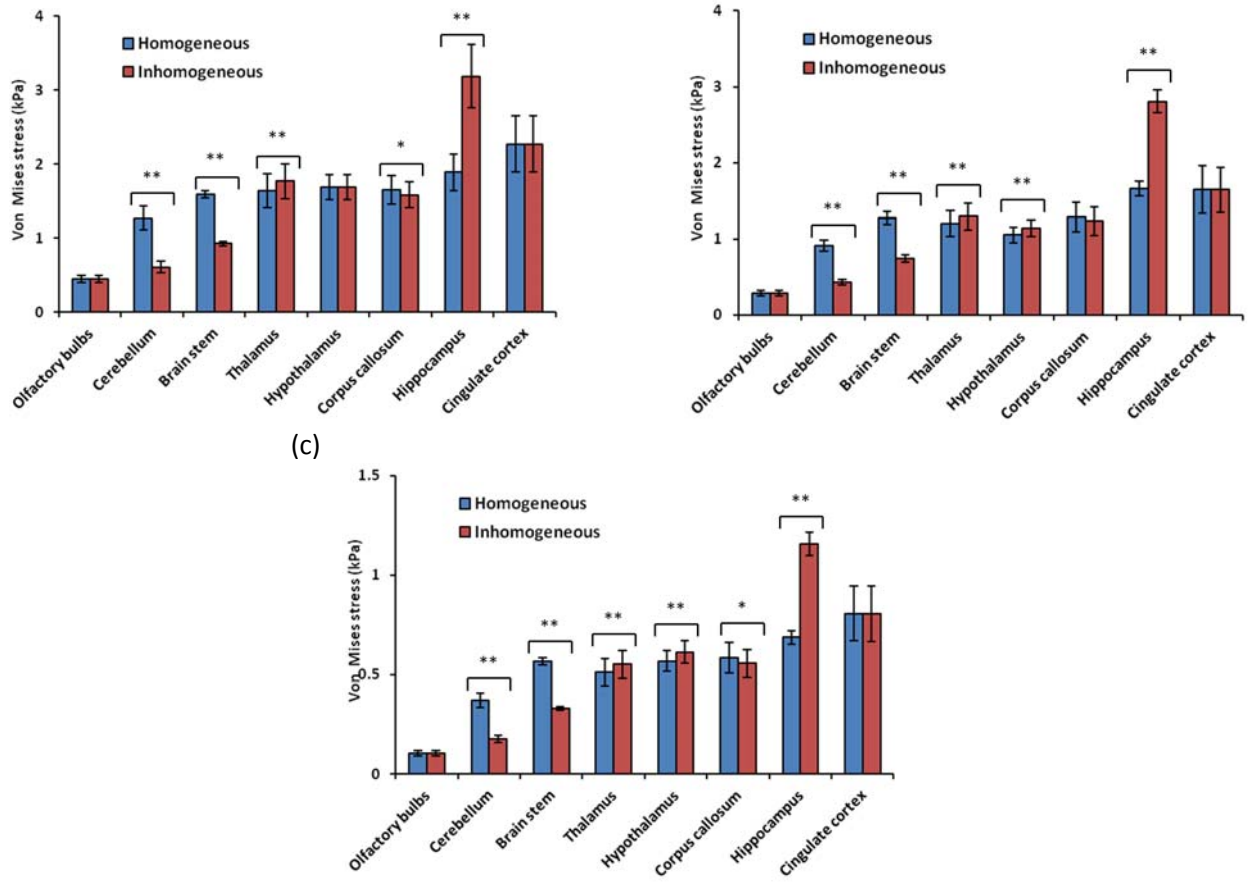

Fig. 7. Peak values of VMS in selected regions: (a) simulations with the high rotational acceleration, (b) simulations with the medium rotational acceleration, (c) simulations with the low rotational acceleration. Data are presented as mean ± standard error of the mean. Horizontal lines above bars indicate significant difference between brain responses of the homogeneous and inhomogeneous models: * represents a significant difference with $p<0.05$, ** represents a significant difference with $p<0.01$.

Maximum principal strain (MPS)

The distribution of MPS responses in the homogeneous model was almost the same as that in the inhomogeneous model, with high MPS responses observed at the cingulate cortex and hypothalamus regions and also in the center areas of the rat brain (as shown in Fig. 8).

As illustrated in Fig. 9, the peak strains of the homogeneous model in selected regions were close to the corresponding values in the inhomogeneous model, while the significant difference ($p<0.05$) was only observed in the hippocampus with a relative error of 2 percent between the homogeneous and inhomogeneous models at the medium rotational acceleration (Fig. 9(b)). Meanwhile, the distributions of the strain responses were consistent with the stress responses in the homogeneous model: the highest peak strain was in the cingulate cortex, followed by the peak strain in the hippocampus, while the lowest peak strain was in the olfactory bulbs.

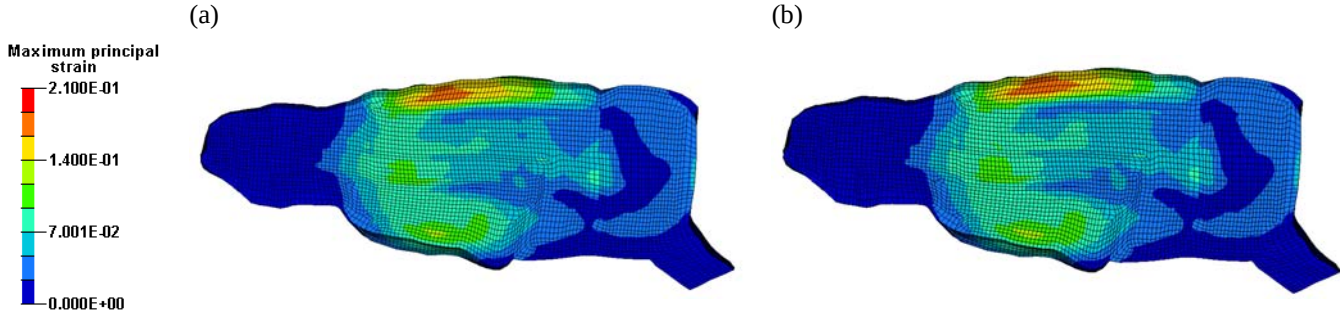

Fig. 8. Contours of MPS at the middle sagittal plane with the medium rotational acceleration. (a) The homogeneous rat brain model, (b) the inhomogeneous rat brain model.

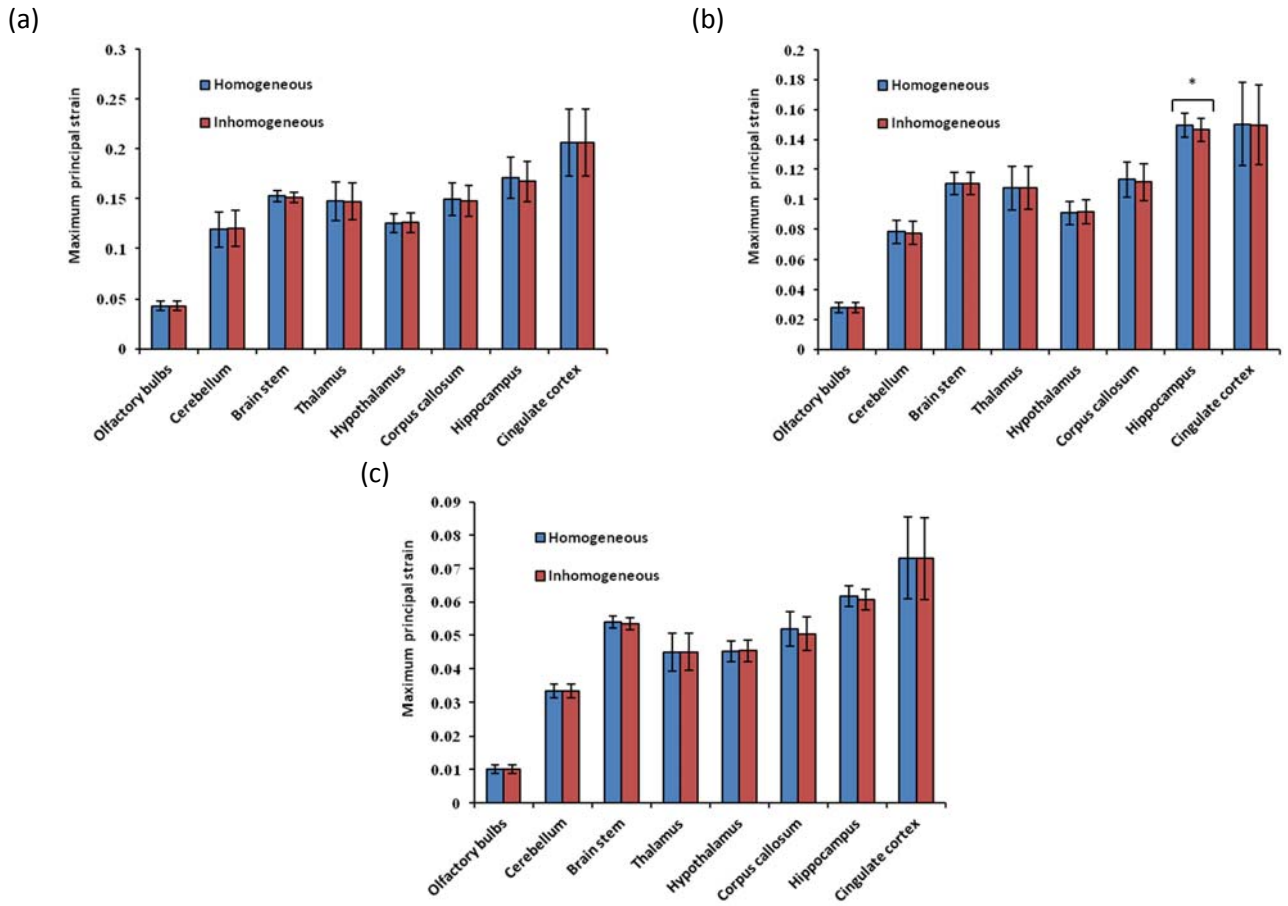

Fig. 9. Peak values of MPS in selected regions: (a) simulations with the high rotational acceleration, (b) simulations with the medium rotational acceleration, (c) simulations with the low rotational acceleration. Data are presented as mean ± standard error of the mean. Horizontal lines above bars indicate significant difference between brain responses of the homogeneous and inhomogeneous models: * represents a significant difference with $p<0.05$.

IV. DISCUSSION

The objective of this study was to investigate the effect of the inhomogeneous brain mechanical characteristic on intracranial dynamic responses relative to head trauma. Therefore, an inhomogeneous and a new homogeneous rat brain FE models were developed based on the previously developed homogeneous model. Three typical rat brain impact tests that represent low brain injury risk, moderate brain injury risk and severe brain injury risk, respectively, were selected for these simulations by using the two new rat brain models.

Rationale for the choice of mechanical parameters

Dynamic responses of rat brain were calculated and compared between the homogeneous rat brain model and the inhomogeneous rat brain model. In the current study, Von Mises stress and maximum principal strain were calculated rather than the intracranial pressure responses. High intracranial pressure was suggested to be the mechanism for coup/countercoup injuries induced by direct impact [14, 26] rather than the mechanism for DAI. Moreover, intracranial pressure did not show any correlations with distribution of DAI in the FE reconstruction of a motocross accident with the brain injury pattern seen in medical images [14]. In addition, intracranial pressure response is dependent on the density of the material used in the FE model [32], and independent of bulk modulus and shear modulus [33]. Also, it has been observed in [26] that almost the same intracranial pressure responses were observed in the homogeneous and inhomogeneous brain models when the brain models were subjected to either a frontal impact or a sagittal plane rotational impact. Thus, intracranial pressure responses were not considered in the current study.

Rationale for the validation of the rat brain FE model

The previously developed homogeneous rat brain model has been validated against dynamic cortical deformation (DCD) experiments [7]. Simulated displacements represented in the previous homogeneous rat brain model were close to the lowest experimentally-measured deformation and around 1.5 times lower than the experimental mean results. Compared with the stiffness of the brain tissue (with a short-term shear modulus of 10 kPa) in the previous homogeneous model, the material properties that were assigned to the brain tissue (with the short-term shear moduli ranging from 1.65 kPa to 5.5 kPa) were a little bit softer but in the same range. It could be predicted that higher displacements and closer similarity to the mean experimental results should be produced in the DCD tests in the new inhomogeneous model compared with the previous homogeneous model. However, considering the objective of the current study, validation of the new inhomogeneous rat brain model against the DCD tests was not included.

Instead, the new inhomogeneous rat brain FE model was validated against the sagittal plane rotational impacts. The experiments, reconstructed for both model validation and inhomogeneity-influence investigation simulations, were conducted by using the same test rig. The magnitude of the acceleration for model validation was between the magnitudes of the medium and high accelerations for the inhomogeneity-influence investigation. As illustrated in Fig. 5, the kinematic responses of the brain tissue that were predicted in the inhomogeneous model were consistent with the experimental result at the outer cortex (0.5 mm below the brain surface). Deduced from the similar strain responses that were predicted in the new inhomogeneous and homogeneous rat brain FE models, the performance of the homogeneous model in the rotational impact for the validation could be similar with the corresponding performance of the inhomogeneous model.

Rationale for the difference in brain responses between the homogeneous and inhomogeneous models

In general, as illustrated in Fig. 6, there were distinct differences between the calculated stress patterns of the homogeneous rat brain model and the calculated stress patterns of the inhomogeneous rat brain model. Sustaining the medium rotational acceleration, the peak value of VMS in the hippocampus increased by 69 percent from 1.66 kPa in the homogeneous model to 2.8 kPa in the inhomogeneous model (Fig. 7(b)). An opposite phenomenon occurred in the brainstem and cerebellum, where the peak values of VMS decreased by 41 percent and 52 percent, respectively. The increased/decreased Von Mises stresses from the homogeneous model to the inhomogeneous model resulted from changed short-term shear modulus between these two models. As illustrated in Fig. 2, the short-term shear modulus of the hippocampus increased by 62 percent from 3.4 kPa in the homogeneous model to 5.5 kPa in the inhomogeneous model, while the short-term shear modulus of the brainstem and cerebellum decreased by 41 percent and 51 percent, respectively. This observation was supported by the parameter studies conducted by Baumgartner et al. [28] which showed that the Von Mises stress increased linearly with the short-term shear modulus. The study of Zhou et al. [26] also revealed that, with the shear modulus of white matter increased by 60 percent, the peak value of shear stress in the genu increased by 31 percent and 59 percent in the frontal impact case and sagittal plane rotational impact case, respectively. Similar to the stress pattern of the inhomogeneous rat brain model in the current study, high stresses were observed close to and at the stiffer brainstem and mid-brain area in the study of Kleiven [14].

The strain responses of brain tissue were not as sensitive as the stress responses to the variation of mechanical properties. The calculated MPS of the two rat brain models were almost the same both in distribution and magnitude (as shown in Figs. 8 and 9). Similar phenomenon had also been observed by Mao and Yang [10] in the simulation of controlled cortical impact tests. In their study, the peak VMS dramatically increased by 383.56 percent with a decrease of 1.54 percent for MPS. Especially, via the implementation of similar relaxation functions as those used in the current study, a rat brain FE model with an inhomogeneous hippocampus was developed for the simulation of the CCI tests [27]. In [27], the contours of the strain responses of the inhomogeneous hippocampus were similar to the corresponding contours of the homogeneous hippocampus. The peak strain values of the inhomogeneous model were close to the corresponding peak strain values of the homogeneous model in most of the anatomical regions in the hippocampus, while the maximum relative error was approximately 23 percent in the dentate gyrus. Dramatic variation of strain responses could be produced when the material properties of whole brain tissue varied by a large range. For example, in the study of Kleiven [14], the FE brain model with stiffer properties (with an effective short-term shear modulus of 831 kPa) produced around 40 percent lower peak values of the maximum principal strain compared with the FE brain model with an effective short-term shear modulus of 415 kPa when

the head FE models were subjected to combined translational and rotational accelerations. However, the range of the short-term shear moduli measured from the rat brain (varied from 1.65 kPa of the cerebellum to 5.5 kPa of the hippocampus) was quite small. Thus, the effect of the inhomogeneity on the intracranial strain responses could be quite less compared with the observations in the studies of Kleiven.

Limitations and future studies

A linear viscous elastic material model was used for rat brain tissue in the current study, which can only represent the characteristics of brain tissue sustaining small deformation [34-35]. Non-linear behavior could be observed when the shear strains exceed the linear viscous elastic limit, while the shear moduli of brain tissue appears to decrease with the increasing strain [36-37]. Hyperelastic behavior and strain rate sensitivity have been observed in dynamic shear, tension and compression tests of brain tissue [16, 38-42]. Moreover, for the investigation of tissue level mechanisms and criteria of brain injuries, not only the inhomogeneous characteristic but also the anisotropic characteristic of the brain tissue should be represented. The crucial role of the anisotropic characteristic of the brain tissue has already been demonstrated in several simulation studies by using multi-scale brain models [43-44] and fractional anisotropic brain models with nerve fibers [45-47]. Consequently, considering the exceeding 25 percent of the maximum calculated MPS, a non-viscoelastic or viscous hyperelastic material model as well as an advanced brain modeling method should be introduced in future studies.

Another limitation in this study was that non-smooth boundaries were used in the definition of anatomical regions in the rat brain. For future FE brain modeling, the boundaries between various anatomical regions of brain tissue should be represented by using more detailed medical images. In addition, the influence of boundary conditions, such as constraints from the spinal cord, on intracranial dynamic responses should be considered in future studies.

Further, traumatic brain injury resulting from direct impacts should also be simulated for the analysis of the influence of the inhomogeneous characteristic on intracranial dynamic responses. In spite of numerous animal experiments (where cerebral concussion or diffuse axonal injury is produced by rotational acceleration only [31, 48]), the real world traffic accident investigation demonstrated that nearly all the severe brain injuries were correlated with direct head impact [49-50]. Additionally, it has been proven by the study of King et al. [51] that the intracranial strains were induced by both linear acceleration and rotational acceleration. Thus, *in vivo* animal experiments with brain injuries induced by direct head impact [52] should be simulated to understand the effect of the inhomogeneous mechanical characteristic on intracranial dynamic responses in real world accidents.

V. CONCLUSIONS

Simulations in this study provided a view of the effect of the inhomogeneous mechanical characteristic on intracranial dynamic responses. Sustaining rapid rotational accelerations, the calculated brain Von Mises stress changed dramatically with the variation of the stiffness (short-term shear moduli) from the homogeneous brain model to the inhomogeneous brain model. Unlike the stress responses, the calculated maximum principal strain remained constant between the homogeneous brain model and the inhomogeneous brain model. As a conclusion, the intracranial stress responses are quite sensitive to the inhomogeneous mechanical characteristic of the brain tissue rather than the intracranial strain responses when the head is subjected to the rapid sagittal plane rotational impact.

VI. ACKNOWLEDGEMENT

This study was supported by the China Scholarship Council (CSC).

VII. REFERENCES

[1] Coronado VG, Xu L, et al. Surveillance for traumatic brain injury-related deaths: United States, 1997-2007. US Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.

[2] Tagliaferri F, Compagnone C, Korsic M, Servadei F and Kraus J. A systematic review of brain injury

epidemiology in Europe. *Acta Neurochirurgica*, 2005, 148(3):255-268.
[3] Bruns JJ, and Hauser WA. The Epidemiology of Traumatic Brain Injury: A Review. *Epilepsia*, 2003, 44(Suppl. 10):2-10.
[4] McGarry LJ., Thompson D, et al. Outcomes and costs of acute treatment of traumatic brain injury. *Journal of Trauma-Injury, Infection and Critical Care*, 2002, 53(6):1152-1159.
[5] Maas AIR, Stocchetti N and Bullock R. Moderate and severe traumatic brain injury in adults. *The Lancet Neurology*, 2008, 7(8):728-741.
[6] Lamy M, Baumgartner D, Davidsson J and Willinger R. Traumatic brain injury investigation using FE modeling of the rat and experimental high amplitude rotations in the sagittal plane. *Proceedings of IRCOBI Conference*, 2013, Gothenburg, Sweden.
[7] Lamy M, Baumgartner D, Yoganandan N, Stemper BD and Willinger R. Experimentally validated three-dimensional finite element model of the rat for mild traumatic brain injury. *Medical & Biological Engineering & Computing*, 2013, 51(3):353-365.
[8] Lamy M, Baumgartner D, Yoganandan N and Willinger R. Mild traumatic brain injury in the rat: Three-dimensional finite element model using experimental data. *Proceedings of IRCOBI Conference*, 2011, Krakow, Poland.
[9] Antona-Makoshi J, Davidsson J, Risling M, Ejima S and Ono K. Validation of local brain brain kinematics of a novel rat brain finite element model under rotational acceleration. *Proceeding of JSAE Annual Congress*, 2013, Yokohama, Japan.
[10] Mao H and Yang KH. Investigation of brain contusion mechanism and threshold by combining finite element analysis with in vivo histology data. *International Journal for Numerical Methods in Biomedical Engineering*, 2011, 27(3):357-366.
[11] Antona-Makoshi J, Davidsson J, Ejima S and Ono K. Reanalysis of monkey head concussion experiment data using a novel monkey finite element model to develop brain tissue injury reference values. *Proceedings of IRCOBI Conference*, 2012, Dublin, Ireland.
[12] Antona-Makoshi J, Davidsson J, Ejima S, Ono K, Brolin K and Anata K. Correlation of global head and brain tissue injury criteria to experimental concussion derived from monkey head trauma experiments. *Proceedings of IRCOBI Conference*, 2013, Gothenburg, Sweden.
[13] Zhang L, Yang KH and King AI. A proposed injury threshold for mild traumatic brain injury. *Journal of Biomechanical Engineering*, 2004, 126(2):226.
[14] Kleiven S. Predictors for traumatic brain injuries evaluated throught accident reconstructions. *Stapp Car Crash Journal*, 2007, 51(October 2007):81-114.
[15] Marjoux D, Baumgartner D, Deck C and Willinger R. Head injury prediction capability of the HIC, HIP, SIMon and ULP criteria. *Accident Analysis & Prevention*, 2008, 40(3):1135-1148.
[16] Elkin BS, Ilankovan A and Morrison B 3rd. Age-dependent regional mechanical properties of the rat hippocampus and cortex. *Journal of Biomechanical Engineering*, 2010, 132(1):011010.
[17] Elkin BS, Ilankovan AI and Morrison B 3rd. A detailed viscoelastic characterization of the P17 and adult rat brain. *Journal of Neurotrauma*, 2011, 28(11):2235-2244.
[18] Finan JD, Elkin BS, Pearson EM, Kalbian IL and Morrison B 3rd. Viscoelastic properties of the rat brain in the sagittal plane: effects of anatomical structure and age. *Annals of Biomedical Engineering*, 2012, 40(1):70-78.
[19] Finan JD, Pearson EM and Morrison B 3rd. Viscoelastic properties of the rat brain in the horizontal plane. *Proceedings of IRCOBI Conference*, 2012, Dubin, Ireland.
[20] Green MA, Bilston LE and Sinkus R. In vivo brain viscoelastic properties measured by magnetic resonance elastography. *NMR in Biomedicine*, 2008, 21(7):755-764.
[21] Kaster T, Sack I and Samani A. Measurement of the hyperelastic properties of ex vivo brain tissue slices. *Journal of Biomechanics*, 2011, 44(6):1158-1163.
[22] Kang HS, Willinger R, Diaw BM and Chinn B. Validation of a 3D anatomic human head model and replication of head impact in motorcycle accident by finite element modeling. *Proceedings of the 41st Stapp Car Crash Conference*, 1997, Lake Buena Vista, FL, USA.
[23] Mao H, Zhang L, et al. Developmetn of a finite element human head model partially validated with thirty five experiemntal cases. *Journal of Biomechanical Engineering*, 2013, 135(11): 111002.
[24] Kleiven S and Hardy WN. Correlation of an FE model of the human head with local brain motion-consequences for injury prediction. *SAE Conference Proceedings*, 2002.
[25] Kleiven S. Evaluation of head injury criteria using a finite element model validated against experiments on localized brain motion, intracerebral acceleration, and intracranial pressure. *International Journal of*

Crashworthiness, 2006, 11(1):65-79.
[26] Zhou C, Khalil TB and King AI. A new model comparing impact responses of the homogeneous and inhomogeneous human brain. *SAE Conference Proceedings*, 1995.
[27] Mao H, Elkin BS, Genthikatti VV, Morrison B 3rd and Yang KH. Why is CA3 more vulnerable than CA1 in experimental models of controlled cortical impact-induced brain injury? *Journal of Neurotrauma*, 2013, 30(17):1521-1530.
[28] Baumgartner D, Lamy M and Willinger R. Finite element analysis of traumatic brain Injuries mechanisms in the rat. *Proceedings of IRCOBI Conference*, 2009, York, UK.
[29] Paxinos G and Watson C. The rat brain in stereotaxic coordinates: hard cover edition. *Academic press*, USA, 2006.
[30] Davidsson J, Angeria M and Risling M. Injury threshold for sagittal plane rotational induced diffuse axonal injuries. *Proceedings of IRCOBI Conference*, 2009, York, UK.
[31] Davidsson J and Risling M. A new model to produce sagittal plane rotational induced diffuse axonal injuries. *Front Neurol*, 2011, 2:41.
[32] Bradshaw DRS and Morfey CL. Pressure and shear responses in brain injury models. *Proceedings of the 17th International Technical Conference on the Enhanced Safety of Vehicles*, 2001, Amsterdam, Netherlands.
[33] Thomas LM, Roberts VL and Gurdjian ES. Impact-induced pressure gradients along three orthogonal axes in the human skull. *Journal of Neurosurgery*, 1967, 26(3):316-321.
[34]Bilston LE, Liu Z and Phan-Thien N. Linear viscoelastic properties of bovine brain tissue in shear. *Biorheology*, 1997, 34(6):377-385.
[35] Nicolle S, Lounis M, Willinger R and Palierne JF. Shear linear behavior of brain tissue over a large frequency range. *Biorheology*, 2005, 42(3):209-223.
[36] Bilston LE, Liu Z and Phan-Thien N. Large strain behaviour of brain tissue in shear: Some experimental data and differential constitutive model. *Biorheology*, 2001, 38(4):335-345.
[37] Brands D, Bovendeerd P, Peters G and Wismans J. The large shear strain dynamic behaviour of in-vitro porcine brain tissue and a silicone gel model material. *Stapp Car Crash Journal*, 2000, 44:249-260.
[38] Miller K and Chinzei K. Constitutive modelling of brain tissue: Experiment and theory. *Journal of Biomechanics*, 1997, 30(11–12):1115-1121.
[39] Miller K and Chinzei K. Mechanical properties of brain tissue in tension. *Journal of Biomechanics*, 2002, 35(4):483-490.
[40] Rashid B, Destrade M and Gilchrist MD. Mechanical characterization of brain tissue in tension at dynamic strain rates. *Journal of the Mechanical Behavior of Biomedical Materials*, 2014, 33(May 2014): 43-54.
[41] Rashid B, Destrade M and Gilchrist MD. Mechanical characterization of brain tissue in compression at dynamic strain rates. *Journal of the Mechanical Behavior of Biomedical Materials*, 2012, 10(June 2012):23-38.
[42] Rashid B, Destrade M and Gilchrist MD. Mechanical characterization of brain tissue in simple shear at dynamic strain rates. *Journal of the Mechanical Behavior of Biomedical Materials*, 2013, 28(December 2013):71-85.
[43] Cloots RJH., Van Dommelen JAW, Nyberg T, Kleiven S and Geers MGD. Micromechanics of diffuse axonal injury: Influence of axonal orientation and anisotropy. *Biomechanics and Modeling in Mechanobiology*, 2011, 10(3):413-422.
[44] Cloots RJH, Van Dommelen JAW, Kleiven S and Geers MGD. Multi-scale mechanics of traumatic brain injury: Predicting axonal strains from head loads. *Biomechanics and Modeling in Mechanobiology*, 2013, 12(1):137-150.
[45] Giordano C, Cloots RJH, Van Dommelen JAW and Kleiven S. The influence of anisotropy on brain injury prediction. *Journal of Biomechanics*, 2014, 47(5):1052-1059.

[46] Sahoo D, Deck C and Willinger R. Development and validation of an advanced anisotropic visco-hyperelastic human brain FE model. *Journal of the Mechanical Behavior of Biomedical Materials*, 2014, 33(May 2014):24-42.
[47] Wright RM and Ramesh KT. An axonal strain injury criterion for traumatic brain injury. *Biomechanics and modeling in mechanobiology*, 2012, 11(1-2):245-260.
[48] Fijalkowski RJ, Stemper BD, Pintar FA., Yoganandan N, Crowe MJ and Gennarelli TA. New rat model for diffuse brain injury using coronal plane angular acceleration. *Journal of Neurotrauma*, 2007, 24(8):1387-1398.

[49] McLean AJ. Brain injury without head impact? *Journal of Neurotrauma*, 1995, 12(4):621-625.

[50] Yoganandan N, Gennarelli TA., Zhang J, Pintar FA., Takhounts E and Ridella SA. Association of contact loading in diffuse axonal injuries from motor vehicle crashes. *Journal of Trauma-Injury, Infection and Critical Care*, 2009, 66(2):309-315.

[51] King AI, Yang KH, Zhang L, Hardy W and Viano DC. Is head injury caused by linear or angular acceleration. *Proceedings of IRCOBI Conference*, 2003, Lisbon, Portugal.

[52] Marmarou A, Abd-Elfattah Foda MA, Van den Brink W, Campbell J, Kita H and Demetriadou K. A new model of diffuse brain injury in rats. Part I: Pathophysiology and biomechanics. *Journal of Neurosurgery*, 1994, 80(2):291-300.