# STRAIN DISTRIBUTION IN BRAIN TISSUE OF RATS SUBJECTED TO CLOSED HEAD INJURY IS AGE-DEPENDENT

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## INTRODUCTION

Traumatic brain injury (TBI) is the dominant cause of death among infants and young children, and most fatal cases are attributed to motor vehicle accidents, falls and abuse [1]. With today's computer power, these injury scenarios can be studied using finite element (FE) computer simulations, but such simulations must be able to represent the unique mechanical characteristics of the infant or young child's brain. In a recent study, we characterized the age-dependent mechanical properties of the rat brain and found that the neonatal rat brain tissue is significantly stiffer than mature brain tissue [2]. Specifically, shear moduli of rat brains post-natal-day (PND) 17 or younger were ~1.9-fold those of rat brains PND 43 or over [2]. Brain tissue strains over ~10% that are induced at rates greater than ~1000% per second are associated with TBI [3,4], but considering the different mechanical properties between neonatal and mature brain tissues [2] (as well as the different sizes and masses), the extent of exposure to critical strains during TBI is expected to differ between neonatal and mature brains even under the same injury conditions. This limits the design of animal model studies aimed at comparing pathohistological and behavioral consequences of TBI across ages. The objective of this study is therefore to determine the strain and stress distributions in mature (PND 43) and neonatal (PND 13-17) rat brains during the same "cortical impact" closed head injury, using FE modeling.

## METHOD

We developed three-dimensional FE models of the rat brain and braincase at PND 13-17 and PND 43 under cortical impact closed head injury. Briefly, the cortical impact injury model in the rat is a well-established, widely-used model which employs pneumatically-driven rigid impactor to deliver mechanical energy to the intact skull of an anesthetized rat [5]. The head of the rat is fixed during delivery of the impact, and velocity (5 m/s) and depth of impact (2.44 mm) are mechanically controlled. By 3-weeks, cell death, hemispheric loss and ventricular expansion appears and progresses chronically 1 year post-injury, with patterns that are known to be age-dependent [5]. Histological evaluation by the neurobiologist of our group (RR) demonstrated widespread cortical damage and ablation of the gray and, to a lesser extent, underlying white matter. Immunohistochemstry further observed axonal changes after mild cortical impact over the parietal cortex while at moderate and high injury severity, contralateral damage and axonal injury in the adjacent white matter, corpus callosum and internal capsule were evident. To simulate these animal studies, we generated a computer reconstruction of the mature rat brain using an anatomical digital database ("The Rat Brain in Stereotaxic Coordinates", Academic Press). Using solid modeling software (Solid Works 2003), we scaled the solid reconstruction of the rat brain geometry to the age of the animal (PND 13-17 and PND 43) based on our previous measurements of rat brain length, width and thickness with age [2]. Next, the solid models were transferred to a FE solver (NASTRAN 2003). A braincase layer was constructed on the brain cortex in the models by projecting the brain surface elements outwards to form the braincase thickness measured for each age group in the rat (0.16 mm for PND 13-17, and 0.4 mm for PND 43, [2]). Brain tissue was considered a viscoelastic solid material with a time-dependent shear modulus *G(t)*:

$$G(t) = (G_\infty - G_i)(1 - e^{-t/\tau}) + G_i \qquad (1)$$

where the instantaneous shear moduli $G_i$ were taken from previous experiments as 3336 and 1721 Pa for PND 13-17 and PND 43, respectively, long-term moduli $G_\infty$ were set as 786 Pa and 508 Pa for PND 13-17 and PND 43, respectively, and the relaxation decay constant $\tau$ was taken as 8 seconds [2]. The braincase layer was considered a linear elastic material with modulus of 6.3 MPa for both age groups [2]. Brain was considered as an incompressible material and accordingly, Poisson's ratio for brain was taken as 0.499. Poisson's ratio of 0.4 was set for the braincase [2]. Models were constrained at the base of the braincase for translation and rotation, and no slip was allowed between the braincase and brain. Concentrated force was applied on the left hemisphere, 19º to the vertical axis and halfway between the Bregma and Lambda sutures to simulate the impactor. Using trial-and-error, this force was increased in each age model stepwise, until it generated maximal braincase deflection of 2.44 mm - which matched the experimental design.

## RESULTS

Values of the peak cortical impact forces required for imposing a 2.44 mm maximal braincase deflection were 14.95 N and 2 N for the PND 13-17 and PND 43, respectively. For these simulation cases, detailed analyses of the state of internal deformations, principal compressive stresses and von Mises stresses in the brain and braincase tissues were conducted. We found that the age of the animal substantially affects the distribution of tissue deformations and stresses under cortical impact. Specifically, peaks of principal compressive stress under the impactor were 80 KPa PND 13-17 and 14.4 KPa PND 43. Peaks of von Mises stress under the impactor were 8.33 KPa PND 13-17 and 2.1 KPa PND 43. We conclude that during a cortical impact experiment, the stiffer tissue in the neonatal brain is subjected to peak stress magnitudes that are 4-fold to 6-fold greater than those in the mature brain. The magnitudes of deformation (Fig. 1) in the central contralateral (right) brain hemisphere during impact were substantially lower in the mature brain (PND 43: under 0.05 mm) with respect to the neonatal brain (PND 13-17: mean 0.34 mm). Likewise, the magnitudes of stresses in the contralateral hemisphere were lower in the mature brain (PND 43: mean 2.4 KPa and 0.35 KPa for principal compression and von Mises, respectively) compared with the neonatal brain (PND 13-17: mean 10.4 KPa and 0.83 KPa for principal compression and von Mises, respectively). We conclude that cortical impact closed head injury studies in the rat impose relatively less mechanical loading on the contralateral hemisphere of the mature brain compared with the neonatal brain. Peak strain rates for brain tissue, however, were similar between PND 13-17 (59426% per second) and PND 43 (57377% per second). Importantly, we found that at the instant of maximal indentation (2.44 mm), the PND 13-17 brain was exposed to substantially greater strain magnitudes than those developed in the 43 PND brain. We quantified the percentage of brain volume subjected to strain levels above 5%, 8%, 11%, 13% 16% and 21%, in each age group and fitted polynomial curves to these discrete FE calculations (Fig. 2). Considering the 10% strain threshold for axonal injury [3,4], we find that 11% of the PND 13-17 brain volume is subjected to strains above 10%, but only 6% of the PND 43 brain volume is exposed to the injuring >10% strains under the same cortical impact experimental conditions (2.44 mm indentation at 5 m/s). The brain volume subjected to strains over 5% is 1.5-fold greater in the PND 13-17 brain (33%). The brain volume subjected to very large strains, over 20%, is less than 0.33% in both age groups (Fig. 2).

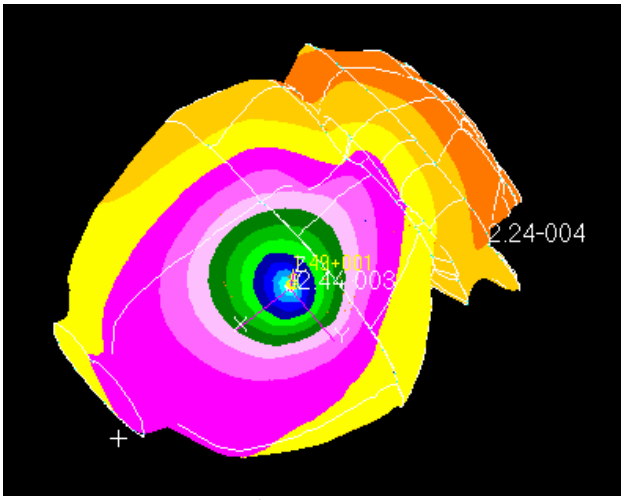


**Figure 1. Distribution of braincase displacements during "cortical impact" closed head injury in a PND 13-17 rat, shown from a superior-lateral view.**

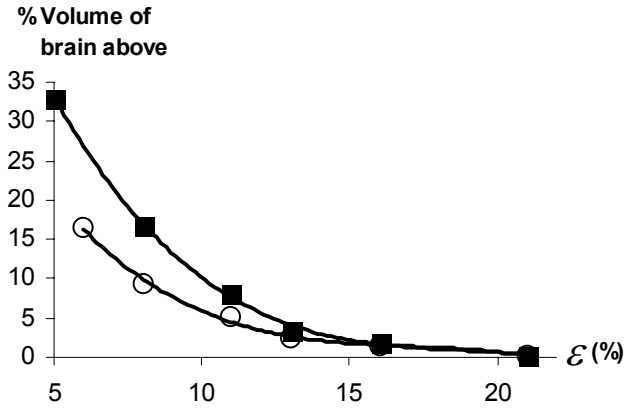


**Figure 2. Percentage of brain volume subjected to strain levels above 5%, 8%, 11%, 13% 16% and 21% in simulations for PND 13-17 (■) and PND 43 (○) rat age groups.**

## DISCUSSION

The neonatal rat brain differs from the mature brain in geometry, mass and material properties [2]. The present FE simulations show that under identical experimental conditions of cortical impact (i.e. same indentation depth and velocity) in two age groups - PND 13-17 and PND 43 - stress and strain magnitudes and distributions will differ substantially, and this should be carefully considered while designing experimental protocols. Fortunately, with the aid of the FE methodology presented herein it is possible to manipulate the indentation depth in order to produce similar tissue strain magnitudes and strain distributions across age groups. This will require studying the strain distributions produced by other indentation depths in search for equivalent effects between age groups. Development of an additional FE model of the adult (90 PND) rat brain is currently underway in our group, to allow scaling of the strain distributions with respect to adult rats. In conclusion, the present simulations indicate that for identical cortical deflections, the neonatal brain is exposed to larger peak stress magnitudes compared with a mature brain due to stiffer tissue properties in the neonate, and larger strain magnitudes due to its smaller size.

## ACKNOWLEDGMENT

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