Diffusion MRI microscopy, voxelwise group analysis and flattened cortex visualization to identify meaningful markers of post-traumatic cortical changes in the mouse.

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Introduction

Non-invasive imaging, in particular MRI, is an advantageous approach for the investigation of TBI in animal models as it is whole brain, high-throughput, longitudinal and quantitative. Additionally, imaging markers identified in these models may be used to develop clinical imaging tools or as powerful outcome measures in animal studies to develop therapies. However, in order to realize the potential of these strengths, it is crucial that imaging markers of post-traumatic abnormalities be well characterized in terms of spatio-temporal course, reproducibility and underlying biology. In this study, we have employed high-resolution ex-vivo diffusion imaging of the mouse brain following mild controlled cortical impact (CCI) to identify consistent and reproducible spatial and temporal patterns of diffusion abnormalities in cortical tissue as well as performed histological analysis to examine the neurobiological basis for these abnormalities.

Methods

Mouse brain samples were obtained following mild CCI to sensory cortex at survival times of 24h (n=6), 1 week (n=5), 4 weeks (n=6) and 12 weeks (n=6). Controls (n=7) were surgically naive. A subset of these extracted brains (n=17) were treated identically with 48 hours post-fix period and storage in saline and these were used for quantitative analysis, while the remaining 15 samples underwent variable tissue processing prior to imaging and were used only for supplemental qualitative comparisons.

Imaging was performed using a 7T vertical bore Bruker microimaging system. Briefly, 297 diffusion weighted and reference images were acquired with b-values up to 10,000 s/mm2 as well as an anatomical reference image. The isotropic resolution for all images was 100 microns. Standard DTI processing was performed using the TORTOISE pipeline and mean apparent propagator (MAP) modeling was performed with IDL software.

Analysis methods included: 1. voxelwise statistics using tensor-based diffeomorphic registration with DTITK and statistical testing by the FSL randomise utility, 2. “Flattening” of the cortical geometry was accomplished by thin plate spline warping of individual brain maps to generate new map volumes with information from the same cortical depth represented in each slice.

Results and Discussion

Whole-brain voxelwise ANOVA with time-point group as a single factor was performed for FA and Trace and regions with significant main effect was found for both indices. The largest region of significance was found in the cortex near the injury site. This was investigated in greater detail using normalized difference maps between each CCI group and the control group. These maps revealed a large region of decreased perilesional diffusivity at 24 hours, this difference was less at 1 week and at 4 and 12 weeks, only a narrow band of reduced diffusivity was found to border the injury site. FA group difference maps revealed decreased FA values at 24 hours in the perilesional region followed at 1 week by a region of increased FA lateral and posterior to the injury site. This regional group difference was progressively larger at 4 and 12 weeks. While many possible interpretations of these findings exist, decreased values of Trace during the acute phase may suggest greater density of cells and/or processes in the perilesional cortex and progressively extending perilesional regions of increased FA, may indicate plasticity or unmasking by cell loss during the chronic phase.

In order to examine these broad group differences in greater detail, a larger set of DTI and MAP MRI maps of the cortex (including FA, Trace, linear and planar anisotropy, directionally encoded color maps, return to the origin probability, non-gaussianity and propagator anisotropy) were "flattened" as described above. This visualization approach revealed a remarkably organized pattern of multiple perilesional subdomains of abnormal tissue regions with distinct diffusion profiles different distances from the injury site. These subdomains were reproducible within each group and demonstrated progressive differences with time following injury.

Conclusion

In this study we used high-resolution diffusion MRI to establish the presence and nature of cortical abnormalities following mild CCI. Using voxelwise analysis, we showed decreased perilesional diffusivity in the day following CCI and a progressive increase in perilesional FA in the months following. Upon examination of greater detail in the flattened cortex, we show highly organized subdomains of diffusion abnormalities following injury.