# Diffusion and Perfusion Imaging in Repeated Concussion

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**Target Audience** Researchers and clinicians with an interest in repeated concussion and mild traumatic brain injury

**Purpose** Although a single brain concussion rarely has lasting effects, recurrent concussions may result in cumulative chronic neurological and neuropsychiatric impairments. These effects may be due to the subsequent concussion occurring while the brain is in a period of increased vulnerability after the initial insult [1]. The current clinical management of concussion is based on assessing for the resolution of neurocognitive impairments, however an asymptomatic state may not accurately indicate that the brain has fully recovered. Magnetic resonance imaging is a potential platform for assessing the brain effects of concussion. In particular, diffusion and perfusion may be sensitive to the subtle pathophysiological changes that occur in the concussed brain and contribute to the cumulative and degenerative effects of repeated concussion. Here we employed a rat model of concussion in conjunction with MRI and behavioural biomarkers to investigate: (a) whether MRI can detect injury and assess recovery from concussion; (b) the relationship between MRI and behavioural biomarkers; and (c) to assess the effects of repeated concussion.

**Methods** The study design consisted of three groups of male Long-Evans rats randomly assigned to each group. The model used was the mild lateral fluid percussion injury and animals were given a combination of either two sham injuries (sham group, n=8), one sham injury and one mild traumatic brain injury (single mTBI, n=8), or two mTBIs (repeated mTBI, n=9), with injuries separated by five days. Imaging was performed on days 1, 3, 5, 7 and 30 days post second injury using a Brüker 4.7 Tesla MRI fitted with BGA12S-HP actively shielded gradient set. Multi-echo $T_2^*$-weighted (TR=4400ms, TE=7.5, 15… 60ms, FOV=28.8×28.8mm$^2$, matrix=160×160, 64 slices, slice thickness=180µm, perfusion (FAIR-RARE with constant recovery time=10,000ms, RARE factor=72, FOV=30×30mm$^2$, slice thickness=2mm, TI=100, 200…2000, 2500, 3000ms, inversion slab thickness=4mm) and diffusion (EPI-DWI, TR=6000ms, TE=35ms, FOV=25.6×25.6mm$^2$, matrix size=128×128, slices=24, slice thickness=600µm, δ=3.5ms, Δ=14ms, 81 directions, 8 non-diffusion, b-value=1200s/mm$^2$) datasets were acquired using volume transmit/4-channel array receive coils. A second cohort of animals in each group underwent behavioural testing at the same time points.

**Results** A single mTBI resulted in transient cognitive deficits to three days post injury with no evidence of behavioural deficits at later time points. Rats in the repeated mTBI group had significantly worse outcomes with persisting cognitive deficits at day 30. In the single mTBI group, hypoperfusion was observed to three days post injury, which extended to five days post injury in the repeated mTBI group (Figure 1). FA template images showed reduced integrity of the ipsilateral corpus callosum in the single mTBI group, which persisted to day 30. In the repeated mTBI group, acute ipsilateral corpus callosum damage was worse and again, persisted to day 30. Disruption of white matter fibres was observed in the cortex, corpus callosum and hippocampus in both single and repeated mTBI groups with persisting abnormalities to 30 days post second injury (Figure 2).

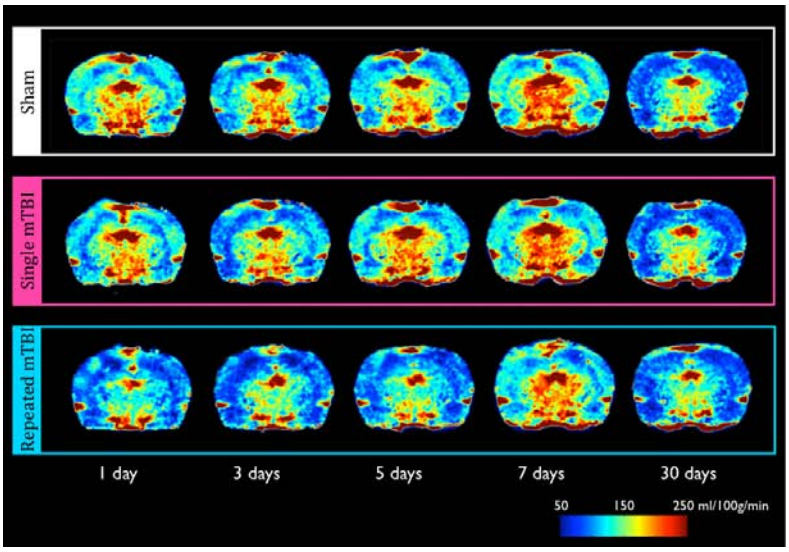


**Figure 1.** Perfusion images at days 1, 3, 5, 7 and 30 post 2nd injury.

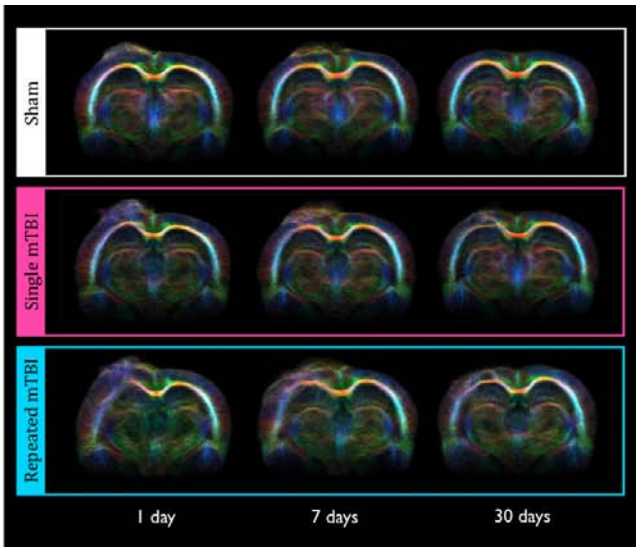


**Figure 2.** Tractography images at days 1, 7 and 30 post 2nd injury.

**Conclusion** Both FA and tractography showed structural abnormalities that were still present 30 days after a single mTBI, despite the relatively early resolution of neurocognitive impairments, suggesting that diffusion is a sensitive biomarker to the changes induced by a single mTBI. A second mTBI given five days after an initial mTBI, when behavioural impairments were no longer present, resulted in short-term motor deficits and clear and persisting cognitive deficits, consistent with previous findings of repeated concussion and CTE [2,3]. MR measures showed prolonged hypoperfusion and widespread white matter injury. While behavioural biomarkers were able to detect both acute and chronic deficits in repeated mTBI, MRI biomarkers were more sensitive to changes induced by a single mTBI. MRI biomarkers derived from streamlines tractography appear to be particularly sensitive to the structural changes occurring in the concussed brain. Furthermore, a second mild TBI given five days after an initial TBI, when behavioural impairments are no longer present, results in exacerbated outcomes.

**References** [1] Prins et al (2013) J. Neurotrauma 30:30-38, [2] Guskiewicz et al (2005) Neurosurgery 57 (4):719-726, [3] McKee et al (2009) J Neuropathol Exp Neurol 68(7):709-735.