showed abnormal MRI findings but seem normal on 3-T examination. Repeat imaging could, therefore, provide information on two fronts: identification of more potential surgical candidates, and prevention of unnecessary surgery.

Cortical dysplasia is often related to a high seizure frequency, but can be difficult to detect on MRI. The most recent classification system[7] differentiates between three types of cortical dysplasia on the basis of the underlying pathology. Type IIb is relatively easy to detect as hyperintensities on fluid-attenuated inversion recovery MRI.[8] Type IIa cortical dysplasia is less visible on MRI, but can often be detected by complementary analysis strategies.[9] A major challenge in future trials is the detection of type I cortical dysplasia.

A recent review of the pathology in MRI-negative epilepsy cases showed that the causes are quite heterogeneous and include patients who do not have a histopathological abnormality, but are postoperatively seizure-free.[10] In such cases, the resected tissue obviously had epileptogenic properties, but neither the neuropathologist nor the neuroradiologist could detect abnormalities with existing tools. This finding underlines the necessity to undertake and improve neuroimaging—with high-definition MRI, electromagnetic imaging, sophisticated nuclear neuroimaging and new innovative tracers—to increase the likelihood of detecting subtle anomalies. With further advances in neuroimaging, precise identification of the extent of the epileptogenic zone and/or of subtle cortical dysplasias—another challenge in imaging—might be possible.

The study by Winston *et al.*[4] illustrates the value of implementing a technical upgrade—to imaging in this instance—in our daily clinical practice. In practical terms, the study reminds us to adopt a more dynamic approach to the management of patients with ongoing seizures, including repeat MRI if technical or analytical improvements have occurred. If curative epilepsy surgery could be offered and was effective in this newly defined group of 5% of patients in whom brain abnormalities remain undetected under conventional MRI (of a total of ~1.2 million patients with pharmacoresistant epilepsy in Europe), a major step forward will have been taken in this not-so-benign condition.

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SPINAL CORD INJURY

Visualizing plasticity and repair in the injured CNS

David W. Cadotte and Michael G. Fehlings

The heterogeneity of traumatic spinal cord injury necessitates large clinical trials to differentiate natural improvements from enhanced recovery due to therapeutic intervention. Recent development of an imaging biomarker to visualize changes in the corticospinal motor system could offer the opportunity to directly visualize anatomical evidence of repair, regeneration and plasticity.

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Traumatic spinal cord injury (SCI) is a devastating event in a person's life, and can lead to loss of independence in activities of daily living.[1] Perhaps the greatest challenge to translation of novel therapeutics into clinical use is measurement of treatment effects in the context of the heterogeneity that exists both in terms of how individuals are injured (primary injury), and the resulting downstream biological effects of the initial trauma (secondary injury). As an illustration of such heterogeneity, up to 20% of individuals with severe SCI show improvement on standard clinical metrics defined by the American Spinal Injury Association (ASIA).[2,3] Large clinical trials and reliable biomarkers are needed to differentiate individuals who recover naturally—presumably because their injury has spared critical structural and functional elements of the spinal cord—from those who respond favourably to a planned intervention.

As recently reported in *The Lancet Neurology*, Freund and colleagues have developed a clever MRI-based method to visualize how the corticospinal tract (CST) changes after SCI and how these changes are ultimately linked to clinical function.[4] Noninvasive imaging techniques offer the potential to characterize residual structure and function of the spinal cord after injury.[5] This approach enables refinement of diagnosis from, for example, 'incomplete SCI'—a clinical diagnosis that stems from the ASIA classification scheme—to one that provides specific metrics of spinal cord structure and function. By reducing heterogeneity in a cohort of patients, clinicians and researchers can conduct more-efficient,

less-expensive clinical trials through use of a stratified randomized block design.

The new study by Freund *et al.*[4] involved prospective MRI investigation of the sensorimotor cortex and CST in patients with acute SCI. Through such methods, the researchers showed changes to the CNS motor pathway as early as 5 weeks after traumatic SCI relative to a cohort of healthy controls. These early imaging results then served as a baseline for subsequent 'snapshots' of CST structure at 2, 6 and 12 months after injury.

Throughout the longitudinal analysis, patients with SCI demonstrated decreased cortical grey matter volume in cortical area M1 in the left hemisphere, decreased subcortical white matter volume of the CST at the level of the corona radiata, internal capsule and medullary pyramid, and decreased spinal cord area rostral to the site of injury. A smaller loss of spinal cord area and less white matter volume change at the level of the internal capsule and cerebral peduncle were associated with better clinical outcomes relative to individuals who showed greater cord atrophy and white matter loss. Collectively, these findings provide strong support that the proposed CST imaging biomarker accurately measures changes in the CNS after SCI, and that changes in this biomarker reflect ultimate clinical function. Whether the proposed CST biomarker can be used to detect subclinical changes in response to a targeted therapeutic intervention remains to be determined.

> "...the researchers showed changes to the CNS motor pathway as early as 5 weeks after ... SCI..."

Response to therapy is currently defined according to either neurological or functional outcome measures, depending on the design of the trial. This approach is appropriate, as neurological capacity and the ability to use that capacity in daily life are key areas of focus for clinicians and researchers. An imaging biomarker, however, could enable detection of response to therapy before changes in neurological or functional outcomes become evident, thereby improving trial efficiency. For example, the evidence of microstructural changes that was detected by Freund *et al.*[4] at 5 weeks could potentially allow an interim analysis of a therapeutic agent long before the current intervals of 3–6 months, when neurological assessments are conducted.

> "...development of other imaging biomarkers will undoubtedly be an area of growth..."

Freund *et al.* should be congratulated for choosing to target the motor system. In a recent systematic review of studies to determine the health priorities of patients with SCI, regaining motor control was among the top-ranked priorities.[6] As imaging tools and data analysis methods continue to improve, development of other imaging biomarkers will undoubtedly be an area of growth. Freund and colleagues focused their efforts on microstructural changes in the CNS that occur together with changes in clinical function, but equally important are the functional properties of spinal and supraspinal circuits.

Early attempts to develop functional imaging biomarkers have focused on both motor and sensory pathways.[7,8] As these functional imaging biomarkers are refined to demonstrate longitudinal changes that correlate with clinical function, an important goal will be to determine the relationship between changes in imaging biomarker metrics and development of symptoms that are largely considered to be a consequence of maladaptive plasticity of functional circuits after traumatic injury—namely, spasticity and neuropathic pain. If, for example, an imaging biomarker can accurately detect the functional 'signature' of neuropathic pain, the biomarker could subsequently be used as an inclusion criterion for a trial that specifically aims to treat pain. This 'revised diagnosis' based on imaging might help to reduce the heterogeneity of treatment and control groups that results from the diverse aetiology of the patients' overall pain state, thereby providing a more efficient trial design. The combination of functional and microstructural imaging biomarkers offers the possibility to address the majority of patient-centred priorities with regard to recovery from SCI.

Considerable efforts have been made to mitigate damage to the spinal cord after traumatic injury. Examples include optimization of management at the scene of an accident, transportation to specialized centres, and early surgical decompression of the damaged bony spinal column.[9] Other novel therapeutics have been studied in preclinical models, and the process of translation for use in humans has commenced.[10] One of the most promising neuroprotective agents under current investigation in a phase I clinical trial is riluzole, a sodium channel-blocking agent that is approved for use in patients with amyotrophic lateral sclerosis.

The ultimate outcome after SCI must be measured in terms of clinical function. The effectiveness of a novel intervention, however, can potentially be measured in a more efficient, less expensive way through use of noninvasive imaging biomarkers. Through characterization of residual structure and function of the spinal cord and associated supraspinal pathways, the opportunity exists to refine the diagnosis of traumatic SCI and more closely follow the effects of novel therapeutic interventions.

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