Head first: Reshaping how traumatic brain injury is treated

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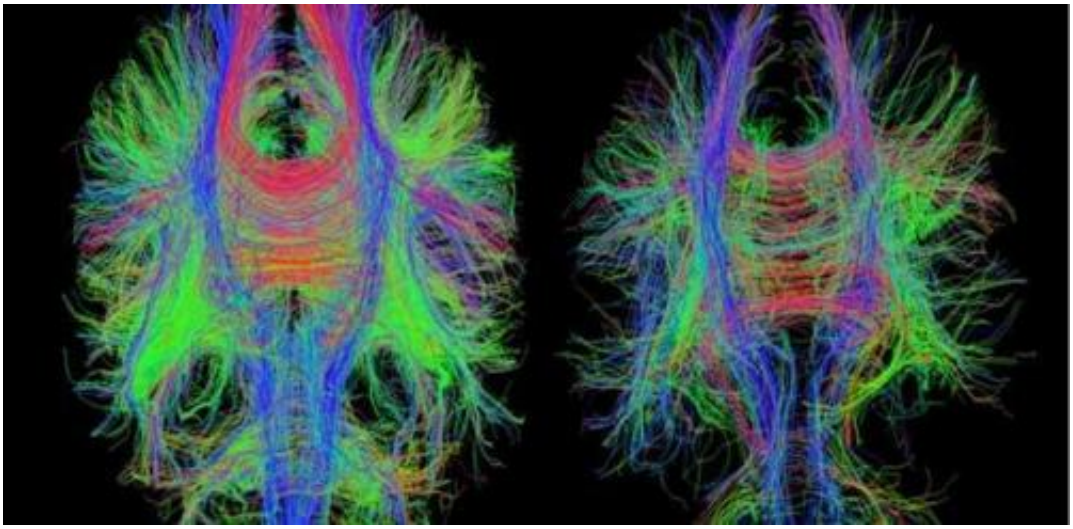

Compared with a normal brain (left), the number of white matter fibres in the brain following a traumatic brain injury (right) can be severely reduced. Credit: Virginia Newcombe, Division of Anaesthesia

(Medical Xpress)—Traumatic brain injury affects 10 million people a year worldwide and is the leading cause of death and disability in children and young adults. A new study will identify how to match treatments to patients, to achieve the best possible outcome for recovery.

The human brain – despite being encased snugly within its protective skull – is terrifyingly vulnerable to traumatic injury. A severe blow to the head can set in train a series of events that continue to play out for

months, years and even decades ahead. First, there is bleeding, clotting and bruising at the site of impact. If the blow is forceful enough, the brain is thrust against the far side of the skull, where bony ridges cause blood vessels to lacerate. Sliding of grey matter over white matter can irreparably shear nerve fibres, causing damage that has physical, cognitive and behavioural consequences. As response mechanisms activate, the brain then swells, increasing intracranial pressure, and closing down parts of the microcirculatory network, reducing the passage of oxygen from blood vessels into the tissues, and causing further tissue injury.

It is the global nature of the damage – involving many parts of the brain – that defines these types of traumatic brain injuries (TBIs), which might result from transport accidents, assaults, falls or sporting injuries. Unfortunately, both the pattern of damage and the eventual outcome are extremely variable from patient to patient.

"This variability has meant that TBI is often considered as the most complex disease in our most complex organ," said Professor David Menon, Co-Chair of the Acute Brain Injury Programme at the University of Cambridge. "Despite advances in care, the sad truth is that we are no closer to knowing how to navigate past this variability to the point where we can link the particular characteristics of a TBI to the best treatment and outcome."

This matching of therapy to the patient is known as personalised medicine. "There are many treatments that show promise. But what we've learned from clinical trials is that it's unlikely any particular intervention is going to be effective in all patients. We need instead to be thinking about customised healthcare based on knowledge of which treatment works best for whom and under what circumstances," he added.

Now, a project led by Menon in the Department of Medicine, together with Professor Andrew Maas of the University Hospital Antwerp, Belgium, aims to provide the evidence on which to base best practice treatment. With funding of £25 million from the European Union, more than 60 hospitals and 38 scientific institutes are participating in the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) project. In total, data will be collected for 20,000–30,000 patients, including extremely detailed data for over 5,000 patients.

"We need collaboration on this sort of scale to characterise TBI as a disease and to identify the most effective clinical interventions," explained Menon. "The burden incurred by TBI provides a strong medical, social and economic imperative to motivate this concerted effort. Similar projects in Asia, Australia and the USA are also now beginning, so we will eventually be able to collapse all the databases together and undertake incredibly statistically powerful analyses."

TBI affects an estimated 10 million people worldwide every year. In India alone, one person dies every 10 minutes as a result of TBI. Survivors can face a lifetime of disability, ranging from dizziness and reduced coordination to cognitive and behavioural problems that are severe enough to require full-time care. In the USA, the annual burden of TBI has been estimated at over $60 billion, with disability-related costs outweighing medical costs by a factor of four. Even mild cases of TBI – many of which go undetected because they are not treated in hospital – can result in problems with concentration and behaviour.

Moreover, epidemiological data suggest that, having suffered a TBI, the chance of developing dementia later in life increases by 2- to 4-fold, or 10-fold if the patient also has a genetic predisposition. In 2013, the US National Football League (NFL) settled a concussions lawsuit for $765 million after dozens of former NFL players developed degenerative

brain diseases, believed to be caused only by repeated head trauma.

For the past 15 years, Menon and colleagues such as Professor John Pickard have been investigating the mechanisms involved in TBI. "We discovered that patients whose injuries may have been classified as being similar had very different underlying brain pathologies," said Menon. "We also found evidence of delayed effects, where structural abnormalities only appeared days or weeks later. This attempt to identify different patterns of TBI that may have differing prognoses and therapy requirements chimes well with the evolving notion of precision medicine, which seeks to provide greater clinical differentiation of different disease trajectories," he added.

Menon was the first Director of the Neurosciences Critical Care Unit at Addenbrooke's Hospital in Cambridge. There, patients with TBIs are finely monitored to make sure that their blood pressure, O2 and CO2 levels are kept constant – even tiny fluctuations can spell further damage and even death. "However, this is an example of where we don't fully know the extent to which a procedure like this helps. Peter Hutchinson, NIHR Research Professor, is currently leading a trial from Cambridge to look at this question, and these data will be fed into the CENTER-TBI project."

Other recent research has been looking in fine-grained detail at changes that happen in the brain following TBI. Work with Dr Alasdair Coles in the Department of Clinical Neurosciences has shown that some patients 'autoimmunise' after TBI, developing antibodies against their own brain cells. "We don't know why or what consequences this might have – it could be protective or it could add to the inflammation and swelling," said Menon. "If we know that autoimmunity is associated with the patient having a good or bad recovery then we can intervene to initiate or prevent the process. If it turns out to be protective, there might even be a case for vaccinating after a TBI to kick-start autoimmunity."

Similarly, working with Dr William Stewart in Glasgow, and colleagues in Pittsburgh and Paris, Menon's team has been looking at the build-up of a brain peptide called beta-amyloid, commonly associated with the development of Alzheimer's disease. Following TBI in some patients, amyloid deposits in the brain can appear within 48 hours of injury and, although these deposits are cleared over weeks to months, their role in worsening brain injury remains uncertain. "We want to know whether this build-up is associated with white matter loss, and whether early intervention might reduce the chance of developing dementia," said Menon. Intriguingly, the collaborating group in Glasgow has shown that patients who survive a previous TBI can show a recurrence of amyloid deposition in later life.

Menon highlights behavioural changes as one of the most invidious aspects of TBI. "There are parts of the brain that make us who we are, that retain memories of our life and allow us to go forward. Injuries here change the person you are, which can have a massive impact on families." Professor Barbara Sahakian in the Department of Psychiatry has been looking at the neuroanatomical basis of impulsivity – one of the behavioural changes frequently seen following TBI. If the researchers can identify which parts of the brain are involved, there may be treatments to prevent some of these longer-term effects.

These research studies, together with the wider activities of the CENTER-TBI collaborating centres, will provide an unparalleled opportunity to refine both the clinical characterisation of an injury and provide individually targeted care. "You could say that the basic concept of the new project is to exploit the variability inherent in TBI," said Menon.

"There may be over 100 interventions we could do at the moment but none is uniformly protective, so we don't know how hard to try with them and it may even turn out that some do harm. If we can refine

characterisation of the injury and determine which clinical interventions are effective to treat those characteristics, this study could benefit millions of people."

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