Susceptibility mapping of brain blood oxygenation and brain network connectivity

Pioneering advanced imaging techniques, **Dr Zhifeng Kou** and his research team at the Wayne State University are exploring the changes that happen to the brain following head injury. Through better identification and diagnosis of vascular abnormalities, their non-invasive, sophisticated imaging tools have the potential to improve patient outcomes after head injury.

Dr Zhifeng Kou's research focuses on the development of non-invasive imaging techniques to investigate brain function following traumatic brain injuries (TBIs). Based upon susceptibility weighted imaging and mapping and other perfusion techniques, His team developed new methods to precisely quantify brain blood oxygenation and brain tissue viability. The team have also developed a novel framework, the connectivity domain, to investigate brain functional and structural networks. Together, these tools have huge potential implications for diagnosis, optimisation of management and the treatment of patients suffering from TBI.

TRAUMATIC BRAIN INJURIES (TBIs)

Traumatic brain injury, often referred to as TBI, is a complex injury that occurs when the brain is injured by an external force, either direct impact or inertial forces. Examples include motor vehicle accidents, falls, assaults or sports injuries. TBIs have a broad spectrum of symptoms and disabilities, and the impact on a person and his or her family can be devastating. With 1.7 million cases every year in the US alone, TBI is a leading cause of death and disability among children and young adults. Currently, over 5.7 million Americans are living with the after effects of TBI-induced disability. There are two types of brain injury following a TBI: primary brain damage that is used to describe the instant damage provoked by the injury, and secondary brain damage that refers to any subsequent damage that evolves over time. Following the primary injury, cerebral ischaemia (low blood supply), or hypoxia (low oxygen supply) and the manifestation of cerebral microbleeds (CMB) are the most important complications that can seriously compromise the health of the patient. It is therefore important to implement efficient methods that allow for the early detection of brain tissue at risk for cerebral ischaemia and hypoxia, thus assessing patients' condition and to implement patient-specific treatment strategies in order to prevent development of secondary injuries.

UNDERDIAGNOSES OF TRAUMATIC BRAIN INJURIES (TBIs)

Although vascular injury to the brain is common during TBI, it is poorly understood. Following the primary brain injury, brain ischemia, hypoxia and CMBs all lead to serious complications that can have a devastating effect on the patient. These include seizures, headaches, memory loss, dizziness, and depression. Despite this, current clinical imaging methods are not sensitive enough to reliably detect CMBs. So it comes as no surprise that current research is focused on introducing innovative strategies to help evaluate the extent to which the brain has been injured.

Dr Kou is introducing innovative strategies to help evaluate the extent to which the brain has been injured

In addition to brain vascular effect, the brain performs cognitive functions through the interactions of different neural networks. Brain injury will likely change the connectivity and dynamics of these neural networks. A novel method developed by Dr Kou's group, called Connectivity Domain Analysis, allows a more reliable way to measure the brain network connectivity across different centres and populations.

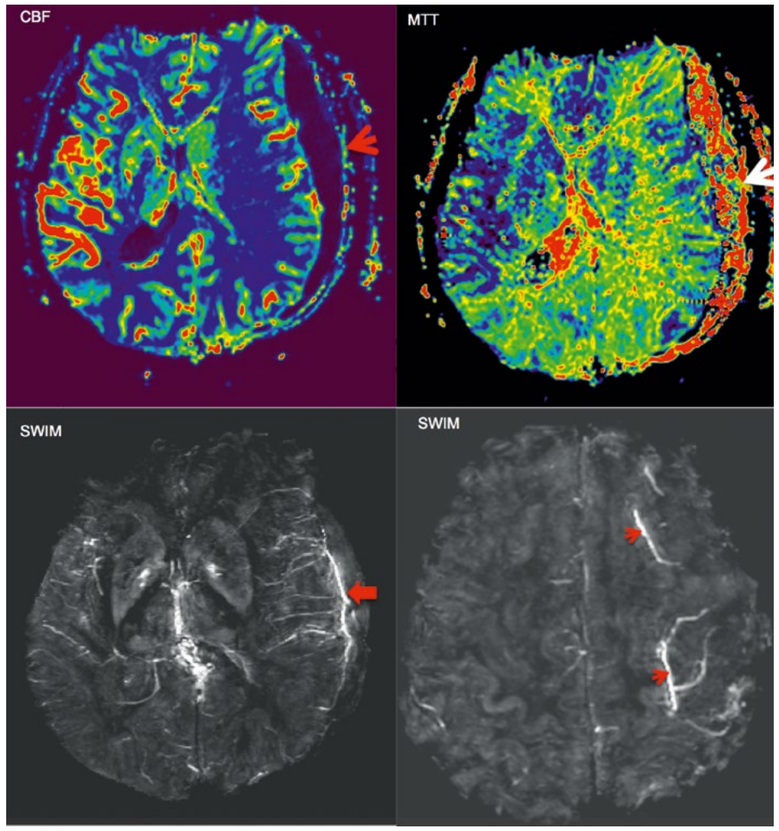
MAPPING MICROBLEEDS AFTER TBI - DEVELOPMENT OF AN INNOVATIVE NON-INVASIVE TECHNIQUE

Dr Kou, an Associate Professor of Biomedical Engineering and Radiology in the Wayne State University, and his team have introduced a novel non-invasive technique that successfully and efficiently assesses regional brain tissue for irreversible ischemic and hypoxia damage in critical care. Set to revolutionise clinical diagnoses of brain injuries in acute clinical settings, Dr Kou's method is based on the detection of important markers that assess the extent of damage following TBI. Firstly, CMBs are heavily associated with patient outcomes. Since the volume and number of CMBs can be efficiently used to predict the presence of brain damage in TBI patients (as compared with neurologically healthy age-matched controls), their detection and tracking over time presents an excellent way of monitoring patients' recovery. Secondly, Dr Kou's tool takes advantage of the fact that abnormal brain metabolism (measured by the

brain's metabolic rate of oxygen, or CMRO2), is associated with poor outcome of TBI patients.

THE IMPORTANCE OF SUSCEPTIBILITY WEIGHTED IMAGING AND MAPPING (SWIM)

Micro bleeds are important diagnostic biomarkers for TBI but very difficult to detect using current imaging methods. Teaming up with Dr E Mark Haacke, a MRI pioneer in the development of susceptibility weighted imaging and mapping (SWIM), Dr Kou's team developed the quantification of cerebral micro bleeds and brain tissue oxygenation in TBI patients. Specifically, their technique is based on a profound estimation of blood oxygenation in major veins – a bit like brain-embedded catheters – which act as markers of draining tissue oxygenation. Their tool has the edge over current methodologies, that are not only highly invasive but also inherently limited to a specific region of the brain vasculature. In a recently published study of 23 TBI patients, SWIM was able to differentiate haemorrhages from normal veins in TBI patients in a semi-automated manner with reasonable sensitivity and specificity. By further integrating SWIM with perfusion techniques, they developed novel methods to measure cerebral metabolic rate of oxygen (CMRO2). They created a patient-specific map of cerebral metabolic rate of oxygen levels (CMRO2). The research team are currently exploring the predictive value of this CMRO2 map for TBI patients' outcome, six months after injury.



Images from a severe head injury case. CBF map (upper left image) shows one side of the brain with reduced cerebral blood flow. MTT map (upper right image) also shows that it takes much longer time for the blood to deliver to the injury side of the brain. Arrows indicate the injury side. Hotter colour means higher value and colder colour means lower value on CBF and MTT maps.
SWIM maps (two bottom images) show high susceptibility signal of draining veins on the injury side of the brain (marked by arrows). This means the regional brain tissue drained by these veins suffers from low blood oxygenation. These veins function just like brain catheters to measure regional brain tissue oxygenation. But it is everywhere in the brain and non-invasive. By combining the blood flow and venous susceptibility, Dr Kou's team is developing a technique to measure brain tissue oxygen metabolism.

BRAIN NETWORK CONNECTIVITY DOMAIN: A MEANS TO INVESTIGATE BRAIN FUNCTION FOLLOWING AN INJURY

Dr Kou and his team clearly highlight the use of clinical non-invasive techniques that can allow measurements of cerebral haemodynamics and the detection of metabolic and connectomic changes of the brain following head injuries. However, Dr Kou's research is not limited to susceptibility mapping of cerebral oxygenation. Another aim is to unfold the underlying brain network connectivity, including both functional and structural networks. In collaboration with Dr Tianming Liu's group from the University of Georgia, Dr Kou's team is developing novel approaches to measure large scale brain network connectivities. This is based on analytical measurements stemming from functional magnetic resonance imaging (fMRI) that can trigger investigations regarding brain connectivity, and hence describe and assess cerebral function. More specifically, brain network connectivity can be generated by making use of theoretical models, which define whether a certain model fits the data exported, and data-driven methods that are based on the extraction of features from fMRI data. However, and as noted by Iraji et al. (2016), the transformation of the respective data is now performed on a new domain – the connectivity domain, as opposed to the conventional time domain – to overcome the cross-individual and cross-center difference. This method provides high levels of sensitivity and specificity that can identify changes of structural and functional connectivity on a connectome scale at the acute stage.

Synthetic biology has great potential in accurately installing modified pathways with unrivalled specificity, far superior to conventional genetic engineering methods

Q&A

Exactly how do you and your research team quantify cerebral microbleeds (CMBs)?

CMB contains hemosiderin, which has very high susceptibility signal. By quantifying the susceptibility signal on a SWIM map, we can quantify the volume and concentration of hemosiderin of the blood product, which is a measure of CMB quantification.

Your novel imaging techniques are non-invasive and have huge potential for guiding optimal treatment and monitoring of patients following a TBI. Are there any limitations or disadvantages of these techniques in clinical practice?

Clinically, a brain catheter is a widely used medical device to measure regional brain tissue oxygenation and metabolism. It gives continuous measurement but is limited to only one brain region and it is invasive. Our imaging technique can give a snap shot of the whole brain oxygenation and metabolism. It is non-invasive. As it is a snap shot, rather than a continuous measurement our method complements the current clinical technique well.

How did you develop the method to examine brain network connectivity?

In the current practice, researchers combine all subjects' brain images together and analyse the brain networks of the group data. This assumes that all individuals within the group share similar patterns of temporal brain network connectivity. However, this method is limited by differences between individuals, such that the repeatability of this method is only about 74%. To overcome this problem, we developed a novel approach, called connectivity domain analysis. Briefly, we first regress out the temporal information of each individual brain to extract their connectivity information at individual level, and then perform group based analysis to look for the overall consistent pattern. As it is not susceptible to individual differences, we have a very good test-retest reliability of 94%.

Can you briefly explain how is the susceptibility map created? Are there any inverse filters used?

SWIM is a phase-based analytical approach. It firstly unwraps the phase information of the brain, then removes the background noise, performs inverse filter to extract the susceptibility information, and finally performs an iterative approach to remove artifacts, yielding the final susceptibility map.

Your clinical research is extremely interesting and clearly has a huge potential impact for the treatment and management of patients with TBI. Does your research have other potential uses?

The approach could be used in many neurological diseases or disorders, including stroke, brain tumour, multiple sclerosis to name but a few.

PROVIDING CUSTOM-BASED SOLUTIONS FOR CLINICAL PROBLEMS

Excitingly, Dr Kou's research presents novel, non-invasive, sophisticated imaging techniques that have the capacity to improve early identification and diagnosis of vascular abnormalities following TBI. Not only does early detection allow accurate assessment of the patients' condition, it is necessary for implementation of patient-specific treatment strategies to prevent secondary injuries from developing. Their non-invasive assessment of brain haemodynamics enhance our understanding of the way that the brain is capable of recovering following a TBI. Furthermore, the development of connectome-scale assessment tools can allow for distinct evaluation and identification of structural and functional connectivity changes provoked by mild traumatic brain injury at the acute stage. The significance of this research is validated by the fact that Dr Kou has been given a mandate from the Office of the Vice-President for Research to create a Center of Excellence in TBI. Dr Kou's research has huge potential for optimal monitoring of patients' recovery and outcomes.

References: Iraji A. et al., 2016. Neuroimage, 134, pp. 494-507

Detail

RESEARCH OBJECTIVES

Using advanced imaging technologies, Dr Kou and his research team provide solutions to clinical problems. As well as specialising in advanced magnetic resonance imaging (MRI) of traumatic brain injury (TBI), the team have also developed novel, non-invasive imaging tools to investigate changes of the brain after head injury.

FUNDING

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- Department of Defense

COLLABORATORS

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BIO

Dr Zhifeng Kou is a translational neuroimaging scientist. He is pioneering MRI investigation of brain concussion patients at emergency departments. He develops imaging-based non-invasive tools to improve the diagnosis and outcome prediction of brain injury patients. His imaging work focuses on brain vascular effects and large scale brain networks after head injury.

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