

# Improving brain health by identifying structure-function relations in patients with neurosurgical disorders

Use of new technology to map which parts of the brain control different functions is leading to better treatment of patients with neurosurgical disorders, say **Liwei Zhang and colleagues**

**B**rain diseases amenable for neurosurgery comprise a group of conditions that are caused by damage to identifiable brain structures. These diseases threaten long term brain health and cause a large burden on both individuals and societies. Tumours originating in the brain, for example, are the most common fatal cancers in children as well as the third most commonly occurring cancers in adolescents and young adults (15-39 years old).<sup>1</sup> Epilepsy is another common neurological disorder that is often caused by specific brain structural abnormalities. Around 10 million patients are thought to have epilepsy amenable to surgery, with 1.4 million new cases globally each year.<sup>2</sup>

Neurosurgery can repair structural problems in the brain that cause dysfunction but may itself affect brain function. A substantial proportion of patients with neurosurgical disorders have some functional impairment. Patients with glioma may experience postoperative

impairment of language, emotional, and psychological processing when the tumours are located in areas controlling those functions (eloquent areas), and roughly 46% of long term survivors have a cognitive impairment, especially in memory and executive function.<sup>3</sup> Psychiatric or neuropsychological testing would probably show that the current data under-report the extent of impairment caused by neurosurgical disorders.

These neurological deficits are challenging because many patients will live for decades and require supportive care, particularly since young patients are disproportionately affected by neurosurgical disorders. For malignant brain cancers, the global disability adjusted life years (DALYs) were estimated at 7.7 million in 2016, roughly 34 times the number of deaths, which was 227 000.<sup>4</sup> Greater use of advanced imaging technology offers the potential to reduce the harms arising from surgery.

## Multidisciplinary approach to protect and restore brain function

Maintaining brain function is vital for quality of life, but in practice, insufficient attention is paid to protecting brain functions when developing plans for neurosurgical intervention. Neurosurgical disorders are complex, and interdisciplinary collaboration is advocated when treating patients. For example, the UK National Institute for Health and Care Excellence suggests referring patients with brain tumour for neurological rehabilitation assessment, including physical, cognitive, and emotional function after diagnosis and at each follow-up.<sup>5</sup>

A typical multidisciplinary team includes neurosurgeons, neurologists, neuroradiologists, neuropathologists, intraoperative neurophysiological monitoring professionals, anaesthesiologists, neuropsychologists, psychiatrists, and therapists. A well functioning

multidisciplinary team can provide neurosurgeons with proper techniques to assess brain function and its implications for long term brain health.<sup>6</sup>

Effective strategies to protect and restore brain function depend on a more fundamental understanding of the relation between brain structures and their various functions, as well as advanced neurosurgical and imaging techniques. Advanced multimodality techniques, such as navigation, awake craniotomy, and intraoperative cortical stimulation mapping have decreased the rate of postoperative neurological deficits in patients with gliomas (box 1).<sup>7,8</sup> According to a meta-analysis of 90 studies, cortical stimulation mapping decreased the rate of late severe neurological deficits from 8.2% to 3.4% while also enabling a more extensive resection in glioma patients with tumours in eloquent areas.<sup>9</sup>

Other non-invasive imaging techniques—for example, functional magnetic resonance imaging (fMRI) and diffusion tensor imaging—enhance the detection of eloquent areas. These techniques have shown that vital functions are often distributed across the brain, with many eloquent areas identified outside the brain structures suggested by historical brain atlases. Improved identification has also facilitated serial monitoring.<sup>7</sup> Invasive and non-invasive techniques have converged to propel neurosurgery into the modern era of precision medicine, to further improve patients' brain health.

Multidisciplinary teams have the strength of overcoming the intrinsic limitations of professionals from a single discipline. For example, neurosurgeons often use preoperative fMRI to guide surgery. However, fMRI has a sensitivity of 44% and specificity of 80% and cannot be a substitute for cortical stimulation mapping in patients having awake brain surgery, which requires input from intraoperative neurophysiological

## KEY MESSAGES

- The incidence of long term brain functional impairment due to damage during surgery for neurological disorders is underestimated
- Such damage can cause significant societal burdens, especially because of the high incidence in younger patients, who require supportive care over their lifespan
- Use of intraoperative imaging can reduce the risk of damage and improve understanding of the structure-function relation in the human brain
- International multidisciplinary research is needed to provide a more accurate brain atlas and high quality evidence on methods to protect brain function

**Box 1: Common intraoperative neurosurgical techniques**

*Intraoperative neurophysiological monitoring* refers to a group of procedures used to monitor neural pathways during high risk operations to help surgeons avoid damage to the nervous system. It includes techniques to identify impending damage and techniques to map the vital structures of the nervous system

*Awake brain surgery (awake craniotomy)* is a neurosurgical technique that allows a surgeon to remove the tumour or epileptic tissue while the patient is awake to avoid brain damage.

Two technical variations, awake-asleep-awake and monitored anaesthetic care (conscious sedation) can be used depending on whether the patient needs to be awake only for cortical mapping or for the entire surgery

*Cortical stimulation mapping* is a type of electrocorticography that involves a physically invasive procedure and aims to identify the function of specific brain regions (usually motor, language, and somatosensory mapping) through direct electrical stimulation of the cerebral cortex. It can be used on anaesthetised or awake patients with brain tumours or epilepsy

monitoring professionals.<sup>10</sup> In one study of patients with gliomas in areas that were assumed to be unresectable based on functional imaging, most were able to have maximal safe resection guided by cortical stimulation mapping without experiencing any functional deficits.<sup>11</sup> This shows how multidisciplinary working can help minimise the probability of brain functional damage and maximise life expectancy.

**Novel insights into brain function from neurosurgical patients**

Although neurosurgical procedures have traditionally focused on targeting specific abnormal brain structures, new knowledge about the pathophysiology of brain changes has been achieved by examining the effects of surgery on patients. For example, study of patients with brain tumours has discovered more refined structural areas related to language, emotional, and psychological processing.

Novel insights into the functional distribution of critical brain structures, especially language, have been attained from patients who received cortical stimulation mapping during awake neurosurgery. This process requires a multidisciplinary team, including the neurosurgeon operating the handheld brain probe, the anaesthetist keeping patients awake but pain free, and the intraoperative neurophysiological monitoring expert assessing language function.

The first bilateral map of human language function in both hemispheres was built from 165 patients having awake mapping for resection of low grade glioma. Interestingly, speech arrest was localised to the ventral premotor cortex, not the classic Broca's area (inferior frontal gyrus), and the right hemisphere was also found

to have a role in language processing.<sup>12</sup> Some bilingual patients with brain tumours experience language disturbance or bilingual switching preoperatively or postoperatively. The structural locations of name switching were found across the left middle frontal gyrus by using cortical stimulation mapping to identify language function in awake brain surgery.<sup>13</sup> These important findings broaden our anatomical based understanding of Broca's area. Insights obtained from these procedures not only extend our conceptualisation of the traditional Brodmann area maps but also reduce damage to patients' language function.

The psychological changes in some neurosurgical patients could provide evidence to update our understanding from preclinical studies. For example, neurosurgeons and psychologists collaborated to find that patients with focal anterior insular cortex lesions displayed decreased empathetic responses to others' pain. By thoroughly assessing the change in patients with insular gliomas, they clarified this psychiatric processing was localised in the anterior insular cortex rather than the anterior cingulate cortices, as suggested by neuroimaging.<sup>14</sup>

Treatment of other neurosurgical disorders also provides an opportunity to better understand brain function. For example, brain mapping and intraoperative stereoelectroencephalography at the cortical-subcortical level is used to detect the areas responsible for epileptogenesis, and this technique can also be used to reveal brain functions that need to be preserved. For patients with Parkinson's disease, precise stimulation of nuclei through deep brain stimulation has been shown to substantially improve motor control and quality of life,<sup>15</sup> leading to a new area of research in neuromodulation.

With ethical approval, neurosurgeons working in collaboration with other disciplines to study brain function could provide important advances for brain health.

**Challenges in brain health**

Brain scientists confront many challenges in research and the clinic. A new brain atlas of advanced human brain functions would meet the demands of clinical and scientific communities and could be achieved through multidisciplinary research. The historical atlases of brain functions are based on non-human models that do not accurately predict the long term effects of neurosurgical disorders on human brain function. The functions of animal brains are different from those of humans, especially for functions unique to humans such as advanced cognition and language.<sup>16</sup>

Although current multimodality imaging and intraoperative techniques benefit neurosurgical patients by preserving their brain functions, the level of evidence supporting their routine use is not high, mostly at level III. A shortage of multidisciplinary teams, brain disease heterogeneity, and insufficient numbers of patients eligible for large clinical trials at a single institution have hindered high quality studies. In addition, because of the limited resources for brain protection techniques and an insufficient number of experts in underdeveloped regions, some neurosurgical skills and research approaches have not been widely implemented. International collaboration is therefore essential to overcome these challenges.

Preserving additional brain function in neurosurgical patients while also prolonging life expectancy is often a difficult balance because of the robust evidence that more extensive resection of the tumour and aggressive treatment correlates with better survival for patients with gliomas.<sup>17</sup> Despite emerging knowledge of the relation between tumour location and the corresponding brain functions, evidence suggests that these relations, and their long term implications, may still be underappreciated. The high incidence of postoperative cognitive decline in patients with low grade glioma could be explained by some functional activity remaining within the tumour mass.<sup>18</sup> Focal brain tumours produce global changes in the functionally complex and networked brain architecture, which may aid in our understanding of patients' larger scale

neurological manifestations and provide a framework for improving plasticity.<sup>19</sup> Of note, recent reports have linked neuronal excitability with growth of gliomas and brain metastases.<sup>20 21</sup> These and other findings highlight the need for a deeper understanding and clearer visualisation of the relations between abnormal brain structures, lesions, and functions from the neurosurgical perspective, which can create new insights in brain health.

Further multidisciplinary research will create an understanding of the pathophysiology of brain function impairments as well as brain plasticity. This will enable greater therapeutic targeting while maintaining function to achieve optimal brain health.

### Future directions

Neurosurgical disorders directly damage specific brain structures and lead to large individual and societal burdens in the long term. Research that focuses on the patient's brain functions during and after surgery should be prioritised to reduce these burdens. This represents a major opportunity for neurosurgery to collaborate with other disciplines to advance our knowledge of brain health.

Establishing a multidisciplinary research alliance, using multimodality technologies, and studying more long term functional changes in neurosurgical patients, will improve our understanding of brain functional localisation and mechanisms of damage in brain disorders. By taking part in research approved by ethics committees, neurosurgical patients can help provide unique insight into brain function and health that could in turn benefit the broader clinical, scientific, and patient communities.

International, large, and diverse prospective trials are also needed to assess changes in patients' brain function attributed to damaged structures in neurosurgical disorders. Initially, the reproducibility and generalisability of brain function observed in patient case series could be validated in a large global population. Such evidence based understanding of brain function and protection techniques could then be used to tailor treatments for a variety of brain disorders.

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We thank Chirag Patel and Weiyu Chen for help in proofreading this analysis.

**Competing interests:** We have read and understood BMJ policy on declaration of interests and declare that this study was supported by the grant from the National Natural Science Foundation of China (81971668) and Beijing Medical Research (2018-7).

**Provenance and peer review:** Commissioned; externally peer reviewed.

This article is part of a series launched at the Chinese Stroke Association annual conference on 10 October 2020, Beijing, China. Open access fees were funded by the National Science and Technology Major Project. *The BMJ* peer reviewed, edited, and made the decision to publish these articles.

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Cite this as: *BMJ* 2020;371:m3690  
<http://dx.doi.org/10.1136/bmj.m3690>