SCIENTIFIC COMMENTARY

Grasping the opportunity: better behavioural diagnoses will lead to better treatments for stroke

This scientific commentary refers to ‘Recovered grasping performance after stroke depends on interhemispheric frontoparietal connectivity’ by Hensel et al. (doi:10.1093/brain/awac157).

One in four adults will go on to have a stroke at some point and 63% of strokes occur in people under the age of 70. There are over 100 million stroke survivors worldwide, most in low and middle income countries. Hyperacute therapies have improved dramatically over the last few decades but our ability to help people achieve their best possible recovery has arguably regressed. How do we turn this around? Firstly, we need to accept that higher doses of behavioural treatments (motor, language, cognitive training) are effective and determine ways of implementing them in a range of health care systems. Secondly, and at the other end of the spectrum, we need to fully explore the possibilities for neural repair via drugs or forms of nervous system stimulation in clinical studies based on an understanding of the underlying neurobiology of stroke recovery. The third key element that has been largely ignored, at least in clinical practice, is diagnostics. If we ask, ‘Why does this person have difficulty using their arm and hand?’ the answer cannot be because he had a stroke because this will not help determine the correct treatment for upper limb dysfunction. Behavioural treatments need an accurate behavioural diagnosis: precisely which aspects of motor control are impaired? Is there additional sensory loss or cognitive dysfunction, for example? Each additional impairment becomes a
therapeutic target. Attempts to target neural repair, on the other hand, need biological, physiological and anatomical diagnoses to define the therapeutic targets (cortical areas, corticospinal tract, reticulospinal tract) and how they must be manipulated. In other words, we must strive to understand the combination of multiple fine-grained behavioural, biological, physiological and anatomical impairments that contribute to the disability of individual patients, because these metrics are the therapeutic targets.

This brings us to the paper by Hensel and colleagues in this issue of Brain, which combines an investigation of fine-grained motor behaviour and underlying biology in one experiment. Functional brain imaging has been used in the field of stroke recovery for several decades now, based on the rationale that stroke is a form of acquired brain injury where patients may well make a reasonable or full recovery despite the fact that the macroscopic structural damage has not been repaired. The only possible explanation is that there must be some form of functional reorganisation of residual brain structures to support recovered behaviour. Many studies, unsurprisingly, have shown alterations in task-related and resting state brain activity in stroke patients, often related to level of impairment (cross-sectional studies) or degree of recovery (longitudinal studies). In the motor domain, there are many areas of the brain where an increase in movement-related activity is seen after stroke, usually in secondary motor areas such as premotor cortices, supporting observations in animal models.

Another brain region of interest is the anterior intraparietal sulcus (aIPS), particularly because of its role in grasping behaviour, and this was the focus for Hensel et al. The authors bring a multimodal technical tour-de-force to bear on the role of aIPS, and in particular contralesional
aIPS, in supporting stroke recovery. They combine resting-state fMRI, motor task fMRI, online-rTMS interference, and 3D movement kinematics in one experiment. The neuroimaging and neurophysiological techniques on display here have been mastered by many research groups, although not always in combination. What is particularly noteworthy here though is the equal attention paid to fine-grained measurement of both brain and behaviour. Hensel et al. measured it all and even then, probably didn’t extract every bit of data that they might have. In their study, 18 chronic stroke patients (who had similar levels of mild to moderate upper limb impairment in the early post-stroke stage) were clustered into those with excellent performance and those with residual mild to moderate impairment based on 3D hand/finger kinematic assessment. A standard neuroimaging analysis showed that better motor performance was associated with higher interhemispheric aIPS–aIPS and M1–M1 connectivity. We have seen this type of result many times before, an associative rather than causal relationship.

The authors next went on to transiently disrupt contralesional aIPS and (separately) M1 function using rTMS, which resulted in the re-emergence of motor deficits in those with better performance. This result certainly strengthens the argument that contralesional aIPS and M1 are key nodes in a brain network supporting recovered motor function. But in the context of accurate diagnostics, ‘recovered motor function’ is not specific enough to be helpful. This is where the approach taken by Hensel et al. comes to the fore. Because they performed detailed kinematic analysis of hand/finger movements in three different tasks, they were able to demonstrate that targeting contralesional aIPS or M1 with rTMS disrupted different behaviours.
Specifically, rTMS to contralesional aIPS impaired grasp-to-lift accuracy in patients with higher aIPS–aIPS connectivity, whereas rTMS to contralesional M1 impaired grasping speed in patients with higher M1–M1 connectivity. A less detailed assessment of behavioural deficit would not have revealed this differential effect. This fine-grained assessment of behaviour is even more important in chronic stroke patients, where the impairments are a combination of lesion-induced deficits, secondary complications and compensatory behaviours adopted in an attempt to achieve functional goals. These must all be unpicked if we are to begin understanding how to treat individual patients. In stroke patients with hand shaping difficulty, we usually think of weakness in the various muscles involved (especially wrist extensors, intrinsic hand muscles and thumb abductors), increased muscle tone, sensory loss or even apraxia (or usually combinations of all these). The current study reminds us that specific patterns of post-stroke cortical network dysfunction can also be involved.

However, the result here is not the most important thing. They will not generalise beyond patients who are relatively well recovered, likely with intact corticospinal tracts and excellent prospects for further recovery. The focus on well recovered patients is common in many studies of stroke recovery, but we should not ignore those with more severe impairments and who have more to gain. Neither does this study point to a way to use non-invasive brain stimulation to promote recovery.

Instead, the most important thing here is the willingness to collect not only highly detailed brain imaging metrics, but also fine-grained behaviour. This is what has been lacking in so many of our studies. For too long, the domain of behaviour, either the deficit or the desired goal, has
taken a back seat. Here, the authors have gone beyond standard clinical measures and by using movement kinematics have been able to make much more specific claims and perhaps get closer to more detailed phenotyping of individual patients. This approach will, ultimately, allow us to answer the question ‘why does this person have difficulty using their arm and hand?’ leading to a rational and mechanistic approach to effective treatment.

Finally, the behavioural and neuroimaging data sets that we can now acquire are so rich and dynamic that we must adopt new ways of analysing them. Often, investigators will reduce the dimensionality of these data sets to make them easier to analyse, but this is no longer necessary with high dimensional approaches\(^5,6\) that can incorporate data from multiple modalities. Embracing the study of behaviour allied to neuroimaging and neurophysiology will form the basis of a more effective approach to reducing the burden of post-stroke impairment.

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**Competing interests**

The author reports no competing interests.


