Name of disorder: Stroke
Title: Targeting stroke treatment to the individual
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New therapies have been developed to help the brain recover after stroke. Individuals or subgroups of patients 'may require different rehabilitation strategies to target specific brain regions' [1] (p.4). Yet currently we do not have effective means of identifying individuals who have potential to benefit from these therapies nor do we have the means of selecting the most optimal therapy. For motor rehabilitation in particular, there are no guidelines or informed predictions of which approach to training is likely to be most beneficial for an individual. Treatment is based on presenting signs and symptoms, such as muscle weakness, abnormal muscle tone and poor neuromuscular control (Figure 1) [2]. As yet there is little utilisation of information about how different types of lesions have interrupted brain networks, and how remaining intact neural tissue and networks may be targeted in therapy. As a result, most patients receive a generalized intervention common to all stroke patients.

Figure 1 – Training for muscle weakness

Current rehabilitation, though it can improve outcomes, is still lacking as 55-75% stroke survivors still have functional limitations months after the infarct [3]. Further, interventions that have demonstrated effectiveness are not necessarily effective for all individuals. Therefore, there is a need to systematically explore how treatment interventions can be improved. One way to do this is to target interventions more specifically to individual patients.

In the past, means of accurately classifying type of lesion routinely after stroke were limited to CT scans or clinical classifications such as the Bamford scale. With the advent of more sophisticated *in vivo* imaging, more accurate definition of how a lesion may interrupt specific brain networks can now be achieved. Techniques such as high resolution structural MRI can be used to reveal changes in brain grey matter density, diffusion weighted imaging and tractography can reveal integrity of brain white matter, and functional MRI, transcranial magnetic stimulation and positron emission tomography (PET) to reveal brain connectivity whilst performing tasks. With these advances it should now be possible to identify specific groups of patients according to their underlying neurobiology and how this impacts on information processing and recovery in the brain.

Recent reviews indicate that there is no single pattern of neuroplastic change observed during recovery from stroke, but that neuroplasticity seems to depend on the patient's deficits and the training intervention, as well as the impact of the lesion on remote locations and networks [4]. These findings reinforce the idea of individually tailored examination and treatment. For example, a neuroimaging study by Shelton and Reding [5] demonstrated that recovery of isolated upper limb movements was more likely for people with purely cortical stroke compared with a subcortical or mixed cortical/subcortical group. One fMRI study identified particular neural substrates for transport of the hand: superior parieto-occipital cortex and rostral superior lobule, and for grasp: bilateral anterior intraparietal sulcus and left ventral premotor cortex [6] . Such studies provide specific information that could shape expectations of degree of recovery or identify areas that may need more intensive therapy for certain individuals. Other studies are linking damaged brain networks to treatment such as one which recently showed that two training approaches for stroke (unilateral and bilateral motor arm training) had different impact on task-related brain activation [7].

The extent to which a lesion interrupts expected motor tracts and/or functional networks in individuals has been shown to predict behavioural gains from treatment in subjects with chronic stroke. For example, inferred interruption to trajectories of corticofugal fibres, characterised in healthy controls using probabilistic tractography, was associated with hand grip performance in individual stroke survivors [8].

Careful analysis of the impact of the lesion on brain networks as well as knowledge of viable brain networks has potential to guide rehabilitation clinicians in individualised stroke rehabilitation. We can map how particular white matter tracts may be interrupted by the lesion, both directly and indirectly. We can also map the residual architecture that may be accessed in therapy. Similarly, the lesion may be mapped relative to functional brain regions and networks that are known to be important for particular functions and tasks.

Individually tailoring treatment according to the neurobiology needs to be underpinned by an expansion of neuroscientific research to inform models of recovery of specific functions that are commonly addressed in therapy. However, research aiming to do this is sparse, for example, a recent review of studies of interventions to improve arm-hand coordination after stroke led by this author found that none of the included studies related results of intervention to individual brain regions and the neurobiological mechanisms underlying improved performance were only minimally discussed [9]. New research is needed to test the effectiveness of interventions that are targeted to the particular groups who are defined by damage to brain areas and networks. These clinical studies also need to be complemented by basic science studies using animal models that reflect the clinical questions asked in order to probe the mechanisms underlying individualised neuroplastic changes.

Models of recovery may provide guidance in predicting which patient will benefit most from which intervention. For example, Stinear et al.'s [10] data-driven algorithm predicts motor improvements after therapy based on neurophysiological and structural integrity of the cortico-spinal tract (CST). For example, observation of functional integrity of cortico-spinal tract (CST) in an individual would recommend intense unilateral therapy, while a lack suggests an augmented or bilateral therapeutic approach for the individual, based on Stinear et al.'s algorithm [10] (Figure 2 below).

Good functional integrity of CST:

Motor evoked potentials in response to TMS

Intense unilateral therapy indicated

Lack of functional integrity of CST:

No motor evoked potentials

Fractional anisotrophy asymmetry < 0.25

Bilateral arm therapy indicated

The future for individualised stroke rehabilitation is emerging. Models of recovery coupled with advances in *in vivo* imaging technologies are paving the way to achieving *real-time* insights into the dynamics of neural plasticity and recovery *in individuals* making targeted treatment more possible. With this knowledge in hand, we can integrate it with evidence of effectiveness of learning-based interventions such as task specific training [11] and enriched environments [12]. Identification of robust biomarkers will be particularly important in this regard. Now is an exciting time for stroke rehabilitation!

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