

# The prospects for poststroke neural repair with vagal nerve stimulation

Nick Ward <sup>1,2</sup>

## Vagal nerve stimulation is a new candidate for promoting neural repair after stroke but there is work to do

Stroke is one of the major global healthcare problems with over 100 million stroke survivors worldwide.<sup>1</sup> It is no longer simply a disease of the elderly, with 63% of the one-in-four adults who will go on to have a stroke being under the age of 70.<sup>1</sup> Treatment to help recovery is often restricted to the first 6 months, despite stroke being a long-term condition from which recovery can be a lifelong process.

There are three key areas where advances will have a major impact. First, accept that higher doses of motor, language and cognitive training are effective and determine ways of implementing them in a range of healthcare settings. Second, recognise that not all patients who have a stroke are the same and so we must ‘re-diagnose’ our patients through fine-grained behavioural, anatomical, physiological and biological phenotyping to understand likely recovery patterns and individual responses to treatments. Third, develop a rational approach to drug or stimulation induced ‘neural repair’ based on the underlying neurobiology of stroke recovery.<sup>2</sup> Neural repair is a curious and confusing term that does not refer to restitution of damaged neural tissue but rather restitution of lost behaviours through manipulation of neural mechanisms, particularly those involving plasticity of some kind. Neural repair approaches have yet to have any clinical impact for one reason or another.<sup>3,4</sup>

In their *JNNP* paper, Gao *et al*<sup>5</sup> consider vagal nerve stimulation (VNS), which has recently entered as a hopeful contender in the field of poststroke neural repair. For the purposes of motor recovery, VNS is delivered concurrently with each practised movement. Work in preclinical stroke models suggests this leads to an increase in the likelihood

of synaptic plasticity in brain regions and networks involved in making the movement.<sup>6</sup> The key thing to remember is that neuromodulators like VNS (or drugs) aim to enhance the effects of behavioural training but do not drive behavioural change on their own. This has not always been appreciated in the design of neural repair trials,<sup>3,4</sup> but the VNS community appear to have got the message.

Gao *et al*<sup>5</sup> performed a systematic review and meta-analysis of the effect of motor training with or without concurrent VNS on motor recovery after stroke. It included the 7 existing randomised controlled trials (RCTs) involving 263 largely chronic, moderate-to-severely affected patients who had a stroke. Training involved upto 20 task-oriented motor training sessions over several weeks (eg, 300 repetitions/session for 18 sessions over 6 weeks<sup>7</sup>). They report a medium effect size ( $g=0.43$ ; 95% CI 0.19 to 0.68;  $p=0.001$ ) in favour of the VNS group. In the largest multicentre RCT,<sup>7</sup> training led to a minimal increase of 2.4 points, and VNS plus training to an increase of 5.0 points of the upper limb Fugl-Meyer score (FMUL). At the end of follow-up, nearly half of all the VNS group, compared with a quarter of the training-only group, had achieved at least an extra six points on the FMUL.

VNS may turn out to be a significant contributor in the field of stroke recovery, but we have been here before, most notably with drugs and non-invasive brain stimulation.<sup>3,4</sup> How to keep things moving? (1) First, there will inevitably be further work on comparing implanted and external devices and assessing the range of stimulation parameters and the results to date probably justify this. One caution is that this type of work has been going on in the field of non-invasive brain stimulation for at least two decades without any discernible consensus or clinical impact. (2) Second, we must pay as much attention to the dose and nature of the training as the technology parameters. In the current studies, VNS is expected to enhance the minimal effects of low dose

training. But higher doses of training have bigger effects,<sup>8</sup> which may in turn lead to bigger VNS effects. When thinking about the nature of the training it is important to consider what impairment is being targeted. Hemiparesis encompasses independent deficits in strength, control/dexterity as well as the intrusion of flexor synergies (in upper limb) and spasticity—which of these might VNS help? Answering this requires aligning the treatment target (strength, control/dexterity), the training regimen and the outcome measure in future trial design. Remember, VNS is not neurorehabilitation in its entirety, it is an impairment-based treatment and should be appreciated and investigated as such. Do not expect it to improve quality of life on its own. Improving strength or control/dexterity may not get someone back to work, but it can enable patients to take part in and benefit from more activity/participation-based work further down the line. (3) Third, what patient phenotype is VNS (or any treatment for that matter) most likely to benefit? For example, what anatomical pathways need to be intact for VNS to work and how do we assess them in individual patients? Stratification will be a key part of future stroke recovery trials.

It remains early days for the field of neural repair (in humans). A better understanding of the field of neurorehabilitation and what we are trying to achieve at each stage of recovery will improve the chances of success.

**Twitter** Nick Ward @dr\_nickward

**Collaborators** None.

**Contributors** NW is sole author.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Commissioned; internally peer reviewed.



## OPEN ACCESS

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

<sup>1</sup>Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK  
<sup>2</sup>Department of Neurology, National Hospital for Neurology and Neurosurgery, London, UK

**Correspondence to** Professor Nick Ward, Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, London, UK; n.ward@ucl.ac.uk



**To cite** Ward N. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [please include Day Month Year]. doi:10.1136/jnnp-2022-330831

Received 5 January 2023  
Accepted 13 January 2023

*J Neurol Neurosurg Psychiatry* 2023;0:1–2.  
doi:10.1136/jnnp-2022-330831

**ORCID iD**

Nick Ward <http://orcid.org/0000-0002-7688-9649>

**REFERENCES**

- 1 Feigin VL, Brainin M, Norrving B, et al. World stroke organization (WSO): global stroke fact sheet 2022. *Int J Stroke* 2022;17:18–29.
- 2 Murphy TH, Corbett D. Plasticity during stroke recovery: from synapse to behaviour. *Nat Rev Neurosci* 2009;10:861–72.
- 3 Ward NS, Carmichael ST. Blowing up neural repair for stroke recovery: preclinical and clinical trial considerations. *Stroke* 2020;51:3169–73.
- 4 Kwakkel G, Meskers CGM, Ward NS. Time for the next stage of stroke recovery trials. *Lancet Neurol* 2020;19:S1474-4422(20)30218-0:636–7..
- 5 Gao Y, Zhu Y, Lu X, et al. Vagus nerve stimulation paired with rehabilitation for motor function, mental health and activities of daily living after stroke: A systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2022;jnnp-2022-329275.
- 6 Meyers EC, Solorzano BR, James J, et al. Vagus nerve stimulation enhances stable plasticity and generalization of stroke recovery. *Stroke* 2018;49:710–7.
- 7 Dawson J, Liu CY, Francisco GE, et al. Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial. *Lancet* 2021;397:S0140-6736(21)00475-X:1545–53..
- 8 Ward NS, Brander F, Kelly K. Intensive upper limb neurorehabilitation in chronic stroke: outcomes from the Queen square programme. *J Neurol Neurosurg Psychiatry* 2019;90:498–506.