Training persons with Parkinson's disease

Cueing training in persons with Parkinson's disease

M A Hirsch, F M Hammond

A groundbreaking study challenges misconceptions about cueing training in Parkinson's disease

The traditionally held belief about the treatment of patients with neurodegenerative conditions is that they cannot benefit from exercise training.² For people with a diagnosis of Parkinson's disease, it was feared that exercise would increase the underlying muscle tone. Exercise might worsen the condition and so was to be avoided.

The paper by Nieuwboer *et al*¹ (see p 134) challenges this assumption. It is groundbreaking in several important aspects. Firstly, with 153 participants, the study is the largest trial on gait training in Parkinson's disease. Results from previous studies have been criticised for their small sample sizes. Owing to its sample size, statistically, the Nieuwboer *et al*'s study is the most powerful trial to date. Secondly, the validity of previous studies has been questioned because of methodological flaws. In the present single-blind, randomised clinical trial, blinded assessors conducted the testing, reducing bias that is known to occur during unblinded assessments. Finally, the training and testing took place in the patients' home environment and included a follow-up period. Rehabilitation studies have a poor track record for performing follow-up tests. Nieuwboer *et al*'s study is a welcome exception.

Notably, in Nieuwboer *et al*'s study, 3 weeks of cueing training (as little as nine 30-min sessions) triggered an improvement in gait function in the later

test even though participants were not cued during later tests, which is an intriguing result. What is the mechanism responsible for the carry-over of external cue training? The basal ganglia are thought to be involved in the execution of automatic and repetitive movements such as gait. Damage to the basal ganglia leads to a reduced supply of internally generated movement cues. Perhaps one explanation is that the external auditory cue training rerouted the movement through a non-automatic pathway, removing it from the automatic basal ganglia pathway. If anatomical and metabolic plasticity in response to cue training could be shown in future studies, it would provide a breakthrough in Parkinson's rehabilitation. The brain may, after all, be more plastic than we thought.

Not surprisingly, the training effect was significantly reduced at the 6-week follow-up. The training frequency, intensity and duration, critical elements of motor learning is to occur, were determined by European insurance reimbursement laws. The study does show that gains can be achieved under the constraints of sub-optimal conditions. Recent studies using animal models of Parkinson's disease suggest that higher intensities of training (ie forced use) are neuroprotective, by reducing striatal dopaminergic loss and promoting improved behavioural outcomes.³⁻⁷ To date, there are no published

studies on forced-use training in people with Parkinson's disease.

Training with external cues would appear to be a logical avenue for the treatment of gait-related dysfunction in Parkinson's disease. Nieuwboer *et al* are to be commended for running this well-designed randomised control trial. It is hoped these results will motivate other centres to mount large-scale studies of this kind.

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Steroid-responsive leucoencephalopathy

Steroid-responsive leucoencephalopathy due to cholesterol embolism

Patrice Laloux

Occlusion of small deep perforating arteries due to cholesterol embolism

The paper by Andreux *et al*¹ (see p 180) reported the first case of multiple cholesterol emboli responsible for a steroid-responsive encephalopathy.

Showers of cholesterol emboli are dislodged from disrupted, ulcerated carotid or aortic atheromatous plaques. The aortic arch is, however, the main source. In the French Study of Aortic Plaques in Stroke, after adjustment for the presence of carotid stenosis, atrial fibrillation, peripheral arterial disease and other risk factors, aortic plaques ≥ 4 mm thickness were found to be an independent risk factor for recurrent stroke.² Cholesterol embolisation can occlude retinal arteries and/or multiple small deep and leptomeningeal brain arteries 17–585 μ m in diameter. Lacunar infarcts, commonly due to lipohyalinosis, can also be caused by cholesterol emboli occluding the small deep perforating arteries.³ Diagnosis may be difficult, especially in patients presenting fluctuating, but also progressive, cerebral symptoms such as confusion and disorientation. Recurrent amaurosis fugax or transient ischaemic episodes, ischaemic stroke, epilepsy, confusion and encephalopathy are the main neurological findings often associated with inflammatory syndrome.⁴ Involvement of other peripheral organs can help in the diagnosis, notably renal infarcts,

pancreatitis, intestinal infarcts and purple toes, as well as the occurrence of acute neurological deficit after vascular surgery or arterial catheterism. Cholesterol crystals can be identified at funduscopy and skin biopsy. Carotid ultrasonography and transoesophageal echocardiography are required to detect the source of embolism. Surgery is recommended for the prevention of cholesterol emboli released from carotid atherosclerotic stenosis, but there has been no randomised controlled trial comparing antiplatelet agents, anticoagulant treatment and statins when the source is in the aortic arch.

The authors report the case of an extensive leucoencephalopathy, with multiple bilateral hypersignals on fluid-attenuated inversion recovery image-weighted magnetic resonance imaging (MRI) suggesting vasogenic oedema in the cerebral white and grey matter, brain stem, cerebellum and basal ganglia. There was no evidence of cytotoxic oedema or infarcts on diffusion-weighted MRI. Follow-up MRI showed complete resolution of lesions after high doses of steroids. Histopathological examination of the brain showed numerous scattered small cortical and subcortical infarcts and multiple cholesterol emboli occluding small leptomeningeal and perforating arteries infiltrated by reactive lymphocytes. The

physiopathological mechanism of this reversible leucoencephalopathy remains unclear. On the basis of histological examination and the dramatic response to corticosteroids, the authors' hypothesis is a localised arterial inflammation at the site of cholesterol occlusion, but endothelial vascular reaction disrupting the blood–brain barrier is another possible explanation, as focal arterial spasm around embolic occlusions and damaging the arterial wall has been reported.⁵ This case requires confirmation, but neurologists should be aware that cholesterol emboli can be responsible for acute encephalopathy likely to respond to corticosteroid treatment. A limiting factor is, however, the inability of steroids to recanalise the arterial cholesterol occlusion and prevent cerebral infarcts. The only expected potential effect, as suggested by the authors, is the reduction of vasogenic oedema underlying the clinical syndrome of encephalopathy.

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TMS and tinnitus

Transcranial magnetic stimulation and tinnitus: implications for theory and practice

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Transcranial magnetic stimulation: a possible treatment modality for tinnitus?

Tinnitus remains an enigma, with no consensus on the pathophysiology or treatment of this condition. Transcranial magnetic stimulation has recently emerged as a possible treatment modality that has shown some promise. The paper by Plewnia *et al.*¹ (see p 152) reported on the efficacy of delivering 10 sessions of low-frequency repetitive transcranial magnetic stimulation (rTMS) over the temporoparietal association cortex to treat chronic tinnitus. Although rTMS is known to effect change in tinnitus perception,²⁻⁴ it is unclear how this change occurs and what method of application is most effective. Plewnia *et al.*¹ provide new information with implications for possible future clinical use. In contrast with previous studies,³ Plewnia *et al.* show only a temporary effect of rTMS on tinnitus, at least with currently used treatment schedules. The study also highlights the fact that blood flow asymmetries associated with tinnitus, and commonly used to target rTMS, can be quite variable among patients. In contrast with previous studies, which have focused on the primary auditory cortex, this study suggests that rTMS may attenuate tinnitus perception by

influencing neural systems related to attention and emotion.

To individually adjust selection of the target area for rTMS, Plewnia *et al.* used [¹⁵O]H₂O positron emission tomography before and after a lidocaine-induced reduction in tinnitus loudness to obtain each patient's maximum of tinnitus-related cortical activity, as measured by regional cerebral blood flow (rCBF). A reduction in tinnitus after active rTMS correlated with change in rCBF in the anterior cingulate cortex immediately after the lidocaine injection. The temporoparietal cortex and the anterior cingulate cortex are known components of neural systems that mediate attention.⁵ Interestingly, deficits in attention in people with tinnitus have been documented in the laboratory.⁶

If rTMS is to be used clinically for the treatment of tinnitus, future studies must consider the following questions. Firstly, what schedule of rTMS can promote long-term change in tinnitus perception? Consecutive, week-long treatment schedules can ameliorate tinnitus in the short run, but booster sessions may be necessary as symptoms return to effect a long-term change. Secondly, do the

asymmetries in rCBF observed in association with tinnitus change as tinnitus improves? Follow-up neuroimaging is necessary to learn whether these asymmetries are relevant and to validate models of tinnitus perception that concern cortical contributions.

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