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Foreword

Brain stimulation and behavioural cognitive rehabilitation: A new tool for neurorehabilitation?

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This special issue of *Neuropsychological Rehabilitation* aims to present new knowledge about a recent and innovative approach that can possibly ameliorate the outcome of the rehabilitation of cognitive deficits, namely: non-invasive brain stimulation (NIBS). The issue includes a series of papers on NIBS and combined rehabilitation studies (reviews and some original contributions), highlighting the challenges, as well as the power, of this novel approach.

The old and time-honoured concept that the brain structure becomes immutable after childhood has been abandoned, based on the evidence that all areas of the brain remain plastic in adulthood and during physiological ageing, with even some evidence for neurogenesis (Berlucchi, this issue).

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This capacity of a neural system to acquire or improve skills, and to adapt to new environments through a learning process has been labelled "neuroplasticity" (e.g., Huttenlocher, 2002). Neuroplasticity refers to the ability of the nervous system to change its structure and function, as part of the processes that underlie learning and memory, to adapt to environmental changes, and to recover function after brain lesions.

In recent years, new techniques have been developed for the understanding and induction of human neuroplasticity. An important contribution has come from the introduction of NIBS (e.g., Wassermann et al., 2008). The development of NIBS techniques to induce neuroplasticity constitutes a main breakthrough in our understanding of the changes in the brain states accounting for behavioural modifiability. NIBS is also relevant to clinical neuroscience as a means to enhance plasticity, and, by implication, cognitive function in individuals with neuropsychological impairments.

Cognitive deficits are a common consequence of traumatic brain injury, stroke, epilepsy, tumours, neurodegenerative and other neurological disorders, and are a primary cause of disability worldwide (Ropper & Samuels, 2009). The rehabilitation of neuropsychological disorders of cognitive function (including aphasia; unilateral spatial neglect and other spatial disorders; amnesia; apraxia; executive deficits and disorders of attention; acalculia) is defined "cognitive rehabilitation" (e.g., Stuss, Winocur, & Robertson, 2008) and represents an expanding area of clinical care and research (Stuss, this issue). Cognitive deficits, which cause an important functional disability for the patient, and represent a burden for society, are a focus of increasing attention, also in their ethical implications. Cognitive impairment is a major public health and financial problem for society in terms of need for assistance, also due to demographic trends including the increase of average life expectancy, and the decrease of mortality in the acute phase of the disease. Cognitive disorders improve both spontaneously and after cognitive training, particularly when intensive and targeted (Cappa et al., 2005; Cicerone et al., 2005; Rohling, Faust, Beverly, & Demakis, 2009). There are many factors that determine the success of cognitive rehabilitation, which, as discussed by Stuss (this issue), should be tailored as much as possible to the neurofunctional characteristics of the patient.

The use of NIBS to study and modulate cognitive function and dysfunction in neurologically unimpaired participants and in brain-damaged patients (e.g., stroke patients and patients with neurodegenerative disorders) has recently received increased attention within the scientific community (e.g., Hummel & Cohen, 2006; Miniussi et al., 2008; Ridding & Rothwell, 2007).

Vallar and Bolognini (this issue) review studies which show evidence of improved performance through NIBS in neurologically unimpaired participants, in the domains of sensation, perception, attention, language, and executive processes. Cotelli et al. (this issue) review the neuropsychological literature concerning the effects of NIBS in aphasic stroke patients; Hesse, Sparing, and Fink (this issue) in patients with unilateral spatial neglect. Overall, the available evidence from both unimpaired participants and brain-damaged patients shows that NIBS may modulate performance, including improvement in unimpaired participants, and reduction of deficits in brain-damaged patients.

The abovementioned studies concerning cognitive deficits, such as aphasia and unilateral spatial neglect, together with the evidence that NIBS may improve motor performance in patients with hemiplegia, may elucidate the mechanisms underlying the effects of NIBS on deranged functions. The effects of NIBS aimed at improving motor performance in brain-damaged patients with hemiplegia have been most extensively investigated (Tanaka, Sandrini, & Cohen, this issue), and the underlying neurophysiological model is much simpler that those concerning cognitive functions, and their impairments. Tanaka et al. (this issue) emphasise that effects on skill acquisition induced by NIBS may differ according to the different types of stimulation protocols, and the tasks used, as well as, importantly, the interaction between the motor cortices in the two hemispheres. Under certain conditions, behavioural facilitation can be explained as a decrease in cortical inhibition of populations of neurons, as suggested by Hesse et al. (this issue) for unilateral spatial neglect (see also Cotelli et al., this issue).

NIBS has also been used for the treatment of dementia of the Alzheimer-type (AD) (Boggio et al., this issue). In these patients, NIBS may be used as a tool to assess the neuroplastic changes due to the neurodegenerative process, revealing alterations of cortical excitability. Given the limited effectiveness of pharmacological treatments for AD, non-pharmacological interventions, such as NIBS, may receive some attention in this important neurological domain. Some recent evidence appears to indicate that NIBS interventions promoting neural plasticity can induce cognitive gains, especially in subjects at risk of or with mild AD (Boggio et al., this issue).

Miniussi and Rossini (this issue) and Paulus (this issue) review the NIBS techniques used to modulate cortical activity; these include transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). NIBS techniques exert their effects on neuronal excitation through different mechanisms, which might also depend on a number of technical parameters that have been extensively investigated. TMS induces a current that can elicit action potentials in neurons. Conversely, tES (including transcranial direct current stimulation, tDCS) brings about a polarisation that is too weak to elicit action potentials in cortical neurons. However, tES effectively modifies the evoked cortical response to afferent stimulation (see Vallar & Bolognini, this issue), as well as the postsynaptic activity level of cortical neurons, by inducing a shift in intrinsic neuronal excitability (Paulus, this issue). Despite these differences, both stimulation techniques induce cerebral plasticity effects that are comparable in many respects: empirical evidence supports this view, as reviewed in most of the contributions in this special issue. Both TMS and tES can transiently influence behaviour by altering spontaneous neuronal activity, which may have facilitatory or inhibitory effects. Importantly, particularly for rehabilitation purposes (see also Berlucchi, this issue), NIBS effects have been shown to outlast the stimulation period, for minutes, hours, and even days (see Vallar & Bolognini, this issue). Relevant mechanisms underlying these behavioural changes include synaptic long-term potentiation and depression (LTP and LTD, see Cooke & Bliss, 2006).

Most of the contributions in this special issue also emphasise that, while NIBS approaches are valuable and have provided exciting results, the use of NIBS in conjunction with concurrent cognitive rehabilitation protocols holds promise for further advances in the treatment of neuropsychological, as well of other neurological disorders. NIBS is indeed an appealing approach to directing adaptive plasticity after structural brain damage, brain dysfunction (i.e., psychiatric disorders), or both.

It is a classical tenet of cognitive neuroscience – at least since the localisation of language functions in the left hemisphere by Paul Broca in the mid 18^{th} century – that "mental faculties", or, using a more modern term, "cognitive functions", are localised in specific parts of the brain, that are currently conceived in terms of complex cortico-subcortical networks (Cappa & Vallar, 1992; Mesulam, 1981, 1998; Vallar, 2000). Particularly, a great deal of evidence from most areas of cognitive neuroscience (cognitive electrophysiology, functional neuroimaging, neuropsychology) suggests that it is the interaction between brain regions organised in functional networks that determines the final function, and the observed behaviour. Miniussi and Rossini (this issue) point out that the general idea behind NIBS is that inducing changes in cortical excitability leads to a recovery or reorganisation of the (dys)functional network responsible for the (impaired) cognitive function. Functions may be restored or compensated for, at least in part, by mechanisms that involve both structural and functional changes to relevant brain circuits. This view also readily accounts for the modulation of sensorimotor and cognitive function, with both reducing and enhancing of performance, or the change of physiological parameters (see Vallar & Bolognini, this issue).

Abnormalities in the interactions of the different components of a relevant neural network may play a critical role in shaping the behavioural manifestations of cognitive and sensorimotor disorders. Hence, any rehabilitation approach of a cognitive function should aim at targeting the whole spatially-distributed network responsible for the function. Activating the appropriate network and reinforcing/changing synaptic interconnections (Berlucchi, this issue) appears thus to be a critical aspect of cognitive rehabilitation. This can be achieved by combining the activation of specific networks through the behavioural techniques of cognitive rehabilitation with a potentiation, through NIBS-induce neuroplasticity, namely: combining "endogenous" (i.e., the targeted behaviour required by the rehabilitation programme) with "exogenous" (i.e., NIBS) neuromodulation. Targeting by NIBS a dysfunctional neural circuitry while it is active, due to a behavioural training, may prove to be a more powerful therapeutic tool, than the mere NIBS of a given cortical area. Notably, in behavioural paradigms inducing plasticity, when a stimulus is associated with reinforcement, its cortical representation is strengthened and enlarged (Blake, Heiser, Caywood, & Merzenich, 2006).

In the same line, combined behavioural-NIBS treatments can also result in favouring generalisation. Those neurons that respond in a similar way ("overlapping of a function") to the task goal may display increased signal-correlation. NIBS, being not focused on specific neurons (e.g., Wassermann et al., 2008), could possibly modulate more effectively the activity of the whole stimulated neural population, if (pre)activated by behavioural training.

Defining network interactions is thus a key point in order to understand brain disorders and brain reorganisation. fMRI has proven to be a useful tool for evaluating the functional status of individuals' brains, during both cognitive rehabilitation, and NIBS (see Cappa, this issue). Likewise, the structural imaging of both grey and white matter in the living human brain can be used to interpret functional data more thoroughly. fMRI, PET, ERP, and MEG methods may be also used to localise and measure the time course of the patterns of activation/deactivation of cortical regions during the performance of a task of interest. This, in turn, may help in optimising the exact timing and positioning for applying NIBS to the identified area(s) (Cappa, this issue). Moreover, information on regional treatment-related activity can be used to define the optimal effect induced by NIBS (see also Miniussi & Thut, 2010). Therefore, combining functional brain imaging data with cognitive rehabilitation is of fundamental importance in future studies.

In summary, NIBS could be used to strengthen and modify networks involved in cognitive functions, both in unimpaired participants, and in brain-damaged or brain-dysfunctional patients, in whom performance is diminished or altered. NIBS applied when the system is in a given appropriate functional state (Ruzzoli, Marzi, & Miniussi, 2010; Silvanto, Muggleton, & Walsh, 2008), also based on cognitive contingencies and affordances, may enhance, and strengthen, specific distributed functional cortico-cortical/subcortical networks, rather than inducing a non-specific arousal or activation of the neural system. This may lead to the stimulation-induced modulation of a specific cognitive function, favouring its recovery. The combination of NIBS with cognitive rehabilitation, although in its beginnings, is poised to deliver novel insights into fundamental aspects of rehabilitation, paving the way for more effective neuromodulatory therapeutic interventions.

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