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Review

The contribution of transcranial magnetic stimulation in the diagnosis and in the management of dementia

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HIGHLIGHTS

- Non-invasive brain stimulation related techniques make it possible an in vivo evaluation of glutamatergic, cholinergic and GABAergic circuits of the human cerebral cortex.
- In patients with dementia they are useful to demonstrate specific abnormalities in the cerebral cortex circuits.
- Brain stimulation related techniques also help to identify possible therapeutic targets, and to measure and monitor pharmacological effects.

ABSTRACT

Transcranial magnetic stimulation (TMS) is emerging as a promising tool to non-invasively assess specific cortical circuits in neurological diseases. A number of studies have reported the abnormalities in TMS assays of cortical function in dementias. A PubMed-based literature review on TMS studies targeting primary and secondary dementia has been conducted using the key words "transcranial magnetic stimulation" or "motor cortex excitability" and "dementia" or "cognitive impairment" or "memory impairment" or "memory decline". Cortical excitability is increased in Alzheimer's disease (AD) and in vascular dementia (VaD), generally reduced in secondary dementias. Short-latency afferent inhibition (SAI), a measure of central cholinergic circuitry, is normal in VaD and in frontotemporal dementia (FTD), but suppressed in AD. In mild cognitive impairment, abnormal SAI may predict the progression to AD. No change in cortical excitability has been observed in FTD, in Parkinson's dementia and in dementia with Lewy bodies. Short-interval intracortical inhibition and controlateral silent period (cSP), two measures of gabaergic cortical inhibition, are abnormal in most dementias associated with parkinsonian symptoms. Ipsilateral silent period (iSP), which is dependent on integrity of the corpus callosum is abnormal in AD. While single TMS measure owns low specificity, a panel of measures can support the clinical diagnosis, predict progression and possibly identify earlier the "brain at risk". In dementias, TMS can be also exploited to select and evaluate the responders to specific drugs and, it might become a rehabilitative tool, in the attempt to restore impaired brain plasticity.

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Contents

1. Introduction

Dementias and other neurodegenerative disorders that affect memory, cognition and behavior are a public health priority across the developed world (European Parliament resolution on a European initiative on Alzheimer's disease and other dementias) (http://www.europarl.europa.eu/sides/getDoc.do?type=TA&language=EN&reference=P7-TA-2011-0016). With an aging population, has been estimated that the number of people with dementia will double every 20 years (Sosa-Ortiz et al., 2012). The impact of dementias on health, quality of life, autonomy and dignity of people with the condition are well recognized (Arrighi et al., 2010; Leroi et al., 2012; Mioshi and Hodges, 2009). Increasingly, national and international agencies are taking into account the potential consequences of the increase of these diseases for the financial sustainability of health and social protection systems (http://www.consilium.europa.eu/ueDocs/cms_Data/docs/pressData/en/lsa/104778.pdf) (Dorsey et al., 2013).

Our understanding of these diseases are far from adequate, as recently evidenced by neuroimaging (Filippi et al., 2012) and neuropathological studies (Taipa et al., 2012). However, perhaps the most pressing challenge is the difficulty in discriminating the different forms of dementia and of recognizing the earliest stages from normal cerebral aging. Today the diagnosis of dementia, whether at a late or early stage, is mostly based upon the clinical evaluation of the subject. The need for screening and early diagnosis tools have focused the search to identify precocious biological and instrumental markers of each dementing illness.

Immunocytochemistry and electron microscopy unveiled the involvement of the different neuronal populations and neurotransmitters in the genesis of dementia (Jellinger, 2012; Taipa et al., 2012; Weiner, 2013). Van der Flier and Scheltens have produced an overview on the different diagnostic strategies in dementia. They took into consideration several diagnostic aids including the contribution of electroencephalography, but did not consider other neurophysiological tests (Van der Flier and Scheltens, 2005). Indeed, neurophysiological techniques, especially transcranial magnetic stimulation (TMS), have emerged as valuable tools for the functional evaluation of cerebral cortex in those patients. Since its introduction, nearly 30 years ago, TMS has increasingly been used to provide novel insights into the pathophysiology of the neural circuitry that underlies neurological and psychiatric diseases. TMS may give information about the excitability of the human brain cortex, the conduction along cortico-spinal tract (Chen et al., 2008), as well as the functional integrity of intracortical neuronal structures and callosal fibers (Kobayashi and Pascual-Leone, 2003). Although not always clearly clinical evident, the involvement of motor areas in dementia has been shown by compelling clinical, neuropathological and neuroimaging studies as discussed below. Changes in motor areas may be secondary to the direct structural alterations caused by the disease process, or more often the consequence of indirect remodeling mechanisms. TMS has a strong talent to unveil motor system impairments in their pre-clinical phase. Moreover, integrated approaches using neurophysiological techniques together with structural and functional imaging have allowed the study of connectivity across motor and non-motor areas (Rossini et al., 2007). By evaluating the effects of agonists or antagonists for specific neurotransmitters, it has been shown that TMS can selectively and non-invasively explore the function of glutamatergic, gabaergic and cholinergic cortical circuits (Paulus et al., 2008).

Although the physiological abnormalities revealed by TMS are not disease-specific (Kobayashi and Pascual-Leone, 2003), there may be specific neurophysiological changes that co-segregate in each dementing illness, consistent with the involvement of distinct neurobiological substrates in the pathogenesis of each disease. With this assumption, we critically reviewed the literature to determine how TMS could be exploited as an additional tool in the differential diagnosis of dementia, especially in the earliest stages.

To this end, we have provided a concise overview of relevant TMS measures, as well as a summary of the literature on TMS studies on primary and secondary dementias. Finally, we propose a common minimum set of basic TMS paradigms to aid differential diagnosis of dementia.

1.1. Transcranial magnetic stimulation techniques

TMS can be delivered as single pulse, pairs of stimuli to the same or different brain areas, paired cortical and peripheral stimulation, or as trains of repetitive stimuli at various frequencies. A single TMS pulse, applied to the primary motor cortex (M1) at adequate stimulator intensity, elicits a motor evoked potential (MEP)