Thirty Years of Magnetic Stimulation: Is it Still Only for the Purpose of Research?

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Thirty years have passed since the first report on a magnetic stimulation device that enabled the relatively painless stimulation of the brain, the proximal segments of the peripheral nerves, and nerve roots that were almost totally inaccessible with conventional electromyography (EMG) devices (1). Although a device with similar stimulation capabilities that uses electrical current had been developed nearly 5 years ago, the pain caused by the stimulation restricted its use, despite the low price of the equipment (2). In magnetic stimulation, on the other hand, the rapidly changing magnetic field induced via a high amount of electrical current flowing through the coil could easily pass through the bones and soft tissues and induce sufficient amount of ionic currents in the deep neural tissues, thereby exciting them. The machinery and coils needed for this purpose were not very expensive, and integrating them into a routine EMG laboratory was the only step needed to begin investigating the many aspects of the nervous system physiology. This magnetic stimulation technique has become highly popular in the research field; a PubMed search during this study revealed 11,876 results for “transcranial magnetic stimulation” (TMS) and 32,743 results for “magnetic stimulation.” In addition, the results as seen for each year, illustrated the continuing trend of the growing number of research using this technique (for the first search: 5 articles in the year 1987 and 1,177 in the year 2013) (3). Could this technique, which has gained such a widespread acceptance in research laboratories, achieve a similar acceptance in clinical diagnoses and treatment? To our knowledge, the answer is “no.” This deficiency becomes more prominent when a comparison is made with the use of other techniques, e.g., magnetic resonance imaging (MRI), which has a nearly similar lifespan in medical use. Therefore, the question is whether magnetic stimulation techniques will someday find a place for feasibly helping physicians in the diagnosis and treatment of their patients or whether they will be considered as obsolete after being tested (or used only for research purposes) for a while.

The initial enthusiasm generated in clinical neurophysiology with the invention of the magnetic stimulation device was with respect to its capability of stimulating the proximal parts of the peripheral nerves, such as the plexi, nerve roots, and the intracranial segments of the cranial nerves, which were nearly inaccessible by the conventional EMG stimulators. These proximal segment stimulations could be very helpful in detecting the lesions involving the abovementioned areas and in determining their axonal or demyelinating nature and severity (4). Furthermore, placing the stimulating coils tangentially over the spine or over the latero-posterior-inferior aspect of the head would excite the nerve roots or cranial nerves at fixed points in or near their exiting foramina, eliciting muscle responses with stable latencies. However, the submaximal intensity of the stimulation reaching into these deep neural structures (accordingly, with respect to the “conduction block” was difficult with magnetic stimulation), the further elevation of the excitability threshold of the nervous tissue due to pathological processes (e.g., inflammation; this precluded the use of magnetic stimulation in Bell’s palsy), and the simultaneous excitation of multiple nerve roots due to the same stimulation were the obstacles against the use of magnetic stimulation in many situations of proximal peripheral nerve involvement. The increased power of newer magnetic stimulators and new coil designs enabled better nerve root stimulations at the foramina, reaching supramaximal levels (5). However, the clinical findings elicited by neurological examinations, standard nerve conduction studies, and needle EMG studies along with imaging findings, if necessary, are also generally sufficient in case of the lesions involving these proximal segments. Consequently, the magnetic stimulation of the proximal nerve segments and nerve roots can provide clinically useful information in only selected rare situations when dysimmune neuropathies that predominantly involve these segments are not revealed via EMG findings in the distal regions, when the axonal/demyelinating nature of the proximally located lesion is needed to be determined, or when the exact site of the lesion responsible for the symptoms cannot be identified via other means.

The other stimulation site at which the evoked responses can easily be recorded and measured is the motor cortex. If the latencies of the muscle responses evoked by the abovementioned nerve root stimulation is subtracted from the latencies of the motor responses evoked via TMS, the conduction time in the upper motor neuron involved in movement can be found. Additionally, the central conduction time for extracting the effect of conduction in the most proximal nerve roots can be calculated using F-wave latencies. Motor evoked potential (MEP) studies using these principles were a long awaited neurophysiological technique, and they were expected to

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provide objective findings about the descending motor pathways. Despite this fact, MEPs did not gain wider use in clinical neurophysiology in the past 30 years in spite of the frequent involvement of pyramidal tracts in neurological disorders. The two major reasons are the effortless elicibility of the clinical findings of upper neuron involvement in most of the patients and the extremely successful competition posed by the modern imaging techniques that could show the presence, characteristics, or absence of the majority of the lesions. However, TMS techniques have some advantages over these clinical and technical competitors. MEPs can be used as a sensitive measure for the diagnosis and follow-up in lesions that cannot be seen via imaging techniques and in those that need to be followed up using quantitative data (e.g., the electrophysiological follow-up of surgically difficult mass lesions until the final decision for operation). The high sensitivity and localizing power of MEPs in compressive and demyelinating lesions have been demonstrated (6,7). In cervical spondylotic myelopathy, for example, it is possible to localize the responsible lesion to a confined spinal segment (by selecting the appropriate recording muscles), to determine the real cause of the clinical deficit among the numerous MRI findings of cervical spondylosis, and to sometimes predict the prognosis (8).

The most important obstacles against eliciting quantitative information about the lesions involving the descending motor pathways are the variabilities in the latency, amplitude, and shape of the motor responses elicited by motor cortex stimulation (predominantly caused by the variable activation level of the target muscle) and the uncertainty about whether, via magnetic stimulation, the whole population of the pyramidal tract fibers can be activated. However, a moderately complicated but sensible method called triple stimulation technique (TST) showed that all the fibers of the descending motor tracts can be activated, and the amount of the lesions in the pyramidal tracts or in the most proximal segments of the peripheral nerves can be measured (9,10). With TST, for example, the presence of upper motor neuron involvement can be shown in amyotrophic lateral sclerosis (ALS) patients in the absence of clinical pyramidal signs, and its severity can be determined and followed up. The main problems related to this method are the relatively painful, but bearable, nature of the procedure (due to electrical stimulations it includes), suitability for only distally situated muscles (most conveniently, the upper extremities), and availability in only some EMG devices that come with an extra cost.

The vast majority of studies performed with TMS are related to cortical physiology. Studies in this category form a large spectrum, and they vary from those pertaining to cortical excitability (including the various techniques for determining the cortical motor thresholds, silent periods for studying intracortical inhibition, and facilitation performed by different neurotransmitters with paired stimulation methods); mapping the cortical areas responsible for executing particular functions and methods containing magnetic interference to the performance of certain functions; and measuring the resultant deficits in the stimulated or remote areas (6). TMS has also attracted the attention of neuroscience researchers to the plastic properties of the brain. The first plastic changes noticed via TMS were the increased excitability and enlargement of the cortical areas in relation to a function being learned (11), which were followed by the introduction of other methods, such as those investigating the sensory-motor integration during the learning of new motor skills (12). These studies provided new non-invasive methodologies for studying the changes occurring in the cortex (most importantly in humans) during the acquisition of new abilities, ranging from increased excitability to synaptogenesis. The development of navigation systems that enable the investigator to place the focal TMS coil precisely over any point of interest on the cerebral cortex provided the opportunity for studying the non-motor areas. TMS also offers a high time resolution (because

the range of milliseconds) for the studies combining neuroimaging and neurophysiology with the use of high spatial resolution of functional imaging. All of these examples are evidences for the extremely impressive contribution of TMS in the understanding of brain physiology. However, the question whether this technology, which seems highly productive for research about neural functions, can help us in the diagnosis of the patients still remains.

Nearly all of the abovementioned methods have been studied in many neurological diseases (e.g., movement disorders), and some clear differences when compared with controls have been found (13,14). However, there are some difficulties against extrapolating these results to wards such as the methodological differences between the studies, difficulties in determining the cut-off values because of the large ranges of the results, and the low level of demand for the products of neurophysiological studies. Nevertheless, TMS can reveal considerably clear values when used in the diagnosis of some neurological diseases. Unilateral or bilateral hypoexcitability of the motor cortex in primary lateral sclerosis has been observed since the early years of TMS practice and has been used as an adjunct in the diagnosis of this disease. In ALS, on the other hand, the finding of decreased short-interval intracortical inhibition and increased facilitation via the newly developed threshold tracking TMS technique has the potential of being a dependable biomarker for the early diagnosis of ALS (15). These observations offer hope for the contribution of TMS in the diagnosis of other neurodegenerative diseases in the future.

The continuation of the inhibitory or excitatory effects of TMS after the end of a series of consecutive stimulations has led to the development of another research area for investigating the therapeutic effects of repetitive TMS (rTMS). For inducing these persistent effects, which are explained by experimentally conceptualized long-term potentiation and long-term depression, rTMS is applied as low frequency (<1 Hz; it generally decreases the excitability in the area it is applied) or high frequency (it generally increases the excitability) repetitions as well as in the form of specified patterns (various forms of "theta burst" stimulation) (6,16). The disorders that rTMS was found to be most successful against are drug-resistant major depression (FDA clearance has been given to two devices for this purpose) and neuropathic or non-neuropathic pain syndromes. rTMS should be administered as a treatment alternative when standard measures have failed in cases presenting with these syndromes. Various rTMS protocols aiming to change the local excitability in the applied area or making plastic changes in the interactions among brain localizations have been found to be effective in numerous neurological symptoms, both individually and alongside with other treatment or rehabilitation methods (16). More accurate guidelines for the treatment methods are expected to be established with increasing experience in the near future.

As seen from the above summarized history, magnetic stimulation methods could not invade the everyday neurological practice with the speed and rate that was expected 30 years ago. Each medical technology has its own process of establishment in the routine practice. The writer began his own neurology training in an era during which all of the patients with a brain disorder would have had an electroencephalography examination, and later, he became a witness of another phenomenon with the surge of extremely useful, but sometimes unnecessary, imaging techniques. Magnetic stimulation methods will gain their modest place in the diagnosis and treatment of neurological diseases at a slower pace. This process might be accelerated by clinicians who have discussions with their clinical neurophysiologist colleagues about the applicability of TMS methods in the diagnosis and treatment of the patients whom they are currently managing.

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