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Synaptic Plasticity in Neurodegenerative Diseases Evaluated and Modulated by In Vivo Neurophysiological Techniques

F. Pilato · P. Profice · F. Ranieri · F. Capone · R. Di Iorio · L. Florio · V. Di Lazzaro

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Abstract Several studies demonstrated in experimental models and in humans synaptic plasticity impairment in some neurodegenerative and neuropsychiatric diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and schizophrenia. Recently new neurophysiological tools, such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation, have been introduced in experimental and clinical settings for studying physiology of the brain and modulating cortical activity. These techniques use noninvasive transcranial electrical or magnetic stimulation to modulate neurons activity in the human brain. Cortical stimulation might enhance or inhibit the activity of cortico–subcortical networks, depending on stimulus frequency and intensity, current polarity, and other stimulation parameters such as the configuration of the induced electric field and stimulation protocols. On this basis, in the last two decades, these techniques have rapidly become valuable tools to investigate physiology of the human brain and have been applied to treat drug-resistant neurological and psychiatric diseases. Here we describe these techniques and discuss the mechanisms that may explain these effects.

Keywords Transcranial magnetic stimulation · Transcranial direct current stimulation · Plasticity · Alzheimer's disease · Parkinson's disease · Huntington's disease

F. Pilato (✉) · P. Profice · F. Ranieri · F. Capone · R. Di Iorio · L. Florio · V. Di Lazzaro
Department of Neurosciences,
Università Cattolica del Sacro Cuore,
Largo A. Gemelli 8,
00168 Rome, Italy
e-mail: fabio.pilato@rm.unicatt.it

Introduction

The term "plasticity" refers to the ability of the nervous system to reorganize its connections functionally and structurally in response to changes in environmental experience, underlying the adaptive development of neuronal circuitry [1], and it is one of the most intriguing properties of the brain. The synapses are not static structures but rather dynamic connections between neurons that are constantly changing in response to neural activity and other influences [2]. Memory storage is thought to depend on activity-dependent modifications in synaptic efficacy, such as long-term depression (LTD) and long-term potentiation (LTP). By these changes, synaptic transmission can be strengthened or weakened. Because the mechanisms underlying LTP and LTD are able to modify the strength of synapses for a long period of time, LTP and LTD are the most widely held candidate mechanism for learning [3, 4]. Mounting evidence suggests that synaptic plasticity and its impairment might represent a pathogenic key point in developing some neurodegenerative diseases such as Alzheimer's disease (AD) [5, 6], Parkinson's diseases (PD) [7], Huntington's disease (HD) [8], and a neuropsychiatric disease such as schizophrenia [9].

Transcranial magnetic stimulation (TMS) is a useful tool to investigate in vivo human brain and specific paradigm of stimulation may be valuable for studying physiology of cortical connections and also investigate neurotransmitters and drugs acting on the neuronal activity [10–12]. TMS has been also used as diagnostic and prognostic tool in different neurological diseases as dementia and AD [13, 14], stroke [15], movement disorders [16], and epilepsy [17]. Repetitive TMS (rTMS) is a stimulation protocol of the TMS technique that investigates human cortical excitability and short-term synaptic plasticity. It is based on TMS applied in a repetitive manner, and it can induce changes in cortical excitability that outlasts the period of stimulation.

In transcranial direct current stimulation (tDCS), weak constant direct currents are delivered by an active anode or cathode placed on the scalp over a targeted cortical area with a reference electrode over the contralateral forehead. Polarizing currents are produced that are able to cross the skull for inducing sustained changes in membrane potential and excitability of cortical cells and fibers that outlast the stimulation [18]. rTMS and tDCS have been introduced in experimental and clinical settings for studying the physiology of the human brain and modulating cortical activity [12, 19, 20]. An interesting theory is that the effects of rTMS and tDCS on the brain are LTD- or LTP-like, as the duration of the effects seems to trigger changes in synaptic plasticity [21]. These noninvasive techniques of transcranial stimulation have advanced our knowledge of the physiology of human motor cortex and also have been used for modulating activity of the human brain.

Modulating Cortical Activity by Noninvasive Neurophysiological Techniques

Cortical stimulation may enhance, inhibit, or otherwise interfere with the activity of different cortico–subcortical networks, depending on stimulus frequency and intensity, current polarity [22], and configuration of the induced electric field [23], and these functional and clinical effects occur during or beyond the time of stimulation [24, 25].

tDCS and rTMS are the most used and promising tools to investigate by stimulating and modulating cortical activity, and these effects may have clinical and therapeutic relevance.

Several studies explored clinical and therapeutic effects of rTMS and tDCS on some neurodegenerative diseases [26–29].

tDCS is a neuromodulator tool because of a low-intensity-induced electric field whereas rTMS is both a neurostimulator and neuromodulator tool depending on the intensity of stimulation (below motor threshold or above) and frequency of induced magnetic field [24].

Moreover, tDCS and rTMS have another important difference about the accuracy of the stimulation. tDCS produces a wide electric field whereas rTMS, using focal coil, may produce a more focal stimulation [10].

rTMS can be an useful tool for evaluating plasticity and predict potential recovery in some neurological diseases like stroke [15, 30], major depression disorder [31], schizophrenia (SCZ) [32], PD [33], AD [34], and HD [28]. The frequency dependence of the outcome of repetitive TMS closely resembles the frequency–response function observed with tetanic stimulation of the Schaffer collateral projection to area CA1 of the rat hippocampus [35]. It has been proposed that rTMS and tDCS may induce long-lasting changes in cortical excitability by synaptic plasticity processes resembling stimulation protocols used in animal models to produce changes in synaptic strength [21, 24].

TMS Versus rTMS

The first TMS devices for clinical use were built in the mid-1980s [36]. TMS is performed using a high-power stimulator connected to a figure-of-eight coil at the optimum scalp position to elicit motor responses in the contralateral muscles [10].

TMS is a noninvasive technique based on Faraday's principle of electromagnetic induction, consisting in the passage of a brief, high-intensity current pulse in a coil of wire, which in turn produces a magnetic field that can reach up to about 2 T and lasts for about 100 ms. When the magnetic field enters the brain, it generates an electric field, and this induced current is able to excite neural circuits. The motor cortex can be activated by TMS producing excitatory and inhibitory phenomena in muscles controlled by the activated cortical areas [37].

TMS allows to evaluate in vivo cortical activity and connectivity even if the underlying mechanisms are not completely understood. The complexity of the interactions between induced currents and neural circuits in vivo, circadian rhythm, hormonal cycles, and genetic polymorphisms might determine the variability showed among subjects [38, 39].

Moreover specific protocols of stimulation, called paired stimulation, have been used to study intracortical circuits. In paired stimulation, two magnetic stimuli or a magnetic and an electrical stimulus are given paired at short or long interval between stimuli [37], and these protocols are named in accordance to stimulus or intervals used as: short latency intracortical inhibition, long latency intracortical inhibition, afferent inhibition, and intracortical facilitation, and have been demonstrated to activate specific neurotransmitter systems such as glutamatergic, cholinergic, and GABAergic circuits [13, 40, 41].

When a coil is used to deliver a repetitive stimulation, it is able to induce changes in cortical activity that outlast period of stimulation depending on frequency and stimulation pattern [23]. This effect may enhance (usually high-frequency stimulation) or reduce (low-frequency stimulation) cortical excitability. In the original low-frequency study, supra-threshold stimulation at 0.9 Hz for 15 min reduced motor-evoked potential (MEP) amplitudes for 15 min after the period of stimulation [42]. The pattern of modulation and duration of effects depends on many factors, but in general it has been noted that low-frequency stimulation (0.2–2 Hz) results in a reduction in excitability, whereas high frequency (5–25 Hz) results in an increase [21].

Moreover, a different repetitive magnetic stimulation protocol called theta burst stimulation (TBS) has been used to induce cortical lasting effects. Patterns of TBS consist of a total of 600 pulses at an intensity of 80 % active motor threshold. The basic element of all of these patterns is a burst of three stimuli at 50 Hz (i.e., 20 ms between each stimulus), which is repeated at intervals of 200 ms (i.e., 5 Hz). These patterns are known as continuous TBS (cTBS) and intermittent TBS (iTBS). cTBS has been demonstrated to reduce cortical excitability whereas iTBS enhances it [43].

General Principles of tDCS

tDCS modulates cortical excitability by application of weak electrical currents (below the perceptual threshold, 1 to 2 mA) in the form of direct current brain polarization [44].

First studies about stimulation using weak currents date back in 1960–1970. In those studies, researchers evaluated the effects of currents in human and animal stimulation. Animal studies demonstrated the effects on the spontaneous activity and evoked response of neurons [45, 46].

tDCS consists in a weak constant direct current delivered by an active anode or cathode placed on the scalp over a targeted cortical area with a reference electrode over the contralateral forehead. Usually a battery-driven portable stimulator is used.

During tDCS, low amplitude direct currents are applied via scalp electrodes and partially penetrate the skull to enter the brain. Polarizing currents, able to cross the skull, can induce sustained changes in membrane potential and excitability of cortical cells and fibers that outlast the stimulation [18]. tDCS has recently been introduced also as a tool to modulate noninvasively the activity of intact human brain, and several studies described potential therapeutic effects in some neurological diseases [29, 47, 48]. Neurobiological mechanisms underlying tDCS effects are not completely defined yet, but some studies explored this topic in animal models [49] and in vivo in humans [22], demonstrating that polarity might induce different changes in cortical excitability: anodal tDCS may increase while cathodal tDCS may decrease excitability [22].

Mechanisms Underlying Plasticity in Transcranial Stimulation

Several neurobiological and neurophysiological studies explored mechanisms underlying neuronal plastic changes in animals and in human subjects [49, 50]. rTMS and tDCS may modulate cortical excitability for a period that outlasts the stimulation and it is conceivable that these effects may be due to changes in synaptic strength; these mechanisms have been studied at the cellular level in brain slices of animals and results have been demonstrated in vivo, in human subjects [21, 49].

At present, a direct link between rTMS, tDCS, and synaptic plasticity has not been demonstrated yet; for this reason, their effects are often described as LTP- and LTD-like effects [21, 34]. Studies regarding genetic polymorphisms show promising results [19, 51, 52]. It has been demonstrated that inter-individual differences in NMDA receptor might influence cortical excitability and plasticity [51], and BDNF that plays an important role in regulating cell survival, proliferation, and synaptic growth in the CNS might modulate NMDA receptor-dependent LTP and LTD [39].

Moreover, in merging neurophysiologic studies with drug studies, new insights have been found in understanding the mechanisms underlying TMS effects. Memantine can block the facilitatory after effect of iTBS suggesting that the effects of iTBS rely on NMDA receptor potentiation [43]. The after effects of DC stimulation on MEPs are abolished for both anodal and cathodal polarities using NMDA receptor antagonists, such as dextromethorphan [22].

Moreover, specific drugs can disrupt or block neuromodulatory effects [22, 53].

Application of Transcranial Stimulation in Neurological Diseases

Recently, there has been a general consensus in valuating abnormalities in synaptic plasticity events as a potential cellular mechanism impairing neural activity in some neurodegenerative diseases [7, 8]. Several drugs have been used to reduce symptoms and to slow down progression in neurodegenerative diseases, but given the limited efficacy of pharmacological treatments, cost, and possible side effects, non-pharmacological approaches have become of great interest. rTMS and tDCS have been used to evaluate motor cortex excitability and synaptic plasticity in ALS, AD, PD, HD, and SCZ [28, 32–34, 54], and results allowed us to better understand the physiology of intracortical neural network and to evaluate the neurotransmission pattern in these conditions.

Mechanisms underlying the effects of rTMS and tDCS are different and results are not completely comparable. rTMS consists in the passage of a brief, high-intensity current pulse in a coil of wire. There are two classical rTMS procedures: low frequency (1 Hz or less) and high frequency (5 Hz or more). When the magnetic field enters the brain, it generates an electric field and it depends on coil orientation and pattern of stimulation. Besides, in tDCS, weak constant direct currents are delivered by an active anode or cathode

placed on the scalp over a targeted cortical area [24]. The differences between these tools make their results not completely comparable. Moreover, neuronal structures involved in the development of LTP and LTD processes are different in rTMS and in tDCS. This might be due to different cortical areas stimulated or different currents or protocols used. For instance, tDCS polarization is considered as a technique of neuromodulation, producing changes in membrane potential of axons, while rTMS is a technique of neurostimulation, eliciting propagated trains of action potentials [24].

In AD patients, TMS has been used to test functioning of cholinergic circuits in human subjects and it has been used as a diagnostic tool in mild cognitive impairment and AD patients [13, 14]. Also, rTMS has been used in AD patients to evaluate plasticity of the brain and also to improve performance and reduce progression of symptoms [34].

Several studies are "proof of principles" studies and small groups of patients were studied but no side effects were reported and a potential beneficial effect in improving ability to relearn or to acquire new strategies for carrying out behavioral tasks were noted [55, 56].

A recent review summarized studies evaluating the effects of transcranial brain stimulation techniques for the treatment of Alzheimer's disease [34]. Three rTMS studies [57–59] evaluated the effects of rTMS over the dorsolateral prefrontal cortex on naming and language of AD patients, and two tDCS studies [47, 48] evaluated the effects of tDCS on temporo–parietal and DLPC regions, and both rTMS and tDCS show promising effects in enhancing naming and language performances and memory in AD patients probably due to enhancement of neuroplasticity in these regions.

In humans, rTMS is able to induce release of subcortical dopamine [60] and this finding has raised interest about a potential benefit of rTMS in PD patients. In PD patients, several rTMS studies evaluated clinical effects on motor performances but most of them are not comparable because of the heterogeneity of stimulation parameters and patients' characteristics such as disease stage, medications, and treatments [61–63]. Another important point is the site of stimulation. In PD patients, two sites have been stimulated: primary motor cortex (M1) that is the most common target area and prefrontal cortex. Albeit these limits, active rTMS seems to be effective compared with sham stimulation in PD patients [64].

So far, few tDCS studies have been performed to evaluate clinical utility in PD patients. Anodal and cathodal tDCS have been both used in primary motor cortex. Results were favorable for anodal stimulation because it may enhance neuroplasticity in the primary motor cortex [29, 65, 66].

Few reports describe the effects of TMS on animal model of HD and in patients [8, 28].

In an animal model of HD, it evaluated the effects of TMS on the free radical production and neuronal cell loss, and results showed the ability of TMS to modify neuronal response to 3-nitropropionic acid [67]. In humans, a neurophysiological TMS study evaluated cortical excitability through an intracortical facilitation protocol of the motor cortex in HD patients, and researchers found an impairment of glutamatergic transmission in early stage of HD [68]. Few rTMS studies have been performed in HD patients [8, 28]. A rTMS protocol called TBS has been used to investigate synaptic plasticity using the human motor cortex-rTMS model and if there was any difference between pre-manifested HD gene carriers and very early manifested HD patients on severity of motor signs. Authors concluded that in HD motor cortex plasticity is abnormal in HD gene carriers but this abnormality is not closely linked to the development of motor signs of HD [8].

An important field in which rTMS and tDCS have been extensively used is neuropsychiatry. rTMS and tDCS have been used in major depression, bipolar disorders, and schizophrenia [31, 69].

The concept of disturbed plasticity in SCZ is supported by different lines of evidence such as dysfunction of glutamatergic transmission (mainly involving NMDA receptor activation); it has been suggested to be a crucial pathophysiological state in schizophrenia leading to neurotoxicity and disturbed plasticity [9]. Several studies have been performed to evaluate the efficacy of rTMS protocols on positive and negative symptoms in non-responders to pharmacotherapy schizophrenic patients [69, 70] [71], and results showed an improvement of symptoms after stimulation of the DLPC and temporo–parietal cortex. However results are not conclusive because of the small group of patients studied, and in a recent meta-analysis, authors warrant further studies of rTMS as a potential treatment of negative symptoms of schizophrenia [72]. Recent studies about neurophysiological and clinical effects of rTMS and tDCS on neurodegenerative diseases are summarized in Tables 1 and 2.

Perspectives

Even if some drugs such as L-DOPA and dopamine agonists are useful in PD patients [73], several pharmacological approaches were tried in AD and HD patients to improve performances or to slow down progression of diseases but clinical relevance of these approaches are still missing [74, 75]. For this reason, great interest was given to new adjuvant non-pharmacological therapies like brain stimulation. These effects were studied in animals and in healthy subjects, and therapeutic approaches were tried in proof of principles studies in patients with neurodegenerative diseases using rTMS and tDCS protocols [47, 55, 76, 77]. Moreover, transcranial stimulation performed in accordance to international standard did not show relevant safety issues [78].

Table 1 rTMS studies in neurodegenerative diseases

Authors	Protocol	Disease	No. of patients	Neurophysiological effects	Clinical effects
Ahmed et al. [76]	20 and 1 Hz rTMS on DLPFC	AD	45	20 Hz reduced transcallosal inhibition	20 Hz improved cognitive functions
Bentwich et al. [55]	10 Hz rTMS and CoG	AD	8 (7)	–	Slight improvement of ADAS score
Koch et al. [82]	1 Hz rTMS and L-DOPA	AD	10	Impairment of LTD-like plasticity	–
Cotelli et al. [56]	20 Hz rTMS	AD	10	–	Improvement in sentence comprehension
Cotelli et al. [58]	20 Hz rTMS	AD	24	–	Improvement in naming performance
Cotelli et al. [57]	20 Hz rTMS	AD	15	–	Improvement in action naming
Inghilleri et al. [77]	5 Hz rTMS	AD	20	Lack of MEP facilitation	–
Orth et al. [8]	cTBS	HD	15	Abnormal motor cortex plasticity	The measure of cortical plasticity was not associated with any clinical ratings
Lorenzano et al. [28]	5 Hz rTMS	HD	11	Impairment of facilitatory intracortical interneurones	–
Filipovic et al. [83]	1 Hz rTMS	PD	9	Enhancement of the excitability of inhibitory circuits	–
Filipovic et al. [62]	1 Hz rTMS	PD	10	–	No beneficial clinical after effects
Grüner et al. [61]	1 Hz rTMS and tDCS	PD	15	–	Beneficial effects of 1 Hz rTMS movements; it is reduced by preconditioning with cathodal tDCS
Hamada et al. [63]	5 Hz rTMS	PD	99	–	Improvement in bradykinesia
Koch et al. 2009 [84]	cTBS-L-DOPA	PD	20	–	Antidyskinetic effect
Sedlackova et al. [85]	10 Hz rTMS	PD	10	–	No significant effects on reaction time
Benninger et al. [86]	50 Hz rTMS	PD	10	–	Safety study
Van Dijk et al. [87]	5 Hz rTMS	PD	13	–	Improvement of sleep
Bäumer et al. [88]	1 Hz rTMS, STN stimulation and L-DOPA	PD	10	Normalization of silent period	No clinical improvement
Brusa et al. [89]	1 Hz rTMS	PD	8	–	Improvement of urinary disturbances
Furukawa et al. [90]	0.2 Hz rTMS	PD	6	–	Improvement of impaired set switching
Filipovic et al. [26]	1 Hz rTMS	PD	10	–	Reduction of dyskinesia
Hamada et al. [27]	5 Hz rTMS	PD	99	–	Slight improvement of motor symptoms
Kim et al. [91]	5 Hz rTMS	PD	9	–	Improvement of motor symptoms
Fierro et al. [92]	10 Hz rTMS, L-DOPA	PD	14	Increase of intracortical inhibition	–
Lomarev et al. [65]	25 Hz rTMS	PD	18	Increase of MEP amplitude	Improvement of gait and bradykinesia of upper limbs
Oh et al. [69]	10 Hz and 1 Hz rTMS	SCZ	10	–	Improvement of clinical symptoms and short-term verbal memories
Barr et al. [70]	20 Hz rTMS	SCZ	24	Reduction of frontal gamma oscillatory activity	–
Barr et al. [71]	20 Hz rTMS	SCZ	25	–	No significant group or time differences on negative symptoms or depressive symptoms
Stanford et al. [93]	20 Hz rTMS	SCZ	5	–	Improvement of negative symptoms
Lai et al. [94]	1 Hz rTMS	SCZ	8	–	Partial efficacy on auditory hallucination
Cordes et al. [95]	10 Hz rTMS	SCZ	35	–	No significant differences in clinical outcome variables
Vercammen et al. [96]	1 Hz rTMS, fMRI	SCZ	18	Enhancement of functional connectivity of the targeted region	Improvement of symptoms
Loo et al. [97]	1 Hz rTMS	SCZ	18	–	Not significant improvement in hallucination scores

Table 1 (continued)

Authors	Protocol	Disease	No. of patients	Neurophysiological effects	Clinical effects
Vercammen et al. [98]	1 Hz rTMS	SCZ	38	–	Improvement of auditory hallucinations and effects on general psycopathology
Montagne-Larmurier et al. [99]	20 Hz rTMS, fMRI	SCZ	11	–	Reduction in severity and frequency of auditory hallucinations

A number of studies used TMS to physiologically characterize AD and to evaluate effects of pharmacological agents [11, 13, 40], while others assessed clinical usefulness of rTMS and tDCS to improve cognitive function and ameliorate symptoms in AD patients [34]. TMS combined with compatible electroencephalography (EEG) can be used non-invasively to determine functional connectivity within the brain by following the spreading of electrical activity after locally applied stimuli [79]. Because altered functional connectivity may precede structural changes in AD patients, an objective method for the investigation of early functional changes might be useful in the diagnostics of MCI and AD, and this approach has been tried using TMS and EEG [80, 81].

These applications are still very early in development, and mechanisms and effects are not completely understood but offer the opportunity of learning from them for future development of these techniques. In next few years hopefully, mechanisms underlying the effects of rTMS and tDCS will be much better defined. This probably will allow using them in clinical setting, but further studies are needed to elucidate which strategies are the most effective and which patients could benefit more from each tool or protocol. Moreover, further studies are needed to evaluate the potential neuroprotective effect of these tools. Therapies might be tailored to the underlying plasticity impairment to enhance or reduce synaptic activity.

Whether these approaches might improve these conditions effectively should be proved by well-designed clinical trials. Based on currently available data, we speculate that therapies targeting synaptic processes have clinical potential, and neurophysiological approaches deserve further explorations.

Genetic state might be a key point in future studies because it might influence individual response to neuromodulatory techniques. Probably, genes involved in neuroplasticity processes might influence individual responses, and its understanding might be helpful to forecast individual responsiveness in specific neurological and neuropsychiatric disorders.

Taken together, these evidences demonstrate utility of in vivo neurophysiological tools that allow us to explore the

Table 2 tDCS studies in neurodegenerative diseases

Authors	tDCS protocol	Disease	No. of patients	Neurophysiological effects	Clinical effects
Boggio et al. [47]	Anodal	AD	10	–	Improvement of visual recognition memory task
Ferrucci et al. [48]	Anodal, cathodal	AD	10	–	Anodal increases recognition memory task, cathodal reduces it
Benninger et al. [29]	Anodal	PD	25	–	Improvement in gait and bradykinesia in upper extremities
Boggio et al. [100]	Anodal	PD	18	–	Improvement in working memory
Fregni et al. [66]	Anodal, cathodal	PD		Anodal increases MEP amplitude and area, cathodal decreases them	Anodal improves motor function
Hasan et al. [101]	Cathodal	SCZ	18	Reduction of RMT and MEP size on non-stimulated hemisphere in healthy but not in SCZ patients	–
Mattai et al. [102]	Anodal, cathodal	SCZ	12	–	Tolerability
Vercammen et al. [103]	Anodal	SCZ	20	–	Failed to improve probabilistic association learning
Hasan et al. 2011 [9]	Anodal	SCZ	44	Failed to increase MEP amplitude and reduced SICI in patients	–
Hasan et al. [104]	Cathodal	SCZ	21	Failed to reduce MEP amplitude and to modulate CSP in patients	–

physiology of the human brain and the possibility to study in vivo synaptic plasticity, and this might be useful in patients for the diagnosis and the treatment of neurodegenerative diseases. However, some mechanisms underlying neuromodulatory effects induced by these neurophysiological tools are not fully understood and still require better understanding of them to reveal their full potential as new therapeutic tools.

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