Measurement and Modulation of Plasticity of the Motor System in Humans Using Transcranial Magnetic Stimulation

Robert Chen and Kaviraja Udupa

Several techniques that involve transcranial magnetic stimulation (TMS) can be used to measure brain plasticity noninvasively in humans. These include paired-associative stimulation (PAS), repetitive transcranial magnetic stimulation (rTMS) and theta burst stimulation (TBS). Some of these techniques are based on the principle of use dependent plasticity or are designed to mimic protocols used to induce long-term potentiation or depression in animal studies. These studies have been applied to certain neurological and psychiatric disorders to investigate their pathophysiology. For example, PAS induced plasticity is enhanced in dystonia and stroke but is reduced in Huntington’s disease and schizophrenia. Furthermore, TMS may be used to modulate brain plasticity and has therapeutic potential in neurological and psychiatric disorders such as stroke, Parkinson’s disease, dystonia and depression.

Keywords: transcranial magnetic stimulation, synaptic plasticity, long term potentiation, depression

Brief History and Physiology of TMS

d’Arsonval (1896) provided the first scientific demonstration of the effects of magnetic field on human brain where sensation of light, vertigo, and syncope were perceived when a subject’s head was placed in a strong magnetic field. Subsequently, other scientists reported the phenomenon of ‘magnetophosphenes,’ visual sensations caused by stimulation of the retina due to changing magnetic fields (Lovsund, Oberg, & Nilsson, 1979). Although there were many claims of using magnetic therapy for various disorders, they lacked vigorous scientific validation. Merton and Morton (Merton & Morton, 1980) first demonstrated noninvasive electrical stimulation of the motor cortex leading to contraction of contralateral muscles using a custom-built high voltage stimulator. However, transcranial electrical stimulation is painful and is not widely used. Five years later, transcranial magnetic stimulation (TMS) was introduced by Barker, Jalinos, and Freeston

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Brain Plasticity and TMS (1985) as a tool to painlessly stimulate the brain and peripheral nerves. A large number of scientific studies have used TMS in research, clinical diagnosis and treatment of neurological and psychiatric disorders (Chen et al., 2007).

TMS is based on the principle that a changing electric current in a wire coil induces a changing magnetic field (Ampere’s law) perpendicular to the current flow in the coil. This changing magnetic field passes unimpeded through the scalp and skull and induces an electric current in the brain that flows in the opposite direction to the current in the coil (Faraday’s law).

The TMS apparatus mainly consists of boosters, control panel connected to a computer and a stimulating coil. Boosters made up of a capacitor discharge system which works with voltages of 500–4000 V and stores energy in the range of 400–2000 J, thus converting electrical energy to magnetic fluxes. The energy is discharged through the coil via thyristor switch. Stimulating coil is made up of wire loops encased in insulated plastic and connected through cable to one or more capacitors. Powerful electrical current passes through the coil for brief period of 100–200 μs. When the current flows through the coil, brief magnetic field of the range of 1.5–2 tesla is generated.

The strength of the induced current is a function of rate of change of the magnetic field, which in turn depends on the rate of change of current in the coil. Magnetic field penetrates the scalp and skull much more easily than electrical energy. The induced electrical current depolarizes axons, most likely at sites of bending. The effects of TMS depend on the intensity of the induced magnetic fields, the shape, and the orientation of the coil.

Brain Plasticity—Long-Term Potentiation (LTP) and Long-Term Depression (LTD)

In neurosciences, plasticity refers to the ability of the neural tissue to modify its structure or functions in response to stimuli and these changes outlast the stimulation period (Butler & Wolf, 2007). According to Rossini et al. (2007), brain plasticity encompasses all possible mechanisms of neuronal reorganization, including recruitment of pathways that are functionally homologous but anatomically distinct from the damaged ones, reinforcement of existing synaptic connections dendritic arborization and synaptogenesis.

LTP and LTD have been extensively studied in animal experiments in the hippocampal region. LTP is generally defined as long-lasting but not necessarily irreversible increase in synaptic strength and LTD the decrease in synaptic activity (Malenka & Bear, 2004). These are considered models for the cellular and molecular mechanisms that underlie learning and memory. Induction of LTP and LTD depends on N-methyl D-Aspartate (NMDA) receptor activation and postsynaptic calcium influx (Massey & Bashir, 2007). A rapid increase in postsynaptic calcium concentration binds the C-terminal of calmodulin and triggers a kinase pathway that increases the density and conductance surface α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors leading to LTP. In contrast, a slower increase in calcium concentration promotes binding to the N-terminal of calmodulin, which operates via the phosphatase pathway and has opposite effect on surface AMPA receptors leading to LTD (Thickbroom, 2007).
LTP is not a unitary phenomenon and mechanisms can differ between different brain regions. Different forms of LTP may occur at the same synapse and these have been termed LTP1, LTP2, and LTP3 (Raymond, 2007). LTP1 is rapidly decaying, protein synthesis independent and lasts up to 3 hr. LTP2 requires protein synthesis, but is independent of gene transcription while LTP3 is the most durable and is dependent on translation and transcription. Different stimulation protocols can produce different phases of LTP and it has been demonstrated that LTP3 requires stronger induction protocols (e.g., 6–8 theta burst stimulation trains) than LTP2 (e.g., 2–4 trains).

A drawback of these stimulation protocols is that the highly synchronous population activity that produces LTP does not occur naturally. According to Hebb’s postulation (1949), a memory trace in an ensemble of neurons become permanently laid down as changes in synaptic weight when a presynaptic neuron repeatedly takes part in the firing of the postsynaptic cell. The presynaptic activity must precede postsynaptic activity for potentiation to occur. Recent studies have confirmed both the associative nature and the temporal constraint of pre- and postsynaptic activity obeys the asymmetric Hebbian learning rule. In several in vitro systems, it was found that presynaptic action potential must be followed by postsynaptic potential in a narrow time window (within ~20 ms) for LTP to occur. Importantly, LTD occurs if the pairing was reversed with postsynaptic potential occurring before the presynaptic action potential (Debanne, Gahwiler, & Thompson, 1998; Bi & Poo, 1999; Zhang & Deschenes, 1998). Computer simulations suggested this temporally asymmetric Hebbian rule for synaptic plasticity supports sequence learning (Paulsen & Sejnowski, 2000). LTD also involves multiple mechanisms that vary depending on the brain region and developmental time point (Massey & Bashir, 2007). Different stimulation protocols are used to induce LTD. Homosynaptic LTD is often induced with low frequency stimulation of 600–900 pulses at 1–5 Hz.

**Synaptic Plasticity and TMS**

Various TMS protocols (Table 1) have been used to induce LTP- and LTD-like changes in the brain and they may have therapeutic utilities in various neurological and psychiatric disorders. In vitro and animal studies have used very high frequency stimulation (e.g., 100–200 Hz for 1–4 s) but such frequencies cannot be used in humans because of risk of seizures and machine limitations. For example, at frequency of 20 Hz, the stimulus duration and intensity that could be safely administered in humans is 1.6 s with a stimulus intensity of 110% of motor threshold (MT) at an intertrain interval of 5 s (Chen et al., 1997b; Wassermann, 1998). Theta burst stimulation (TBS) was devised in an attempt to produce greater effects than regular rTMS by using parameters similar to TBS in animal studies (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). TBS usually involves short bursts of 3–5 pulses repeated at 5 Hz (theta frequency), typically 10 bursts in one train. These different stimulation paradigms are discussed in greater detail in following paragraphs.
Paired Associative Stimulation (PAS)

It is possible to induce LTP- and LTD-like changes in the sensorimotor system in human by means of a validated experimental intervention known as PAS (Stefan, Kunesch, Cohen, Benecke, & Classen, 2000; Wolters et al., 2003; Wolters et al., 2005). PAS refers to a paradigm of repetitive, low-frequency single pulse electrical nerve (usually median) stimulation or a train electrical stimuli applied to motor point of muscles (Ridding & Taylor, 2001), followed by TMS over the contralateral motor cortex. It is based on the principles of associative LTP in experimental animals and the Hebbian concept of spike-timing-dependent plasticity with two inputs paired to arrive at a single neuron at approximately the same time.

PAS-induced changes in cortical excitability share a number of physiological properties with LTP. In human, it takes about 20 ms for the fastest sensory impulses from the median nerve to reach the sensory cortex. The integration of the information from sensory cortex to M1 takes about 2–5 ms. If the TMS is applied ~25 ms (PAS25) after median nerve stimulation, M1 neurons are synchronously activated by the afferent input (presynaptic) and TMS (postsynaptic activation). If a weak

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**Table 1 Plasticity Inducing Protocols in Humans**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Description of the procedure</th>
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<tr>
<td>Typical LTD-inducing protocols</td>
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<tr>
<td>PAS25</td>
<td>Median nerve stimulation at the wrist at 3 times sensory threshold paired with TMS to the contralateral M1 delivered ~25 ms later, at 0.1 Hz for 30 min (180 pulses)</td>
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<tr>
<td>High frequency rtms</td>
<td>rtMS applied to cortical region of interest is stimulated usually at frequencies between 5 and 25 Hz. (the actual parameters varied among studies)</td>
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<tr>
<td>iTBS</td>
<td>3 TMS pulses at 80% active MT is given at 50 Hz, with bursts repeated at a 5 Hz. Two second trains of TBS applied every 10 s for a total of 190s (600 pulses)</td>
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<tr>
<td>Typical LTP inducing protocols</td>
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<tr>
<td>PAS10</td>
<td>Stimulation paradigm is identical to PAS25 except that time between median nerve stimulation and TMS is 10 ms instead of 25 ms</td>
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<tr>
<td>Low frequency rtMS</td>
<td>rtMS applied to cortical region of interest at 1 Hz or lower</td>
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<tr>
<td>cTBS</td>
<td>Similar to iTBS, except that TBS is applied continuously for 40s (600 pulses)</td>
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Abbreviations: cTBS = continuous theta burst stimulation; iTMS = intermittent theta burst stimulation; LTD = long term depression; LTP = long term potentiation; MT = motor threshold; PAS = paired associative stimulation; rtMS = repetitive transcranial magnetic stimulation.
excitatory synaptic input repeatedly arrives at a neuron shortly before the neuron has fired an action potential, then the strength of the connection is increased. If the timing of the stimuli is reversed so that the input arrives just after neural discharge, then the strength of the connection is reduced (Wolters et al., 2005). There are also cases in which the rules are reversed such that synaptic strengthening occurs if the weak input arrives after rather than before the postsynaptic action potential (Kujirai, Kujirai, Sinkjaer, & Rothwell, 2006). In human PAS studies, it is likely that the median nerve stimulus and TMS both evoke inputs onto a shared neuron in the cortex. Repeated pairings then result in an increase in the net efficiency with which subsequent TMS pulses can activate corticospinal neurons (Kujirai, Kujirai, Sinkjaer, & Rothwell, 2006). Thus, repeated pairs of PAS25 lead to enhance M1 excitability, which can be measured by TMS parameters such as decreased motor threshold, increased MEP amplitude, decreased silent period duration. In contrast, repeated pairs of PAS10 (TMS pulse given 10 ms after median nerve stimulation) reduce the M1 excitability since the postsynaptic activation (TMS) precedes the presynaptic activation (afferent input) at the M1 (Wolters et al., 2003). Changes in M1 excitability induced by PAS occur rapidly, last for at least 60 min, are topographically specific occurring selectively in median nerve innervated muscles and are blocked by dextromethorphan (NMDA receptor antagonist) or nimodipine (L-Type voltage-gated Ca\(^{2+}\) channel blocker; Stefan, Kunesch, Benecke, Cohen, & Classen, 2002). Thus, the physiological and pharmacological profile of PAS share the features of the Hebbian LTP, such as associativity, input specificity, and cooperativity (Bear & Malenka, 1994), suggesting that LTP/LTD-like mechanisms likely underlie cortical plasticity induced by PAS (Stefan et al., 2000; Stefan et al., 2002). The effects of motor learning (Ziemann, 2004) and how different sessions of PAS interact are also consistent with PAS being mediated by LTP (PAS25) and LTD (PAS10; Muller, Orekhov, Liu, & Ziemann, 2007).

**PAS in Stroke**

In chronic subcortical stroke, previous studies found enhanced interhemispheric inhibition (IHI) of the affected side by the unaffected side before movement onset (Murase, Duque, Mazzocchio, & Cohen, 2004). In contrast, a recent study reported normal IHI in subacute stroke patients tested at rest (Butefisch, Wessling, Netz, Seitz, & Homberg, 2008). To modulate the possible imbalance in IHI, a recent study in ten stroke patients (Jayaram & Stinear, 2008) applied inhibitory PAS (120 pairs at 0.5 Hz) with stimulation of the common peroneal nerve innervating the nonparetic tibialis anterior muscle followed by TMS of the contralesional motor cortex. As expected, this slightly decreased the excitability of the contralesional motor cortex but also increased the motor cortical excitability of the lesioned side assessed during walking. This may be achieved through decreasing the enhanced interhemispheric inhibitory drive from the contralesional to the ipsilesional primary motor cortex. In a study involving two chronic stroke patients (Castel-Lacanal, Gerdelat-Mas, Marque, Loubinoux, & Simonetta-Moreau, 2007), PAS was able to induce lasting changes in the excitability of corticospinal projection to wrist muscles of the affected side, suggesting that associative plasticity may occur in the cortex affected by stroke. Further studies in more patients are needed to
examine whether functional improvement in hand motor function occurs follow-
ing PAS and to evaluate the therapeutic utility of PAS in stroke rehabilitation.

**PAS in Movement Disorders**

Morgante et al. (2006) and Ukei et al. (2006) found that LTP-like changes induced
by PAS is impaired in Parkinson’s disease (PD) and is restored by dopaminergic
medications. Furthermore, Morgante et al. (2006) observed restoration of PAS in
PD patients without levodopa-induced dyskinesia but not in patients with levodo-
pa-induced dyskinesia, suggesting that abnormal synaptic plasticity in the M1
play a role in the development of levodopa-induced dyskinesia.

It has been observed that LTP-like changes is enhanced in patients with focal
arm dystonia (Weise et al., 2006; Quartarone et al., 2003) in response to PAS pro-
tocol. Tisch et al. (2007) studied PAS in primary generalized dystonic patients
with deep brain stimulator (DBS) implanted in globus pallidus internus (GPi).
They concluded that DBS reduced LTP-like motor cortex plasticity since increased
motor cortex excitability was observed in healthy subjects and GPi DBS OFF
patients but not with GPi DBS ON following PAS. In another study with Hunting-
ton’s disease patients, Crupi et al. (2008) observed impaired cortical and brain-
stem LTP-like plasticity following PAS although these patients had normal soma-
tosensory evoked potentials and blink reflex.

**PAS in Schizophrenia**

Frantseva et al. (2007) found that LTP-like plasticity measured by PAS is impaired
in patients with schizophrenia and this deficit correlates with performance in
motor skill learning.

**Repetitive Transcranial Magnetic Stimulation (rTMS)**

rTMS involves regularly repeated stimulation of the cerebral cortex by trains of
magnetic pulses. By convention, stimulating frequencies greater than 1 Hz is
referred to as high frequency rTMS whereas stimulating frequencies lower than 1
Hz is referred to as low frequency rTMS (Wassermann, 1998). Low frequency
rTMS has been shown to decrease corticospinal excitability. Chen et al. (1997a)
demonstrated that a 15-min train of supra-threshold 0.9 Hz rTMS applied to the
M1 reduced MEP size for at least 15 min after the end of stimulation. Similar
results have been reported by other investigators (Siebner et al., 1999; Muellbacher,
Ziemann, Boroojerdi, & Hallett, 2000; Fitzgerald, Brown, Daskalakis, & Kulkarni,
2002) and the effects are stronger with suprathreshold than subthreshold pulses.

High frequency rTMS has opposite effects and may result in increased M1
excitability. It has been demonstrated that MEP facilitation during a train of rTMS
varied with stimulus intensity and frequency (Pascual-Leone, Valls-Solé, Wasserm-
mann, & Hallett, 1994). With 5 Hz rTMS at 150% of resting motor threshold
(RMT), there was clear MEP facilitation. At 10 and 20 Hz rTMS with lower inten-
sity (110% RMT), there was also consistent facilitation. Several other studies
have also demonstrated that MEP size increases with high frequency rTMS (Jah-
anshahi et al., 1997; Berardelli et al., 1998). Although how rTMS alters cortical
excitability remains unclear, many investigators have suggested that decreased excitability is related to LTD (Chen et al., 1997a) whereas increased excitability is related to LTP (Wang, Wang, & Scheich, 1996). However, there is considerable intersubject variability in the response to rTMS. A distinct subgroup of healthy controls demonstrated opposite effects with 1 Hz stimulation leading to increased cortical excitability whereas 20 Hz stimulation was associated with reduced cortical excitability (Gangitano et al., 2002). Moreover, rTMS has different effects on the motor cortex depending on its state. For example, 0.1 Hz rTMS applied to the deafferented motor cortex produced by ischemic nerve block increased cortical excitability whereas the same stimulation applied the naïve motor cortex had no effect (Ziemann, Corwell, & Cohen, 1998).

rTMS is being studied as a treatment for neurological and psychiatric disorders. High frequency rTMS has been reported to improve symptoms of PD (Lomarev et al., 2006; Khedr, Rothwell, Shawky, Ahmed, & Hamdy, 2006), myoclonus (Lefaucheur, 2006a), chronic neuropathic pain (Lefaucheur, 2006b) and is promising treatment for depression (O’Reardon et al., 2007; Stern, Tormos, Press, Pearlman, & Pascual-Leone, 2007; Gross, Nakamura, Pascual-Leone, & Fregni, 2007). Low frequency rTMS has potential for treatment of levodopa-induced dyskinesia in PD (Koch et al., 2005; Wagle-Shukla et al., 2007), epilepsy (Tergau, Naumann, Paulus, & Steinhoff, 1999), and auditory hallucination in schizophrenia (Hoffman et al., 2003). In stroke, high frequency rTMS has been applied to the affected side or low frequency rTMS applied to the unaffected side to promote recovery (Fregni & Pascual-Leone, 2007). Webster, Celnik, and Cohen (2006) concluded that TMS is a powerful tool for modulating brain activity and cognitive function in stroke patients and may contribute to neurorehabilitation of these patients.

**Theta Burst Stimulation (TBS)**

In an attempt to produce more powerful changes in cortical excitability in human, (Huang & Rothwell, 2004) examined the effects of rTMS applied in TBS mode (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Animal studies have used intermittent TBS (iTBS) to facilitate synaptic transmission (Capocchi, Zampolini, & Larson, 1992; Hess, Aizenman, & Donoghue, 1996; Heynen & Bear, 2001) and some have used longer trains of continuous TBS (cTBS) to produce synaptic suppression (Heusler, Čebulla, Boehmer, & Dinse, 2000; Takita, Izaki, Jay, Kaneko, & Suzuki, 1999). Maximal TBS in the rat CA1 is induced with 8–16 TBS trains (Raymond, 2007).

Huang et al. (2005) used a TBS protocol consisting of 3 weak TMS pulses (80% active motor threshold) at 50 Hz frequency and the bursts repeated at a frequency of 5 Hz (i.e., 200 ms, theta frequency). iTBS consists of 2 s trains of TBS applied every 10 s for a total of 600 pulses (190 s) and produces ~50% decrease in MEP amplitude that lasted about 60 min (Di Lazzaro et al., 2005). In contrast, cTBS consists of 40 s of uninterrupted TBS (600 pulses) and produces ~50% increase in MEP amplitude that lasted about 20 min. These changes appear to be of greater magnitude and longer duration than conventional rTMS paradigms and are due to changes in cortical rather than spinal excitability (Huang et al., 2005;
Di Lazzaro et al., 2005). They likely involve LTP (iTBS) and LTD (cTBS) based on similarity with induction protocol used in animal experiments and these changes are blocked by NMDA receptor antagonist (Huang, Chen, Rothwell, & Wen, 2007).

Even though TBS was described only three years ago, it has garnered much interest among investigators (Martin, Gandevia, & Taylor, 2006; Huang et al., 2007; Ishikawa et al., 2007; Talelli, Cheerin, Teo, & Rothwell, 2007). In stroke patients, it was demonstrated that both facilitatory TBS over the stroke hemisphere and inhibitory TBS over the intact hemisphere enhance the excitability of the motor cortex of the lesioned hemisphere (Di Lazzaro et al., 2008). In another study (Talelli, Greenwood, & Rothwell, 2007), iTBS over the stroke hemisphere transiently improved motor behavior and corticospinal output in the paralyzed hand. Thus, TBS is a promising strategy for promoting stroke recovery. TBS also demonstrated abnormal cortical plasticity in patients with dystonia (Edwards, Huang, Mir, Rothwell, & Bhatia, 2006). Prolonged response to cTBS was observed in DYT1 gene carriers with dystonia and healthy volunteers compared with DYT1 gene carriers without dystonia. This suggests lack of response to ‘plasticity probing protocol’ in genetically susceptible but clinically normal individuals.

**Conclusions**

TMS can be used to measure and induce brain plasticity in humans. It has immense potential both as an investigative tool as well as a therapeutic option. It is likely that future studies will provide further information on the mechanisms of brain plasticity in humans, new insights on the pathophysiology of neurological and psychiatric disorders, and novel treatment for these conditions.

**References**


