

# Neural Plasticity: Influencing Elements and Modulation Techniques

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## Abstract

It is believed that neural plasticity plays an important role in the process of human cognition and motor practicing. Tremendous researches on neural plasticity have been done in the past 30 years. In this paper, we discussed the factors that may affect neural plasticity and the widely used modulation techniques. The purpose of this review is to present the current-state-of-art of neural plasticity studies and help readers to envision the future research directions.

**Keywords:** Neural plasticity; Motor training; d-amphetamine; Sensory input; Repetitive transcranial magnetic stimulation; Transcranial direct current stimulation; Brain-derived neurotrophic factor

## Introduction

Neural plasticity, also known as brain plasticity, cortical plasticity and other terms, refers to the structural and functional reorganization ability of brain and nervous system as a result of input from the environment. It was formerly thought to exist only in early postnatal periods [1]. However, recent researches have shown enough evidences of modulating the neural plasticity in adult human subjects. A classic well-known experiment of modulating neural plasticity in adult human subject was performed by Classen et al. [2]. In their research, transcranial magnetic stimulation (TMS) is applied over the subjects' motor cortex to elicit directional thumb movement. After the preferred direction of thumb movement is established, subjects are asked to repetitively move their thumb to the opposite direction for a period of 30 minutes. Once the motor training is done, TMS is applied to the same area of the motor cortex again. At this point, it is observed that the direction of subjects' thumb movement elicited by TMS change to the trained direction which is opposite to the original thumb movement direction. This experiment shows that active motor training induces rapid change in cortical representation of the thumb. Therefore it is considered as a supportive evidence of the assumption that neural plasticity of adult human subject can be modulated by appropriately designed motor task. Neural plasticity is believed to play an important role in the process of motor learning, skill acquisition [3] and memory formation. Tremendous researches have concluded that modulation of neural plasticity can assist the function restoration from brain lesion and spinal cord injury and may facilitate the recovery of patients suffering from stroke, depression, and Parkinson disease. Neural plasticity modulation may be influenced by many factors including age, pharmacology, motor training, sensory input, non-invasive brain stimulation and gene expression. In this article, these factors are discussed separately in following sections.

## Age

Neural plasticity may reduce with advancing age. Rogasch et al. [4] examined changes in corticomotor excitability and plasticity after a thumb abduction training task in 14 young (18-24 yr) and 14 old (61-82 yr) adults. The training task consisted of 300 ballistic abductions of the right thumb to maximize peak thumb abduction acceleration (TAAcc). TMS of the left primary motor cortex was used to access changes in abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles motor evoked potentials (MEPs) and short-interval

intracortical inhibition (SCSI). After motor training, 77% and 24% improvement in peak TAAcc were observed in young and old group respectively. Meanwhile, the APB MEP amplitude increased 50% in young subjects, while no changes were found in old subjects. These experiment results suggest that neural plasticity diminishes in older adults. Todd et al. [5] also examined the age effect to neural plasticity by applying inhibitory repetitive transcranial magnetic stimulation to young (25±4 yr) and old (67±5 yr) groups. Their experiment results indicate that the MEP amplitude recorded from first dorsal interosseus (FDI) muscle after 10 minutes of rTMS reduced 15% in the young group, with no changes in old group. It is supportive to the hypothesis that age is accompanied by reduced neural plasticity. Possible causes of the neural plasticity decreasing in older people may include the reduction in the number of synapses [6], the size of compound excitatory post-synaptic potentials [7], the number of cells (Henderson, Tomlinson et al. 1980), the volume of gray matter [8] and atrophy of spinal motoneurons [9]. Several researches have confirmed that advancing age is associated with neural plasticity diminishing. However, Cirillo et al. [10] recently published a paper arguing that although an age-related decline in motor learning occurred for the dominant hand, use-dependent corticomotor plasticity was not altered with advancing age in a simple thumb-training task. The mechanism of this age-related maintenance in neural plasticity remains to be determined.

## Pharmacological modulation

Pharmacological modulation has been utilized to improve recovery of motor function. As early as in 1981, Feeney et al. [11] reported that a single dose of d-amphetamine (AMPH) given the day following a unilateral sensorimotor cortex ablation resulted in improved motor recovery in rats. This initial study introduced the positive effect of d-amphetamine to the recovery of motor function and triggered tremendous further researches on humans [12-15]. Butefisch et al. [16] investigated six subjects' performance of a simple motor task under

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the effects of placebo and AMPH in a randomized, double-blind, counterbalanced experiment. The results suggest that AMPH induces increased magnitude, faster development and longer lasting duration of use-dependent plasticity and confirm the hypothesis that AMPH has facilitatory effect on neural plasticity. The mechanisms underlying the effect of AMPH are not completely understood, but they may include AMPH induced presynaptic release of the monoamines norepinephrine, dopamine and serotonin, inhibition of their reuptake [17-20], and enhancement of alpha adrenergic neurotransmission secondary to amphetamine-dependent release of norepinephrine [21]. It is also reported by Sawaki et al. that drugs that antagonize the effects of norepinephrine, such as prazosin, decreased the effectiveness of motor training in eliciting use-dependent plasticity measured by TMS [22]. Although AMPH may bring transient side effect including irritability, increased alertness, and a feeling of being detached from the environment [16], it is conceivable that d-amphetamine enhances the neural plasticity thought to contribute to functional recovery after brain injury and cortical lesions [11,23].

### Motor training

Motor training has been proved capable of modulating neural plasticity [2,24]. Although the within-session effect of motor training is still controversial [25-27], consistency has been reported in the slowly developing increase of activation [27-29]. The plasticity modulation effect of motor training may also depend on the complexity of the motor task presented to the subjects. While many studies have confirmed that elementary motor training can change neural plasticity [30-32], researches also provided evidences that skilled motor training is more beneficial to the neural plasticity modulation [33,34]. Smyth et al. [35] analyzed the performance outcome of a wrist flexion-extension waveform-tracking task in two groups of 10 subjects, with one group was given 100% feedback (FB) and the other group was given only 50% FB during the task [35]. Interestingly, although no cortical excitability changes were observed during the acquisition, the 50% FB group had elevated primary motor cortex excitability at retention (24 hrs after motor training). This effect may be due to the increased cognitive complexity in the 50% FB group, which additionally modulated the learning associated plasticity [36,37]. Motor training induced motor cortex excitability may reduce in skilled subjects compared to non-skilled subjects when performing the same motor task [38-40]. This effect has been explained as diminished neural effort is required for a particular motor task with a history of intense motor training [32].

### Sensory input modulation

It has been reported that manipulation of sensory input has the ability to modulate the excitability of the primary motor cortex in animal model [41,42]. Further studies on human cortex demonstrated that rapid motor representation may be incurred by disruption of sensory input, such as amputation, ischemic nerve block, or blood pressure cuff [24,43]. Kaelin-Lang, et al. [44] analyzed the MEPs recorded from abductor pollicis brevis (APB), first dorsal interosseous (FDI) and abductor digiti minimi (ADM) muscles after a 2-hour period of ulnar nerve electrical stimulation at the wrist and concluded that somatosensory stimulation elicited a focal increase on corticomotoneuronal excitability that outlasts the stimulation period and probably occurs at cortical sites. Khaslavskaja et al. [45] also reported increased motor cortex excitability after electrical stimulation measured by TMS in tibialis anterior (TA) muscle.

### Non-invasive brain stimulation

Non-invasive brain stimulation techniques have been developed rapidly in the past two decades as a useful and promising tool for neuroscientists. Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), two techniques that can purposefully enhance or decrease excitability in focal areas of the brain, allow researchers to explore the facilitate activity in specific cortical areas in motor learning in an attempt to improve motor function [46].

Single pulse transcranial magnetic stimulation (TMS) elicited MEPs have been widely used as effective measurement of neural plasticity. It operates by creating a pulse magnetic field, which induces focal current flow that activates the targeted cortical brain area [47]. TMS under the frequency of 0.1 Hz are considered unable to induce neural plasticity. However rTMS protocols including theta-burst stimulation (TBS) [48] have been proved as safe and noninvasive techniques that have the ability of neural plasticity modulation [49,50]. Generally, low-frequency rTMS (i.e. 1 Hz) induces inhibitory effects on motor cortical excitability [51] while high-frequency rTMS (5-20 Hz) usually increase cortical excitability [52,53]. It is believed that rTMS is able to interfere with the motor learning, skill acquisition, memory consolidation and reconsolidation process through stimulation on the primary motor cortex [54-62] and non-primary motor cortices [63-68]. Different motor tasks may be more dependent on motor cortex or non-motor cortical areas like premotor cortex, posterior-parietal area and basal ganglia [69,70]. Therefore, TMS effects on behavior cannot be automatically conjectured from its effects on motor cortical excitability [71]. rTMS is also utilized as a useful tool in studies of interaction between hemispheres [72-74] and believed to be able to enhance the treatment effect in depression patients [75-78].

tDCS is another non-invasive procedure of cortical stimulation which uses weak direct current to polarize target brain area. Depending on the polarity of the stimulation, tDCS can be divided as anodal tDCS and cathodal tDCS that increase and decrease cortical excitability in the stimulated brain regions respectively [79]. tDCS has the ability to modulate neural plasticity and thereby enables the investigation of the causal relationships between brain activity. With several advantages over TMS, such as producing less artifact, low cost and great potential for cognitive and motor enhancement without seizure reported, tDCS is considered not only a complementary tool to TMS, but also a unique technique in current neuroscience [80].

### Gene expression

A recent popping up question in neural plasticity studies is whether plasticity in human motor cortex is in part genetically determined? According to de Geus et al.'s review [81], there are about 100 genes currently considered have influence to human brain function and cognition, in which brain-derived neurotrophic factor gene (BDNF) is believed to be the most promising way to better understand the multifaceted role of BDNF variants in different plasticity protocols [82,83]. BDNF, as a key neural signal that orchestrate synaptic plasticity [84], is elevated within motor cortex in response to motor training [85]. Kleim et al. [86] studied the relationship between cortical plasticity and BDNF with a val66met polymorphism by investigating the MEP amplitude recruitment curve (RC), cortical representational area, normalized map volume and center of gravity (COG) in 9 Val/Val, 11

Val/Met and 6 Met/Met subjects [86]. Their experiment results indicate that although no baseline differences were observed in corticospinal output or motor map area between Val and Met subjects, a brief period of motor training enhanced corticospinal output and increased motor map area in Val/Val, but not Val/Met or Met/Met subjects [86]. This outcome is consistent with former researches [87,88] and supports the hypothesis that BDNF is involved in mediating use-dependent plasticity of human motor cortex. Cheeran et al. [89] studied human cortical plasticity in subjects with BDNF polymorphism by using different protocols [89]. The significant differences of cortical plasticity changes in Val/Val subjects and Met allele carriers drove them to hypothesize that BDNF polymorphism and the number of alleles may be associated with cortical plasticity modulation. Missitzi et al. [82] furthered Cheeran et al. [89] research by studying paired associative stimulation (PAS) induced neural plasticity in monozygotic (MZ) and dizygotic (DZ) twins [82]. It was found that the intrapair differences in MEP amplitudes measured 25-30 minutes post-intervention at APB muscle were almost double for DZ in comparison to MZ twins. This result more convincingly supports the hypothesis that interindividual variability in excitability changes of the motor cortex may due to the BDNF polymorphism and implicates that genetic factors may contribute significantly to the interindividual variation of neural plasticity.

## Summary

Neural plasticity, as the reorganization ability of human or animal's neural system adapting to the environment input, has been studied for more than three decades. In this review, we discussed the factors that may affect neural plasticity and the available modulation techniques that can be utilized to induce neural plasticity. With abundant evidences, age, medicine (d-amphetamine), and gene expression have been proved as important factors that may affect neural plasticity. Motor training and modulation techniques, such as sensory input, rTMS and tDCS, have been widely used to induce neural plasticity in humans. Despite of the great progresses that have been achieved in neural plasticity studies, there are still many blank areas need further explorations. For example, the mechanisms of the maintenance of neural plasticity in older subjects, the medicine assisted neural plasticity modulation, the design of skilled motor task that enhances neural plasticity modulation and the relationship between gene expression and variation of neural plasticity. Future researches should also include the clinic use of the neural plasticity modulation techniques and the development of more effective modulation protocols by combining the available techniques, while stay alert to the influencing factors.

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