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Non-Invasive Brain Stimulation and its Supposed Site of Action in the Rehabilitation of Parkinson's Disease and Stroke

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Two non-invasive brain stimulations have spread all over the world: repetitive trasncranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). TMS is based on the current induction with a changing electromagnetic field in the nervous system [1] while tDCS changes the polarity of cell membranes [2].

General Aspects of TMS and tDCS

TMS is widely used in research and daily medical practice. It was introduced as a diagnostic tool about thirty years ago to test functioning of motor pathways [3]. The motor evoked potential (MEP) and the measurement of the central motor conduction time (CMCT) has entered into daily practice. The other parameters of the electrophysiological examination assessed by TMS are mainly used in scientific work [4]. TMS aids the diagnosis of multiple sclerosis, furthermore the prognosis of stroke can be indicated by TMS [5]. Different paired pulse stimulations with TMS give a new insight into the function of the brain. In recent years, sophisticated brain plasticity can be detected by the measurement of intracortical excitability [6,7]. We learnt from these studies how different conditions can modify brain plasticity. It can be changed by different diseases, altered by drugs [8] and strongly influenced by non-invasive stimulations [2,9]. The single TMS and one session of repetitive stimulation have a short after-effect. However the effect of repeated stimulation for days exceeds the stimulation period and many times it lasts for months. This effect of rTMS has made it useful for therapy for the last 20 years. The low and high frequency stimulation, continuous theta burst stimulation (cTBS), intermittent theta burst stimulation (iTBS), anodal or cathodal stimulation are used for therapy. The intensity of rTMS was around the motor threshold and the duration of stimulation was 7-10 days. This paper reviews the most frequently studied symptoms of Parkinson's diseases and stroke although rTMS has been tried to treat all disorders of the central nervous system (CNS).

Parkinson's Disease (PD)

The first protocol was low frequency, low intensity monophasic stimulation for 7 days which improved the Parkinsonian symptoms and its results were maintained for several months after the stimulation [10,11]. The authors performed a "dose (intensity) response" curve with 1 Hz stimulation and they indicated that there is an optimal intensity using 1 Hz [12]. We learned from these studies that the therapeutic effect of rTMS develops after a delay in time of a few weeks. The improvement can be maintained for several months. The later studies confirmed these observations not only in PD but other diseases. Although, the high frequency stimulations over the primary motor cortex [13,14] had the same effect on the Parkinsonian scores but the after-effect lasted for a shorter time. iTBS over the dorsolateral prefrontal area improved the depression without effecting on bradykinesia [15]. The studies concentrated on varying the frequency which was applied but they did not try to find the optimal intensity for high frequency stimulation. Using the optimal intensity will produce longer lasting therapeutic effects. The cure of levodopa induced dyskinesia is far more can not be solved. Although, the dyskinesia induced by levodopa can be decreased by low frequency rTMS over the primary motor cortex or cTBS over the cerebellum [16,17]. rTMS over the motor cortex induced dopamine release in ipsilateral putamen assessed by [11C] raclopide PET study, which also contribute to the effect of rTMS in PD [18]. The regularly repeated rTMS periods may decrease the development of PD [19]. This observation needs further confirmation. The motor deficit of Parkinson's disease can be influenced by tDCS applied parallel over the motor and prefrontal area [20]. Similarly to the rTMS, one of the supposed sites of action of tDCS - according to animal studies - is the dopamine release in the striatum [21]. These promising results urge the involvement of non-invasive brain stimulation in the treatment of Parkinson's disease because the respond for dopaminergic therapy is less effective over years.

Influence on Different Symptoms of Stroke with Non-Invasive Brain Stimulation

The most frequently observed stroke happens in the area of the artery of the cerebral media. It may cause different symptoms such as paresis, spasticity, aphasia, neglect dysphagia and cognitive decline.

There is a mutual inhibition between the two hemispheres which is destroyed by a lesion caused by stroke. The goal of the treatment with non-invasive brain stimulations is to restore the decreased excitability of the lesioned hemisphere and decrease the over activity of the non-lesioned hemisphere [22]. Low frequency stimulation and cTBS stimulation are applied over the non-lesioned hemisphere to decrease the excitability, while the high frequency and iTBS stimulation enhances the excitability and they are used over the lesioned hemisphere. Both treatments led to a faster movement in the paretic hand, and decreased the reaction time in slight cases of stroke [23-26]. The 3 Hz stimulation showed a more pronounced effect than 10 Hz stimulation assessed by NIHSS after one year [27]. The best results were achieved after 1 Hz stimulation [28] which induced new movement in the paretic hand years after the onset of stroke [29]. A meta-analysis confirmed that 1 Hz rTMS over the unaffected hemisphere may be more beneficial for the motor outcome than the high frequency rTMS over the affected hemisphere [30]. The motor deficit of stroke can also be treated by tDCS.

The same positive results with tDCS as rTMS confirmed the effectiveness of anodal and cathodal stimulations for 6 days. Both stimulations were superior to sham stimulation over the primary motor cortex in a three month follow up study [31]. The usefulness of tDCS in chronic stroke was summarized by Stagg [32]. There are controversy results in the long term usefulness of speech therapy in fluent aphasia, but the non-invasive stimulation over the language area can improve

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the object naming, although, several weeks after the stimulation. It was demonstrated by rTMS [33-36] and tDCS [37,38]. There is a reversion of the imbalance of interhemispheric inhibition, speech induced activity shifts to the left side instead of both sides or right side and formation of a new language network which may responsible for the better outcome of aphasia several weeks after stimulation.

In addition, both neglect and dysphagia can be improved by non-invasion brain stimulation. Neglect makes the improvement of paretic extremities more difficult. It can be ameliorated by one Hz stimulation over the right parietal cortex [39]. Dysphagia is a life threatening symptom of a brain injury. It is caused by pseudobulbar paralysis or a lesion in the brain stem which was improved after rTMS [40,41]. In addition to the wide therapeutic application of rTMS the spasticity can also be decreased by rTMS with low and high frequency stimulation [25,42].

Cognitive impairment appears not only in Alzheimer's disease, but it accompanies many diseases. The most prominent examples are brain injuries, stroke and different neurodegenerative diseases. The working memory and executive function can be improved by low and high frequency stimulation over the dorsolateral prefrontal cortex but not over the primary motor cortex in patients with stroke [43]. The working memory and visuo-motor learning were facilitated by tDCS [44,45]. The effect of non-invasive stimulations depends on the tasks performed in the study which may contribute to the great variability of the results. It was summarized by Miniussi [46].

Depression is an independent entity but many times accompanies other chronic diseases. No unified protocol for the treatment of depression has been settled. The FDA accepted treatment with high frequency stimulation of drug resistant cases. Similarly to the previous symptoms, depression can be improved by low and high frequency stimulation of rTMS [47,48]. The right dorsolateral prefrontal cortex (DLPFC) was stimulated by low frequency while the left DLPFC was treated with high frequency stimulation. Both were equally effective according a meta-analysis [49]. The previous symptoms can be influenced at the same time by non-invasive stimulations. This possibility is the great advantage to these therapies.

Proposed Site of Action of Non-Invasive Brain Stimulation

The question is whether the change in intracortical excitability is responsible for the therapeutic effect of the brain stimulation. At the beginning, the therapeutic use was based on influencing brain plasticity but there is a time delay in the two effects of rTMS. The effect on brain plasticity develops immediately and ceases at the end of the stimulation but the therapeutic effect develops over a period of weeks or months. This discrepancy in time led to the conclusion that TMS and tDCS influence both of them but the two effects are partly independent from one another [50].

In animal studies, the production of stem cells under the subventicular zone and their migration to the lesioned area was increased after rTMS [51,52]. If this is true in humans as well, rTMS will not only be a symptomatic treatment but it could be used to influence the etiology of the disease. BDNF is the regenerating hormone for the nervous system and rTMS and tDCS increases its production [53-56].

The effects of rTMS and tDCS are not localized but the activity of the central nervous system is increased or decreased far from the place that was stimulated. We cannot exclude the possibility that non-synpatic transmission contributes to the effect of non-invasive stimulations because the non-stimulated parts of the brain are also activated by non-invasive stimulations [57]. GABA is increased in the cortex after low frequency stimulation [58,59]. After high frequency stimulation, the glutamate is increased [60]. There is a new balance between the inhibitory and excitatory neurotransmitter system which is achieved by the rTMS and tDCS [61].

Therefore the mode of action of rTMS and tDCS may be similar in restoring impaired neuronal activity which prepares the intact part of the brain for better functional activity.

Difficulties in Therapy with Non-Invasive Brain Stimulation

The results of different publications are hardly comparable because of the great variations of protocols. Two modes of TMS stimulation are applied, monophasic and biphasic, which basically differ from each other. Consequently the same intensity and frequency do not mean the same electric current induced by the stimulation. Furthermore intracortical excitability can be facilitated by high frequency stimulation and inhibited by low frequency stimulation but the individual values present a great variability which may lead to different therapeutic effects. The variability depends on which interneuron network is affected by TMS in the subject [62]. The heterogeneity of a group of patients may lead to divergent results.

Conclusions

Both non-invasive brain stimulations improve different symptoms of central nervous diseases. The effect develops slowly and can be maintained for months after the stimulation. It seems that both the low and high frequency stimulations effective but the intensity and duration of stimulation must be adjusted to each other. They influence both neuroplasticity and symptoms of the disease but their effect may partly independent from each other. The therapeutic effect may be attributed to the elevated brain stem production, increased levels of BDNF, a new balance in the inhibitory and excitatory neurotransmitter and in addition the non-synaptic transmission may play a role in the healing effect of non-invasive stimulation.

While the stimulation of motor pathways quickly spread all over the world, therapeutic use of repetitive stimulation remained restricted to electro physiologists and has hardly touched the daily practice of neurology and rehabilitation. During the last twenty years nearly one thousand patients with different diseases were involved in the studies where results showed a significant improvement in most cases. These are safe methods (guidelines exist) and we have to use them to benefit our patients.

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