Chapter 3

Motor Cortex Hyperexcitability, Neuroplasticity, and Degeneration in Amyotrophic Lateral Sclerosis

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Abstract

Neuronal hyperexcitability is a well-known phenomenon in amyotrophic lateral sclerosis and other neurodegenerative diseases. The use of transcranial magnetic stimulation in clinical and research practice has recently made it possible to detect motor cortex hyperexcitability under clinical conditions. Despite numerous studies, the mechanisms and sequelae of the development of hyperexcitability still have not been completely elucidated. In this chapter, we discuss the possibilities for detecting motor cortex hyperexcitability in patients with amyotrophic lateral sclerosis using transcranial magnetic stimulation. The potential relationship between hyperexcitability and neuronal degeneration or neuroplasticity processes is discussed using the data obtained by navigated transcranial magnetic stimulation and neuroimaging data, as well as the data of experimental studies.

Keywords: transcranial magnetic stimulation, amyotrophic lateral sclerosis, hyperexcitability, excitotoxicity, neuroplasticity

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease affecting the upper and lower motor neurons. Despite the significant advance in molecular biology and genetics over the past years, many aspects of etiology and pathogenesis of ALS remain unstudied; neither biomarkers of the disease nor effective treatment methods have been designed [1].

A significant advance in understanding the pathophysiological mechanisms of the development of the neurodegenerative process of ALS has been made over the past years after novel neurophysiological and neuroimaging techniques were introduced into the research and clinical practice [2–4]. Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation method that is used to evaluate the functional status of the upper motor neuron in ALS patients. It has been shown in the recent studies that different TMS parameters are altered in ALS patients [4]. TMS is currently viewed as a valuable research and diagnostic tool in ALS.

Development of hyperexcitability of the primary motor cortex and the entire motor system is a well-studied phenomenon in ALS. Motor cortex hyperexcitability can be determined using TMS as reduced resting motor threshold and increased motor evoked potential (MEP) amplitude, decreased silent period, reduced effectiveness of short-interval intracortical inhibition (SICI), and increased intracortical facilitation (ICF) (see review [4]). Most authors attribute motor cortex hyperexcitability in ALS patients to enhanced glutamatergic neurotransmission in the neocortex and reduced gamma-aminobutyric acid (GABA)ergic inhibitory neurotransmission, thus suggesting that hyperexcitability provokes degeneration of motor neurons [5–7]. However, no direct evidence has been obtained yet that would unambiguously demonstrate the relationship between motor cortex hyperexcitability in ALS patients and its degeneration. There is an alternative opinion that hyperexcitability can potentially be related to neuroplasticity processes taking place in the motor cortex and compensation for the lost function.

We would like to discuss the potential relationship of motor cortex hyperexcitability with motor neuron degeneration and neuroplasticity in ALS patients, as well as the possible methods to solve this problem using modern neurophysiological and neuroimaging methods.

2. Motor cortex hyperexcitability in ALS

Although the term 'hyperexcitability' is widely used, it still does not have a commonly accepted definition. According to Bae et al. (2013), it 'means an increased or exaggerated response to a stimulus, which may usually have been expected to evoke a normal response' [7]. We deem that hyperexcitability is discussed in modern TMS studies more broadly: as the ability to respond to stimuli that normally do not evoke any response and, speaking more generally, as the predominance of excitation over inhibition.

Hyperexcitability in ALS patients can be determined using various methods at different levels of the motor system. It can be detected at the level of individual neurons and ion channels in cell cultures in transgenic animals, clinically (presenting as the well-known phenomena, such as fasciculation or cramps) or using the modern neurophysiological techniques such as electromyography (EMG) and TMS [7].

Motor cortex excitability is a complex integral parameter that depends on numerous factors. Hence, the hyperexcitability phenomenon is also a complex and multifactorial process that

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depends on glutamate synthesis and release, its reuptake and degradation, expression and functional status of several types of glutamate receptors, excitable properties of neuronal membranes, and the status of inhibitory GABAergic neurotransmission. A number of experimental studies demonstrated that all the aforementioned processes are disturbed in ALS [8, 9]. **Table 1** summarizes the results of some key studies.

Mechanism	Supporting facts
Decreased Glutamate reuptake	• A 70-80% decrease in expression of high-affinity astroglial glutamate transporter EAAT2 (excitatory amino acid transporter) in the motor cortex and spinal cord in ALS patients as a result of posttranslational modifications, oxidative stress, and other factors [10, 11]
	• Early reduction of glutamate transporter expression in mSOD1 transgenic animals [12]
	• Degeneration of motor neurons in the motor cortex and spinal cord as glutamate reuptake is inhibited *in vitro* in an organotypic cell culture [13]
	• The absence of compensatory increase in glutamate transporter expression by glial cells under excitotoxic conditions and oxidative stress [14]
Dysfunction of inhibitory GABAergic neurotransmission	• Degeneration of inhibitory interneurons in the motor cortex and spinal cord in ALS patients according to pathomorphological and animal model studies [15–17]
	• Decreased GABA level in the motor cortex according to the MR spectroscopy [18] and reduced ^{11}C-flumazenil binding according to the PET data [19]
	• Decreased level of mRNA of GABA(A) receptor subunits in a postmortem study [20]
Changes in excitability of motor neuron membranes	• Increased density and excitability of voltage-gated sodium channels in SOD1 transgenic animals [21, 22]
	• Decreased conductance of potassium channels Kv 1.2
	• Hyperexcitability of individual motor neurons in a cell culture [23, 24]
Changes in expression and functions of glutamate receptors	• Decreased expression of the GluR2 subunit blocking calcium delivery to the cell in ALS patients with transgenic animals [25]
	• Disturbance of posttranslational modification of GluR2 subunit increasing permeability to calcium ions [25]

Table 1. Potential mechanisms of development of motor neuron hyperexcitability in ALS patients.

Today, TMS is the key and actually the only method for clinical investigation of motor cortex excitability. The use of the entire range of TMS parameters allows one to perform a relatively differentiated study of various factors contributing to motor cortex excitation [26]. TMS can be employed for assessing the functional status of the corticospinal tract due to the ability to excite motor cortex neurons by induced electrical current followed by propagation of excitation to alpha motor neurons of spinal cord. This causes contraction of muscle fibers within a certain motor unit, which can be recorded by cutaneous electrodes as a MEP [27]. TMS assesses the functional status of neuronal contours of the motor cortex [28].

Motor threshold is the key parameter used to assess motor cortex excitability. The motor threshold represents the density of corticospinal projections and can be regarded as a biomarker of neuronal membrane excitability [26]. Decreased motor threshold is considered to be one of the key signs of motor cortex hyperexcitability.

According to most studies, the motor threshold in ALS patients is increased, probably being indicative of degeneration of cortical motor neurons [29–35]. Meanwhile, a paradoxical decrease in the motor threshold when examining patients at the onset of the disease was shown in some studies [36–39]. The motor threshold is likely to decrease at the onset of ALS, probably until clinical signs appear, and subsequently increases as motor neurons die. A statistically significant direct correlation between the motor threshold and disease duration was demonstrated in some studies [29, 40].

Physiologically, the motor threshold is primarily determined by rapid AMPA receptor (AMPAR)-mediated glutamatergic neurotransmission in the neocortex and excitability of motor neuron membranes that depends on voltage-gated sodium channels [41]. In ALS, AMPA receptor-mediated glutamatergic neurotransmission increases and properties of sodium channels change (presenting as increased conductance) [23, 24, 42, 43]. Alteration in functional properties of potential-gated sodium channels has been revealed: more rapid recovery after inactivation, increased permeability to sodium, and increased density of ion channels [21]. Pieri et al. demonstrated a decrease in the action potential threshold, an increase in pulse frequency, and an increase in persistent sodium current in cortical motor neurons isolated in G93A mutant mice [22].

MEP amplitude is determined by the number of reduced motor units and the number of activated alpha motor neurons in the spinal cord. Increased stimulation intensity enhances MEP amplitude due to superimposition of late I-waves and I1-wave [28, 44]. Like the motor threshold, MEP amplitude is determined by the density of corticospinal projections. Meanwhile, MEP amplitude to a greater extent represents the function of neurons with lower excitability or those located farther from the stimulation site [4]. GABAergic drugs reduce MEP amplitude, which results from the scheme of generation of late I-waves modulated by inserted inhibitory GABAergic interneurons [41]. Noteworthy, the motor threshold and MEP amplitude are modulated by drugs belonging to different pharmacological classes, thus emphasizing the difference between the mechanisms of their formation.

Identically to the motor threshold, MEP amplitude in ALS patients changes in opposite directions depending on stage of the disease. MEP amplitude decreases in most cases, being accompanied by increased motor threshold and representing a decrease in motor neuron number and reduction of density of corticospinal projections [4]. On the contrary, some patients with the reduced motor threshold may have increased MEP amplitude and the ratio between MEP amplitude and M-response amplitude [45, 46]. The increased slope ratio of the amplitude vs intensity curve is additional evidence to motor cortex hyperexcitability in ALS patients as it demonstrates a more pronounced amplitude increment with increasing stimulation intensity compared to the norm. The increase in MEP amplitude and the slope ratio of the amplitude vs intensity curve in ALS patients is probably related to both enhanced glutamatergic and reduced inhibitory GABAergic neurotransmission in the neocortex [4].

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The *cortical silent period* (cSP) represents inhibition of voluntary muscular activity during a certain period after a magnetic stimulus was applied [47]. It has been demonstrated that the first one-third of cSP is mostly controlled by inhibitory mechanisms at the spinal cord level, while the remaining two thirds are of cortical origin and are related to inhibitory neurotransmission through GABA(B) receptors [27].

It was demonstrated in most studies that patients with sporadic and familial ALS had either decreased cSP or no cSP at all, which is regarded as significant evidence attesting to intracortical inhibitory dysfunction in ALS patients [48–50].

Paired pulse stimulation is used to assess intracortical inhibition and excitation processes. The method involves sequential generation of two pulses: the conditioning (S1) and testing (S2) pulses. The physiological effects of paired pulse stimulation are determined by the intensity of S1 and the interval between S1 and S2 pulses. Application of the sub-threshold S1 pulse 1–6 ms before the supra-threshold S2 pulse reduces MEP amplitude compared to isolated application of a supra-threshold stimulus [51]. This phenomenon is known as SICI. Contrariwise, an increase of the interstimulus interval to 8–20 ms rises the amplitude of MEP to the testing pulse (ICF). Several protocols have been proposed where the conditioning pulse has the supra- and sub-threshold intensity. MEP amplitude increases at the long interstimulus interval (long-interval intracortical inhibition, LICI) and decreases at the short interval (short-interval intracortical facilitation, SICF) [27].

The neurophysiological mechanisms of formation of these phenomena remain insufficiently studied; however, it has been demonstrated rather convincingly that they have the predominantly intracortical origin. Thus, SICI and LICI protocols cause suppression of amplitude and the number of late descending waves [51, 52]. Intracortical inhibition processes are assumed to be caused by activation of neocortical inhibitory interneurons under the action of the conditioning pulse; SICI being mediated by inhibition through GABA(A) receptors and LICI, through GABA(B) receptors. The ICF phenomenon is presumably caused by activation of glutamatergic neurotransmission through NMDA glutamate receptors [26].

Disruption of intracortical inhibition and facilitation under paired-pulse stimulation is currently believed to be the most convincing evidence that motor cortex hyperexcitability develops in ALS patients and has been detected in numerous studies [6, 53, 54, 55]. It should be mentioned that a decrease in efficiency of SICI is revealed at the earliest stages of the disease, including asymptomatic SOD1 mutation carriers, and correlates with axonal degeneration of peripheral motor neurons [45]. Assessment of the disruptions of intracortical inhibition using the new threshold tracking technique is considered to be a potential diagnostic tool in ALS demonstrating high sensitivity and specificity [56, 57].

The role of inhibitory interneurons dysfunction in pathogenesis of ALS has been actively studied over the past years [58–60]. Degeneration of inhibitory interneurons both in the spinal cord and in the motor cortex was demonstrated in several pathomorphological studies carried out in the 1990s. Nihei et al. (1993) reported a reduced amount of parvalbumin-positive interneurons in the motor cortex in ALS patients [61]. In addition, Petri et al. (2003) demonstrated that the level of GABA(A) receptor alpha-1 subunit mRNA decreases in ALS patients

[20]. Dysfunction of inhibitory neurotransmission in the neocortex has also been confirmed in neuroimaging studies presenting as a decrease in GABA amount according to magnetic resonance spectroscopy [18] and decreased ^{11}C-flumazenil binding as shown by PET [19].

The TMS data additionally confirm that inhibitory neurotransmission in the neocortex is disrupted in ALS patients. It should be mentioned that TMS has been used to show the disturbance of inhibition in the motor cortex both mediated by GABA(A) (decreased SICI) and by GABA(B) receptors (decreased LICI and sCP), being indicative of degeneration of interneurons or GABA metabolism disruption rather than dysfunction of receptors of this mediator in the postsynaptic membrane.

Other factors that cause SICI disruption in ALS patients are being discussed. Thus, riluzole was reported to induce partial recovery of SICI in ALS patients, which gives grounds for suggesting that enhancement of glutamatergic neurotransmission plays a role in disturbance of intracortical inhibition in ALS patients. NMDA receptor antagonists, memantine and amantadine, were shown to increase SICI and decrease ICF in several pharmaco-TMS studies [41]. These data suggest that decreased intracortical inhibition in ALS patients can be related not only to reduction of inhibitory GABAergic neurotransmission but also to enhancement of glutamatergic neurotransmission through NMDAR.

Increased intracortical facilitation is another evidence for involvement of NMDAR in pathogenesis of ALS. This phenomenon is currently predominantly attributed to glutamatergic neurotransmission through NMDAR, which is confirmed, in particular, by its reduction due to antagonists of these receptors [41].

Hence, a large body of data attesting to the development of motor cortex hyperexcitability in ALS patients can currently be obtained by TMS. Signs attesting to degeneration of the upper motor neuron are detected simultaneously (**Table 2**). Importantly, some TMS parameters (MEP threshold and amplitude) can change in opposite directions and attest to motor cortex hyperexcitability at onset of the disease and degeneration as the disease progresses. Meanwhile, such signs of hyperexcitability as decreased cSP and efficiency of SICI are detected even in patients with pronounced degeneration of motor neurons. This phenomenon in ALS patients was referred to as 'dying but overactive' [7]; it can cause difficulties for interpretation of TMS results in a specific patient.

Hyperexcitability	Degeneration
• Resting motor threshold decreased	• Resting motor threshold increased
• MEP amplitude increased	• CMCT increased
• SICI reduced and ICF increased	• MEP amplitude decreased
• SP decreased	• Central conduction failure (triple stimulation technique)

Table 2. Motor cortex hyperexcitability and degeneration in ALS: TMS findings.

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Table 3 summarizes the TMS data on the potential mechanisms responsible for the signs of motor cortex hyperexcitability in ALS patients. It should be mentioned that the variety of TMS procedures makes it possible not only to reveal the dysfunction of individual mediator systems but also to perform differentiated evaluation of neurotransmission through different types of glutamate and GABA receptors in ALS patients.

Sign	Mechanism
Decreased motor threshold	• Increased glutamatergic neurotransmission through AMPAR
	• Increased sodium current due to an increase in density and/or alteration in functional properties of sodium channels
Increased MER amplitude	• Increased glutamatergic neurotransmission through AMPAR
	• Decreased inhibitory GABAergic neurotransmission
Decreased silent period	• Decreased inhibitory GABAergic neurotransmission through GABA(B) receptors
Decreased SICI	• Decreased inhibitory GABAergic neurotransmission through GABA(A) receptors
	• Increased glutamatergic neurotransmission through NMDAR
Increased ICF	• Increased glutamatergic neurotransmission through NMDAR

Table 3. Potential mechanisms of formation of TMS signs of motor cortex hyperexcitability in ALS.

Based on TMS findings, it is rather promising and reasonable to suggest that motor cortex hyperexcitability and the underlying molecular events (e.g., excitotoxicity) cause degeneration of motor neurons in ALS patients. We attempt to discuss the specific potential mechanisms underlying motor cortex hyperexcitability in ALS and present the evidence for its pathogenetic relationship with degeneration of motor neuron.

3. What does motor cortex hyperexcitability mean?

3.1. Is hyperexcitability bad?

The evidence that motor cortex hyperexcitability plays a role in pathogenesis of ALS is still rather sparse [62]. Hyperexcitability is registered at different stages of the disease, including

the pre-symptomatic ones [23, 45]. However, this fact tells nothing about its role in pathogenesis of the disease. It is still unclear when true onset of neurodegeneration occurs; however, the results of studies using transgenic animals demonstrate that the pathological process in ALS may start at the earliest stages of embryogenesis (e.g., at the stage when neural networks are formed) [63]. In this situation, all the objectively detectable alterations may be either primary or secondary (i.e., emerge as one of nonspecific stages of neurodegeneration or via the compensatory mechanism).

The enhancement of excitatory glutamatergic neurotransmission and reduction of inhibitory GABAergic neurotransmission in the neocortex, which underlie hyperexcitability in ALS patients, are believed to damage motor neurons via the excitotoxicity mechanism [4, 7]. The role of excitotoxicity as one of the universal mechanisms causing neuronal death in various nervous system diseases has currently been demonstrated [8, 9, 64]. High sensitivity of motor neurons to excitotoxicity can be related to high expression of glutamate receptors and low expression of calcium-binding proteins [9].

An important argument in favor of the role of hyperexcitability and the underlying molecular processes in ALS pathogenesis is that this phenomenon can be early detected using TMS in asymptomatic SOD1 mutation carriers. Vucic et al. (2008) demonstrated a decrease in SICI in three SOD1 mutation carriers who were asymptomatic at the time the study was performed but developed clinical signs of the disease during a prospective study within 3 years. It is interesting that no neurophysiological signs of motor cortex excitability were revealed in 14 other asymptomatic carriers and they did not present with any clinical manifestations of the disease within the entire study period [45]. Early development of signs of hyperexcitability of neurons of the motor cortex, spinal cord, and even the extramotor areas such as hippocampus (e.g., see [23]) were demonstrated in a large series of experimental studies using a culture of neurons isolated from transgenic animals. Additional evidence is that signs of motor cortex hyperexcitability in ALS patients can be detected before the pyramidal pathways are affected and EMG signs of degeneration of the lower motor neuron emerge. A recent study carried out by Menon et al. (2015) showed that 24 patients with ALS had a statistically significant decrease in motor threshold, duration of cSP and intracortical inhibition, while simultaneously having an increased MER amplitude and intracortical facilitation at onset of the disease [5]. No signs of alterations in central motor conduction time (CMCT) were detected in these patients, thus attesting to the fact that the conduction function of the pyramidal pathway was retained and there were signs of denervation and reinnervation process according to the EMG data. The results of this study demonstrated that motor cortex hyperexcitability precedes degeneration of both the upper and the lower motor neurons and is the earliest neurophysiological signs of neurodegeneration. This supports the hypothesis proposed by Charkot back in 1869 that the upper motor neuron is the first one to be affected in ALS patients ('dying-forward') [65].

The certain effectiveness of riluzole in treating ALS also indirectly confirms the pathogenetic role of hyperexcitability and excitotoxicity. Despite the diversity of its mechanisms of action, riluzole is primarily considered to be a medication reducing excitotoxicity [66]. It has been demonstrated that riluzole can partially normalize SICI and reduce excitability of peripheral nerve axons in ALS patients [67].

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The indirect evidence to the pathogenetic role of excitotoxicity was also obtained in studies on using therapeutic repetitive magnetic stimulation in ALS. High-frequency repetitive TMS increases neuronal excitability in the stimulated area (see reviews [68] and [69]). It has been demonstrated in a small study conducted by Di Lazzaro et al. (2004) that high-frequency stimulation may accelerate onset of the disease, while low-frequency stimulation may inhibit it [70]. Hence, high-frequency stimulation may increase excitotoxic degeneration of motor neurons and motor cortex excitability, having an unfavorable effect on the course of the disease.

3.2. Is hyperexcitability good?

Excitotoxicity and hyperexcitability have been for a long time regarded only as damaging phenomena facilitating neuronal death. However, findings obtained in a number of studies suggest that hyperexcitability can also have a compensatory effect, at least at early stages. Furthermore, molecular alterations that accompany excitotoxicity are similar to the processes taking place when neuroplasticity is ensured. We present the results of some studies confirming the validity of this alternative view of the hyperexcitability problem in patients with ALS and other neurodegenerative diseases.

3.2.1. Motor cortex excitability and neuroplasticity

The term 'neuroplasticity' means brain's ability to alter structurally and functionally in response to internal and external factors. This ability is currently attributed both to strengthening or weakening of the existing neural connections and to the formation of new connections or destruction of the old ones [71]. Starting with the first description of cellular mechanisms of neuroplasticity, this universal property of neural tissue is inseparably associated with alteration in neuronal excitability. Long-term potentiation was shown to be predominantly of postsynaptic origin and is mostly connected to the glutamatergic system [72–74].

A series of studies have shown the alteration in motor cortex excitability and reorganization of the cortical representation of muscles after motor learning and acquisition of new skills [75, 76]. The TMS data confirmed that there is a relationship between neuroplastic alterations and an increase in motor cortex excitability [77–79]. Thus, Tyč and Boyadjian (2011) performed TMS mapping of cortical representation of the deltoid and brachioradialis muscles in healthy volunteers before and after a 6-week training (playing darts three to four times a week). The boundaries of cortical representation of the muscles under study were expanded after training, which was accompanied by an increase in the slope ratio of the amplitude-intensity curve, being indicative of the increase in motor cortex excitability [80]. According to Perez et al. (2004), a 32-minute training causes statistically significant increase in the slope ratio of the amplitude-intensity curve and a decrease in intracortical inhibition [81]. Increased motor cortex excitability presenting as increased MER amplitude and reduced motor threshold is observed in healthy volunteers not only after actual training but also after they had imagined the movements [82]. Professional sportsmen and musicians were found to have increased motor cortex excitability and increased ability of the motor cortex to undergo plastic alterations [83, 84].

To sum up, the aforementioned facts indicate that motor cortex excitability and glutamatergic neurotransmission increase during neuroplastic alterations.

3.2.2. Hyperexcitability and neuroplasticity in pathology

The most forcible evidence for the possible relationship between hyperexcitability and neuroplasticity was observed in patients with Alzheimer's disease (AD). Neurodegeneration in this disease is not limited to the structures involved in the cognitive function and affects other brain regions as well, including the primary motor cortex. At the late stages of the disease, AD patients often have motor disorders, including spasticity and pathologic plantar responses, attesting to involvement of the upper motor neuron [85]. Furthermore, lesions of the motor cortex, predominantly giant pyramidal cells of Betz, were detected in AD patients in pathomorphological studies [86]. In this connection, investigation of the structural and functional status of the motor cortex in AD patients is of interest as a model of clinically asymptomatic neurodegeneration of the motor cortex.

In AD patients, identically to those with ALS, motor cortex hyperexcitability can be recorded using TMS. It has been demonstrated in many studies that the motor threshold decreases in AD patients. Decreased intracortical inhibition and short cSP duration were also detected in some studies (although not all of them) (see reviews [87, 88]). There is controversy in data on disrupted inhibitory neurotransmission in AD patients; however, decreased SICI in AD is most probably not associated with dysfunction of the GABAergic system [89]. The enhanced glutamatergic neurotransmission is currently the predominant conception of the development of motor cortex hyperexcitability in AD patients.

It is interesting to mention that motor cortex hyperexcitability in AD patients is predominantly attributed to neuroplasticity processes. Hyperexcitability is believed to develop via the compensatory mechanism as a response to disruption of associative connections [90].

Motor cortex hyperexcitability in AD patients is accompanied by reorganization of the cortical representation of muscles according to TMS mapping presenting as displacement of the center of gravity of the cortical representation in the frontomedial direction with respect to localization of hot spots in patients without motor disorders [90]. Ferreri et al. (2011) believe that this may attest to plastic brain alterations aimed at maintaining normal motor activity as the neuron number decreases progressively [91]. fMRI studies in patients at early stages of AD, identically to those with ALS, showed areas with increased activation, which is also regarded as a result of compensatory changes [92]. In their recent study, Guerra et al. (2015) demonstrated the relationship between motor cortex hyperexcitability and neuroplasticity. Examination of seven patients with vascular dementia and nine AD patients showed a statistically significant decrease in motor threshold compared to healthy volunteers of comparable age. Parameters related to motor cortex excitability (the area of cortical representation of muscles and the area of active cortical points) showed a statistically significant correlation with neuroplastic reorganization of the motor cortex assessed based on the distance between the center of gravity of the maps and hot spot localization. The authors drew a conclusion that motor cortex hyperexcitability may promote neuroplasticity [93].

As opposed of the cortical motor zones, most AD patients at the dementia stage have decreased connectivity and activation of the hippocampus, medial temporal, and prefronal cortex when performing cognitive tasks involving short-term memory [94]. Meanwhile, activity of these areas is increased in AD patients at the moderate cognitive impairment stage and in asymptomatic carriers of mutations in the presenilin-1 gene [95–97]. This is believed to result from turning on of the compensatory mechanisms. It should be mentioned that transgenic animals at the presymptomatic stage and stage of initial manifestations (which approximately corresponds to the moderate cognitive impairment stage in humans) showed an increased expression of a number of genes promoting synaptic plasticity [98]. In particular, transgenic mice showed enhanced expression of the AMPAR subunit genes at the early stages of the pathological process [99]. Furthermore, experimental studies revealed an increase in synaptic plasticity and hyperexcitability in hippocampal neurons, which preceded β-amyloid deposition [100, 101]. Schneider et al. (2001) reported that hippocampal neurons in transgenic mice with presenilin mutation are characterized not only by hyperexcitability and reduced threshold to excitotoxic damage but also by facilitation of long-term synaptic potentiation [102]. In their pathomorphological study, Bell et al. (2007) showed that patients with moderate cognitive impairments had increased density of presynaptic boutons in glutamatergic synapses, while the density of presynaptic boutons in AD patients was reduced [103]. On the contrary, expression of the genes involved in synaptic plasticity and energy exchange was shown to decrease at the late stages of the disease [98, 104]. These data give grounds for assuming that the increase in neuronal excitability in AD patients at early stages of the disease may occur via the compensatory mechanism.

3.2.3. Compensatory hyperexcitability in ALS: evidence from fundamental research

Several recently published studies using transgenic animals expressing mSOD1 have compromised the conception of the pathological role of excitability of motor neurons in ALS. Saxena et al. (2013) demonstrated that hyperexcitability can be a defense mechanism preventing degeneration of motor neurons. Thus, reduced excitability of motor neurons decreased accumulation of mutant SOD1, whereas increased excitability was accompanied by the greater number of intracellular aggregates and quicker death of motor neurons. It was also demonstrated that mutant protein accumulation increases after AMPAR blockade and decreases when AMPA is introduced. Stronger excitatory stimulation may contribute to the decrease in severity of endoplasmic stress and accumulation of abnormal proteins, thus exhibiting protective properties. Interestingly, mutant SOD1 accumulation was first detected in the least excitable fast fatiguing (FF) motor neurons of the spinal cord [105]. Leroy et al. (2014) studied the excitability of various populations of spinal cord motor neurons isolated from G93A mutant mice [106]. In this study, the electrophysiological signs of hyperexcitability were revealed only in degeneration-resistant motor neurons. The authors believe that their findings indicate that hyperexcitability does not cause degeneration; instead, it can be a defense mechanism [106].

3.2.4. Neuroplasticity in ALS: evidence from fMRI studies

Nowadays, fMRI is the key method for studying neuroplasticity in ALS patients. Numerous studies have revealed the changes in activation patterns of various brain regions in ALS both in rest and using various paradigms [2]. In this publication, the changes in activation patterns in ALS patients performing motor tasks are of special interest.

In the study performed by Konrad et al. (2002), ALS patients and healthy volunteers underwent fMRI as they performed a motor paradigm (bending fingers) [107]. Significant changes in the patterns of cortex activation were observed: a forward displacement of the activation cluster, into the supplementary motor area, and an increase in its volume. Activation volume in the inferior frontal gyrus (Brodmann area 6) in the contralateral hemisphere and parietal lobes increased bilaterally. The authors have put forward a hypothesis that these changes represent the structural and functional rearrangement of the motor system induced by degeneration of the upper and lower motor neuron [107]. Lule et al. (2007) reported that an increase in activation of the primary motor and premotor cortex in ALS patients is revealed not only when performing the movement but also when imaging it [108]. Stanton et al. (2007) detected that activation in the sensorimotor cortex (Brodmann areas 1, 2, and 4), the inferior parietal lobule, and the superior temporal gyrus increased when the ALS patients performed a motor task, while activation in the dorsolateral prefrontal cortex decreased [109]. It is noteworthy that these changes were observed when comparing ALS patients not only to healthy volunteers but also to patients with peripheral nerve disorders [109]. This confirms that involvement of the upper motor neuron plays a crucial role in development of these changes and does not give grounds for considering them as just a response to the development of muscle fatigue.

Thus, an analysis of the results of fMRI with the motor paradigm in ALS patients demonstrates that the activation areas expand when a motor task is being performed. Interestingly, the changes in activation during fMRI can have a prognostic value. Poujois et al. (2013) reported that activation in the somatosensory and parietal cortex increases in ALS patients performing a simple motor task compared to the control group. The dynamic follow-up for 1 year has shown that activity of the contralateral parietal lobe has a statistically significant negative correlation with the rate of disease progression ($p = 0.001$) [110].

These findings give grounds for suggesting that expansion of activation areas as an ALS patient performs a motor task has the compensatory mechanism and is probably aimed at maintaining the motor function in response to progressive degeneration of cortical motor neurons. Meanwhile, certain researchers believe that the activation areas can increase due to degeneration of inhibitory interneurons [2]. The relationship between alterations in activation patterns in ALS patients according to fMRI data and changes in motor cortex excitability according to TMS data has not been studied yet. It should be mentioned that the positive prognostic significance of neuroplastic alterations demonstrated by Poujois et al. (2013) is in contrast with the views about the negative role of hyperexcitability in this disease.

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4. Navigated TMS mapping in ALS

Navigated TMS (nTMS) is today considered to be the most promising method to answer the question about the relationship between hyperexcitability and neuroplastic alterations in the motor cortex under kinetic conditions. On the one hand, nTMS is a neuroimaging technique and allows visualization of the location of cortical representation of certain muscles on individual MR images and provides an opportunity to assess the changes in their size and displacement with respect to anatomical landmarks. On the other hand, nTMS is a neurophysiological method that allows one to assess various parameters showing the excitability and degeneration of the motor cortex. The nTMS method uses the brain of a person being examined as a landmark when applying stimuli for an individual MR model; the stimuli can be accurately applied to a certain area with allowance for the area of interest, the individual anatomy, and topography of the gyri [111].

In our recent study, we mapped the cortical representation of m. abductor pollicis brevis (APB) in 30 ALS patients and 24 healthy volunteers [29]. It was demonstrated that ALS patients exhibit a statistically significant increase in the resting motor threshold and a decrease in the MEPs amplitude, as well as a statistically significant reduction of the volume of cortical representation of APB ($p < 0.001$). The latter observation agrees with the results of the findings of Carvalho et al. (1999) who demonstrated a progressive decrease in size of the cortical representation in ALS patients [112]. This phenomenon is probably based on the neurodegenerative process that reduces motor cortex excitability and decreases the number of cortical motor neurons. According to our data, the volume of cortical representation statistically significantly correlates with disease duration and negatively correlates with strength of the corresponding muscle and disease severity according to ALS Functional Rating Scale Revised (ALS FRS-R). These data give grounds for hypothesizing that the size of cortical representation can be regarded as a neurophysiological marker of disease severity, which opens new avenues for using it both in fundamental research and in clinical trials of new therapy methods. Further studies are needed to determine the sensitivity and specificity of this marker compared to other neurophysiological parameters and to determine its diagnostic significance.

The capabilities of navigated TMS made it possible not only to determine the size of cortical representation but also to accurately localize the maps within the anatomic landmarks. In most ALS patients, the maps were localized within the precentral gyrus (Brodmann area 4); some active sites, similar to those in healthy volunteers, were detected within the postcentral gyrus (Brodmann area 1) and the premotor cortex.

Meanwhile, we detected expanded boundaries of individual maps of the APB in some ALS patients, usually presenting as a displacement of the greatest portion of the map toward the postcentral gyrus. It was found by analyzing these cases that the aforementioned reorganization is mostly typical of patients at onset of the disease or when the disease course is relatively benign (**Figures 1** and **2**). It is important to mention that the motor threshold in these cases remained within the normal values or was decreased.

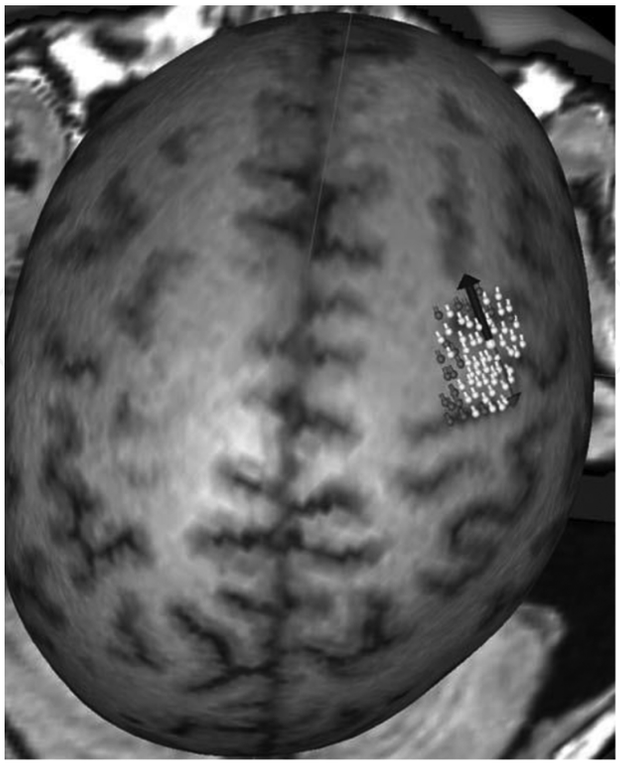

Figure 1. Map of cortical representation of the APB in a healthy volunteer (28 years old, motor threshold—43%). Here and in other figures, the points whose stimulation provides MEPs with amplitude over 50 μV from the contralateral APB are shown in white.

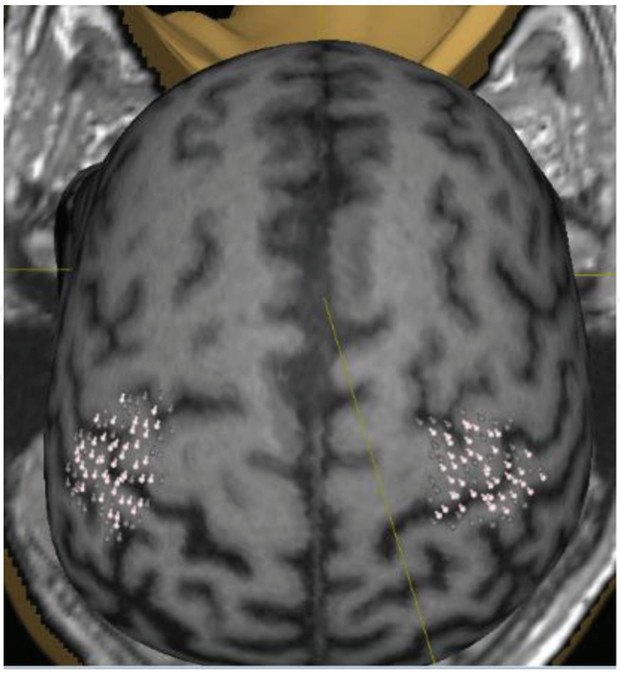

Figure 2. Maps of cortical representation of the APB in ALS patient with the relatively benign course of the disease (54 years old, right-side motor threshold—31%, left-side motor threshold—35%, duration of the disease—25 months, APB strength is bilaterally reduced to MRC score 4).

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Although we have not performed mathematical analysis of the relationship between motor cortex excitability and reorganization of cortical representation, we suppose that hyperexcitability can be one of the mechanisms of the aforementioned neuroplastic alterations. Thus, a statistically significant relationship between the passive threshold as an excitability marker and the volume of cortical representation has been revealed. So the largest cortical representation was revealed in patients with lower thresholds. This made it possible to rule out the possible role of higher-intensity stimuli in expansion of the map boundaries in ALS patients compared to the control group. Indeed, the motor threshold in some patients was 100% and we used this intensity in mapping. However, only single MEPs were detected in the aforementioned cases and the size of cortical representation was very small (**Figure 3**).

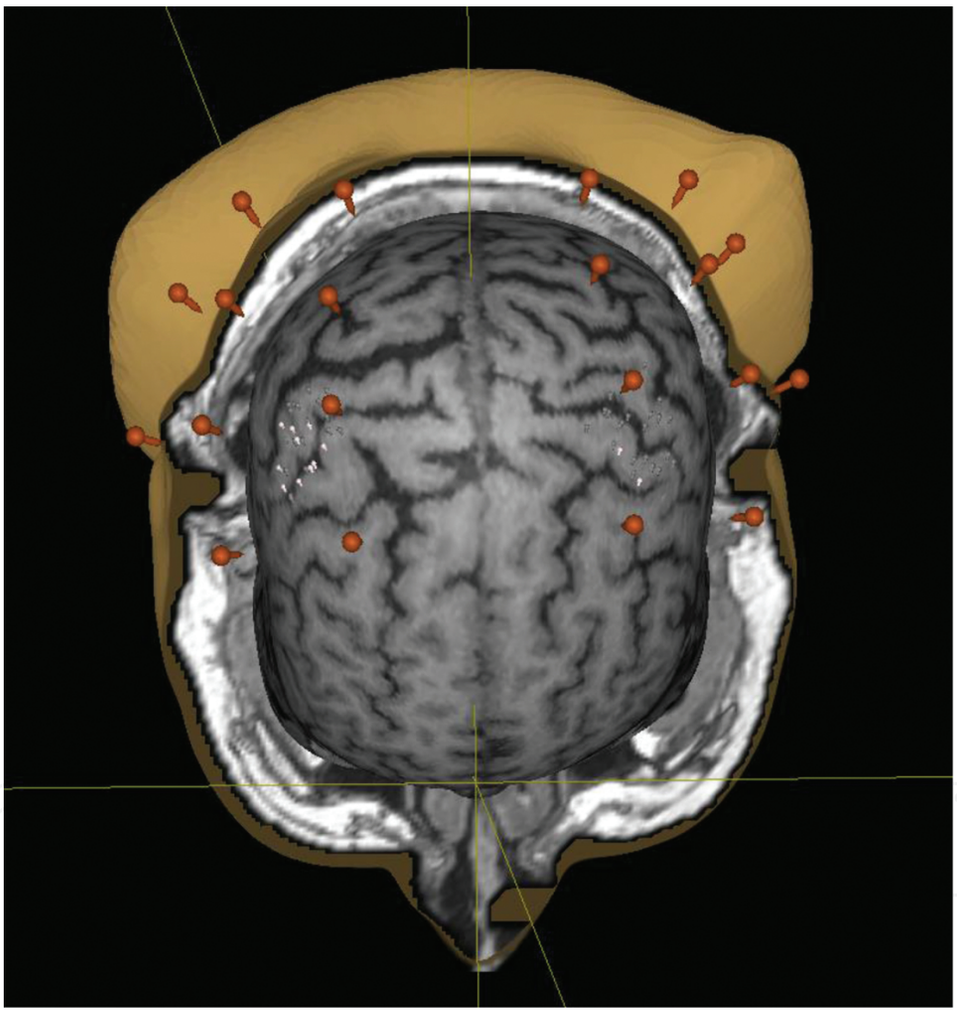

Figure 3. Maps of cortical representation of the APB in a 62-year-old female patient with ALS. Upper-limb form of the disease; disease duration—8 months. ALS-FRS-R—38. APB strength is bilaterally reduced to MRC score 2. Motor threshold on the right and left sides—100%. The volume of cortical representation is significantly decreased.

Our findings agree with the fMRI data described above that attest to expansion of the activation areas in ALS patients performing a motor task. Like fMRI, visual assessment of nTMS mapping data allows one to detect displacement of cortical representation. Our preliminary data

demonstrate that displacement of the boundaries of cortical representation as a result of neuroplastic alterations can be caused by decreased motor cortex excitability. Hence, the phenomenon of motor cortex hyperexcitability can have the compensatory function in ALS patients.

5. Conclusions and future perspectives

Motor cortex hyperexcitability in ALS patients is a well-studied phenomenon that can be of significant interest as a biomarker of neurodegeneration. However, despite the large number of studies, the reasons and sequelae currently remain poorly studied. Since motor cortex hyperexcitability in ALS patients was first described, this phenomenon has been attributed to the development of excitotoxicity and weakening of inhibitory neurotransmission in the neocortex, thus ensuring its pathogenetic role in the development of neurodegeneration. However, no direct evidence to the fact that motor cortex hyperexcitability in ALS patients attests to development of excitotoxicity and precedes its degeneration has been obtained yet. Meanwhile, hyperexcitability can be one of the mechanisms of neuroplastic alterations, thus having the compensatory (sanogenetic) rather than pathogenetic value. This theory has been supported by the data on interaction between decreased motor cortex excitability and neuroplasticity in the norm and in some pathologic conditions such as Alzheimer's disease and vascular dementia. Furthermore, expansion of the cortical representation of certain muscles was demonstrated for ALS patients in fMRI and nTMS studies, which can be a manifestation of neuroplasticity and related to increased motor cortex excitability.

It should be mentioned that hyperexcitability is not a specific sign of ALS and is also revealed in other neurodegenerative diseases. More and more data supporting the similarity between pathophysiology of neurodegeneration in various diseases and its relationship with intracellular accumulation of abnormal proteins have been obtained. This may result in dysfunction of synaptic connections and a compensatory increase in expression of the genes ensuring increased excitability and synaptic plasticity.

A hypothesis can be put forward based on these data that hyperexcitability plays different roles at different stages of the disease (**Figure 4**). At onset of the disease, this phenomenon can develop via the compensatory mechanism in response to reduced number of functioning motor neurons and disruption of synaptic connections. Hence, increased hyperexcitability can be regarded as a method for maintaining functioning of the system as the number of its components decreases. In addition, hyperexcitability can have a protective effect at the cellular level as it prevents accumulation of pathologically altered proteins. As the disease progresses, hyperexcitability may start to have a pathological effect and induce excitotoxicity. Does this mean that our effect on motor cortex excitability in ALS patients needs to be differentiated depending on disease stage? Further research involving various methods and focusing on patients at different stages of the disease needs to be carried out to answer this question.

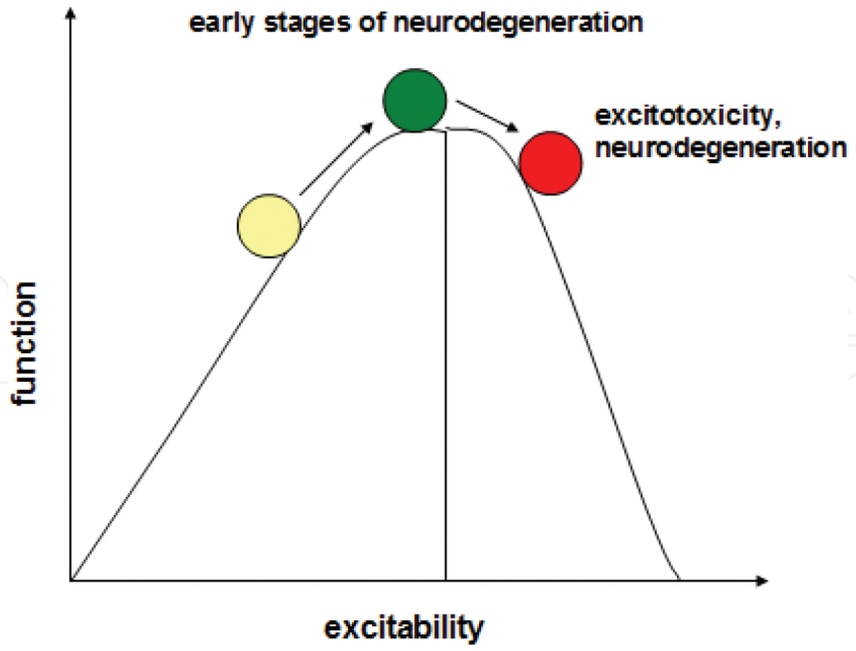

Figure 4. A link between excitability and function.

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