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Paper title

Computational models and motor learning paradigms: Could they provide insights for neuroplasticity after stroke? An overview.

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Key words

motor learning, computational models, stroke, neuroplasticity, neurorehabilitation

Highlights

Computational models can be used to better understand motor control mechanisms

Neuroplasticity occurs in case of permanent changes of brain structure and function

Neuroplasticity is modulated by administration of drugs

Motor learning is sustained by positive interaction with external environment

Internal models has been described to explain the activation of voluntary movements

Abstract

Computational approaches for modelling the central nervous system (CNS) aim to develop theories on processes occurring in the brain that allow the transformation of all information needed for the execution of motor acts. Computational models have been proposed in several fields, not only to interpret the CNS functioning, but also its efferent behaviour. Computational model theories can provide insights into neuromuscular and brain function allowing us to reach a deeper understanding of neuroplasticity. Neuroplasticity is the process occurring in the CNS that is able to permanently change both structure and function due to interaction with the external environment. To understand such a complex process several paradigms related to motor learning and computational modeling have been put forward. These paradigms have been explained through several internal model concepts, and supported by neurophysiological and neuroimaging studies. Therefore, it has been possible make theories about the basis of different learning paradigms according to known computational models.

Here we review the computational models and motor learning paradigms used to describe the CNS and neuromuscular functions, as well as their role in the recovery process. These theories have the potential to provide a way to rigorously explain all the potential of CNS learning, providing a basis for future clinical studies.

Key words

motor learning, computational models, stroke, neuroplasticity

1. Introduction

Stroke is the third cause of death and the first cause of disability among adults regardless of ethnicity, worldwide [1]. At least half of the patients have neurological impairments limiting their independence and about 20% of patients are completely dependent on their care-givers [2].

It is widely acknowledged that cortical reorganization of the motor areas occurs in patients recovering after stroke [3]. Passive movements of the hemiplegic side in stroke survivors have been shown to activate the same brain areas, as described for voluntary active movements in the contralateral side [4]. Changes of cerebral activation in the sensory and motor systems occur early after stroke and may be the first step toward recovery of motor functions. Functional re-organization of the motor system after focal stroke in primates depends on compensatory mechanisms supported by the intact motor cortex, as well as on the amount and intensity of motor training provided [5]. Recent research on motor control and learning provides emerging neurophysiological evidence that could be feasibly translated into rehabilitation practice. During motor activities, neurons from several areas are connected within the same hemisphere and across the contralateral one [6]. The existence and activity of these networks have been documented both in primates and humans

[7]. The human motor system consists of several brain areas cooperating for the production of motor tasks. Among those, the most important are: the primary sensorimotor cortex in both hemispheres, the parietal and lateral premotor cortex, the cerebellum, and the basal ganglia (considered as secondary motor areas) [8, 9]. The balance between the primary sensorimotor cortex and the secondary motor areas changes when part of the network is disrupted as a result of a stroke. Clinical studies with functional Magnetic Resonance Imaging (fMRI) have shown that after a stroke, there is a reorganization of the overall network the activity of which is higher depending on lesion extension, while activity decreases with the progression of brain reorganization [6]. Furthermore, many studies have shown that learning new motor skills stimulates brain plasticity and allows functional improvement. Plasticity in the central nervous system (CNS) is assumed to be preserved throughout the whole life of an individual, regardless of age [10]. Results from fMRI and Transcranial Magnetic Stimulation (TMS) studies have revealed that the cerebral cortex maintains the capacity for functional adaptation, both early and after a long time following a stroke [11-13]. Other results from studies in primates suggest that cortical reorganization is promoted by rehabilitation after injury of the M1 area (primary motor cortex), but reorganization only occurs when learning new motor abilities and not due to repetition of non-finalized movements [11, 14, 15].

The aim of this paper is to review the theoretical bases underpinning the organization and functioning of the brain after a lesion, while performing motor tasks.

2. Neuroplasticity and brain repair after stroke

Plasticity of the nervous system is the ability to create permanent structural and functional changes under the influence of external stimuli. Such stimuli can be understood also like information processed from the external environment. The plasticity of neuronal tissues (neuroplasticity) is intended as the biological substrate of learning and memory and is among the main factors influencing recovery after stroke. Neuroplasticity after brain lesion is due to spontaneous cortical reorganization. However, increasing evidence indicates that intensive stimulation provided with rehabilitation therapy is essential to increase improvement of motor function after stroke, thus potentially promoting neuroplasticity for learning new motor skills [4, 16-18]. Many studies on both animals and humans have demonstrated that various changes occur in the CNS both at the molecular and synaptic level, when interacting with the external environment [17]. The plasticity properties of the CNS are preserved throughout the whole life in humans and are intensified in case of injury or adaptation to new environments. Such examples are the mechanisms of “self-repairing” and reorganization of neuronal connections exploiting new paths that are functionally consistent but anatomically different from those impaired [19]. Cortical plasticity can occur either as a result of training of different skills or of the same task at different levels of difficulty [20]. This plasticity can be assessed by means of non-invasive technologies (e.g. fMRI,

Magnetoencephalography – MEG, TMS, High Density Electroencephalography – HD-EEG, Positron Emission Tomography – PET) [4, 21, 22]. Recently, several neurophysiological studies using neuroimaging techniques have provided insight on the mechanisms involved in neuroplasticity during recovery after stroke. Neuroplasticity refers to the brain's capacity to repair neural networks and its reorganization for information processing between neurons. Thus, neuroimaging techniques can help us to decipher brain connectivity patterns, which occur during motor task execution by means of network analysis approaches, such as structural, functional, and effective connectivity. Structural (anatomical) connectivity refers to a network of synaptic connections (fiber pathways) representing morphological change and plasticity. However, only invasive tracking studies are capable of revealing significant direct axonal connections. Functional connectivity is defined as a statistical dependency among remote neurophysiological events, and it is related to studies of patterns of functional connectivity among cortical regions and based on coherence or correlation. However, correlations can arise in a variety of ways. These studies have provided evidence for a fractal organization of functional brain networks [23]. The plasticity of intrinsic functional connectivity patterns was investigated in a clinical study and it revealed that the impact of rehabilitation can be measured on resting-state fMRI, and that the functional connectivity can provide prognostic insight for later motor recovery [24]. Effective connectivity describes networks of directional effects of neural elements i.e. providing significant differences between a given set of brain regions when estimated in different tasks, which is important for showing the time- and task- dependent nature of these patterns. Thus, effective connectivity could be seen as the union of both structural and functional connectivity [23]. The hypothesis that effective connectivity between cortical areas exists during execution of motor tasks has been tested by EEG and MEG. Thus, this activity might be used as biomarker to predict motor recovery in experimental paradigms. This connectivity can be measured observing two sources of signals (i.e. neuro-electrical and neuro-chemical) with the aim to study the relationship between cortical activity and movement [25, 26]. However, some authors have reported that through these techniques, the neuro-electrical and neuro-chemical processes that mediate cerebral function cannot be measured directly [27]. For example, the brain activity that can be observed with fMRI techniques is inferred via measurements of focal hemodynamic changes in blood-oxygen-level dependent (BOLD) contrast imaging, whereas, in EEG or MEG measurements of the cortex, activity is inferred via measurements of extracranial electric or magnetic fields, respectively. Therefore, non-invasive and indirect measurement of activity occurring in the brain is a fundamental limitation.

An fMRI clinical study [4] carried out with stroke patients revealed that neuroplastic changes occur after motor rehabilitation and may be specifically fostered by the intervention provided. After specific rehabilitative treatment patients showed varied patterns of fMRI changes related to improvement of upper limb motor function [4].

Neurophysiological and neuroimaging studies suggest that neuroplasticity happens in the sensorimotor cortex of the affected hemisphere with task-specific training [28].

A large number of studies have considered repetitive TMS (rTMS) as a potential therapeutic technique for rehabilitation of neurological disorders, aimed to enhance the effect of conventional rehabilitative training [29]. This method has an impact on cortical activity and may be inhibitory or facilitatory depending on whether low (≤ 1 Hz) or high (≥ 1 Hz) frequency magnetic pulses are administered, and also depending on the length or intensity of stimulation. Generally, low frequency stimulation has an inhibitory impact while frequency higher than 1 Hz enhances cortical excitability [30]. Several pieces of evidence have reported that rTMS is effective for treatment of aphasia and visuospatial neglect after stroke. In the study by Martin et al., rTMS was used to stimulate Broca's area in patients with expressive aphasia [31]. The authors reported excessive activation of homologous structures to Broca's area in fMRI images [31]. Whereas, in the clinical study by Oliveri et al., rTMS was used to stimulate the contralesional parietal area during the execution of a motor task in patients who experienced visuospatial neglect [32]. These authors revealed that rTMS in the parietal part of the head on the unaffected side transiently decreased the magnitude of visuospatial neglect; however, the improvement was present only during the rTMS stimulation [32]. Thus, this method could be potentially integrated as an additional intervention to neurorehabilitation.

Homologous cortical areas of the primary motor cortex (M1) are connected through the axons of the corpus callosum [16, 33]. Some studies suggest that communication between homologous areas (M1) plays an essential role in the control of single limb movement. The activity of the two hemispheres is balanced by means of "silent" inhibition guaranteed by the fibres in the corpus callosum, and this inhibition process can be impaired as a consequence of stroke [34]. As an example, in finger movement tasks, the M1 area increases its inhibition towards the injured hemisphere through the connections of the corpus callosum causing a decrease in excitability [35]. Studies in patients after stroke reported an increase in M1 area activity and abnormal inhibition in the damaged part, resulting from an imbalance in activity between the two brain hemispheres [36]. Nonetheless, it is not clear whether these changes in cortical excitability are caused by the non-use of the paretic limb or by overuse of the unaffected limb [30]. Generally, these results support the hypothesis that a decrease in excitability of the unaffected hemisphere can contribute to an improvement of motor function in the paretic limb after stroke. This hypothesis was tested in a study on healthy subjects, whose upper limb was immobilized for ten hours, showing a decrease in cortical excitability of the opposite M1 area and inhibition between the two brain hemispheres [33].

Impairment of motor function is the most disabling consequence of stroke, affecting patients' quality of life heavily. Brain plasticity is paramount for the recovery of motor function after stroke and the combination of specific training with general exercises is still the basis of motor rehabilitation approaches. However, even after applying intensive

physical training, 15 – 30% of patients still experience severe disability after stroke [37]. Nowadays research is aimed at developing new therapies that could stimulate neuroplasticity by means of rehabilitation. This area of study can be divided into three branches, which are at a relatively early stage of development. The first branch of investigation concerns the study of molecular and cellular mechanisms of normal movement as well as the pathophysiological processes leading to paresis after stroke [38, 39]. The understanding of pathophysiological mechanisms associated with post-stroke paresis should lead to improvement of impaired functions and more effective recovery than those currently available. In depth, these findings can provide new insights to improve the quality of rehabilitation programmes. The second branch of research is related to the development of pharmacological, biological, and electrophysiological techniques potentially enhancing exercise-induced plasticity [40]. Both research branches aim to understand basic mechanisms, with the common goal to enhance plasticity in the CNS through rehabilitation. The degree of neuroplasticity that can occur in the adult brain is unknown, however. Thus, the third branch of research deals with progression in biomedical engineering (e.g. neurostimulation or robotics) to promote functional recovery. Although these branches aim to improve understanding of plasticity that can occur after stroke and to potentially speed-up recovery, they cannot be compared as they represent separate study areas on different progress stages. However, the translation of findings between research areas should be maintained.

Several approaches have been used to demonstrate that neural reorganization occurs after stroke [3], and both the primary motor cortex and dorsal premotor cortex areas have been identified as potential targets of neuroplasticity. Research using neuroimaging and electrophysiological techniques indicates that non-primary motor areas (i.e. premotor cortex and supplementary motor cortex) can significantly influence the improvement of movement recovery in the paretic limb after stroke [41]. Pharmacological treatment may also potentially increase the effectiveness of post-stroke rehabilitation, which influences the neurotransmitter system able to stimulate neuroplasticity. Studies on animals revealed that using amphetamine increases dopamine and noradrenaline release and also inhibits re-uptake of neurotransmitter by presynaptic neuron, which may have a therapeutic effect after brain injury [42]. Motor training can be reinforced by the administration of amphetamines, which potentially decrease motor impairment, as was demonstrated in several clinical trials [43]. Drugs increasing activity of the cholinergic system (i.e. Donepezil, Galantamine, Rivastigmine, Tacrine), which is responsible for modulating neuronal activity in the cerebral cortex, are also considered helpful in improving the effects of post-stroke rehabilitation [43]. Moreover, the pharmacotherapy used for improving memory and executive functions in Alzheimer disease is also associated with the improvement of sensorimotor functions in patients following stroke [43]. Studies on treatments with selective serotonin reuptake inhibitor (SSRIs) suggest also that SSRIs may enhance recovery after stroke [44]. Furthermore, in several studies thrombolytic drugs have shown to be effective in reducing brain lesion and enhancing functional outcome, but they can

be administered for a short-time window intravenously or intra-arterially. Other drugs that have shown a tendency to improve functional outcomes after stroke are dextroamphetamine and levodopa [45, 46]. Therefore, it is not well-understood whether the ability to learn motor skills could be the direct consequence of reinforced rehabilitation or just the result of drugs administration.

Therapies which directly stimulate the peripheral or central nervous system can increase neuroplasticity during rehabilitation time after stroke and may help in overcoming motor deficits in individuals after stroke. For example, devices used for electrical stimulation of muscles and peripheral nerves can help patients in performing movements with the paretic limb. Furthermore, stimulation of the peripheral nervous system can influence the CNS through afferent fibres [47].

Imaging techniques detecting metabolism of the brain have revealed that the contralesional motor cortex is highly activated after stroke [4]. The functional role of this activity is unknown. However, electrophysiological data indicate that inter-hemispheric inhibition is continuous during movements of the hemiparetic side. These data support the hypothesis that the interaction between the two brain hemispheres may be a factor influencing rehabilitation after stroke [4]. Few studies have demonstrated improvement of limb function (as scored by validated outcome measures) in patients treated to reduce excitability in contralesional M1, both in the sub-acute and in the chronic phase after stroke [48].The ability to recover motor functions after stroke is strongly influenced by the integrity of high-speed fibres connecting M1 to the spinal cord [14]. Since brain plasticity is virtually maintained regardless of age, changes in environmental conditions may impact the reorganisation of the cerebral cortex [49]. These findings indicate that there is potential for functional plasticity in the cerebral cortex of adults and suggest that rehabilitation programmes may influence this process.

3. Computational approaches to the motor system

Computational approaches for the modelling of the CNS aim to develop theories on processes occurring in the brain that allow the transformation of all information needed for the execution of motor acts [50]. The following paragraphs will outline how the motor system manages and controls in real time such a large amount of information and how sudden changes of information result in the modification of movement behaviours. The ability to perform complex motor tasks can be controlled by a simple feedback process which gathers sensory information that can be recalled later if needed [51]. Considering the number of muscles composing the human body (600 at least), each able to contract and relax, a potential combination of all the possible states could be calculated as 2^{600} [50]. The possibility that the complete system could be controlled by feedback mechanisms is not plausible because the loop would be too slow to maintain the reliable flow of information needed for fast adaptation [52]. The process of transforming meaningful information from

the environment for motor coordination relies on the possible presence of so called internal models, which hypothetically represent the anticipatory and inverse dynamics and kinematics of the body in a given environment. According to the literature the term “internal model” refers to the neural mechanisms modelling afferent and efferent stimuli from, and to, the motor system components [51]. Several kinds of computational models have been described to explain the motor control strategies potentially occurring in the CNS. Among them, the forward internal model transforms motor commands into appropriate actions exploiting the process of real-time updating coming from internal sensory information. Such a model would be able to predict the sensory response activated by a motor command as well as the expected result of the command, and would estimate the position and velocity of the body segment when moving in real time (Figure 1) [53, 54]. Forward dynamics of this model have been used in determining theoretical internal forces that cannot be experimentally measured such as, for example, in the joints. However, this can be useful to study pathological motor behaviours and their rehabilitation. The existence of forward models have been tested in studies of coordination between reaching and grasping, these data described precisely the control of grip force under normal conditions [55]. Furthermore, fMRI studies have revealed cerebral activity specific for the coupling of grip-force and load-force, suggesting that forward models can be encoded in the cerebellum [56]. Another model, called the inverse internal model represents internal activities associated with the desired modification of the environment [50]. This model converts the expected motor behaviour into the respective motor commands, which are calculated along with the information collected from the surrounding environment in order to obtain a desired trajectory of movement (Figure 2) [53, 54]. Hypothetically, the creation of internal models would allow the CNS to handle both kinematic and dynamic data [57]. The planning and control of movement execution requires knowledge of the dynamics of the controlled extremities to generate an appropriate efferent command in order to achieve the target. Such planning and control of motor action presuppose that the CNS must be able to manage forces and constraints acting on the limb. Furthermore, the inverse dynamics consists of using the outputs of the real system as inputs to a computational model, the dynamics and predicted behaviour of which do not necessarily match with the real system.

However, as useful forward and inverse models are, so experimental validation of those computational approaches is challenging. The translation of the internal model idea into rehabilitation deals with the ability of the patient to update the "state" of their own body as long as it changes with movement propagation in the smallest dimension out of the overall sensorial stimuli [50, 53]. From a computational perspective, the ability to efficiently control the motor system relies on the ability to adapt motor commands within the context of a due task. In these conditions, movement can be analyzed periodically as in sensorimotor loops (Figure 3). The complexity of a sensorimotor loop has been presented in three main stages. The first stage determines which motor commands have to be generated in the CNS to handle a particular state and task to be performed by the motor system (Inverse Model). The second stage determines the changes

occurring to states because of specific motor commands (Forward Sensory Model). In the third stage, the sensory feedback is determined by the newly generated state (Forward Dynamic Model) [50].

The possibility to adapt internal models to the environment in patients following a stroke has been examined in studies which used the manipulation of end-effector robots [58]. The results showed that the ability to adapt and carry out internal models is deteriorated after stroke. Thus, when the motor impairment is severe the ability to adapt and implement new internal models is lower. According to the authors, improvement of motor function depends on the possibility to restore the overall adaptability abilities or through rehabilitation [58].

Each process of motor learning comes from interaction with the environment and requires a change of behaviour. Considering rehabilitation as a process of motor learning, the manner in which the CNS determines the performance of movements should be considered. Thus, motor re-learning could be viewed as the process of acquiring both forward and inverse internal models, appropriate for different tasks [59]. The process of acquiring and retaining the internal models is a computational approach aimed at adapting to different situations quickly [60].

Several concepts of internal models have been presented in neuroscience and most of them have been supported by neurophysiological and neuroimaging studies [53, 55, 59, 60]. The internal model paradigm has its origin in control theory, and robotics and was studied in the sensory system for processes other than motor control. Nowadays, internal models have been studied thoroughly as one of the most known mechanisms underpinning motor control and learning. Several studies have explored the existence of specific structures and the involvement in learning and functioning of internal models [61-63].

The study by Shidara et al., [61] provided evidence that an inverse-dynamics model exists for eye movements. The authors revealed that the ventral paraflocculus of the cerebellum includes a major dynamic part of the inverse dynamics model and is complemented by other brain regions [61]. The cerebellum is connected to cerebral areas that sub-serve a range of sensory and motor functions. It is assumed that the cerebellum calibrates internal model estimates through an error-based learning process. This adaptation was observed in some studies showing improvement of motor adaptation in patients with cerebellar lesions when force-field perturbations were introduced gradually over several movements rather than suddenly in one step [62]. Learning with endpoint feedback may rely more heavily on updating of feed-forward models. The finding that cerebellar patients can adapt to a gradual visual rotation when cursor feedback is provided may reflect an ability to use compensatory online feedback corrections to improve reach accuracy [63].

In recent years, much attention has been devoted to innovative technologies and its impact related to computational approaches [64-68]. From a technological perspective, computational models allow us to design and generate very complex systems. From this point of view, engineers tend to apply an inductive approach and build models from the beginning. In those models the constructive parts represent computational implementations of physics and mechanics.

In contrast, neuromuscular models are mostly used for scientific inquiry through a deductive approach, based on behavioural observations in a particular regime, and measured accurately to create models that can be used as a computational implementation of a hypothesis of the overall behaviour. In one clinical study, the kinematic features of the same movements performed in both a real and virtual environment were compared in healthy participants and stroke patients [69]. These authors observed that both groups used the same motor actions in both real and virtual environments [69]. One of the hypotheses confirming the efficiency of this method is that the use of a multimodal environment for rehabilitation could assist the continuous reorganization of sensory stimuli and, consequently, stimulate the updating of internal models [70].

Different kinds of computational models have been studied and developed. Computational models have been proposed in several fields, not only to interpret the CNS functioning, but also its efferent behaviour. At present, several packages are available to model the musculoskeletal systems (e.g. OpenSim – National Center for Simulation in Rehabilitation Research) [71]. The musculoskeletal models operate in a lower dimensionality than a simulated sensorimotor system because it simplifies the mathematical implementation and analysis, or simply a low-dimensional model is considered to be sufficient to simulate the analyzed task. Kinematic dimensionality is often reduced to limit motion to a plane, when arm motion is stimulated. Furthermore, the number of muscles controlled independently is often reduced for simplicity and computational convenience [72, 73]. Fuglevand et al., proposed models to investigate muscle physiology, electromyography, and force variability, but these were limited to the study of single muscles [74]. Therefore, Cheng et al., developed the Virtual Muscle software package to integrate motor recruitment models into a software package of multi-body dynamic models [75].

Computational motor control theories are widespread, providing theoretical information about dynamic systems, how they are controlled, and their performance. In the context of neuromuscular modeling, the dynamics of system could be described as the sample of control vectors determining the forces acting to vary the states of the same system [76]. This means that the goal for an optimal control framework is to control the dynamical system. Moreover, to consider the control framework as an optimal control theory, the controller should have direct access to the state and output variables and should quantify the performance of the system [76]. The first method based on linearization of dynamics was the Iterative Linear Quadratic Regulator introduced for the optimal control of nonlinear neuromuscular models [77].

As a whole, the idea of internal models has been a meaningful step ahead in producing plausible explanations for motor control issues while, at the same time, providing a concrete solution to operate simulation of human kinematics and dynamics. In recent years, computational performance in the field of applied informatics has increased hugely, making real time emulator of human movements possible. Access to these types of applications represents an intriguing opportunity for rehabilitation; in fact such a detailed avatar might be exploited like a trainer of compromised functions,

following injuries of the CNS and of the musculoskeletal system. Firstly, computational models can provide precise methodology for understanding mechanisms of recovery. Secondly, application of these models could be used in designing new and more effective clinical experiments. Thirdly, computational models have the potential to enhance treatment of patients through optimized therapy selection in terms of content, dosage, and timing (e.g. X therapy and Y period for Z disorder, etc.). Although some components of internal model paradigms are already an integral part of post-stroke rehabilitation programmes, they are still not fully implemented in clinical practice. Therefore, computational models should be studied in the clinical field to better understand motor control mechanisms, which in turn could be applied to rehabilitation practice.

4. Motor control and learning

Learning new movements implies a process of selection of motor actions to perform the requested task. Theoretically, the best movement should be repeated, emulating a reference model as exactly as possible, with the aim to achieve the best motor performance. In fact, a person performs and memorizes a set of movements more or less similar to the correct movement, improving performance on the basis of practiced motor experience. Doya [78] suggested that different areas of the brain (the cerebellum, the basal ganglia and the cortex) are involved in the process of movement learning through their cellular architecture. According to known computational models, each brain structure might implement three different learning paradigms, which are: Supervised Learning, Reinforcement Learning, and Unsupervised Learning [78, 79].

In supervised learning, the external environment provides an appropriate target for each stimulus. The aim of the task proposed is to teach the movement pattern using information coming from the surrounding environment. Learning efficiency may be defined as the discrepancy between the output signals from the CNS and the effectiveness of achieving the target. The cerebellum is engaged in fine adjustment of movement in real-time, by means of its feed-forward structures based on several synaptic connections from granule cell axons (parallel fibers) to Purkinje cells, which send inhibitory connections to the deep nuclei of the cerebellum and the inferior olive. The circuit of cerebellar connections is capable of implementing a supervised learning paradigm, which consists of error driven learning behaviors [78, 80]. Some supervised learning methods go beyond producing a functional mapping and also anticipating confidence threshold for each predicted output. An example of this method is the Gaussian process regression. This regression is based on the input-output relationship with a linear combination of basic functions.

In reinforcement learning, the subject directly estimates information from the performed movement. The neural substrate for reinforced learning is based on the multiple inhibitory pathways of the basal ganglia that permit the reward predicting activity of dopamine neurons and change of behavior in the course of goal directed task learning [78, 79].

Depending on task settings, each stimulus and its response, which are directed to the musculoskeletal system, provide feedback in the form of “rewards” or “punishment”. This learning process based on a trial and error paradigm is promoted by augmentation of Knowledge of the Results (KR - feedback related to the nature of the results produced in terms of the movement goal) and on the Knowledge of the Performance (KP - feedback related to the nature of the movement pattern which was produced) [54, 65, 80]. The difference between supervised and reinforced learning is that the external environment determines only whether the task was done correctly or incorrectly and does not have to provide feedback for each stimulus throughout the whole duration of the task.

In unsupervised learning, the environment provides input to the motor system, but does not set a desired target nor any measure of “rewards” or “punishment” [54, 81]. The main problem of unsupervised learning is the lack of guarantee that the initiated learning process has a functional effect on the motor system. Some authors have suggested that after stroke, if no therapy is given, plasticity due to unsupervised learning may become maladaptive, thereby augmenting the stroke‘s negative effect [82]. In the absence of supervised learning or reinforcement learning, motor functions worsen regardless of the number of undertaken therapy trials. On the other hand, if unsupervised learning is not present, the motor performance improves but at a later post-stroke stage [83].

Motor learning could be seen as the ability to predict or generalize commands in new situations. Theoretically, according to the principles of synaptic plasticity, motor learning depends on structural changes in brain tissue or on the structure of the nervous system [51]. Some authors suggest that movement re-learning depends more on the architecture of the CNS and on its internal organization than on its anatomical structure [84]. Thus, to exhaustively explain the process of motor learning it is necessary to understand the organization of the CNS structure.

5. Conclusions

This paper describes theoretical approaches to rehabilitation after stroke, providing examples from studies in animal and human models, of which the rationale should be translated in clinical practice and trials. Therefore, the aim of this paper was to provide an overview of the theoretical bases related to the organization and functions of the brain during the performance of motor tasks.

Rehabilitation can be intended as a re-learning process aimed at regaining movements with functional purposes to satisfy personal needs [39]. Using the regenerative capacity of the CNS, rehabilitation therapy can be deployed as a process of movement re-learning targeted to recovery of motor function [11]. Nevertheless, current knowledge on recovery processes after stroke and on the best available rehabilitation approaches is yet not sufficient to clearly understand the mechanisms involved in each specific intervention.

Computational models of the neuromuscular system can be profitably used to better understand the mechanisms sub-

serving motor control, thus providing useful perspectives to investigate different control hypotheses. These can also potentially allow us to reach a deeper understanding of motor function and clinical rehabilitation. Moreover, computational models could serve to create and explore new hypotheses as well as to design future experimental studies. Computational models are the fundamental blocks for building models of neuromuscular function since they can provide information on movement parameters (i.e. both kinematics and dynamics) that are hard to detect experimentally.

Computer models, therefore, can be used to simulate the neuromuscular system, to analyze the energetics of movement execution, and to plan rehabilitation programmes. Thus, considering an undefined action of the CNS during the execution of a task, computational modeling can be seen as providing pre-clinical insights into neuromuscular and brain functions to allow us to reach a deeper understanding of neuroplasticity. This approach is of interest for building models that allow the simulation of motor control mechanisms for generating sequences of motor commands. The literature, however, does not provide definitive methods for a unique computational approach or for the application of the optimal control theory to the neuromuscular system. Therefore, for future clinical studies it is important to model such computational paradigm, which would be based on the potential learning of defined dynamics and which would rigorously explain all the potential for CNS learning.

The take-home message from above presented studies is that even small amounts of available neurophysiological and behavioural studies, which focused on internal models, have provided vital information for understanding neural reorganisation and possible movement trajectory planning. Such studies are important for showing the existence, structures, learning, functions and anatomy of internal models, and should be considered in specific rehabilitation programmes. Nonetheless, computational methods cover wide, multidisciplinary aspects, the exploration of which is already possible in established fields such as machine learning, control theory, and estimation-detection theory. These fields interact with a combination of several techniques derived from engineering, statistics, computer sciences, or applied mathematics, which are routinely used. For example, reinforcement learning can be categorized within both machine learning and control theory. Thus, its interaction can be studied in both fields as an unique computational learning model. The categorization, therefore, of those fields and their combination could simplify computational models characterization as well as establish bases for parameters variability for future models' implementation.

Conflict of interest

The authors declare that they have no conflict of interest.

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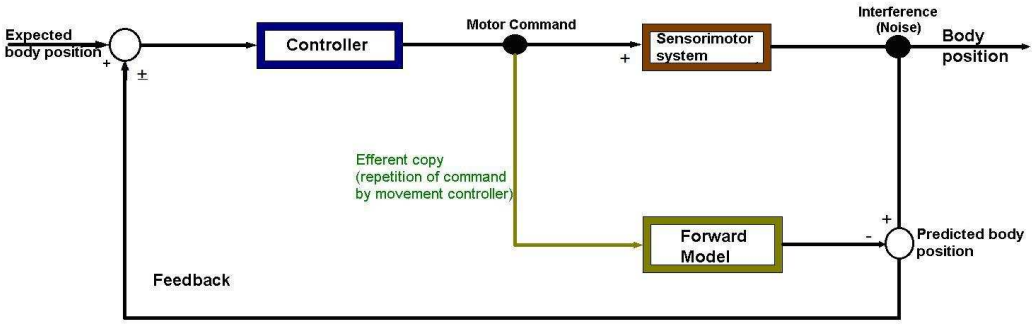

Figure 1. The forward internal model. The expected position of the body is the starting point for a hypothetical controller generating the necessary motor commands. This command is sent to the sensorimotor system to change body position while the efferent copy of the motor command is sent to the forward model. The results of the outcome of the forward model (predicted body position) are compared with the result of the outcome of the sensorimotor system (body position). Interference from the system or the surrounding environment may cause differences between the actual and expected body position. Bias (difference) between the actual and the predicted position can provide feedback to improve the movement execution and update the forward model.

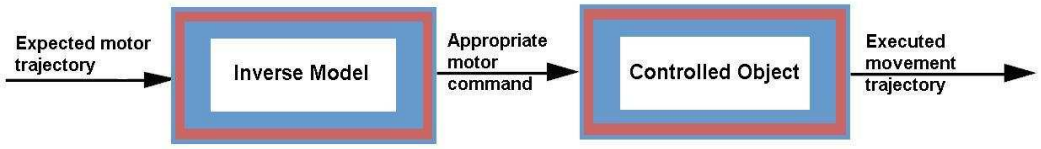

Figure 2. The inverse internal model. As a result of the expected motor trajectory, the inverse model converts motor behavior and generates the appropriate motor command to adapt to specific activities and executes the expected trajectory. The expected motor trajectory represents an input for the inverse model, which generates an output motor command. The generated motor command is associated with the desired modification of the environment (controlled object) to execute previously converted movement trajectory.

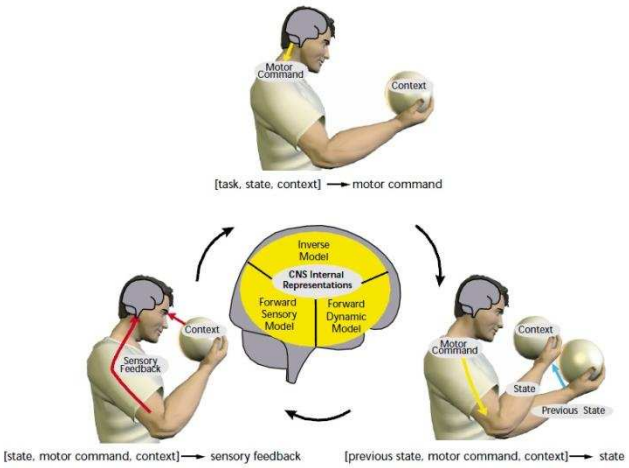

Figure 3. The sensorimotor loop, showing motor command generation (top), state transition (right) and sensory feedback generation (left). Center, internal representation of these stages within the CNS. (reproduced with permission from the author and from the Nature Neuroscience journal – Nature Publishing Group, License Number: 3800680205586) [50].