Insights into Neurorehabilitation

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EMOTION-DRIVEN MOTIVATION IS CRUCIAL FOR MOTOR CONTROL

Key questions

- What is the neural substrate for emotion–motion interaction?
- What is the unique role of the cingulate motor area in motor control among cerebral motor cortices?

During motor rehabilitation, it is often found that patients are more willing to complete motor training tasks integrated into fun games in comparison with conventional training programs. Therefore, various games are increasingly applied in motor rehabilitation, including EMG biofeedback games and virtual reality games. The positive effects of emotional stimuli provided by the games indicate that emotion plays an important role in motor training and motor rehabilitation.

Origination of Brain motor cortices

Structure of the frontal lobe

The human frontal lobe consists of the prefrontal cortex, frontal eye fields, premotor cortices, and primary motor cortex (M1). The prefrontal cortex (PFC) is located on the most anterior portion of the frontal lobe medially, laterally, and orbitally. On the lateral side of the brain, the frontal lobe is located rostral to the central sulcus. In the frontal lobe, the lateral prefrontal cortex, frontal eye fields, premotor cortex, and primary motor

cortex lie in a rostral to caudal order.

The dorsolateral prefrontal cortex (DLPFC) covers the entire dorsolateral surface of the frontal lobe, including most parts of the superior, middle, and inferior frontal gyri. The DLPFC is bounded posteriorly by several brain motor areas. The superior frontal gyrus consists of the prefrontal cortex, pre-supplementary motor cortex (pre-SMA), and supplementary motor cortex (SMA) from rostral to caudal.

The medial prefrontal cortex (mPFC) lies on the entire medial surface of the frontal lobe and envelops the corpus callosum ventrally, anteriorly, and dorsally (and thus the anterior cingulate cortex, ACC, is included) [1]. However, in some literature, on the medial side of the brain, the paracingulate sulcus is considered as (roughly) the border between the frontal lobe and the cingulate cortex of the limbic lobe (and thus ACC is not included) [2]. The cingulate motor cortex lies in the dorsal/middle portion of the cingulate cortex. The primary motor cortex is called M1, the supplementary motor cortex called M2, the rostral cingulate motor cortex called M3, and the caudal cingulate motor cortex called M4, though M2, M3, and M4 are rarely seen in recent literature.

The ventral part of the frontal lobe is the orbitofrontal cortex (OFC), which is located on the floor of the anterior cranial fossa, just above the orbits [2]. Orbital-ventromedial Prefrontal Cortex Contributes to Emotional Control of Behavior [1, 3].

Projections of brain areas in the frontal lobe

Orbitofrontal cortex (OFC)

The OFC receives inputs from all five types of sensory modalities and from the viscera.

1) The primary olfactory and gustatory cortices (mainly the insula) send olfactory and gustatory projections to the posterior OFC.
2) Unimodal parietal/temporal association areas (responsible for each sensory modality) send visual/somatosensory/auditory signals to the OFC. Especially, the somatosensory cortex sends somatosensory inputs in terms of mouth and hands, possibly indicating a role in feeding.
3) The nucleus of the solitary tract sends the fullness sensation to the OFC through the ventroposterior medial thalamus and agranular insula.

These inputs reach the posterior OFC and then are relayed to anterior OFC regions.

All three pathways relay appetitive- and feeding-related inputs (smell and taste of food, somatosensory information of mouth and hands, and fullness). In humans, feeding-related information and other rewarding stimuli are represented in the OFC [4].

Medial prefrontal cortex (mPFC)

The ventral mPFC areas receive inputs from the OFC. The dorsal mPFC areas receive inputs from the DLPFC. The ACC receives inputs from other mPFC areas and from the posterior cingulate cortex and parietal and

temporal association cortices. Additionally, the mPFC receives relatively strong dopaminergic and serotonergic projections. The output projections of the mPFC reach the thalamus, amygdala, entorhinal cortex, and subiculum. Additionally, there is a unique relationship between the mPFC and subcortical brain areas related to the autonomic nervous system including the hypothalamus, PAG, and the dopaminergic, serotonergic, and noradrenergic brainstem nuclei.

These connections indicate that the mPFC is involved in the emotional processing of sensory stimuli. Abnormalities of the mPFC are detected in mood disorders, schizophrenia, substance use, and some other psychiatric problems [1].

Dorsolateral prefrontal cortex (DLPFC)

The DLPFC receives projection from multimodal association cortices, including the parietal lobe (somatosensory and visuospatial ["where" visual stream] information), and temporal lobe (auditory and visual object related information ["what" visual stream]. Strong dopaminergic and serotonergic inputs also reach the DLPFC.

DLPFC outputs mainly arrive at adjacent brain motor areas, that is, the M1, PMd, PMv, and SMA. It also connects the thalamus, striatum, and medial temporal lobe (MTL). The MTL encodes/ stores/retrieves specific memories, and marks the emotional values of the object and situation (the OFC and mPFC have stronger projections to the MTL than the DLPFC).

Such connections indicate that the DLPFC is closely related to cognitive processing rather than emotional and autonomic functions.

Function of motor cortices

- The prefrontal cortex (PFC) maintains the intention of goal-directed movements. Patients with a lesion in the PFC cannot remember their intentions and thus may devise plans one by one but abandon them immediately [3].
- Premotor cortices form motor plans, that is, generating an "abstract representation" of an intended motor action, e.g., which combination of limbs will be used or what is the sequence of movements.
- SMA and pre-SMA play a key role in selecting appropriate actions based on internal and external contexts. Lesions in this region lead to difficulties in initiating/suppressing movement. The initiation deficits manifest the loss of self-initiated movements of contralesional limbs or speech; the suppression deficits manifest the release phenomena, e.g., forced grasping when the hand touches an item, irrepressible reaching/searching movements towards an object), and the hand of the patient moving without being directed by the patient's own will.
- M1 execute skilled motor acts.

To sum up, in the frontal lobe, all brain areas participate in the motor control process. These areas are connected in series, forming a functional hierarchy. The dorsolateral prefrontal cortex (DLPFC) is responsible for the cognitive control of movement, especially the intention to perform movements. The signal then flows from the DLPFC to the premotor cortex (PMd, PMv, and SMC) and finally reaches M1 [3].

Emotion and cingulate cortex

The cingulate cortex is a neural interface between emotion, motivation, reward, sensation, and action, which is achieved by anatomical connections between the cingulate cortex and brain regions closely associated with each of such functions [5-8].

The exact functional subregions of the cingulate cortex remain unclear. Base on cytoarchitecture features, Brodman's area 24 is often referred to as anterior cingulate cortex (ACC) whereas Brodman's areas 23 and 31 are referred to as posterior cingulate cortex (PCC) [5, 9, 10]. As an alternative, the cingulate cortex may be divided into the ACC, MCC (middle cingulate cortex), and PCC [11]. Therefore, some parts of the MCC may be introduced as the ACC in other studies [12].

Motor tasks often evoke activations in the middle part of the cingulate cortex, a region called the cingulate motor area (CMA). The CMA is located mainly in the scope of the MCC whereas more anterior and posterior extensions may appear in movement-evoked activations [13, 14].

Several motor cortices participate in motor control. Through direct corticospinal projections, the primary motor cortex (M1) controls fractionated movements to execute a skilled motor act, such as opposing fingers to pick up a pen [14]. Projecting directly to the spinal cord, the dorsal and ventral premotor cortices (PMd and PMv, respectively), supplementary motor area (SMA, or more broadly, SMA and preSMA, called supplementary motor complex, SMC), and cingulate motor area (CMA) are main premotor areas that encode a general goal-directed command of a motor action. A motor task is thought to be divided into

multiple subtasks, with each subtask managed in parallel by one of the cortical motor areas [15]. Then, a project is formed to move the fingers in the premotor areas. PMd has roles in movement preparation and guidance where PMV appears to play a major role in visually guided arm movements. SMA is responsible for initiating, programming, and planning movements [16]. M1 executes the movement. However, the role of CMA in brain motor control largely remains unclear. Neural activities in SMA and CMA are reported to be very similar during movement [17]. As a cortical region near SMA and sharing similar neural activities with SMA in motor control, the question of whether CMA has any unique function compared with those of SMA and other premotor areas should be answered.

Here, we directly compare the activation scopes evoked by stimulation/tasks rather than tangle with the nomenclature (ACC and PCC vs. ACC, MCC, and PCC). The emotion/motivation-evoked activity in the cingulate cortex is found to overlap those evoked by motor tasks: emotion/motivation-evoked activity are distributed over the anterior, middle, and posterior parts of the cingulate cortex, whereas activities evoked by motor tasks are distributed mainly in middle and anterior parts of the cingulate cortex (called cingulate motor area, CMA) [11, 12]. For example, motivation-induced brain activities are detected in the anterior and middle parts of the cingulate cortex [18], whereas the middle part can also be activated by motor tasks [13, 14].

The functional overlap suggests that the CMA may bridge the brain emotional/motivation processing network and motor control network. This is supported by several lines of evidence. First, stimulating the MCC/CMA region evokes both affective and motor responses [19].

Furthermore, brain activations in the MCC/CMA are observed in emotional (gentle or rude) hand movements, by using the direct contrast of gentle (or rude) hand movements vs. controlled hand movements. That is, MCC/CMA activations found in the study contain two parts, those evoked by the motor component of the hand movements and those evoked by the emotional component [20]. Additionally, emotion stimuli were found to evoke signal changes in the amygdala, middle insula, and MCC in a functional MRI study, whereas only the MCC activity presented a pattern similar to observed motor behavior changes, indicating that among all three emotion brain regions, only the MCC is closely related to motor outputs [21]. All these findings are direct evidence that MCC/CMA is a hub to integrate emotional and motor processing. In the brain motor areas, this role is unique.

The convergence of brain emotional network and motor network in MCC/CMA can be achieved by connections among MCC/CMA and other brain regions. A subregion of the cingulate cortex presents most strongly anatomical/functional connects to its adjacent brain areas and therefore possesses similar functions. For example, the posterior ACC is located adjacent to the orbitofrontal cortex, and both are responsible for emotional and motivational information processing. The dorsal ACC is adjacent to the lateral prefrontal cortex and pre-SMA, and all of them are involved in abstract cognitive processes. The MCC, overlapping the scope of the CMA, is adjacent to the SMA and M1, all of which participate in motor control. The posterior cingulate and retrosplenial cortex are located adjacent to the parietal and parahippocampal regions, and both process spatial information [5].

Each portion of the cingulate cortex also connects other brain regions in addition to those immediately adjacent areas. The cingulate cortex performs emotional and motivational processing via strong reciprocal projections to brain areas related to reward processing, e.g., the orbitofrontal cortex, basal ganglia, insula, and lateral prefrontal cortex [5]. Strong reciprocal connections also exist between the cingulate cortex and brain motor areas. Specifically, the MCC not only projects to M1, SMA, putamen, and spinal cord [22], but receives direct/indirect inputs from emotion-processing brain areas [23]. Connectivity analysis demonstrates that the MCC links the prefrontal and premotor cortices in addition to the M1 and SMA [19].

Therefore, the connections between the cingulate cortex and emotion/ motivation/reward-processing brain areas and connections between the cingulate cortex and brain motor areas, especially the MCC, endow the CMA as a hub to bridge brain motor and emotion-motivation networks. Such a role well explains the unique function of the CMA in the brain motor system.

Emotion influences motor behavior to meet various needs, from basic survival requirements to social activities. Emotion concepts are critical in choosing appropriate actions and maintaining ongoing physiological balance [24]. Basic survival needs, such as food intake and predatory hunting, are regulated by the amygdala, which performs a primary role in processing emotional responses [25, 26]. Adolescents with a stronger emotion-driven impulsiveness tendency show a higher snacking frequency [27]. Unpleasant stimuli generate better force output in both healthy people and patients suffering from functional neurological symptom disorders

than do pleasant stimuli [28]. In sports science, pleasant emotions such as happiness are thought to be associated with poor performance, whereas unpleasant emotions such as anxiety and anger are associated with good performance [29]. Emotion can even guide actions in ways we are often unaware of. For instance, although the task of dog owners walking their dog appears to be constructed as "for the dog", dog owners represent the dog's needs in a hidden manner, which is actually aligned with their own. The most important reason for dog walking is to meet the emotional needs of the owner rather than as a requirement for the dog's physical activity [30].

Movement also influences emotion. Walking or ergometer cycling positively affects depression and anxiety [31, 32]. High-intensity exercise leads to greater enjoyment due to elevated feelings of reward, excitement, and success than moderate-intensity exercise [33]. This result indicates a dose-dependent effect of movement on emotion. By contrast, inactivity due to bed rest for 10 days induces a decrease in positive emotions in healthy people [34].

Human behavior is either heavily influenced or motivated by emotions [35, 36]. Movement is a process in which motivation is actualized. PMd, PMv, and SMA are brain regions that plan and prepare motor acts, while M1 executes movements. CMA acts as a key area that introduces emotion–motivation drives to the brain motor system. Thus, the role of CMA is different from those of SMA, PMd, and PMv.

Brain emotion network may exert motivation to drive the brain motor network via CMA during non-emotional situations. This driving effect is

supported by a previous finding that the directional ACC→SMA influence is greater during the motor task state than in the resting state in non-emotional situations [37]. The driving effect of emotion on motor outputs is also supported by the fact that amygdala neurons generate motivation for movement during situations without emotional stimuli [25].

To sum up, brain emotion and motor systems are tightly integrated; they are not only hard-wired in the brain across jawed vertebrates [25] but are seen among brain regions as revealed with functional MRI [38] and in the behavioral level [28, 30, 33, 34, 39]. CMA (mainly in MCC) bridges brain motor and emotion networks, thereby providing a neural substrate for emotion–motion interaction. With the CMA, the emotion network drives the brain motor system. Such a driving role may be explicit or latent, depending on the nature and magnitude of emotional changes. Thus, CMA plays a different role in motor control compared with other promotor areas such as SMA.

Emotion is the basic component of brain motor outputs

The brain emotion system influences the motor system in many ways. In the frontal lobe, the initiation to exert a motor behavior begins in the orbitofrontal-ventromedial prefrontal cortex (OFC and mPFC), and then flows along projections from the OFC and mPFC to the dorsolateral prefrontal cortex (DLPFC) [3]. Afterwards, the DLPFC mainly projects to the nearby motor, premotor, and supplementary motor areas. This OFC/mPFC-DLPFC-Premotor/SMC/M1 pathway represents an emotion-cognition-movement sequence in that the OFC/mPFC is more closely associated with emotional processing whereas the DLPFC is

more closely associated with cognitive functions [1, 3]. This emotion-cognition-movement sequence also demonstrates the crucial role of emotion in initiating and controlling motor behavior. However, the CMA, as the interface/hub between brain emotional and motor systems, appears to directly integrate emotion and motor processing. The multi-level/area integration between brain emotional and motor systems strengthens the role of emotion, as a basic component, in brain motor control processing.

Emotion and motivation are closely related processes

Tomkins argued that emotion drives the behavior of a person as the basis of human motivation (to be concise, affect, emotion, and mood are not distinguished in this chapter). Motivation derived from the emotional system can amplify biological activities [40]. As an example, negative emotions including anxiety and depression can increase people's motivation to drink to achieve psychological relief [41, 42]. The concept that emotional systems act as the basic motivational system is supported by others [43]. Motivation and emotion systems in the brain share a number of common brain areas (e.g., the ACC and medial prefrontal cortex) and are tightly integrated [7, 18, 44], thereby often introduced together, e.g., the emotional-motivational system [45], emotional and motivational systems [43], emotional/motivational impact [46], and emotional-motivational brain functions [45].

The role of emotion/motivation in motor rehabilitation

Under most conditions, patients receive motor training via a cognitive process. That is, the medical professionals, caregivers, and patients realize the functional deficits and the necessities to restore the deficits. Then, a motor training course is given although the course may (and actually often) be boring, tedious, and lacking in variations. The course usually is composed of a number of motor tasks.

Because motor function deficits caused by a neurological disease (e.g., stroke) often lead to a heavy burden, patients usually follow the arrangement of the therapeutic exercise despite of abovementioned issues. However, the negative emotional status may lead to clinical problems to various extents, from mood swings to post-stroke depression. These problems impede the recovery of motor function and should be avoided. Thus, positive emotion should be built in a motor rehabilitation program, and negative emotion is to be avoided. In this way, the brain emotional system exerts a positive impact via CMA (and other brain emotion-motion interfaces) on the brain motor system, thereby promoting motivation to stick to motor training.

Practically, such a positive emotion-motivation impact can be achieved by using various approaches.

First, attractive content and appearance of the motor training program should be applied, such as adopting music, dance, and action video games in motor training. Music can lead to mood improvement [45], which improves emotional/motivational status and motor function in stroke patients [47]. The action video games are far more fun than the “boring”

games commonly seen in healthcare facilities for training various functions of the patient. An example of an attractive appearance can be seen in a dolphin game (http://blam-lab.org/index.php/kata-design-studio/). The lifelike dolphin in the game exhibits a vivid, lively appearance, which can stimulate the interests of the patients. If possible, the motor training program should be designed and implemented as games instead of motor "tasks". A task implies a piece of work to be undertaken, whereas playing games is an activity for enjoyment rather than work and thus tends to cultivate initiative and even enthusiasm.

Secondly, challenge/difficulty levels of the contents of motor training should be carefully adopted. Similar to playing a game, a suitable challenge level can inspire participation whereas a level being too hard or too easy is hardly attractive for the patient. For example, when performing motor rehabilitation, the ability of a patient should be examined and the optimal level should be determined. Afterwards, the challenge/difficulty level of the motor action can be slightly increased beyond the optimal level, step by step. When successfully completing each training action one by one, the patient experience a series of success, and the motivation to keep training can be built. Such a process does not imply adopting challenges easy to be overcome. Instead, a challenge that can be overcome by using a certain amount of effort is preferred, which may induce a stronger imprint in the nervous system than easy-come-easy-go changes.

Additionally, the feedback should be timely presented to patients. A simple way to use feedback in motor training is to indicate muscle activities or limb movements with some type of biological signals, e.g., surface electromyography. However, an advanced approach is to

determine the key components of a motor action, and trace its activity when performing motor training; the training may be to activate the muscle (from no voluntary muscle contractions to presenting stable voluntary contractions and from weak voluntary contractions to strong voluntary contractions) and to enhance functionality (improving endurance, selectivity, and dexterity of muscle contraction). Endurance is the ability to maintain enough duration when a muscle contracts; selectivity is the ability to contract relevant muscles but not irrelevant muscles for a motor action; dexterity indicates skillful rather than rigid or jerky movements and the ability to switch among concentric, eccentric, and isometric contractions. In each training session, no matter how tiny the progress is, the progress should be timely presented to the patients. The functional improvement can invigorate the patient if the function of the patient is continuously improved and positive feedback is timely given. As previously introduced, tight interaction exists among brain emotion and motivation systems. Additionally, the central role of the cingulate cortex in emotional- motivational processing is highlighted by its strong reciprocal connections to brain reward centers including the orbitofrontal cortex, basal ganglia, and insula, e.g., the ACC is the main target area of midbrain dopamine neurons and these neurons release dopamine to modulate reward responses [5]. Thus, the positive emotional/motivational modulation stemmed from a properly arranged training program and feedback can activate reward mechanisms, which enhances the impact of the emotion-motivation systems on brain motor outputs.

Summary

Human movements can be cognitively and/or emotionally motivated. It is a cognitive process to learn the possible effects of motor training on motor function recovery after neurological diseases such as stroke, which drive the compliance of a patient to receive training. Emotion-driven motivation may be explicit or latent and has a crucial impact on motor output because the brain emotion network and motor control network are tightly integrated via the CMA and other interfaces/hubs where the two systems converge. Thus, in motor training programs, positive emotions should be built to optimize the effect of therapeutic exercise.

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ARE HUMAN WALKING CPG IMPORTANT FOR WALKING TRAINING?

Key questions

- What is the neural mechanism of human walking?
- How to restore walking function after stroke or other neurological diseases leading to limb paralysis?
- Is the spinal CPG a target for training walking?
- Are body weight support treadmills and walking robotics useful for human walking training?

Spinal CPG alone cannot drive normal walking in adults

Rhythmic movement is a basic type of movement in humans and many animals, such as walking, running, breathing, chewing, swimming, and flapping wings during flight. Once initiated, rhythmic movements can be automatically repeated without intentional control to maintain the rhythm. The rhythmic activity originates from rhythmic action potentials generated by neurons in the central pattern generator (CPG). The CPG neurons may burst rhythmically spontaneously or when neuromodulators (or neuromodulatory substances) present [1-3]. In the circuits of a CPG, a small number of neurons generate strong rhythmic signals, whereas some neurons produce platform-shaped action potentials to exert effects over a relatively longer period [4].

Walking is one of the fundamental motor skills in humans. Rhythmic muscle activities, left–right alternating leg movements, and multi-joint movements of the lower limbs are core factors of human walking, which are considered the basic components of locomotion/walking movement patterns controlled by the CPG [5]. In animal experiments, these components are used to determine whether the lower limb motor actions are walking-like movements (and thus driven by the walking CPG). However, different from quadrupedal animals, a person must support the body and maintain balance during walking with two legs.

Previously, the alternating contractions of flexors and extensors of lower extremities during walking were considered as results of rhythmic activities in the central nervous circuits by which antagonistic muscle groups are suppressed by each other [6]. However, after removing timed sensory inputs, the locusts are still able to develop rhythmic movements (wing cycling) [7], suggesting that the rhythmic movement is not driven by spinal cord reflexes. In vertebrates such as Petromyzon [8] and neonatal rats [9], isolated spinal cords (or brainstem-spinal cord) can produce locomotion-like movements without peripheral sensory inputs, that is, periodically alternating left- and right-side contractions of the torso muscles (for Petromyzon) or extensor- and flexor-contractions of limb muscles (for rats).

The locomotion/walking CPG exists in the spinal cord in quadrupedal animals such as cats or rats. Walking-like movement patterns can spontaneously occur in decerebrated mammals [10], and the walking CPG in mammals comprises rhythm-generating and pattern-generating circuits in the spinal cord [11]. The rhythm-generating circuit consists of excitatory,