Overview of neurophysiology of movement control

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ABSTRACT

The motoneuronal outputs from cortex and spinal cord have quite different patterns of organisation. The cortex consists of a highly intermixed mosaic of small output zones whereas the motoneurones in the cord are located in clearly defined columns of cells, that all project to the same muscle. I describe the pattern of innervation between cortex and cord, indicate the importance of cortical plasticity in allowing flexible control of spinal circuits, and show how these inputs interact. Finally I discuss some of the new methods of stimulating descending motor pathways in humans.

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1. Introduction

The process of movement has in the past been expressed in terms of a sequential flow of information, often expressed as: Idea—Plan—Select—Move. In this scheme, movements were believed to start with an idea that defined a goal to be reached. This was then converted into a plan of action which detailed the best way to achieve the goal. The muscles to be used were then selected and energised to produce movement. Evidence in favour of the distinction between idea and plan came from observations in apraxic patients who could know what they wanted to do but be unable to formulate the best method to achieve the goal. An example would be a patient trying to put on a jacket but mistaking the back from the front or the arm holes for trouser legs. The patients were said to know what they wanted to do but were unable to do it. The evidence for conversion of the selected plan of action into a suitable pattern of muscle activity was less clear since many conditions have movements that are accompanied by abnormal muscle activity, such as dystonia or Parkinsons disease. However, whether this is truly a faulty conversion of an accurate plan or simply or poor planning is not clear.

Although this approach has the benefits of simplicity it probably underestimates the degree to which these elements are performed in parallel, not only in time but in space, being executed simultaneously in many different areas. The benefits of such a parallel organisation are that it is robust; damage to any one structure (at a particular time) can be compensated, at least to a certain extent, by activity in other structures. One disadvantage is the resulting complexity, since a given group of neurones can participate in more

than one different task. In addition, if this is to work efficiently there must be good communication and feedback between the elements.

2. Summary of supraspinal motor organisation

The motor areas of cortex are defined by the fact that all of them send axons to the spinal cord, and are interconnected with each other. They are the primary motor area (Brodmann's area 4, mainly located in the anterior bank of the central sulcus), premotor cortex (the lateral part of area 6 of Brodmann), which is usually divided into dorsal and ventral in human studies, the supplementary motor area (the medial part of Brodmann's area 6) and 3 regions of the cingulate cortex ventral to the supplementary motor area [1]. The primary motor cortex contributes about 40% of the corticospinal fibres, the cingulate and supplementary areas about 20% each and the premotor areas about 10% [2]. All of these areas of cortex also project to brainstem areas that give rise to reticulospinal tracts, giving them an indirect route to spinal cord as well as the direct corticospinal route. The primary motor cortex is thought to have fewer of these indirect connections than other motor areas.

The corticospinal tract travels in the lateral column of the spinal cord and has the densest terminations among distal muscles of the arm and leg, but also innervates all sections of the cord. About 90% of the projections are crossed. A smaller proportion project ipsilaterally. The reticulospinal tracts arise from areas of the pontine and medullary reticular formation and tend to project bilaterally to innervate more proximal and axial muscles, although recent electrophysiological work suggests that they may even have some connections to the most distal muscles of the hand [3].

Consistent with this general anatomical picture, lesion studies in primates show that corticospinal section (pyramidotomy)

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produces mainly a disorder of distal muscle control, leading to a lack of fractionated finger movements. Despite the loss of such a large tract, the animals can still use the contralateral limbs quite well (especially after some weeks recovery) to climb the bars of a cage or to run around the room [4].

Isolated lesions of the reticulospinal system are impossible to achieve because the fibres are intermixed with other tracts along most of their path, in the lateral and ventromedial columns, to the spinal cord. Experiments by Lawrence and Kuypers [5] suggest that lesion of these tracts produces much more profound deficits in overall motor control than a pyramidotomy. The animals cannot balance, have no righting reflexes and need a good deal of care to enable them to survive. The conclusion is that the reticulospinal systems are an important contributor to movement, as evidenced by the relatively well-preserved overall function of pyramidotomised animals.

There are no similar studies in human patients. The lesion of the internal capsule that is common in subcortical stroke, disrupts both the direct and indirect cortical connections to the spinal cord. Thus we see, to a mixed degree, the combined effect of a corticospinal and reticulospinal lesion. Rare surgical cases show that the effect is quite different from a pure corticospinal lesion. Bucy and colleagues [6] sectioned the middle third of the cerebral peduncle, which is mainly devoted to the corticospinal tract, to control abnormal involuntary movements (hemiballismus) caused by a natural unilateral lesion of the subthalamic nucleus. They reported that the lesion abolished the involuntary movement but that there was no spasticity and movement control remained good. However, there were no detailed descriptions about hand function that we can compare with the monkey data.

Parts of three other subcortical structures are viewed as part of the supraspinal motor system: the vestibular system, the cerebellum and the basal ganglia. The vestibular system is the only one with a direct projection to spinal cord in the vestibulospinal tract. This runs in the ventromedial fasiculus and terminates mainly on proximal and axial muscles, often bilaterally. It is thought to provide direct input to control balance and posture. The cerebellum and basal ganglia have no direct motor outputs. The cerebellum has projections to reticular centres where it may access reticulospinal tracts, but most of the output is to thalamus and cortex. The cerebellum also receives input from many areas of cortex via relays in the pons as well as direct sensory input from spinal cord through the spinocerebellar tracts. In motor control, the cerebellum is seen as being in a position to compare outputs from the cortex with sensory inputs that it receives. The basal ganglia have no direct sensory inputs or motor outputs, but a large part of the nuclei is devoted to processing information from sensorimotor areas of cortex and then sending the transformed information back to the same or nearby cortical areas.

A simplified account of these areas of the motor system would probably state that

(1) The corticospinal system, particularly the projections from the primary motor cortex is important for fine finger control.
(2) Reticulospinal and vestibulospinal systems are important in gait and balance.
(3) Primary motor cortex is a common output path through which a large proportion of the motor command is funnelled to reach the spinal cord.
(4) Dorsal premotor cortex is involved in performing movements that are triggered by arbitrary cues in the environment (such as visual shapes, or auditory tones) whereas the ventral premotor cortex is involved in controlling (particularly hand) movements that relate to real objects in the environment within reach of the body.

(5) Supplementary motor area is involved in performance of sequences of movement, particularly if these have to be made in the absence of any external cues.
(6) Cerebellum is important for adapting movements to changes in feedback, such as using a computer mouse to move a cursor on the screen even though the movement of the hand is much less than the cursor on the screen. It is thought to do this by comparing the sensory inputs it receives with the outputs that caused the movement to occur and then to use this information to update the relationship between the commands to move and the expected sensory consequence.
(7) The basal ganglia automatise movement. They do this by analysing input from cortex and using it to predict likely future actions.

Although such an account is useful for explaining some of clinical features of lesions or disease, it fails to highlight the degree of overlap between functions in the different structures and the interconnections between them. In fact, PET and fMRI images during performance of even the simplest movement show that large areas of cortex and subcortex are active, consistent with the idea that any task requires the cooperation of a widely dispersed network of cells. Similarly, neurophysiological recordings have always shown that there are a small number of cells in any brain area that do not necessarily discharge in the "canonical" pattern typical of the majority of cells such as visually sensitive neurones in motor cortex. Such a dispersed organisation allows the CNS to reorganise after damage since damage to one structure rarely removes the only element capable of performing a certain type of calculation.

3. Spinal cord organisation

Recent work on development of spinal cord in mice models has suggested that location and types of neurone within the grey matter, as well as the connections that each receives depends to a large extent on the dorso-ventral and medio-lateral position of the progenitor cells of each subpopulation [7]. In the mouse the motoneurones that will innervate distal leg muscles are located dorsally in the ventral grey matter whereas the proximal motoneurones lie ventral. The fact that motoneurones innervating the same muscle lie close together increases the likelihood that they will receive common inputs. In addition they tend to be located near to other synergist muscles that also will share more of the input than motoneurones pools that are located at a distance. Motoneurone pools usually occupy several adjacent spinal segments, forming columns within a spatially segregated part of the ventral grey matter. Motor columns from synergist muscles likewise group together over several segments.

The terminations of sensory afferents that grow back to the spinal cord also seem to produce terminals and synapses that are position dependent. Thus inputs from the proximal muscles terminate more ventrally in the cord than inputs from distal muscles so that they tend to synapse with homonymous motoneurones. This organisation is complemented by a similar organisation of spinal interneurones, which also appear to develop, at least partially, according to their initial position in the cord. For example, Renshaw interneurones are located only in ventral parts of the spinal grey. Here they tend to receive inputs from and project to motoneurones that innervate proximal muscles with far fewer connections to distal motoneurones. The organisation of other groups of interneurones is less well studied, but work suggests that there may be over one hundred different types of neurone, each clustered within specific areas of cord and projecting to specific populations of motoneurones [7]. Position for them, as for motoneurones may

be an important factor in determining the inputs they receive as well as the output connections that they make.

It is likely that similar rules govern the organisation of the human spinal cord. In this case, however, motoneurones that innervate distal motoneurones lie laterally whereas those innervating proximal muscles are medial. Flexor motoneurones are dorsal to extensor motoneurones. This organisation then accounts for the termination pattern of the different descending motor systems. Those in the lateral columns, and in particular the corticospinal tract, tend to innervate distal muscles whereas those in the ventral columns innervate proximal motoneurones [2].

Almost all of the connections between descending tracts and motoneurones are via interneurones located among the motoneurones or in the intermediate grey matter. This means that inputs will tend to diverge and innervate more than one motoneurone pool. Indeed, each descending fibre may have branches at several segments in the spinal cord, innervating motoneurones throughout their spatially organised columns. Importantly, these interneurones will also receive inputs from other interneurones and sensory afferents which can then potentially control the degree to which descending input can access the motoneuronal output.

4. Comparison of spinal and cortical motor organisation

The spinal cord appears to have a highly patterned spatial organisation in which groups of motoneurones and interneurones with common projection targets are located in close proximity. This means that the inputs that project to spinal cord, which seem also to terminate in particular spatial locations, will recruit outputs in a relatively restricted pattern. Effectively this means that certain output patterns are "wired into" spinal cord organisation. This anatomy may well account for the patterned outputs that are often reported after intraspinal stimulation.

The organisation of the motor cortex is much more of a mosaic than that of the spinal cord [1]. Although groups of neurones that project to distal and proximal limb muscles are located in common areas of cortex, within those areas the outputs intermingle to a far greater degree than occurs in the spinal grey matter. For example, in the forelimb region of cortex, outputs to hand muscles can be spread throughout the area and can intermingle with flexor, extensor and synergist muscles in seemingly random patterns. Work suggests that although the groups of neurones with common output targets are more intimately connected than those that have different targets [8], this distributed organisation may provide the cortex with more flexibility than can occur in the spinal cord.

Many experiments in animals and in humans have shown that learning new tasks is accompanied by synaptic plasticity in the primary motor cortex [9]. This involves strengthening existing synapses and production of new synapses between inputs to and output from the cortex. Initially a large number of new connections are formed and then as skill becomes consolidated, the number is trimmed until only a small fraction of the initial numbers remain permanently changed [10]. The mosaic nature of the cortical circuits may allow a given input to connect potentially to a wide variety of output zones, and it may therefore be that the initial stages of learning are associated with an increase in this connectivity. As learning progresses, these connections can be trimmed back to the ones that are most effective in producing the movement that is required.

This flexibility in the cortical circuitry allows the brain to change the pattern of connections between inputs and outputs and thereby modulate the output of motor commands to the spinal networks. Interestingly, such plasticity is not easy to demonstrate in spinal networks, where the "wiring" appears to be much more stable. At one level this may be a useful distinction since if the lower level wiring changes, then all the motor programs sent down from a cortical level will be affected. It is probably better to maintain the lower level "hardware" relatively constant and change movement by changing the upper level "software" command structure. The result is a system that is flexible to a certain extent but which is limited in the final analysis by the imposed connectivity within the circuitry of the spinal cord.

5. Studying descending inputs to spinal cord in humans

It is possible to access corticospinal, reticulospinal and probable vestibulospinal pathways non-invasively in humans. The most commonly used method is transcranial magnetic stimulation (TMS) of the primary motor cortex [11]. This employs a large time varying magnetic field to induce electric current in the brain underlying a stimulating probe. The stimulus produces a stimulus similar to that from a conventional nerve stimulator (around 200 µs duration) which then activates axons of neurones in the brain. When held over the motor cortex it tends to activate presynaptic inputs to corticospinal output neurones which then cause contraction of muscles on the opposite side of the body. TMS does not stimulate as focally as a direct electrical stimulation of the exposed surface via a metal probe; however, it can distinguish between motor cortical output zones to hand, upper arm, trunk and legs very easily.

The muscular contraction produced by TMS is produced mainly through conduction in large diameter corticospinal neurones that have monosynaptic excitatory connections with motoneurones. However, there are also later effects that are best observed by using indirect methods (such as monosynaptic reflex testing) after giving TMS pulses that are below threshold intensity for eliciting direct EMG activity. These show that the initial excitation is followed by an immediate period of inhibition that is probably caused by activation of Ia inhibitory neurones in the spinal grey matter. After this there is a further period of increased excitability that could be due to activity in spinal interneuronal pathways, or to arrival of inputs travelling in smaller diameter, slowly conducting, corticospinal fibres. Reflex testing can also reveal corticospinal inputs to other interneurones such as the C3–C4 propriospinal neurones that innervate extensor muscles in the arm during reaching movements [12].

The input from a TMS pulse can be quite complex because it can recruit interneuronal activity within the cortex as well as the spinal cord. There are two other forms of stimulation that can avoid this complexity and activate corticospinal axons directly. They are transcranial electrical stimulation (TES) and cervicomedullary stimulation. TES was the first form of non-invasive brain stimulation that was used before the advent of TMS [13]. It employs a special electrical stimulator to deliver high voltage stimuli directly to electrodes attached to the scalp. If the anode is placed over the hand area of motor cortex and that cathode at the vertex, this tends to activate corticospinal fibres to the hand in the white matter underlying the primary motor cortex. Although successful the method is uncomfortable since the stimulus also causes local contraction of scalp muscles and pain.

Cervicomedullary stimulation uses a specially shaped TMS coil placed over the rear of the scalp to activate corticospinal tract fibres at the level of the medullary pyramids [14]. However, this is associated with strong contraction of muscles, in this case at the rear of the neck, which can cause some discomfort. Collision studies using TES indicate that cervicomedullary stimulation activates the same fibres as TES although the stimulation site is some 2 ms conduction time more caudal.

TES and cervicomedullary (CM) stimulation produce a single descending volley in large diameter axons with monosynaptic

input to spinal motoneurones. Taylor and colleagues have made use of these methods to investigate some of the physiology of this connection [15]. In particular they have found that it may be possible to increase the effectiveness of this connection by an LTP-like process. To do this, they used a spike-timing dependent procedure that is similar to that used in many animal studies to induce synaptic plasticity in CNS pathways. An electrical stimulus was given to a motor nerve to evoke an antidromic volley to the motoneurones and this was paired with a CM stimulus timed so that the efferent volley would reach the motoneurones before the antidromic volley. The pairs were repeated 50 times. For about 20–30 min after this procedure CM stimulation alone evoked large muscle responses than before conditioning, suggestive of an increase in excitability of the corticomotoneuronal synapse. If correct this may be a very useful way to increase the effectiveness of volitional inputs to motoneurones in patients with partially severed corticospinal pathways.

The properties of reticulospinal and vestibulospinal inputs to spinal cord have been studied in much less detail. The startle reflex is thought to be conducted in the reticulospinal system [16]. There is excellent evidence for this in rats; in humans the same is likely to be true since [1] startle can be observed in anencephalic children born with no cerebral cortex, and can even be exaggerated in some patients with dense motor stroke [2]; EMG studies of the spread of the startle reflex in healthy humans shows that the response begins in muscles innervated by caudal cranial nerves (sternocleidomastoid, XI nerve), spreading up the brainstem to innervate mentalis (VII nerve) and then masseter muscles (V nerve); some patients with excessive startle have lesions located in brainstem areas.

Consistent with a reticulospinal projection, the startle reflex primarily affects proximal muscles and is rarely seen, for example, in the hand. Although it is most prominent in flexor muscle, the distribution of the response varies with posture, in a manner that suggests that it always acts to maintain body stability whilst protecting the face and abdomen [17].

Finally, the vestibulospinal input to spinal cord can be activated with transmastoid "galvanic" electrical stimulation [18]. This consists of a DC current of around 1 mA applied to electrodes on the mastoid processes at either side of the head. The current polarises the afferent terminals on hair cells in the vestibular apparatus, causing an imbalance between the signals from the two sides of the head. This is interpreted as a rotation in the direction of the negative terminal (cathode). Thus, in a person standing upright and looking forwards, galvanic vestibular stimulation (GVS) causes a compensatory body sway towards the anode. Intriguingly, if the head is then rotated by 90° so that participants look directly towards the left or right, the sway is now in the posterior–anterior direction (again in the direction of the anode). The response to GVS therefore takes into account the position of the head in space relative to the base of support on the ground. Postural responses to GVS can be observed and may even be increased in patients with spinal cord injury and are normal after stroke [19,20]. Responses are also modulated during gait, being largest during stance, indicating that the inputs that are activated must converge on a common spinal premotor mechanism.

6. Conclusions

The motoneuronal outputs from cortex and spinal cord have quite different patterns of organisation. The cortex consists of a highly intermixed mosaic of small output zones whereas the motoneurones in the cord are located in clearly defined columns of cells, that all project to the same muscle. This may give a greater degree of flexibility between inputs to and outputs from the cortex. Learning new skills subtly changes the pattern of these connections by stimulating processes of synaptic plasticity.

Descending inputs to spinal cord show a highly divergent pattern of connections to many different motoneuronal pools. This distributed organisation is more robust to damage than highly dedicated systems, although it means that activation limited to individual muscles (or small groups) requires a highly patterned descending drive. Apart from some direct monosynaptic corticospinal terminations on motoneurones (corticomotoneuronal), all descending inputs converge onto spinal motoneurones which can be viewed as a final filter on the primary motor command.

Techniques now exist in humans for stimulation of corticospinal, reticulospinal and vestibulospinal inputs to cord, allowing us to study interactions with spinal motoneurones and interneurones.

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