Motor Areas of the Cerebral Cortex-New Vistas

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= ABSTRACT=

On the basis of morphological and functional studies, it is now established that there exist multiple motor representation areas in the frontal lobe of subhuman primates. Recent development of analysis on cerebral cortical organization in human subjects, utilizing novel techniques of PET and MRI, provides evidence of corresponding motor areas. Each area has its unique sources of inputs from the thalamus and from other parts of the cerebral cortex. To understand functional roles of these multiple motor areas, it is necessary to study neural activity while subjects are performing a variety of motor tasks. In view of high accuracy in spatial and temporal resolution, the analysis of single cells in relation to specific aspects of motor behavior remains to be a powerful research technique. It is with this technique that a number of novel concepts on functional roles of multiple motor areas have been proposed.

Key Words: Motor areas, Frontal lobe of subhuman primates, PET, MRI

About forty years ago, Woolsey and his collaborators (Woolsey et al, 1952) published results of their extensive mapping studies on cortical motor areas in the Old World monkeys that resulted in the two "simiusculi", that have been reproduced in numerous textbooks. Although their achievement in establishing separate motor areas (primary motor area (MI), and the supplementary motor area (SMA)) in the cerebral cortex and in determining basic topographical organization was astonishing in view of only crude techniques available at that time, their famous drawing must now be corrected in many ways. First of all, the existence of the premotor cortex (PM) just rostral to the MI in the lateral hemishpheric surface is established (Wise, 1985). Second, two new motor areas have been defined in the cingulate cortex (CMAr and CMAc) (Barbas and Panya, 1987) (Dum and Strick, 1991a). In addition, an area

just rostral to the supplementary motor area is now defined as the presupplementary motor area (preSMA) (Matsuzaka et al, 1992). Furthermore, it has recently been proposed that each of MI, PM, and CM can be divided into more than two subareas (Humphrey and Tanji, 1991). The PM, for instance, is now viewed to be composed of dorsal (PMd) and ventral (PMv) parts (Kurata, 1993). It seems to be a trend in this research field that cortical motor areas are rapidly growing in number, just as are the cortical visual areas.

ANATOMICAL CONNECTIONS

All cortical motor areas of primates receive both corticocortical and thalamocortical afferent inputs. Sources of afferent inputs are different among different areas, though they may share common inputs to a certain extent. Corticocortical inputs to the MI originate from

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the SMA, the PM, the primary and secondary somatosentory cortex (SI and SII), and parietal area 5 (Chavis and Pandya, 1976; Strick and Kim, 1978; Dum and Strick, 1991b; Kunzle, 1978; Leichnetz, 1986; muakkassa and Strick, 1979; Pandya and Kuypers, 1969). The input form the cingulate motor areas to the MI has also been reported (Dum & Strick, 1991b; Martino and Strick, 1987; Muakkassa & Strick, 1979; Shima et al, 1991). The SMA is previously thought to receive afferents from the lateral part of the prefrontal cortex (around the principal sulcus). However, it is now made clear that the prefrontal cortex projects to the preSMA (Luppino et al, 1990), that in turn projects to the SMA. Thus, there is a pathway of information flowing from the prefrontal cortex -preSMA -MI. The projection from the principal sulcal area to the PM exists, but limited to a small portion in the posterior bank of the arcuate sulcus. The posterior parietal cortex projects to the ventral part of the PM (PMv). This pathway seems important in visual guidance of arm movements. Fig. 1 shows some of the flow of information viewed to be essential for intercommunication of cortical areas used for motor control.

The subcortical inputs from the thalamus to different motor areas has been extensively studied (Kievit and Kuypers 1977; Strick 1976; Jones et al, 1979). Although the exact origin of the thalamocortical inputs to each of multiple motor areas is still under a considerable dispute, different areas receive inputs from separate portions in the thalamus. As for the input to the MI, it has been a general belief that a subdivision of the ventrolateral thalamus, ventralis posterior lateralis pars oralis (VPLo) is the major source of projection to MI (Darian-Smith et al, 1990; Ghosh et al, 1987; Holsapple et al, 1991; Matelli et al, 1989; Schell and Strick 1984). However, recent studies have found that the projection from another subdivision, ventralis lateralis pars oralis (VLo) is also substantial (Hoover and Strick 1991). This issue is of critical importance, because VPLo is known to be a major thalamic projec-
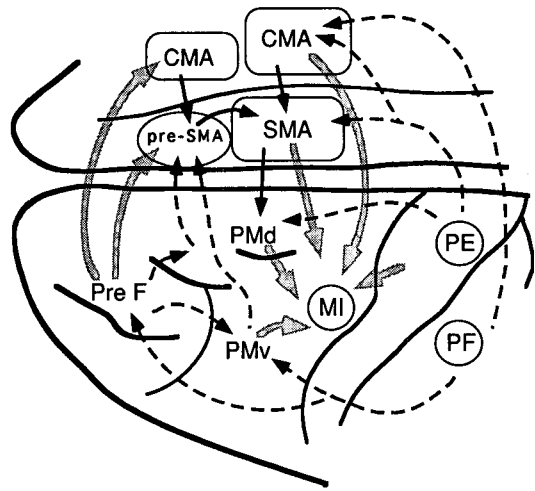

Fig. 1. Schematic drawing of the flow of information through corticocortical connections, directed toward the primary motor cortex(MI). Illustration is limited to main pathways only. Abbreviations: MI, primary motor cortex; SMA, supplementary motor area; pre-SMA, pre-supplementary motor area; CMA, cingulate motor area; PMd and PMv, dorsal and ventral premotor cortex; PreF, prefrontal cortex; PE and PF, superior and inferior parietal association cortex.

tion site of the cerebellar nuclei, whereas VLo is known to be the projection site of the basal ganglia. Thus, according to the present knowledge, both cerebellar and basal ganglia pathways are able to gain access to the MI through the thalamus. On the other hand, The SMA receives information predominantly from the basal ganglia by way of the subnucleus VLo, and some from VLm (Schell & Strick 1984). The PMd receives its main input from rostral VLc, while the PMv receives inputs from the subnucleus X. This means that the cerebellar nuclei send strong information to the PMv. Much more information is needed as for subcortical input sources of the cingulate motor areas. The sources of subcortical inputs are summarized in a simplified diagram in Fig. 2.
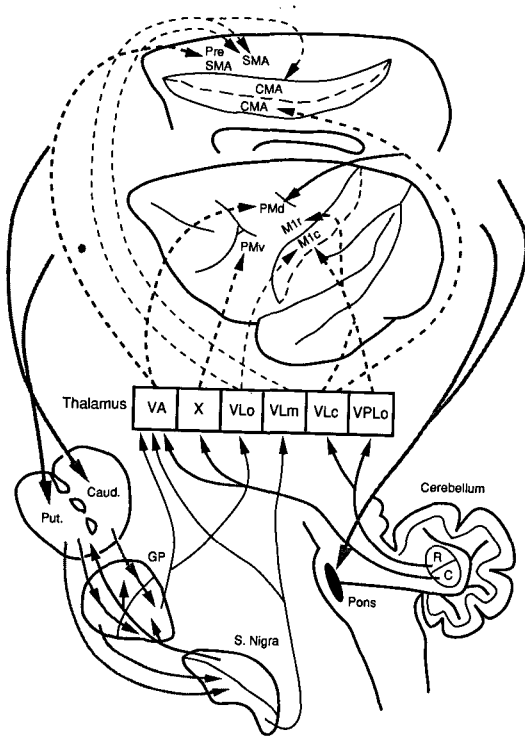
Fig. 2. *Schematic drawing of subcorticocortical pathways connecting the basal ganglia and cerebellum, by way of the thalamus, to motor areas. This figure is shown to facilitate general principles of subcortico-thalamo-cortical connections. Only principal pathways are included. Some controversies still exist concerning details of pathways. VA, X, VLo, VLm, VLc, VPLo are all subnuclei in the ventral thalamus. Put, putamen; Caud, caudate nucleus; GP, globus pallidus; S. Nigra, substantia nigra; MIr and MIc, rostral and caudal part of the primary motor cortex.*

ANALYSIS OF NEURONAL ACTIVITY IN RELATION TO VOLUNTARY MOVEMENTS

Movement-related neuronal activity in different motor areas

It is well known that the neurons in the multiple nonprimary motor areas exhibit activity changes closely related to the execution of movements (Wiesendanger, 1981). In relation to simple motor tasks (like pushing keys or moving a handle), the activity appear to be similar to that in the primary motor area (Tanji, 1984). Comparisons have been made of the neuronal activity onset In the SMA and MI, and in the PM and MI. In some reports, the activity onsets in SMA and PM were found earlier than in MI, but in other reports they were not distinguishable (Tanji and Kurata, 1983). It seems that the comparison of neuronal onset times in possible only when the animal's motor behavior is well controlled and stable (Tanji and Kurata, 1989). In recent studies, it was found that the movement related activity was also found in such newly defined motor areas as the rostral and caudal cingulate motor areas (Shima, et al, 1991), and the preSMA (Matsuzaka, et al, 1992). It is important to note that neuronal activity in each of the nonprimary motor areas is related to distal, as well as proximal, limb movements (Tanji and Kurata, 1979). Therefore, it is a mistake to regard either SMA or PM as areas primarily related to postural control.

In addition to the movement related activity starting immediately preceding the movement onset, the neuronal activity in the period of motor preparation of 'motor set' have been found (Tanji and Evarts, 1976). Although the activity of this type has been studied most extensively in the PM (wise and Mauritz, 1985), it can also be found in other motor areas (Tanji and Kurata, 1985). Thus, neuronal activity in multiple motor areas seems to play at least some part in the preparation for and execution of relatively simple movements.

Different properties of neuronal activity in nonprimary motor areas from that in primary motor area

The above findings led to a view that multiple motor areas may be operating in a similar way in parallel. However, this view does not explain the reason why individual areas have different input sources with corticocortical and thala mocortical connectivity. Indeed, differenc-

es in neuronal activity properties among indi-
vidual areas have increasingly been found.
Even in relation to relatively simple motor
tasks, quantitative analysis revealed differences
of activity properties of PM and SMA on one
hand, and MI on the other. In PM, only a mi-
nority (10~15%) of cells displayed a discharge
pattern that was significantly correlated with
such movement parameters as velocity and ac-
celeration (Kubota and Hamada, 1978). Simi-
larly in SMA, the activity onset of only a small
number of cells was correlated with the animal'
s reaction time (Tanji and Kurata, 1982). This
is in contrast to the abundance of MI neurons
exhibiting significant correlation to motor pa-
rameters. In both PM and SMA, neuronal
activity time-locked to visual or auditory sig-
nals have been found (Kurata and Tanji 1985).
Such signal-locked responses are rare, if any, in
MI. Furthermore, with regard to the presence
or absence of a selective relationship to a limb
movement initated differently, significant dif-
ferences have been found. In MI neurons, if a
particular neuron is active prior to a move-
ment, the amount of activity changes remain
similar regardless of whether the movement is
triggered with visual or auditory signals, or ini-
tiated by the animal without sensory trigger-sig-
nals. In contrast, in many SMA and PM neu-
rons, the movement-relations is selective. For
instance, a neuron may be active with a visual-
ly triggered movement, but inactive with an au-
ditory triggered movement. Another (PM or
SMA) neuron may be active when a movement
is self-initiated, but not when the movement is
triggered by any sensory signals (Kurata and
Tanji 1986). These findings indicate closeness
of MI neurons to output structures in the
motor pathway, as opposed to closeness of PM
and SMA neurons to input sources providing
information for movement initiation.

Furthermore, the neuronal activity in the
SMA and PM was found fundamentally differ-
ent from that in MI in relation to selection of
ipsilateral, contralateral, or bilateral hand
movements (Tanji et al, 1987; Tanji et al,
1988).

DIFFERENCES OF ACTIVITY
PROPERTIES IN PM AND SMA

Although PM and SMA have a number of
activity properties in common, their functional
differences have been inferred from a phyloge-
netic study (Sanides 1964), from histological
studies employing tracer techniques, from clini-
cal observations on localized cerebral lesions
(see(Goldberg 1985) for review), and from
studies utilizing measurements of cerebral
motor potentials (Lang et al, 1991), as well as
regional cerebral blood flow (Roland et al,
1980). On the basis of these reports, a
hypothesis has been proposed that SMA takes
part in self-initiated movement whereas PM is
involved in movements guided or triggered by
sensory signals (Eccles, 1982; Rizzolatti et al,
1983 ; Goldberg, 1985). The validity of this
hypothesis has been studied extensively in our
laboratory. In early stages of experiments, rela-
tively simple motor task was employed to com-
pare single cell activity in PM and SMA
(Okano and Tanji 1987). Key-press movements
were either triggered by a visual signal or initi-
ated in a self-paced manner. It was found that
differences were not sufficiently dramatic to
support a simple dichotomy hypothesis that
SMA primarily takes part in self-paced move-
ment and PM is only involved in visually trig-
gered movement.

In the second series of experiments, we se-
lected a more demanding motor task of sequen-
tial movements to study possible differences in
the two areas (Mushiake et al, 1991). In one
condition of this experimental paradigm (visu-
ally triggered task), monkeys had to touch three
pads placed in a front panel by following lights
illuminated individually. In the other condition
(internally guided task), they had to remember
a predetermined sequence and press the three
pads without visual guidance. A majority of
PM neurons were more active during the visu-
ally triggered task. In contrast, a majority of
SMA neurons were more active during the in-

ternally guided task. These findings indicate that the PM is more important in guiding movements on the basis of sensory (especially visual) cues, whereas the SMA is more involved in memory-guided motor behavior.

INVOLVEMENT OF NMDA AND NON-NMDA GLUTAMATE RECEPTORS IN MOTOR-TASK RELATED ACTIVITY IN MI

It is well known that glutamate is a major ex-citatory neurotransmitter in the mammalian CNS and that postsynaptic receptors for gluta-mate can be classified into different subtypes. The role of the NMDA receptors has been a subject of particular interest in relation to their involvement in plastic changes in synaptic transmission. However, it was not known to what extent the NMDA receptors (as opposed to non-NMDA receptors) are involved in pro-viding excitatory activity in the motor areas of behaving animals. To answer this question, we compared the responsiveness of neurons in the monkey MI to iontophoretically applied APV (NMDA antagonist) and CNQX (non-NMDA antagonist) (Shima and Tanji 1993). We found that APV often blocked the activity of neurons that received excitatory input from the SMA and that were active during a preparatory peri-od of a forthcoming movement. On the other hand, MI neurons having excitatory inputs from the SI, and exhibiting movement-related activity were often blocked by CNQX. These findings suggest that NMDA and non-NMDA subtypes of glutamate receptors in MI neurons are differentially involved in the preparation and execution of movement.

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