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Abnormal sensory gating in basal ganglia disorders

Abstract Basal ganglia encompass four to five distinct loops to allow parallel processing of information. Among them, the most intensively studied is the motor loop, which includes two distinct *direct* and *indirect* pathways. The direct pathway exerts facilitatory influence upon the motor cortex, whereas the indirect pathway exerts an inhibitory effect. Overall, this dual system provides a center(excitatory)-surround-(inhibitory) mechanism to focus its effect on selected cortical neurons, and several lines of evidence suggest that this center-surround mechanism is used to focus the output on a specific group of muscles required for performing a specific task. This operation is made possible through opening the sensory channel for the expected sensory feed-back afferents during movement. Thus, one of the important functions of basal ganglia seems to be the gating of sensory input for motor control. Dystonia may be caused by a mismatch between sensory input *versus* motor output, and parkinsonism may be viewed as a disorder of gain control of this sensorimotor integration.

Key words dystonia · Parkinson's disease · sensorimotor integration · somatosensory evoked potentials · gating · motor loop

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Introduction

Basal ganglia is a term to denote subcortical nuclei, consisting of the striatum (putamen or PUT and caudate nucleus or CN), the pallidum (internal and external globus pallidus or Gpi and GPe), sunthalamic nucleus (STN), and substantia nigra (pars compacta or SNc and pars reticulata or SNr).

These structures are situated intermediate between the cerebral cortex (mainly frontal lobe) and the thalamus, and have dense fiber connections between them. Notably, these connections form four to five distinct loops or circuits to allow *parallel processing* of information through them [1]. Here we focus subsequent discussion on the *motor loop*.

The basic anatomical connection of the motor loop is depicted in Fig. 1A. There are two distinct pathways in the loop; *direct* and *indirect*. The direct pathway is driven by dopaminergic D1 receptor and disinhibits the powerful inhibition of Gpi/SNr upon VL thalamus with the net result of facilitatory influence upon the motor cortex. The indirect pathway, on the other hand, exerts the net inhibitory influence. Overall, this dual system forms a *center-surround* mechanism to focus its effect on selected cortical neurons (Fig. 2). Although putative transmitters, inhibitory or excitatory nature of these projections and their receptors are mostly known, the functional role of the loop in motor control is not precisely understood.

Physiological studies in monkeys and intra-operative recordings in man document a large amount of unit activities responding to sensory inputs, when they are relevant to motor control [7, 11]. Numerous neurons in the supplementary motor or premotor cortex discharge in response to a sensory cue long before the movement on-

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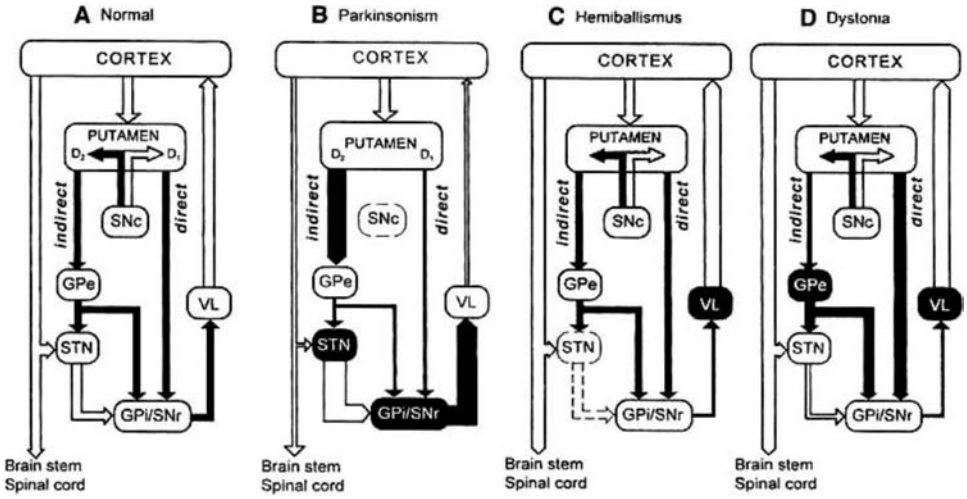

Fig. 1 Overview of the motor loop according to the Alexander and Crutcher model

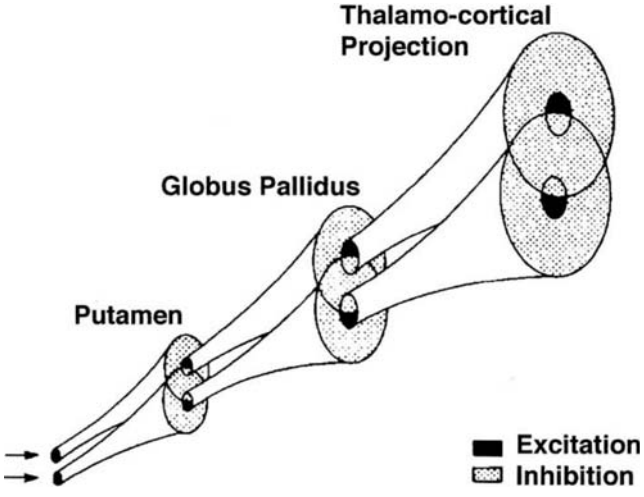

Fig. 2 Center(excitatory)-surround(inhibitory) mechanism in the motor loop

set, and they appear to encode a specific movement parameter. Such *set-related* activities or *context-dependent* discharges are also seen in the basal ganglia [15]. Despite these, the exact pathway through which the sensory input reaches the basal ganglia remains elusive [8].

Pathophysiology of Parkinson's disease, hemiballism and dystonia

Parkinson's disease is a degenerative disorder that primarily affects nigrostriatal dopaminergic neurons. The biological mechanism of the selective vulnerability of this system is still unknown, but a number of hypotheses have been advanced, including environmental or genetic susceptibility of these neurons to impaired oxidative phosphorylation. Clinically, the disease is characterized by *akinesia* (lack or poverty of movement), *bradykinesia* (slowness of movement), *rigidity* of muscles, disturbed postural reflex and tremor. Hallett and Khoshbin [4] studied the physiological mechanism of bradykinesia using surface EMGs in a ballistic elbow flexion movement. They found a fractionated pattern of agonist-antagonist muscle bursts (Fig. 3), which were actually repetitions of the normal triphasic (agonist-antagonist-agonist) muscle activation. The basic abnormality, therefore, seemed smaller-than-normal scaling of movement excursion at each burst, which was compensated by repeating the normal triphasic pattern. Intriguing is the benefit of the external sensory cues for initiating and performing movements (*kinesie paradoxale*). Auditory or visual input dramatically corrects the small excursion of movement. This suggests that abnormal scaling of movement is secondary to disturbed utilization of proprioceptive sensory input, but not to exteroceptive input disturbance. In support of this idea, Walshe [14] demonstrated that blockade of muscle afferents with local anesthetic normalized the small excursion of elbow movement in a boy with post-encephalitic Parkinsonism (Fig. 3).

Fig. 1B illustrates the mechanism of clinical symptoms in Parkinson's disease. Because the striatonigral dopaminergic projection acts as inhibitory input to the indirect pathway (D2 receptor) and as excitatory input to the direct pathway (D1 receptor), its absence leads to the overactive indirect pathway and hypoactive direct pathway. The overall effect is excessive inhibitory influence upon the motor cortex, which underlies bradykinesia or akinesia.

Hemiballism is a hyperkinetic state caused by a focal lesion in the subthalamic nucleus (STN), giving rise to a thrust-like or violent involuntary movement of the limbs contralateral to the lesion. This is explained as shown in Fig. 1C. Because of the lack of facilitatory in-

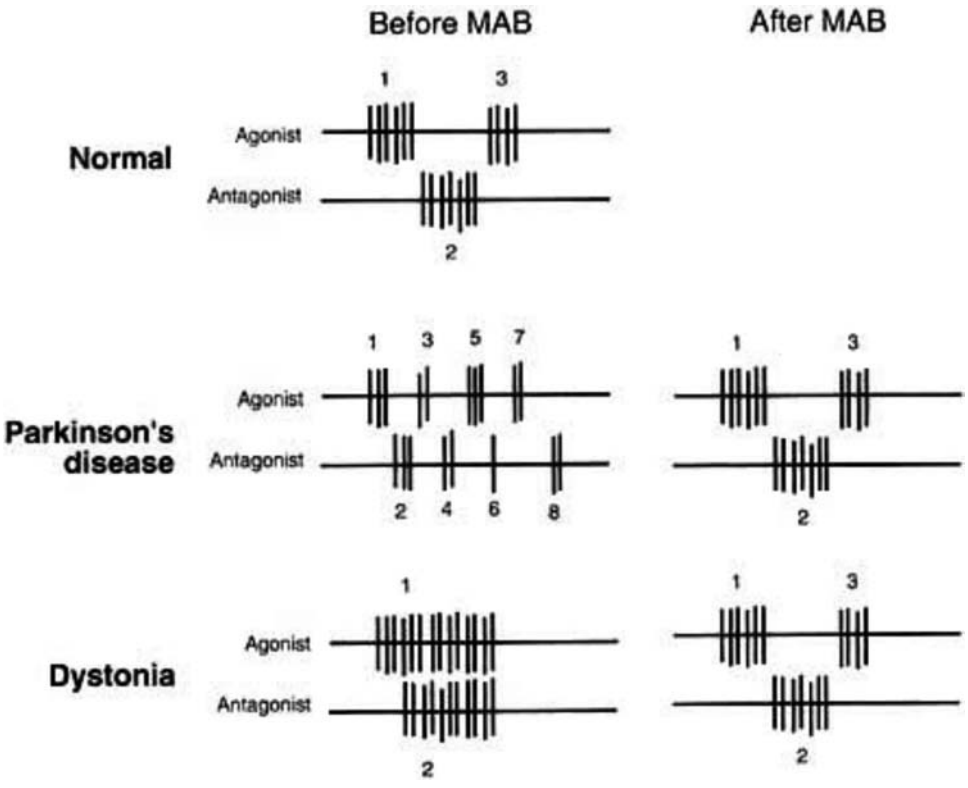

Fig. 3 Representative surface EMG recordings in ballistic elbow flexion movement from agonist (biceps brachii) muscle and antagonist (triceps brachii) muscle before (left) and after (right) muscle afferent block (MAB)

put from STN, tonic discharges of GPi/SNr are lost. Since the latter normally inhibits VL thalamus, the net effect is to disinhibit the thalamocortical projection, leading to the hyperkinetic state.

Dystonia is defined as a syndrome of sustained muscle contractions frequently causing twisting or repetitive movements or abnormal postures. Examples of focal type include blepharospasm, spasmodic torticollis (or cervical dystonia) and writer's cramp (or hand dystonia). One of the clinical features is *sensory trick*, in which a tactile or proprioceptive sensory input to the body part nearby dramatically improves abnormal posture or contraction. In case of blepharospasm, reducing the amount of light or brightness is equally effective. This phenomenon clearly points to sensory-motor mismatch in dystonia [5].

Another important feature in dystonia is that it often affects only a specific task (*task-specificity*). Writer's cramp usually begins as a task-specific disorder only affecting writing, but may later involve other tasks as well. Other task-specific dystonias include pianist's cramp or other musician's cramp, typist's cramp and telegrapher's cramp, all of which affect activities of frequently or repetitiously used motor acts.

Dystonia is regarded as one of the basal ganglia disorders, because focal lesions in the motor loop cause dystonia in the limbs contralateral to the lesion (*hemidystonia*), and because trihexyphenidyl, an anti-cholinergic agent frequently used for Parkinson's disease, is also effective in treating this condition. Of note is that some dystonias such as writer's cramp affect only specific task (*task-specificity*). Their symptoms are mostly *stereotypical*: the neck rotation in spasmodic torticollis is always in the same direction, and the abnormal contraction in writer's cramp remains the same. Electromyographic analyses showed simultaneous contraction of agonist and antagonist muscles (*co-contraction*) or contraction of surrounding muscles (*overflow*) (Fig. 3).

These findings suggest that dystonia is a disorder of a frequently used motor program or *subroutine*, in which motor output is matched to a fixed sensory input [8]. This idea is also supported by the finding of the abolishment of dystonic muscle contractions by blocking muscle afferents (Fig. 3) [6]. This motor subroutine is probably stored as connectivities in the motor loop. If the surround inhibitory mechanism in the motor loop is disrupted (as depicted in Fig. 1D), the lack of inhibition of antagonist or surround muscles causes co-contraction or overflow phenomena.

Sensory function of the basal ganglia viewed from the clinical domain

As reviewed above, the diagram shown in Fig. 1 gives an account of the mechanism of action of therapeutic

agents or surgical options. However, it remains unsolved how these multiple inhibitory connections affect movement or what kind of information processing takes place.

Although the basal ganglia are commonly regarded as a center for motor control, the benefit of external sensory cues in Parkinson's disease and the sensory trick in dystonia highlight sensory aspects implicated in these basal ganglia disorders. Animal studies indicate that sensory inputs reaching the basal ganglia significantly differ from those in the lemniscal exteroceptive system in that they show encoding of information that appears to be relevant to motor control [8]. Indeed, the basal ganglia appear to 'gate' sensory inputs at various levels [12, 13].

Stimulation of the basal ganglia inhibits auditory and visual cortical evoked responses. Lemniscal and extraleminiscal components of the somatosensory system are modified by the basal ganglia. For example, the sensory responsiveness of second order neurons in the trigeminal sensory nucleus is altered by activation of CN or GP [12]. Lesions of the basal ganglia mostly affect automatic movements that need sensory guidance. It is, therefore, likely that the basal ganglia control automatic or highly trained movements in relation to relevant sensory inputs [3, 10].

Tasks impaired in writer's cramp or other occupational cramps are among these. In accord with this, hand representation in the somatosensory cortex was found disorganized in writer's cramp [2]. Head control and blinking are other examples of such automatic movements impaired in spasmodic torticollis or blepharospasm. These motor programs or *subroutines* are encoded in the association of a fixed sensory input and a motor output [5]. There are now converging pieces of evidence indicating that this sensory gating for motor control is lost in dystonia [9] and is scaled less than normal in Parkinson's disease.

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