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VIEWPOINT

Parkinson's Kinesia Paradoxa Is Not a Paradox

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Kinesia paradoxa is defined as "the sudden transient ability of a patient with Parkinson's disease (PD) to perform a task he or she was previously unable to perform."[1] Classic accounts report how persons with PD were seen running when triggered by a life-threatening event (fire, earthquake). Even some wheelchair-bound patients with advanced disease could run.[2] Apparently, these patients could use locomotor abilities no one suspected to be present.[3] Similarly, it is frequently seen that patients have difficulty walking slowly, yet are able to run swiftly when chasing a ball, for example, in tennis or hockey.

As first author of this article, I am living with PD (7 years), and my professional specialty is the neural control of gait, which is also the topic of this viewpoint. In particular, as a patient with PD, I am fascinated by the fact that I am very poor at walking slowly yet can still manage to play some tennis and run for about 1 hour a day. This has brought my attention to kinesia paradoxa. Here we will argue that kinesia paradoxa may have been viewed too narrowly in the context of life-threatening situations. Would it not be great to be able to understand kinesia paradoxa and use this knowledge to help persons with PD to increase mobility and physical activity? The striking feature is the contrast between a malfunctioning, slow system and the apparently normal functioning of a faster system. This viewpoint has a focus on locomotion, but paradoxical kinesis can affect other motor acts as well (eg, gripping, throwing). In terms of locomotor circuits, the solution may be simple: perhaps there are multiple locomotor systems.

The idea that there are several alternative motor pathways is not new. Evidence for alternative motor paths was obtained in studies on reactions to gait perturbations.[4] Many stepping reactions are so fast that they have to bypass the usual pathway (over the visual cortex and the [pre]motor areas) and instead have to rely on shorter pathways bypassing the primary motor cortex. For example, there is a fast pathway from primary visual cortex to parietal cortex to the pons. In addition, there are fast subcortical paths possibly involving the colliculus and/or the cerebellum.[4,5] Similar alternative locomotor circuits may exist for kinesia paradoxa. Under given circumstances, alternative locomotor circuits may be able to take over when the primary locomotor path is defective. According to the available literature, there are at least 2 possible candidates for these alternative pathways, and they are not mutually exclusive.

Let us first consider the basics. It has long been known that human locomotion depends critically on spinal central pattern generators (CPGs)[6] that in turn rely on the activation of the brainstem mesencephalic locomotor region (MLR). The MLR in turn depends on corticostriatal input, particularly when locomotion needs to be initiated or altered (eg, a change in gait speed).[7] Electrical stimulation in the MLR region elicits locomotion of cats in the absence of connections to the cortex.[8] Recent evidence indicates that the authors of that study presumably stimulated primarily 1 part of the MLR, namely, the cuneiform nucleus (CnF), and not the other part (the pedunculopontine nucleus [PPN]).

This evidence for a primary role of the CnF in triggering locomotion derives from c-Fos immunohistochemistry in combination with electrical stimulation of the

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MLR.[9] Other convincing data were obtained from experiments using optogenetics, a method that optically stimulates selective groups of genetically identified neurons. In brief, the technique relies on "opsines," proteins that are light sensitive. These opsines are made specific for a particular transmitter, allowing the specific activation of neurons using that transmitter. When the technique was applied to glutaminergic cells in the MLR, it was discovered that both parts of the MLR could induce slow walking, but only the activation of glutaminergic cells in 1 part of the MLR (in the CnF) made the animal run, as if to escape some threat.[10] In contrast, activation of the glutaminergic cells in the PPN always made the animals to walk slowly, as in exploration of the environment.

Hence, there is good evidence for 2 locomotor systems, both converging in the MLR.[11] These 2 systems were termed "the emotional (ventral) locomotor system" and "the cognitive (dorsal) locomotor system."[12] Both rely on input from the basal ganglia, but it is plausible that the cognitive pathway is more vulnerable in patients with PD. If so, then these 2 locomotor pathways have important implications for the treatment of gait disorders in PD if methods are found to exploit the relatively intact emotional pathway. As Naugle and colleagues stated, "It is plausible that activation of affective circuits could bypass impaired basal ganglia systems and provide an alternative route to "energize" locomotor centers and drive the CPGs."[13] The situation is reminiscent of blindsight in which some form of vision persists even when the primary visual pathway is lesioned.

Knowledge of the various locomotor pathways has important clinical consequences. For example, recently it was already argued that deep brain stimulation (DBS) should target the CnF, the emotional locomotor path, rather than the cognitive part of the PPN.[14] It was shown that there is evidence that DBS of the CnF is more effective to improve freezing of gait compared to PPN stimulation. Similarly, in another study the most effective site for gait improvement in persons with PD was with DBS of the CnF.[15] Furthermore, histological verification has shown that in many successful cases, the presumed DBS stimulation in the PPN was in effect stimulation of the CnF,[16] although its exact mechanism needs to be unraveled. The superiority of the CnF for DBS does not exclude the possibility that genuine PPN stimulation can also be effective in DBS (for a review, see reference 17) The PPN is part of the ascending reticular activating system and can have an effect on heightened arousal and indirectly on increased speed for example. In addition, there is evidence for cells in the PPN that are responsive both for wakefulness and locomotion.[18] Finally, PPN DBS can restore StartReact in patients with PD with severe gait freezing, and this could be considered as overcoming a motor block akin to the action of kinesia paradoxa.[19] The effectiveness of CnF may derive from its role in the noradrenergic system involved in "fight or flight."[20] Connections from the CnF exist with the periaqueductal gray, amygdala, hippocampus, prefrontal cortex, and locus coeruleus.[21,22] The locus coeruleus projects to the pontine reticular formation, which connects to the spinal CPGs,[12] but there is also the potential of a direct noradrenergic projection from the locus coeruleus to the spinal cord.[23] These pathways were to be expected because the application of noradrenergic drugs induces locomotion in spinal animals.[24]

In a study on compensation strategies for walking it was observed that some patients with PD used running to compensate for gait difficulties.[3] It was argued that a generic increase in attention may be involved in kinesia paradoxa (eg, the ability to run while perceiving severe difficulties to walk).[3] Such a generic increase in attention involves a noradrenergic cortical and subcortical network, which includes the CnF.[25] Hence the issue is not whether the CnF underlies either fast locomotion or high arousal because both functions may overlap but, rather, the issue is primarily how to recruit the CnF in situations that are less dramatic than "fight or flight."

A key to understanding how a switch from 1 (slow) system to another (fast) is made was provided by recent optogenetic data on cells from the brainstem dorsal raphe nucleus (DRN). This nucleus receives commands from the CnF and forms the basis of the serotonergic (5-hydroxytryptamine) system, known to play an important modulatory role in the control of locomotion.[22] In a recent study, it was shown that stimulation of the dorsal raphe serotonin neurons suppressed locomotion when there was no threat but facilitated running when a shock had to be avoided.[26] Hence DRN activation can have opposite effects of locomotion depending on context. These authors pointed to paradoxical kinesia as a typical example of a switch induced by behavioral environment. Furthermore, it was shown that DRN stimulation by itself (without MLR involvement) can initiate gait (picrotoxin injection),[27] thereby demonstrating the potential of alternative pathways.

A second alternative explanation for kinesia paradoxa is that the cerebellum is strongly involved because many of the kinesia paradoxa examples involve cue-induced movements (eg, hitting an approaching ball).[1,2] Basic research supports a role of the cerebellum in goal-directed gait. Electrical stimulation of a region in the cerebellum was shown to induce locomotion in the decerebrate cat.[28] Furthermore, the cerebellum has the appropriate afferents and efferents to underlie cue-guided behavior.[1] In humans, it is of interest that the cerebellar locomotor region is strongly activated during running imagery, even in the absence of cues.[29] When people are asked to imagine running, they strongly activate the cerebellar locomotor region. It should be added

that explaining kinesia paradoxa does not necessarily require making the choice between the noradrenergic or cerebellar hypothesis because these ideas are not mutually exclusive. Indeed, Mori and colleagues showed that stimulation of the CnF and cerebellum MLR can have cumulative effects.[28] Hence both systems may be involved with perhaps a dominant contribution of the adrenergic system in arousal and a leading role of the cerebellum in cue-induced motion.

With respect to cue-induced locomotion, it should be mentioned that there is also evidence for a switch between alternative pathways in the basal ganglia. In a previous communication,[3] it was pointed out that patients with PD tend to have the greatest deficit in the posterior putamen (linked to automatic movements), while keeping the potential to use the rostro-medial striatum, a structure known to be concerned with goal-directed movements (as reviewed in Redgrave and colleagues).[30] In line with this, it is recognized that patients with PD can walk more easily with attention (goal-directed) than without active control of steps (automatically).[31] Interestingly, Redgrave and colleagues also pointed out the relative sparing of a third modular part of the basal ganglia, the limbic territories (next to the automatic and the goal-directed section).[30] Activation of these limbic parts (fed by the mesolimbic dopamine system and the limbic cortex) could "energize" the emotional locomotor system, as is indeed observed in kinesia paradoxa. Hence, cue-induced movements—which are known to increase gait speed and reduce freezing of gait[32]—may induce a switch to a different basal ganglion module: from automatic to goal-directed or to emotional, thereby relying increasingly on spared parts of the locomotor system.

Whatever the correct kinesia paradoxa mechanism, it seems worthwhile to consider the possibility of using kinesia paradoxa as a rehabilitation tool, especially in light of the overwhelming evidence for the beneficial effects of exercise in the early stages of PD.[33-36] The underlying mechanisms of the benefit are only beginning to be revealed. For example, mice with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)–induced PD show the potential of some neurons to replace the deficient dopaminergic input to the striatum.[37] In addition, in PD rats, it was shown that treadmill running is beneficial by inhibiting apoptosis in the cerebellum.[38] The application of cues to elicit kinesia paradoxa in rehabilitation may lose its effectiveness over time, but it is yet unclear whether this is attributed to habituation or whether the alternative locomotor circuits become affected when PD progresses. Habituation may be prevented by introducing unexpected events (which is, for example, possible when using virtual reality).[39]

Kinesia paradoxa is only a paradox for those who believe that there is just 1 motor system. However, there is enough evidence that there are several locomotor systems and therefore there is no real paradox in kinesia paradoxa, instead there is the observation that kinesia paradoxa shows that effective use can be made of alternative systems when the primary motor system fails.[3] In nonaffected humans, these parallel systems coexist as well, but their expression overlaps better than in persons with PD, where the contrast between the deficient slow system and the spared fast system leads to the perception of an apparent paradox.[40] We argue that kinesia paradoxa can be successfully used as a compensation strategy and exercise tool in the early and moderate phases of PD.

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