

Université de Montréal

**Contribution of the subthalamic nucleus to visually guided
locomotion**

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Résumé

Les ganglions de la base (GB) jouent un rôle important dans le contrôle locomoteur. Ceci est illustré par les troubles locomoteurs dont souffrent les patients atteints de maladies dégénératives qui affectent les GB, telles que la maladie de Parkinson, caractérisées par de petits pas lents et traînants, ainsi qu'un gel de la marche (*freezing of gait*). Une structure centrale dans les GB est le noyau sous-thalamique (NST), de par son rôle de structure d'entrée et ses projections vers le globus pallidus. Cependant, la nature de la contribution du NST au contrôle de la locomotion, ainsi que les caractéristiques de son activité cellulaire durant la marche, sont peu connues.

Afin de mieux comprendre cette contribution, nous avons examiné les propriétés de l'activité neuronale du NST lors de la locomotion non-obstruée et celle sous guidage visuel. Ainsi, nous avons effectué des enregistrements neuronaux chez un chat intact, entraîné à marcher régulièrement sur un tapis roulant et à franchir des obstacles se déplaçant à la même vitesse. Nous avons enregistré 40 cellules montrant une activité reliée au mouvement du membre antérieur, dont 30 ont montré une activité phasique au cours de la locomotion non obstruée liée aux différentes phases du cycle de la marche, principalement la phase de balancement. Au cours de la modification volontaire de la marche, un groupe de 37/40 cellules, incluant certaines qui étaient modulées pendant la locomotion non-obstruée, ont changé leur fréquence de décharge par rapport à l'obstacle. Ces changements étaient principalement des augmentations de fréquence, mais parfois des diminutions ou une diminution suivie d'une augmentation. Ces modifications se produisaient soit avant l'enjambement de l'obstacle (*step-advanced*), soit lors de l'enjambement de l'obstacle (*step-related*). L'activité des cellules *step-advanced* était indépendante des membres (*limb-independent*), tandis que celle des cellules *step-related* était spécifique aux membres (*limb-dependent*).

Cette étude est la première à examiner les caractéristiques de décharge du NST lors de la marche et montre que cette structure contribue au contrôle de la locomotion non obstruée ainsi que la modification volontaire de la marche, en jouant un rôle dans la planification et l'exécution de cette dernière.

Mots-clés : Ganglions de la base, noyaux sous thalamiques, locomotion, modification volontaire de la marche, locomotion sous guidage visuel.

Abstract

The Basal ganglia (BG) plays an important role in locomotor control. This is emphasized by the impaired walking of patients with neurodegenerative disorders that affect the BG such as Parkinson's disease. One important structure in the BG is the subthalamic nucleus (STN), which acts as an input structure for the BG and projects to its output structures. Although the STN has been shown to display movement-related activity during reaching, the nature of its contribution to the control of locomotion, together with the characteristics of its neural activity during locomotion, is poorly known.

In order to better understand this contribution, we examined the properties of the neural activity in the STN during unobstructed and visually guided locomotion. To do so, we recorded single neurons in an intact cat trained to walk steadily on a treadmill and to step over obstacles attached to the treadmill belt and moving at the same speed. We recorded 40 neurons which activity was related to the movement of the forelimb during the task. We found that during unobstructed locomotion, many of these cells (30/40) showed phasic step-by-step modulation of their activity pattern, mostly during the swing phase. Most of these swing-related cells discharged throughout the swing phase with no relationship to changes in the pattern of different muscle groups. During voluntary modifications of gait, 37/40 cells, including both cells that were and were not modulated during unobstructed locomotion, changed their firing rate in relationship to the step over the obstacle. The changes observed were mostly increases of activity, but a few cells showed decreases of activity and some showed a decrease followed by an increase of activity. These changes occurred either before the modified step and were classified as step-advanced activity, or they occurred during the modified step and were classified as step-related activity. Step advanced cells mostly showed limb-independent activity, while step related cells showed limb-specific activity.

This is the first detailed account of the contribution of the STN to the control of locomotion and our results indicate that the STN is involved in the control of both unobstructed and visually guided locomotion. The results suggest that during unobstructed locomotion, the STN contributes to the general control of the limb trajectory and to both the planning and execution of voluntary changes of gait.

Keywords: Basal ganglia, subthalamic nucleus, locomotion, voluntary gait modification, visually guided locomotion.

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Liste des abréviations

BG: Basal Ganglia

CMA: Cingulate motor areas

co: Contralateral

CPG: Central Pattern Generator

EMG: Electromyographic

EN: Entopeduncular

FOG: Freezing of gait

FRA: Flexor Reflex afferents

GABA: γ -Aminobutyric acid

GP: Globus pallidus

GPe: Globus pallidus pars externa

GPI: Globus pallidus pars interna

GTO: Golgi tendon organ

i: Ipsilateral

i.v: Intravenous

LVST: lateral vestibulospinal tract

MI: Primary motor cortex

MLR: Mesencephalic locomotor region

MPTP: 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine

MRF: Medullary reticular formation

MSN: Medium spiny neurons

MT: Movement time

MVST: Medial vestibulospinal tract

PD: Parkinson's disease

PEH: Peri-event histogram

PMd: Dorsal premotor area

PMRF: Pontomedullary Reticular Formation

PMv: Ventral premotor area

PPC: Posterior parietal cortex

PPN: pedunculopontine nucleus

RN: Red nucleus

RST: Reticulospinal tract

SMA: Supplementary motor cortex

SNpc: Substantia nigra pars compacta

SNpr: Substantia nigra pars reticulata

STN: Subthalamic nucleus

VST: Vestibulospinal tract

To you mom, for the masters you never got to finish.

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General introduction

Survival critically relies on an animal's ability to navigate its environment in order to search for food, escape predators and reproduce. Since the 1900s, extensive studies have been conducted to better understand the control of locomotion by investigating the contribution of various parts of the nervous system to the production of stepping. Sherrington was the first to recognize the importance of the spinal cord in producing a locomotor rhythm through what he described as spinal reflexes. From his findings, multiple lines of research have contributed to the understanding of the neural networks behind the basic control of locomotion, which stem from the spinal cord and of brainstem nuclei. However, these structures alone cannot produce visually guided and voluntary gait modifications of locomotion. Such skilled motor behaviors are controlled by a complex network of supraspinal structures that has yet to be fully understood. Most of the major advances relative to this network have concentrated on the contribution of different cortical areas, particularly the primary motor cortex and more recently the posterior parietal cortex. Although clinical evidence also strongly suggests that the basal ganglia play an important role in controlling locomotion, there is little information concerning this contribution at the single neuron level. It is therefore in an effort to better understand the role of the basal ganglia, and more specifically the subthalamic nucleus in the control of visually guided locomotion, that this research project was conducted.

I. Literature review

1. Neural control of locomotion

Although locomotion may seem like a simple and stereotypical motor task, it requires a complex and dynamic neural control that involves multiple structures of the central nervous system, each controlling a specific aspect of the gait. In order to produce the basic pattern of stepping, a complex signal is produced by central pattern generators at the spinal level, which then activates the appropriate muscles. When external perturbations occur, reflex adjustments and postural adjustments triggered by proprioceptive and cutaneous inputs are superimposed on the centrally generated pattern to maintain balance when walking. When negotiating obstacles on a path, visual information is essential and is processed through complex cortical and subcortical networks to guide the gait modifications needed. In this section, we will be discussing all of these processes and the neural structures involved in the generation of the basic locomotor pattern as well as voluntary gait modifications in response to environmental cues.

a. Basic locomotion

i. Half centre theory

The first studies suggesting that the generation of locomotion was intrinsic to the spinal cord were conducted by Sherrington (1910a, 1910b). He observed that after a brief period of spinal shock following a spinal cord transection, the hindlimbs were capable of executing ‘reflex stepping’ which strongly resembled a natural step. In decerebrate acute spinal preparations, stepping movements were induced when the animal was lifted and hindlimbs were left suspended. He also showed that stepping could be evoked by continuous, non-rhythmical stimulation of the skin or of the spinal cord. With his results, Sherrington showed that the rhythmic movements elicited by stimulation were intrinsic to the spinal cord. He described the basic motor pattern for walking as a “chain of reflexes” native to the spinal cord, where the activation of one group of muscles would trigger the contraction of another muscle group until the end of the step cycle. Furthermore, this “chain of reflexes” would be evoked by proprioceptors and result in an alternation of flexion and extension movements.

This work was complemented by Graham Brown, who described independently the potential existence of a spinal neuronal network for locomotion. He challenged the idea of reflexes as a source of stepping when, under some conditions, he found that alternating activation of flexor and extensor muscles could be evoked after deafferentation of the studied limb. In one of his experiments, spinal cats with a complete transection of all lumbosacral dorsal roots showed alternating rhythmic contraction of flexor and extensor muscles (Brown 1911, Brown 1914). In addition to that, his study of locomotor movements in fetal cats showed their ability to produce rhythmic progression, both alternating and in-phase (Brown 1915). Brown concluded from his results that rhythmic progression could occur in the absence of any external rhythmic stimulation.

Overall, he concluded from his studies that reflexes rising from sensory afferents were not necessary to the production of the locomotor rhythm and suggested that the spinal cord possessed an intrinsic mechanism that could produce the alternating activation of flexor and extensor muscles in stepping. He further showed that this intrinsic mechanism was innate rather than a learned capability of the central nervous system. He then proposed a ‘half-center’ model comprised of two groups of spinal neurons, reciprocally organized and mutually inhibiting each other, capable of producing the basic rhythm for locomotion.

This idea received little study until it was revitalized by Lundberg and his associates who provided the first direct evidence of Graham Brown's model by using extracellular recordings of flexor and extensor interneurons (Jankowska et al 1967a, Jankowska et al 1967b, Lundberg, 1965). They identified segmental pathways, composed of interneurons located in the lumbar segments of the cord (specifically in the lamina VII) activated by high-threshold afferents (flexor reflex afferents, FRA), that were organized in accordance with Brown's half-center hypothesis. These FRA pathways, normally inactive in spinal cats, became active following intravenous (i.v) injection of monoaminoxidase inhibitors and L-3,4-dihydroxyphenylalanine (L-DOPA). In this preparation, they observed that single trains of FRA stimulation could evoke rhythmic activity in flexor and extensor nerves (Lundberg 1979) and proposed that the spinal pathways activated by these FRA responses represented the rhythm generator for spinal locomotion (Lundberg 1979). Lundberg and Engberg (1962, 1969) also analyzed the step cycle in unrestrained walking cats and observed that extensor muscle

activity started before the foot touched the ground, concluding that the generation of the alternating pattern of activity in contralateral flexor and extensor muscles was not due to reflexes, but rather centrally programmed in the spinal cord.

Following these findings, Lundberg and Engberg (1969) further suggested that intrinsic limb reflexes “sculpted” the basic rhythmic activity produced by the spinal cord, as the half-center hypothesis could not account for the complexity of the observed locomotor pattern. Their studies on the pattern of afferents coming from muscle spindles to motor nuclei led them to conclude that proprioceptive reflexes play a role in “assisting stepping “as proprioceptive reflexes modify a simple centrally generated program to result in the detailed locomotor pattern observed in intact cats (Engberg & Lundberg 1969, Lundberg 1969).

ii. Central pattern generators

Although the experiments of Graham Brown showed that locomotor movements could occur after dorsal root transection, the degree of normality of the pattern was open to debate, since no objective inspection of the coupling between muscles had been conducted. This issue was addressed by Grillner and Zangger (1975) who examined the locomotor pattern in chronic and acute spinal cats after injection of a noradrenergic precursor (DOPA) or agonist (Clonidine). They showed that, after transection of all dorsal roots in such preparations, a complex pattern of rhythmic alternating movements was obtained during (bilateral or sometimes unilateral) stimulation (5-100 Hz) of cut dorsal roots (Grillner & Zangger 1974, Grillner & Zangger 1975). According to their experiments, the activity in flexors and extensors was clearly reciprocal (Grillner & Zangger 1974). The normality of the locomotor activity was demonstrated in this deafferented preparation by objective inspection of the locomotion using EMG recordings from individual muscles. Such activity could also be evoked after curarization, which excludes the possibility that any phasic sensory activity reaches the spinal cord (Grillner & Zangger 1974, Viala & Buser 1971). Further, the persistence of complex activity patterns following bilateral deafferentation of the hindlimbs in decerebrate cats performing locomotor movements showed that the isolated spinal cord deprived of descending control and of phasic sensory input contains sufficient neuronal elements to produce a complex motor output (Grillner & Zangger 1974, Grillner & Zangger

1975, Grillner & Zangger 1979). These neural elements, likely organized in groups of premotor interneurons, were termed central pattern generators (CPGs) (Grillner 1981, Grillner & Wallen 1985). Further evidence of centrally generated locomotor patterns was presented by Pearson and Rossignol (1991) who recorded the fictive locomotor pattern in cats previously subjected to a thoracic transection (T13).

iii. Interlimb coordination

In order to generate quadrupedal locomotion, the movement of the four limbs must be coordinated in order to maintain equilibrium. The question of whether this coordination is achieved by one CPG controlling four limbs, or by separate CPGs controlling each limb and synchronized through connections, has been thoroughly investigated. Results of multiple studies have suggested that each limb is controlled by its own CPG, which can generate the appropriate motor pattern for its limb (Grillner 1981). In cats walking on a split-belt treadmill with different speeds in the left and right sides, the stance and swing phases of the “fast” leg and the “slow” leg are adjusted separately according to the speed of the treadmill (Forssberg et al 1980b, Frigon et al 2013, Halbertsma 1983). More direct evidence of the existence of separate CPGs for each limb was provided by a study in the spinal rabbit, in which central locomotor activities were recorded from nerves of the fore- and hindlimbs (Viala & Vidal 1978). The locomotor pattern of the limbs was studied in cervical transected preparation (C1), then after a second low thoracic transaction (Th12). The study found that the rhythm of the hindlimbs stayed unchanged after the thoracic transection, but that the burst frequency of forelimb flexors was significantly reduced. Viala and Vidal concluded that both the cervical and the lumbosacral spinal cord have distinct locomotor pattern generators, but that hindlimb CPGs might be driving the rhythm of forelimb GPGs.

Analyzing more complex patterns of locomotor activity such as backward walking and climbing led to the suggestion that a CPG could exist for each joint of each limb (Grillner 1981). Activity from these “units” would be tightly coupled during normal walking but individually controlled by supraspinal input to produce different types of motor patterns. In turns, the locomotor system could be conceived as a group of unit burst generators that,

through connections, could control the limbs to produce a variety of locomotor patterns such as walking forward, backward, as well as different types of gait such as trotting and galloping.

In conclusion, animals with spinal transection can generate the essential and basic features of the step cycle as well as coordinating the limbs and shift from one type of gait to another. However, although the spinal cord plays a major role in the production of basic locomotion, some aspects of the locomotor control are lacking (Grillner 1975). These aspects will be discussed in the next sections.

iv. Adaptive capacities

The central pattern generator is regarded as a central framework for the production of stereotyped locomotor movements. These movements, however, must also be adapted to the environment and compensate for various types of external perturbations or other stimuli. Such adjustments are primarily the result of reflex responses, and therefore are intrinsic to the spinal cord. They arise from somatosensory inputs that produce a range of behaviourally appropriate adjustments to the movements of locomotion. In considering the role of somatosensory input in stepping regulation, Sherrington made a distinction between proprioceptors, located in muscles and joints, and exteroceptors, located in the skin (Sherrington 1910).

Proprioceptors regulate timing of stepping

The implication of proprioceptors in the entrainment of locomotor rhythm was first proposed by Sherrington (1910a) when he saw that stepping movement could be induced simply by lifting the thorax of a spinal cat or dog. Since the removal of the skin did not abolish the response, he concluded that this was due to proprioceptors located in the limbs. Later studies showed that spinal cats walking on a treadmill can adapt their locomotor rhythm to the treadmill speed (Budakova 1973, Forssberg & Grillner 1973, Forssberg et al 1980a, Forssberg et al 1980b). One explanation for these phenomena was that the hip joint angle, signaled by afferents from the hip, was an important factor for swing initiation (Andersson et al 1978, Grillner & Rossignol 1978). These afferents were activated as a result of the periodic stretch of muscles around the hip (Andersson & Grillner 1983, Kriellaars et al 1994) and were identified as being produced by Ia afferents of flexor muscles located around the same joint (Hiebert et al 1996). Other muscle spindles were also shown to modulate the locomotor

rhythm based on studies in decerebrate cats that revealed that phasic sensory signals from specific muscle spindle afferents such as Ia from ankle extensor (Guertin et al 1995) and II from flexors (Perreault et al 1995) can entrain and reset the rhythm to extension. These studies support the idea that Ia afferents from primary spindle endings of flexor muscles around the hip as well as Ia from ankle extensor and II from flexors contribute to regulating the stance-to-swing transition (Guertin et al 1995, Perreault et al 1995). A recent study examined the locomotor capabilities of genetically modified mice lacking group Ia/II afferents and found that the absence of proprioceptive feedback from muscle spindles affected the locomotor pattern due to the change of timing of muscle offset during the swing phase (Akay et al 2014). Overall, these studies show that afferent group Ia/II from muscle spindles contribute to regulating the stance-to-swing transition.

Although Grillner and Rossignol showed that a necessary condition for the swing phase to be initiated was that the hip be extended beyond a critical angle, Duysens and Pearson (1980) noticed that it wasn't a sufficient condition for swing initiation. Indeed, they found that stepping could be inhibited by holding the ankle in a flexed position, even when the hip was extended beyond the angle at which swing would normally be initiated. They suggested that proprioceptors signaling increased load of the extensor muscles could inhibit the central generation of swing. When group I afferents are stimulated during the extensor burst in decerebrate anesthetized cats with a spinal transection at Th12, extensor activity was prolonged while initiation of the following flexor burst was delayed (Conway et al 1987). This effect was mediated at pre-motoneuronal levels resulting from inhibition of centers generating flexor bursts and excitation of centers generating extensor bursts. Conway and colleagues then proceeded to activate Ia and Ib afferents in isolation and found that the main input to rhythm generators arose from Golgi Tendon Organs (GTO) Ib afferents. In the same study mentioned previously (Akay et al 2014), feedback from muscle spindles played a more critical role in pattern generation when feedback from GTO Ib afferent was absent, indicating that both afferents provide essential and distinct functions in the patterning of locomotor output.

Overall, proprioceptive inputs are important for the stance to swing transition. During stance, group Ia and II inputs are activated by extensor muscle stretch, group Ib inputs are activated by load signals coming from the GTO, and afferents signaling hip joint angle all

maintain the stance phase by activating extensor muscles. At the end of the stance phase, when the hip is at its optimal angle and the ankle starts to be unloaded, flexor activity is facilitated and the swing phase is initiated.

Cutaneous stimulation causes phase dependent responses

The neural control of locomotion in animals incorporates mechanisms for coping efficiently with obstacles or painful stimuli occurring at any moment of the locomotor cycle. These mechanisms generate patterns of responses that must be adapted to the ongoing phase of locomotion. Evidence that such mechanisms exist within the spinal cord was first provided by Forssberg (1979) who showed that spinal animals can execute what he termed a “stumble-corrective reaction” during stepping. In the spinal cat, tactile stimulation of the dorsum of the hindlimb paw during the swing phase induced short latency responses in flexor muscles, while the same stimulation during the stance phase induced a marked extensor activity (Forssberg 1979). These responses were abolished after applying a local anesthetic (Xylocaine) to the dorsum of the foot, ruling out activation of muscle or joint receptors as a source of the response (Forssberg et al 1977). Similar reflexes were recorded in the hindlimb of conscious cats, which were abolished after anesthesia of the dorsum of the foot (Prochazka et al 1978). These studies showed that light cutaneous stimulation applied to the dorsum of the paw during the swing or the stance phase yields two opposed responses which occur in synergy with the ongoing locomotor phase.

This switch between extensor and flexor responses was also observed in forelimb muscles when electrical stimulation was applied to the superficial radial nerve of unrestrained cats walking on a treadmill (Drew & Rossignol 1985, Drew & Rossignol 1987). These experiments revealed that the observed phase dependent responses did not necessarily always match the period of locomotor activity, indicating a central modulation of cutaneous reflex responsiveness.

These results show that the “stumbling corrective reaction” does not simply result from the activation of motoneurons that are discharging when the stimulus is applied. Instead, cutaneous inputs during locomotion evoke complex organized responses that are well integrated into the step cycle and recruit flexors and extensors in a very precise sequence, determined by CPG responsiveness to cutaneous reflexes. This emphasizes the importance of

cutaneous afferents in contributing to the control of motor responses to unexpected perturbations.

Cutaneous information in highly demanding motor tasks

It has been shown that cutaneous denervation does not prevent the expression of the locomotor rhythm in undemanding situations such as level walking on a treadmill although cutaneous denervation does cause temporary and minor deficits such as foot drag during swing, and a higher lift during stepping (Bouyer & Rossignol 2003, Sherrington 1910a). However, the deficits become more apparent in more demanding locomotor situations such as walking across a horizontal ladder (Bouyer & Rossignol 2003). These results suggest that cutaneous afferents from the paw are used for fine control of foot placement in locomotor conditions demanding a precise positioning of the foot. Moreover, cats that underwent full cutaneous denervation quickly recovered their locomotor pattern. However, when spinalized, the same cats showed persistent deficits in foot placement and weight bearing of the hindlimbs (Bouyer & Rossignol 2003). This indicates that cutaneous feedback is essential for the expression of spinal locomotion.

b. Supraspinal control of locomotion

Besides the basic locomotor pattern produced at the spinal level, well-controlled locomotion requires three principal functions (Grillner 1976); 1) initiation of locomotion 2) modification of locomotor posture to adapt to different requirements, and 3) adaptation of each step to the environment. The main structures controlling initiation and posture will be discussed in this section.

i. Initiation

To initiate locomotion, a signal has to be produced somewhere in the nervous system to activate the appropriate structures. Acutely prepared decerebrate animals for example (precollicular-post- mammillary section), do not walk spontaneously, suggesting that the brainstem rostral to the lesion contains a structure essential for locomotor initiation (Wetzel & Stuart 1976). In order to find structures responsible for locomotor initiation, a research group which included Shik, Arshavsky, and Orlovsky, analyzed the brainstem contribution to the initiation of locomotion by systematically applying electrical stimulation throughout the

mesencephalic, pontine and medullary regions of the brainstem (Arshavsky & Orlovsky 1986). An important finding of this group was that tonic stimulation of a region just below the inferior colliculus in supported decerebrate cats triggered controlled quadrupedal locomotion (Shik & Orlovsky 1976). Increasing the strength of the stimulus increased the speed and eventually produced a transition from trot to gallop (Shik 1966). This effect was also seen in the absence of afferent feedback during fictive locomotion (Jordan et al 1979), showing that stimulation of this region is sufficient to produce rhythmic activity in motoneurons in the lumbar spinal cord without any need for afferent inputs. They termed this region the mesencephalic locomotor region (MLR) which was later identified as the cuneiform nucleus and the pedunculopontine nucleus (PPN) (Grillner et al 1997, Jordan et al 1979, Takakusaki et al 2004).

However, the MLR doesn't directly activate the CPG, as it does not project to the spinal cord. Rather, it is thought that the action of the MLR is exerted through the medullary reticular formation (MRF) (Bayev et al 1988, Steeves & Jordan 1984). Anatomical evidence for this connection was presented by Garcia-Rill and his colleagues in a study using anterograde tracing, showing that the MLR projected to the reticular formation (Garcia-Rill et al 1983). Other studies have shown that cooling of the MRF blocks MLR induced locomotion (Shefchyk et al 1984) and electrical stimulation of MRF in combination with treadmill movements can induce locomotion (Garcia-Rill & Skinner 1987, Mori 1987). The locomotor initiating signal is then transmitted to the spinal cord through the reticulospinal tract that descends in the ventrolateral region of the spinal cord as demonstrated by the fact that destruction of this part of the spinal cord can prevent MLR induced locomotion (Mori et al 1992, Steeves & Jordan 1980).

ii. Posture

Postural control is an essential element of locomotor control. On the one hand, animals need to produce sufficient muscle tonus in antigravity muscles to maintain an adequate weight support, and on the other, they need to be able to maintain equilibrium in the face of perturbations.

Although the neural mechanisms controlling these postural adjustments are not fully understood, studies have shown that lesions in low thoracic level (T11 or T13), restricted to the ventral and the ventrolateral part of the spinal cord (containing the reticulospinal tracts (RST) and the vestibulospinal tract (VST) cause major postural deficits and in some cases rendered cats unable to support their weight or walk on their hindlimbs (Brustein & Rossignol 1998). These finding indicated that the specific brainstem structures from which the RST and the VST originated play an important role in postural control.

The vestibular system is important for maintaining weight support and equilibrium primarily by modifying the excitability of extensor and antigravity muscles, but also through inhibition of reciprocal flexor muscles that constitute mainly axial and proximal limbs muscles. This modulation of muscular tonus is controlled by medial and lateral (Deiters') nuclei which receive vestibular information and projects to muscles in the neck, trunk, and limbs through the lateral vestibulospinal tract (LVST) and the medial vestibulospinal tract (MVST). The LVST mainly controls extensor muscles and axial muscles, but also ipsilateral and contralateral flexor muscles through its projections in the ipsilateral cervical and lumbar spinal cord, allowing the body to maintain an upright posture. The MVST mainly innervate neck extensor muscles and lateral neck motoneurons. It activates neck muscles to counter head movement caused by acceleration, allowing the head to stay stable (Markham 1987).

The Pontomedullary-Reticular-Formation (PMRF), which projects to the spinal cord through the RST, is the other principal structure responsible for postural control during movement (Mori 1987, Mori et al 1992). Postural control is facilitated by reticulospinal neurons (RSN) that project to both cervical and lower levels of the spinal cord through the RST and establish connections with spinal interneurons and motoneurons activating both flexor and extensor muscles (Peterson et al 1975, Peterson et al 1979). During locomotion, stimulation of the PMRF in decerebrate (Drew & Rossignol 1984, Orlovsky 1972a) and chronic cats (Drew 1991, Drew et al 1986) evokes EMG responses in flexor and extensor muscles that are reciprocal, phase dependent and adapted to the locomotor rhythm (Drew & Rossignol 1984). In addition, because the PMRF receives strong projections from the primary motor area of the cat, it was suggested that cortico-reticulospinal projections to the RS neurons are part of the neural pathway that integrates motor commands and postural adjustments

(Drew et al 2004, Matsuyama & Drew 1997, Matsuyama et al 2004, Rho et al 1997). The PMRF is also thought to play a role in the control postural adjustments accompanying voluntary movement, such as voluntary gait modification to step over an obstacle (Prentice & Drew 2001).

c. Voluntary gait modification

When navigating uneven terrain, animals frequently have to avoid or step over obstacles. For this voluntary adaptation to happen, visual information about the object is used to produce an appropriate motor program that constitutes planning and executing the appropriate gait modification. In the next section, we will discuss some important structures that are involved in each of these two processes.

i. Execution

Motor cortex

It is when anticipatory locomotor adaptations dependent on visual information are needed that the cortex plays an essential role in locomotor control. Indeed, inactivation of the motor cortex (Beloozerova & Sirota 1988, Eidelberg & Yu 1981) or transaction of its efferent pathway, the pyramidal tract (Liddell & Phillips 1944) or of the corticospinal tract (Jiang & Drew 1996) causes very limited motor deficits during unobstructed treadmill. Nonetheless, cells in the motor cortex are rhythmically active and were suggested to contribute to the step-by-step control of locomotion, particularly in regulating the transition period between stance and swing during unobstructed locomotion (Armstrong & Drew 1984a, Armstrong & Drew 1984b, Armstrong & Drew 1985, Beloozerova & Sirota 1988, Orlovsky 1972c, Rho et al 1999).

However, lesions to the motor cortex have much more serious consequences when animals are required to negotiate obstacles in their path. For example, Magoun and Ranson (1938) reported that large, bilateral lesions of the cortex rostral to the ansate sulcus resulted in an inability of cats to “scramble over the rungs of a low stool in their path.” Similarly, Liddell and Phillips (1944) emphasized that a unilateral pyramidotomy left the cats unable to walk along a narrow beam or a horizontal ladder because they were placing their foot too far

forwards, a motor symptom referred to as hypermetria. These motor symptoms persisted in these cats even when they resumed their ability to walk on flat ground. Similar deficits were described by Beloozerova and Sirota (1993) who reported that cats knocked over obstacles placed in their path following cortical ablation. Based on these observations, it seems that for what might be called 'skilled' locomotion, in which the feet must be guided towards specific points in the environment, the integrity of the motor cortex and the corticospinal tract is essential.

Furthermore, studies in a variety of challenging locomotor tasks including walking on circular or horizontal ladders, or stepping over barriers or obstacles, have shown that motor cortical neurons, including those neurons that project towards the spinal cord via the pyramidal tract, significantly change the phase and/or magnitude of their discharge activity when gait has to be modified (Amos et al 1990, Beloozerova & Sirota 1993, Drew 1993, Drew et al 2008a, Drew et al 1996).

The motor cortex, therefore, plays a role in the execution of gait modifications and is involved in specifying limb trajectory and paw placement (Drew et al 2008a, Drew et al 2008b, Krouchev & Drew 2013, Krouchev et al 2006). Changes in limb trajectory are likely the result of the modification of the activity of groups of synergistic muscles active at different times during the gait cycle (Drew & Marigold 2015).

Red Nucleus

The red nucleus (RN) gives rise to the rubrospinal tract (RST) which descends to provide excitatory synaptic terminals at all segmental levels of the cat cord. In general terms, the pathway is flexor-facilitatory (Shapovalov 1975) and microstimulation of the RN in mesencephalic and thalamic cats as well as in intact cats causes responses preferentially in physiological flexor muscles during the swing phase (Orlovsky 1972c, Rho et al 1999).

Lesion studies in the RN have shown that destruction of this structure, especially in the caudal magnocellular part, causes minor deficits such as a slight unsteadiness in gait as well as dysmetria and ataxia (Evans & Ingram 1939, Ingram et al 1934, Ingram et al 1932, Mussen 1927) and therefore does not play a major role in the in generating the basic locomotor synergy. However, Ingram and Ranson (1932) reported stronger deficits when the cats walked

in a cluttered environment, indicating an increased loss of control in a more challenging context. This comment suggests that the RN, like the motor cortex (see previous section, motor cortex), might contribute more strongly to the regulation of locomotion when the cat has to adapt its gait to the environment.

Recording studies have shown that rubrospinal neurons are modulated phasically during unobstructed locomotion, mainly at the end of stance and during the swing phase (Orlovsky 1972b), and increase their discharge frequency during voluntary gait modifications (Lavoie & Drew 2002) in a similar manner to cells in the motor cortex (Drew 1993). From their results, Lavoie and Drew suggested that both structures contribute to the modifications of the pattern of EMG activity that are required to produce the change in limb trajectory needed to step over an obstacle. However, the multiple activations of some neurons time-locked to both contralateral and ipsilateral swing suggest an additional role for the RN in regulating intra- and interlimb coordination. Indeed, while cells in the motor cortex are correlated almost exclusively to the patterns of muscle activity in the contralateral limbs, cells in the RN show correlations with both contralateral and ipsilateral muscles. Moreover, unit recording and microstimulation studies indicate that the RN may also influence the activity of extensor muscles at the end of the swing and during stance phase (Lavoie & Drew 2002, Rho et al 1999). Taken together, these studies strongly suggest that the motor cortex and the RN may play a complementary role in controlling the execution of voluntary gait modifications during visually guided tasks.

ii. Planning

Animal behavior is expressed through two types of movements; reflexive movements generated in response to external or internal stimuli, and voluntary movements that are a “centrally generated intention to act” (Rizzolatti et al 2014). This intention to act could be induced by external stimuli and the goal to interact with it or avoid it. In order for this goal to be achieved, the animal has to plan a series of voluntary movements (Rizzolatti et al 2014). The precise and complex planning of these movements requires the contribution of multiple cortical and subcortical structures including the premotor cortex (PMC), the basal ganglia (BG) and the posterior parietal cortex (PPC). The contribution of only one of these structures (the PPC) has been studied with respect to the planning of visually-guided locomotion.

Posterior parietal cortex

The posterior parietal cortex (PPC), which includes area 5 and 7 is located within and caudal to the ansate sulcus in the cat and projects strongly to all regions of the motor cortex (Andujar & Drew 2005, Andujar & Drew 2007). Moreover, functionally the PPC is located between the primary visual areas and the motor cortex and has been shown to integrate motor and visual information (Beloozerova & Sirota 2003). These projections provide the anatomical basis through which the PPC could directly modulate visually guided motor activity.

Bilateral lesion of the anterior and middle suprasylvian cortex (that includes area 5) in cats trained to press on a moving lever resulted in significant deficits in the ability of the cat to perform the task, although its ability to press on an immobile lever was unaffected (Fabre & Buser 1981) which suggests a role in the spatial adjustment of visually guided arm movements. During visually guided locomotion, unilateral lesion of the PPC in freely moving awake cats resulted in errors in the accuracy of paw placement reflecting errors in motor planning (Lajoie & Drew 2007).

Moreover, neural recording studies (Andujar et al 2010, Beloozerova & Sirota 2003) have shown that cells in the PPC discharge before and during gait modification. In many of these cells, the increase of discharge was best related to the first limb stepping over the obstacle, regardless of whether the limb was ipsilateral or contralateral to the recording site. Because the increase occurred several steps after the obstacle became visible to the animal, this limb independent activity is thought to represent a motor plan that would be later executed when the cat steps over an obstacle. In order to better understand the nature of this motor plan, neural activity in the PPC was recorded when visual input during the approach of the obstacle was briefly interrupted (Marigold & Drew 2011). They found that the largest proportion of recorded cells did not change their discharge following occlusion and concluded that the PPC is not simply involved in processing visual information, but is rather involved in the “visuomotor transformations necessary to plan gait modifications” (Marigold & Drew 2011). Later they suggested that this signal could contribute to the estimation of the position of the limbs and body relative to the location of the obstacle (Marigold & Drew). These studies show that the PPC contributes to the planning of locomotion by providing an estimate of the position of an animal with respect to objects in its path.

2. The Basal Ganglia

As presented in the previous section, locomotor control requires the contribution of multiple structures that project directly to the spinal cord to modulate the pattern produced by central pattern generators. However, the cerebellum and the basal ganglia (BG) are known to exert their effect indirectly. The former has received extensive study over the years (Armstrong & Marple-Horvat 1996, Armstrong 1988) while the contribution of the latter is little studied, despite the major deficits in locomotion observed in patients with Parkinson's disease (see section 2.b). The present study forms part of a program to better understand the contribution of the basal ganglia to the control of locomotion in the intact cat. In the following sections, I detail the organization of the basal ganglia as well as information concerning its contribution to motor control. The emphasis is placed on the subthalamic nucleus which is the subject of the current report.

a. Structure and pathways of the basal ganglia

The basal ganglia (BG) are a group of sub-cortical nuclei spread across the telencephalon, diencephalon, and midbrain (Lanciego et al 2012). In primates, they are composed of the striatum (divided into the caudate nucleus and the putamen), the globus pallidus (GP, composed of the external and internal segment; GPe and GPi), the substantia nigra (SN, composed of pars reticulata and pars compacta; SNpr and SNpc) and the subthalamic nucleus (STN) (Fig.1). In the cat, the GPi is referred to as the entopeduncular nucleus (EN) and the GPe as the globus pallidus (or pallidum). In the text that follows, the terminology of the primates will be used.

The striatum, pallidum, STN, and SN are strongly interconnected through intrinsic BG pathways that transmit information from the afferent to the efferent targets of the BG. Afferent projections to the BG originate from various cortical areas that have different functions. Information from each type of area is transmitted through BG pathways to the BG output structures and is sent back to the same cortical areas. This creates what is referred to as cortico-basal ganglia functional loops. Three main functional loops have been identified (Alexander & Crutcher 1990, Alexander et al 1986, Middleton & Strick 2000): the associative (oculomotor and prefrontal), limbic, and motor loops (Fig.2).

The motor loop starts with cortical areas, mainly from the frontal cortex that project onto the two main BG input structures from which the three major BG pathways originate; the direct, the indirect and the hyperdirect pathways. The first and main input structure is the striatum which gives rise to the direct and indirect pathways. It receives cortical projections mainly onto its GABAergic medium spiny neurons (MSN). These neurons can express one of two different types of dopamine receptors, D1 or D2 (albeit with a small degree of overlap) through which the SNpc dopaminergic projections modulate the striatum. Expression of these neurons corresponds to their implication in the direct and indirect pathways. Indeed, in the direct pathway, MSNs with D1 receptors project monosynaptically to the GPi and the SNpr while the indirect pathway constitutes MSNs with D2 receptors that project polysynaptically to the GPi/SNpr via the GPe (GABAergic projections) and the STN (glutamatergic projections). The GPi and the SNpr, therefore, receive GABAergic input from both the striatum, as part of the direct pathway, as well as a glutamatergic input from the STN as part of the indirect pathway (Fig.3A). More recent studies have found that the GPi also receives projections from the GPe (Fig.3B) (Smith et al 1998).

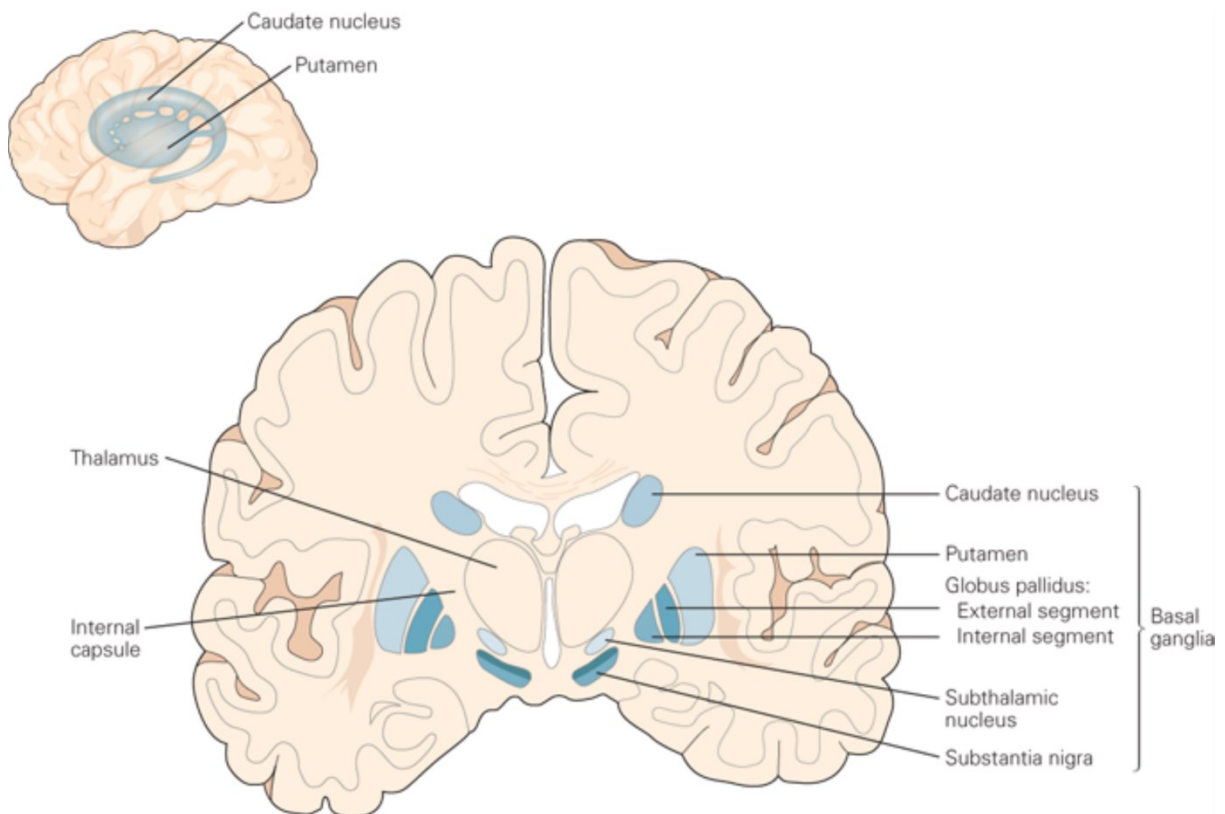


Figure 1. (Kandel 2012): The basal ganglia and surrounding structures in the human brain. A: The image in the top left shows a 3D representation of the striatum, composed of the caudate nucleus and the putamen. **B:** Coronal section of a human brain showing the nuclei of the basal ganglia, identified on the right of the section.

The second input structure of the BG is the STN which receives strong glutamatergic projections from the cortex and projects directly to the BG output structures through what is referred to as the hyperdirect pathway (Nambu et al 2002).

The BG output structures project first to the motor thalamus (Alexander et al 1986), to eventually project back to the cortex. This motor loop is not completely closed since the BG also projects to the pedunculopontine nucleus in the brainstem through the GPi (Redgrave & Coizet 2007). These pallidal projections to the thalamus and the pedunculopontine nucleus are not completely segregated, as a proportion of GPi neurons project to both structures through collaterals (Parent & Hazrati 1995a). Amongst the different BG loops, the motor loop has received a lot of attention mainly because of the various motor disturbances that result in pathological BG motor output. This link between BG dysfunction and motor disorders has resulted in numerous studies investigating the contribution of the BG activity in the production of motor symptoms. In the following text, we will briefly introduce some of the best-known motor disorders that have been linked to BG pathological activity.

b. Basal ganglia pathological activity

Dysfunction of the BG motor circuit that involves the thalamus and the cortex causes a spectrum of motor disturbances that range from hypokinetic to hyperkinetic motor disorders (DeLong 1990).

Hypokinetic disorders are characterized by akinesia (impaired movement initiation and poverty of movement), bradykinesia (slowness of movement), muscular rigidity, and tremor at rest. One of the best-known examples of hypokinetic disorders is Parkinson's disease (PD), which is caused by a relatively specific dopaminergic loss in the SNpc, which results in a deregulation of striatal activity and by extension, in the direct and indirect pathway. Because

striatal neurons involved in these two pathways express two types of dopamine receptors (D1 and D2) that polarize MSN differently when bound to dopamine, dopaminergic loss causes an imbalance of activity between the two pathways which ultimately results in increased GPi activity (this will be discussed in more detail in the STN section). This increased motor output from the BG results in an increased inhibition of the motor thalamus which in turns causes reduced activity in the thalamo-cortical projections ultimately resulting in hypokinesia (DeLong 1990).

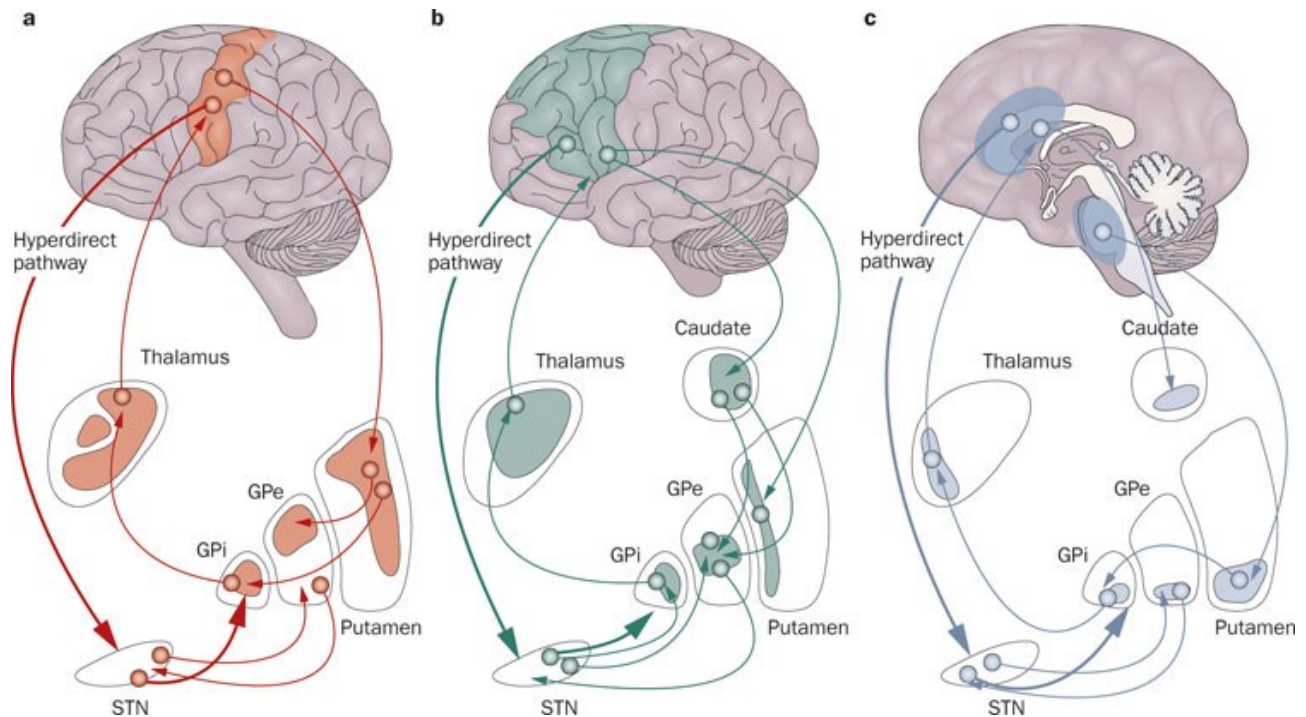


Figure 2. (Volkman et al 2010): The basal ganglia form anatomically and functionally segregated neuronal circuits with thalamic nuclei and frontal cortical areas. a: The motor circuit involves the motor and supplementary motor cortices, the posterolateral part of the putamen, the posterolateral globus pallidus pars externa (GPe) and pars interna (GPi), the dorsolateral subthalamic nucleus (STN), and the ventrolateral thalamus. **b:** The associative loop (that includes the oculomotor and the prefrontal loops) and **c:** the limbic loop connects the prefrontal and cingulate cortices with distinct regions within the basal ganglia and thalamus. In the STN, a functional gradient is found, with a motor representation in the dorsolateral aspect of the nucleus, cognitive–associative

functions in the intermediate zone, and limbic functions in the ventromedial region. Via a 'hyperdirect' pathway, the STN receives direct projections from the motor, prefrontal and anterior cingulate cortices that can detect and integrate response conflicts (Nambu et al 2002, Frank 2004). This pathway is a powerful contact to influence basal ganglia outflow. (the substantia nigra is not shown).

On the other hand, hyperkinetic disorders are characterized by dyskinesia, defined by excessive motricity expressed through involuntary movements. One example of a hyperkinetic syndrome is hemiballismus, which involves proximal musculature of the limbs (Buruma & Lakke 1986, Lakke 1981, Sellaal et al 1992, Whittier 1947) and has been linked to STN lesions in humans (Whittier 1947). These lesions were found to cause hypoactivity in the GPi that equates reduced BG motor output (Hamada & DeLong 1992b) resulting in a hyperactivity in the thalamo-cortical pathway, thought to account for the observed dyskinesia (DeLong 1990).

These two examples emphasize that strong clinical manifestations arise when one or multiple parts of the BG show pathological neural activity, causing an imbalanced activity within the BG pathways. In the next section, we will summarize the contribution of one of these nuclei, the STN, to the maintenance of an appropriate motor output, and how deregulation of subthalamic activity contributes to hemiballismus and PD.

3. The Subthalamic Nucleus

The subthalamic nucleus is a small oval-shaped structure located ventral to the thalamus. It can be divided into three functionally distinct subparts which have been categorized based on afferent cortical projections; a sensorimotor area in the dorsal part of the nucleus, an associative area located ventrally, and a smaller limbic area in the medioventral part of the nucleus (Fig.4) (Nambu 2011). The sensorimotor STN holds a central anatomical position in the motor circuit of the BG considering its role as an input structure as well as its strong excitatory projections to the GPi, the main motor output structure of the BG. The functional importance of these connections is supported by clinical studies linking various motor symptoms to dysfunctional subthalamic activity and by electrophysiological studies in primates. In the following section, we will present the most important connections of the STN as well as its role in motor disturbances and its contribution to motor control.

a. Anatomical connections

i. Afferent projections

The subthalamic nucleus receives strong excitatory projections from the cerebral cortex and a dense inhibitory projection from the GPe (Carpenter et al 1968, Smith et al 1990a). Other less prominent inputs include projections from the excitatory centromedian-parafascicular complex of the thalamus have been described in the rat and the cat (Groenewegen & Berendse 1990, Sugimoto et al 1983) and the pedunculo-pontine tegmental nucleus and the raphe nucleus in primates (Rinvik et al 1979). Since projections from the cortex and the GPe are the main sources of input to the STN, they will be the focus of this section.

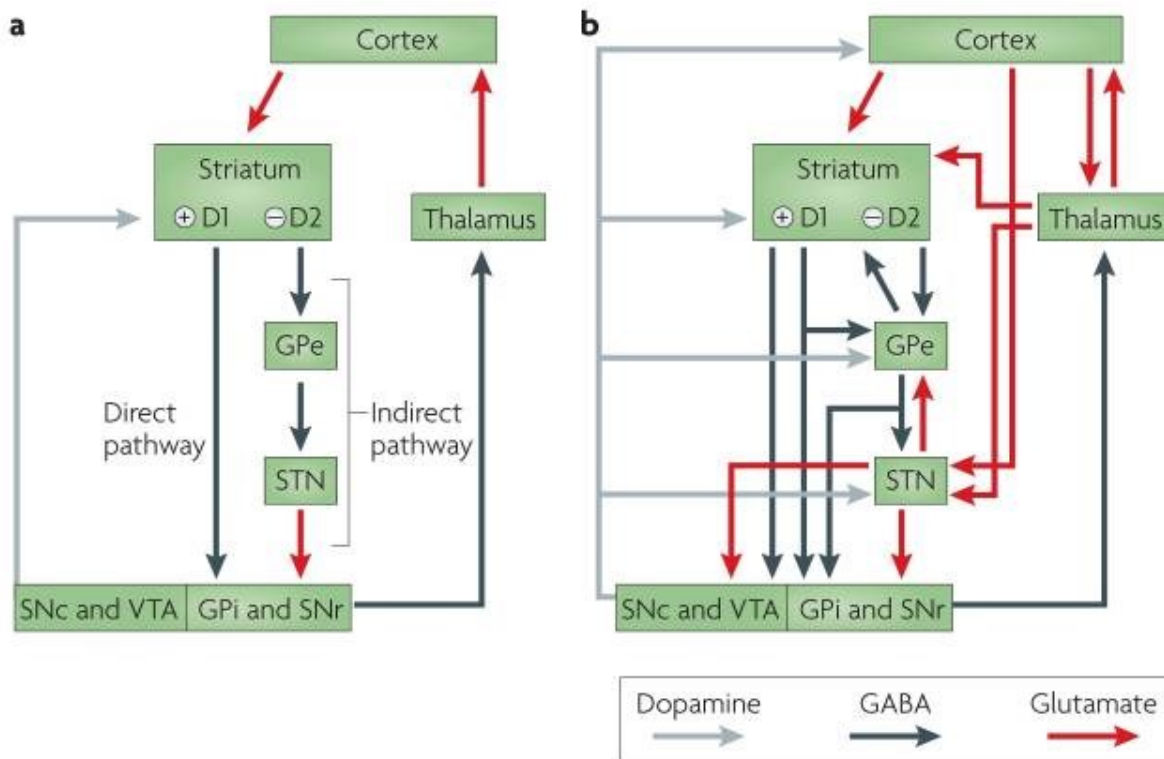


Figure 3. (Redgrave et al): Organization of intrinsic connections within the basal ganglia. A: Model based on the influential proposal by Albin and colleagues (Albin et al 1989), according to which the output of the basal ganglia is determined by the balance between the direct pathway, which involves direct striatopallidal inhibitory connections to the GPi and the SNr, and the indirect pathway, which involves relays in the external

globus pallidus (GPe) and subthalamic nucleus (STN) that eventually project to the GPI and the SNr. The balance between these two projections is thought to be regulated by afferent dopaminergic signals from the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA) acting on differentially distributed D1 and D2 dopamine receptors. **B:** Recent anatomical investigations have revealed a more complex organization in which the transformations that are applied to the inputs to generate outputs are less easy to predict. Grey arrows indicate dopaminergic projections, blue arrows GABAergic projections, and red arrows glutamatergic projections. SNr, substantia nigra pars reticulata.

Cortical projections

The STN receives inputs primarily from the M1, the supplementary motor cortex (SMA) and the premotor cortex (Bankiewicz et al 1986). The largest of these inputs is from the M1, which projects mainly to the dorsolateral part of the ipsilateral STN (Monakow et al 1978). In primates, these projections are somatotopically organized into face, forelimb and hindlimb areas on the mediolateral axis (Nambu et al 1996). On the other hand, the dorsomedial part of the STN receives cortical inputs from the SMA and the dorsal and ventral premotor areas (PMd and PMv) (Nambu et al 1996, Nambu et al 1997). The SMA projections to the STN have a somatotopical organization that is a mirror image of the one found in the M1 region (Fig.4) (Nambu et al 1996). The face, forelimb and hindlimb regions of the M1 and the SMA also project in their respective territories to the corresponding body representations, creating a certain level of overlap. Projections from the forelimb representations in the PMv and PMd were found to overlap with each other and with the SMA projections.

Other less prominent cortical inputs to the STN originate from the cingulate motor area (CMA) and the pre-SMA. The caudal cingulate motor areas (CMAc) projects to the lateral STN while the rostral CMA (CMAr) and the pre-SMA project to the medial STN (Inase et al 1999, Takada et al 2001). These anatomical connections show that the STN funnels information from a wide range of cortical areas through the hyperdirect pathway to the BG motor output.

Pallidosubthalamic projections

Although connections between the STN and the pallidum have been the subject of many studies, the topography of these connections is still not clear. According to one study,

the ventral GPe projects onto the dorsolateral STN which in turns projects to the ventromedial sensorimotor part of the GPi (Fig.5) (Shink et al 1996). This study is in line with the idea of functional segregation of the intrinsic BG connections where functional parts of each nucleus only project to areas of the same function. On the other hand, studies from Parent and Hazarti have suggested a complete segregation of pallidosubthalamic projections and subthalamopallidal projections (Parent & Hazrati 1995a, Parent & Hazrati 1995b). These results refute the existence of the GPe-STN-GPi connections, known as the indirect pathway (see next section).

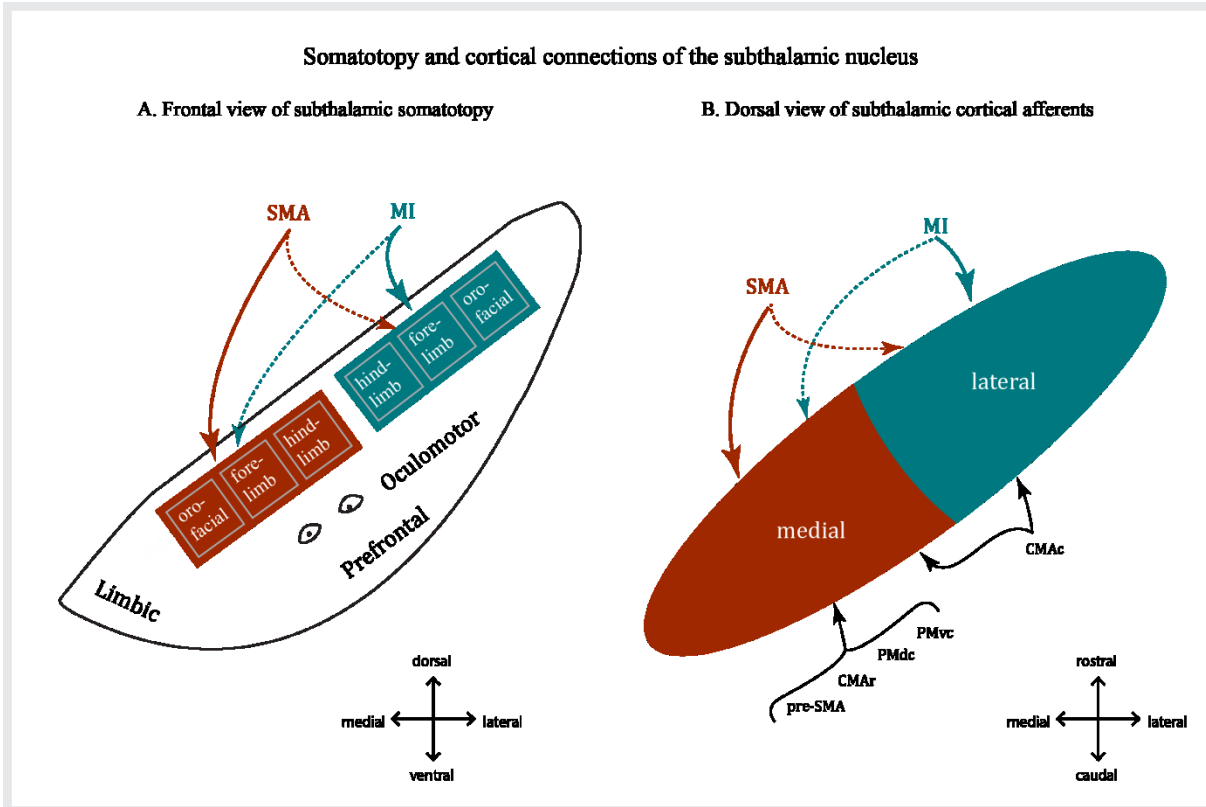


Figure 4. (Modified from Nambu 2011): Somatotopy of the subthalamic nucleus (STN) in the primate. A: Somatotopy of the STN is shown in a frontal section. In the dorsal part of the STN, the lateral part receives somatotopic inputs from MI (solid blue arrow), and the medial part from the SMA (solid red arrow). MI also projects partly to the medial part (dotted blue arrow), and the SMA to the lateral part of the STN (dotted red arrow). Ventral to the motor territory, there exist the oculomotor and prefrontal territories. The most medial part is occupied by the limbic territory. **B:** Input from motor cortices to the STN is schematically shown in a horizontal section.

ii. Efferent projections

Subthalamopallidal projections

According to a primate study, the majority of efferent subthalamic neurons have axon collaterals that project to both the GPi and the GPe (Sato et al 2000). These projections are thought to originate from the dorsal STN and project onto the sensorimotor part of the GPi located in its ventrolateral two thirds, as well as to the ventral GPe (Fig.5) (Shink et al 1996). On the other hand, the ventromedial part of the STN projects to the non-motor parts of the GPi and the GPe (Shink et al 1996).

Subthalamonigral projections

The SNpr is one of the biggest recipients of STN efferent projections, second to the pallidum (Nauta & Cole 1978). These projections originate mainly from the ventromedial third of the STN (Parent et al 1984, Parent & Smith 1987, Smith et al 1990b). They enter the SNpr from its dorsal or ventral parts and terminate in a patchy manner (Carpenter et al 1981). Although the majority of the STN projections to the SN terminate within the SNpr, some fibers ascend along the dopaminergic cell columns of the SNpc that go through the SNpr (Smith et al 1990b). In both the SNpr and the SNpc, the STN neurons seem to preferentially project onto non-dopaminergic neurons (Nauta & Cole 1978).

b. Clinical implications of subthalamic dysfunction

In order for the BG to produce an appropriate motor output, balanced activity between all the nuclei is essential. Because of the high connectivity between the STN and other important nuclei such as the GPi, an insult to the STN can strongly affect activity in the GPi which results in an inappropriate motor output to the motor thalamus and impedes proper motor control. In this section, we will present how pathological subthalamic activity contributes to BG-related motor disorders.

In the case of hemiballismus, lesion of the STN in primates has been shown to cause motor symptoms closely resembling human hemiballismus (Carpenter et al 1950, Hamada & DeLong 1992b), further supporting the link between reduced STN activity and dyskinesia.

This effect seems to be conveyed by the GPi since lesions to the STN also causes a reduction of GPi activity (Hamada & DeLong 1992a) and a subsequent lesion of the GPi abolishes STN-induced dyskinesia (Carpenter 1961, Carpenter et al 1950). These results show that the STN plays a role in suppressing involuntary movements through the subthalamopallidal pathway. They also suggest that the STN is an important modulator of the BG motor since its hypoactivity is related to a reduced BG motor output that is significant enough to result in dyskinesia.

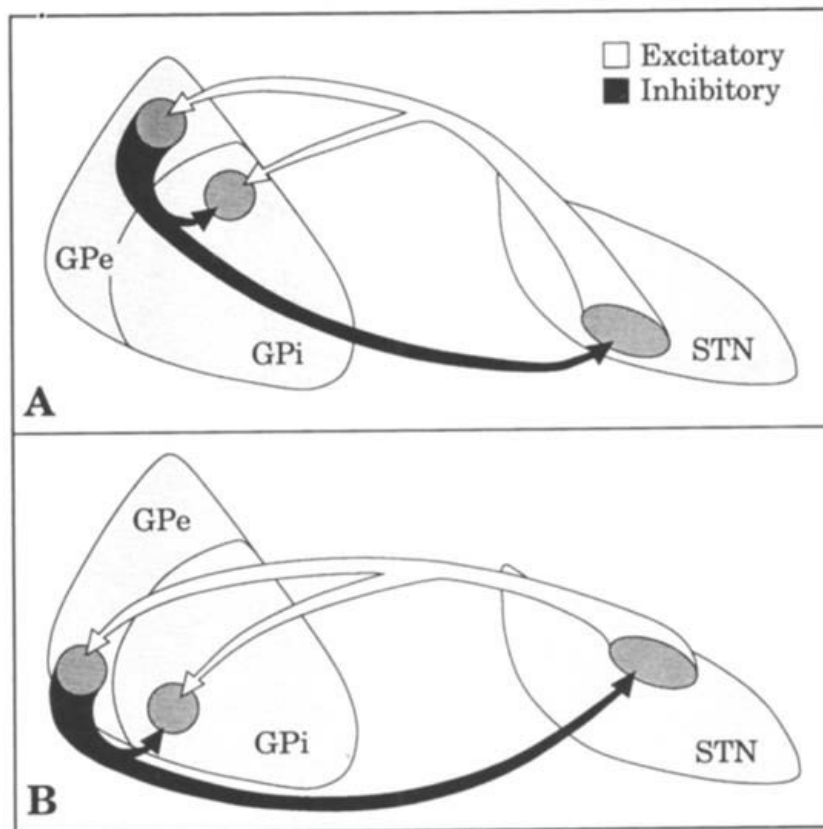


Figure 5. (Shink et al 1996): Anatomical connections between the STN and the pallidum. Schematic diagram to summarize the relationships between the two pallidal segments (GPe and GPi) and the STN. Small groups of interconnected neurons in the associative (A) and sensorimotor (B) territories of GPe and STN innervate, via axon collaterals, a common functionally-related region in the GPi.

In the case of PD, activity in the STN was found to be increased. Indeed, loss of SNpr inhibitory dopaminergic projections to striatal D2 neurons (involved in the indirect pathway) increases their GABAergic projections to the GPe. This causes reduced activity in the GPe which releases the STN from its tonic inhibition. This, in turn, causes an increased activity in the STN which sends stronger excitatory glutamatergic projections to the GPi (Bergman et al 1994, Miller & DeLong 1987). Furthermore, when this hyperactivity is countered with STN lesions in parkinsonian 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primates, there is a reduction of all of the major motor disturbances in the contralateral limbs, including akinesia, rigidity, and tremor (Aziz et al 1992, Aziz et al 1991, Benabid et al 1993, Benazzouz et al 1993, Bergman et al 1990, Guridi et al 1993). This improvement of motor disturbances that follows STN lesion can be explained by its effect on the GPi. Indeed, one study showed that lesion of the STN in MPTP primates reduces the hyperactivity of the GPi (Wichmann et al 1994b).

These studies show that increased subthalamic activity results in increased inhibition of thalamocortical neurons by GPi output which eventually results in the hypokinetic motor disturbances that characterize parkinsonian symptoms. These studies in primates provided sufficient evidence for clinical studies to use deep brain stimulation on human patients which allows reversible lesioning of the STN or the GPi (Rodriguez-Oroz et al 2005, Samuel et al 1998). This has been successful in reducing pathological BG motor output and in turn, reduces motor symptoms in patients (Wichmann & DeLong 2003).

These clinical studies emphasize the importance of the sensorimotor STN in the control of movement. In the next section, we will present studies that have investigated the role of the STN in motor control.

c. Relationship of subthalamic activity to movement

Neural activity of the STN in relationship to movement has been mainly studied in monkeys, with a few studies in cats, and was found to correlate to different movement parameters. In primates executing a reaction time task, the relationship between the discharge frequency and each movement parameter was tested during both the reaction time (RT) and movement time (MT) (Georgopoulos et al 1983). The results showed statistically significant

relations of cell activity to the direction, amplitude, and peak velocity of the movement, predominantly during movement time, but also during reaction time before the movement occurred (Georgopoulos et al 1983). In an arm tracking task, cells that significantly changed their discharge in relation to the movement responded to either extension or flexion of the arm during application of elbow torque pulses, and some cells were active in both situations, although their responses to each direction were different (Wichmann et al 1994a). In the cat, the activity of subthalamic neurons related to motor performance was studied during a lever-release movement (Cheruel et al 1996). The results showed that most of the cells were task related (85%) as they presented significant changes in activity in relation to the lever-release movement.

Changes of cell activity in relationship to movement in the STN are expressed mainly as an increase in discharge activity (Cheruel et al 1996, Georgopoulos et al 1983, Wichmann et al 1994a), and occurred before movement related changes in the GPe and GPi by 60 to 66 ms (Georgopoulos et al 1983). These results suggest that movement-related subthalamic activity originates from excitatory inputs from the motor cortex, through the hyperdirect pathway. Neural activity in the STN was also found to relate to the active and passive movement of individual body parts in wake monkeys (DeLong et al 1985, Wichmann et al 1994a). In both types of movements, cell discharge was found to occur in relation to either arm, leg or orofacial movement (DeLong et al 1985, Wichmann et al 1994a). In these studies, cells that showed responsiveness to either passive or active movement tended to be distributed along the rostrocaudal extent of the nucleus, mainly in the lateral part. Cells that discharged in relationship to a body part were clustered where the lateral region contained arm responding cells, and in a more medial region, leg responding cells (Wichmann et al 1994a). This is in accordance with the somatotopically organized projections from M1 to the dorsolateral STN where a face, arm, and leg representation are found on the mediolateral axis (Nambu 2011). Stimulation of the STN did not evoke any movement (Wichmann et al 1994a). In summary, these studies show that the STN exhibits movement-related activity that is mostly expressed in terms of increased activity that occurs before and during the movement.

d. Relationship of subthalamic activity to locomotion

Although clinical evidence suggests a strong causal relationship between increased subthalamic activity and hypokinesia, and reduced subthalamic activity and hyperkinesia, the implication of subthalamic activity in gait control is still far from clear.

In humans, bilateral stimulation of the STN has been shown to be effective in increasing gait velocity and stride length in parkinsonian patients (Stolze et al 2001, Xie et al 2001). However, freezing of gait can be insensitive to pharmacological treatment (Schaafsma et al 2003) and in that case, does not improve with DBS in the STN (Xie et al 2001).

As far as fundamental research goes, I was only able to find one study investigating STN activity during locomotion (Shi et al 2004). Multi-unit recording in freely moving rats performing treadmill locomotion showed that the STN increased its neural activity when walking in comparison to resting state. However, this study did not investigate the relationship between neural activity and different phases of the step cycle nor activity during voluntary modification of gait.

4. Objectives

As reviewed in the preceding sections, clinical and fundamental research present evidence that STN strongly contributes to movement. On one hand, the STN shows strong movement-related activity during arm reaching, on the other, deep brain stimulation of the STN has proven effective in treating most Parkinsonian motor symptoms. However, very little is known about the contribution of the STN to the control of locomotion and no studies have examined the properties of subthalamic cellular discharge during visually guided locomotion.

The present study was designed to gain a better understanding of the contribution of the STN in the control of locomotion, and more specifically, on characteristics of the cellular discharge underlying the control of visually guided locomotion. To this end, we recorded activity from single neurons in the STN of chronically implanted cats trained to perform unobstructed locomotion, and visually guided locomotion by stepping over obstacles.

The major questions addressed in this study were;

1) *is neuronal activity in the STN related to the rhythmical activity of limb muscles during basic, unobstructed locomotion?*

2) *do neurons in the STN show modifications of activity prior to, or during, the visually-guided, voluntary gait modifications required to step over an obstacle?*

3) *how do the characteristics of the neuronal activity in the STN relate to different aspects of control of visually guided locomotion?*

The findings from this study will show the extent to which neuronal activity in the STN is related to different aspects of locomotor control. As such, it will provide important insights regarding the contribution of the basal ganglia to the control of locomotion, as well as a better understanding of how deficits in locomotor activity might be treated in patients with Parkinson's disease.

II. Methods

Training and surgery

We trained two male adult cats (weight 5 - 5.6 kg) over a period of 2-3 months to step over obstacles attached to a treadmill moving at a speed of 0.4m/s. Obstacles of two different sizes and shapes were used: a large cylindrical obstacle (10 cm cross-sectional area) and a smaller rectangular obstacle (3 cm wide by 2 cm high). The two obstacles were placed 1.55 m apart, allowing for 2-3 step cycles between each obstacle, and were visible to the cat 2 steps before it stepped over either one of them.

Following training, the cat was prepared for recording procedures during surgery made under general anesthesia and under sterile conditions. It was first pre-medicated with antibiotics (Cefovecin, 8mg/kg), then anesthesia was induced with ketamine (11 mg/kg), Atravet (0.05mg/kg) and Rubinol (0.01mg/kg). The cat was subsequently intubated and anesthesia was maintained throughout the surgery with isoflurane (2–3% with oxygen). The animal was then placed in a stereotaxic frame using atraumatic ear bars coated with lidocaine ointment 5% (Xylocaine) and petroleum jelly (Vaseline) was applied to the eyes to prevent drying of the cornea. During the surgery, fluids and corticosteroids (Solu-Medrol, 15 to 30 mg/kg) were administered through a catheter to prevent cortical swelling, and an analgesic

(Buprenorphine, 0.005mg/kg) was administered subcutaneously. Heart rate and body temperature were monitored continuously throughout the procedure.

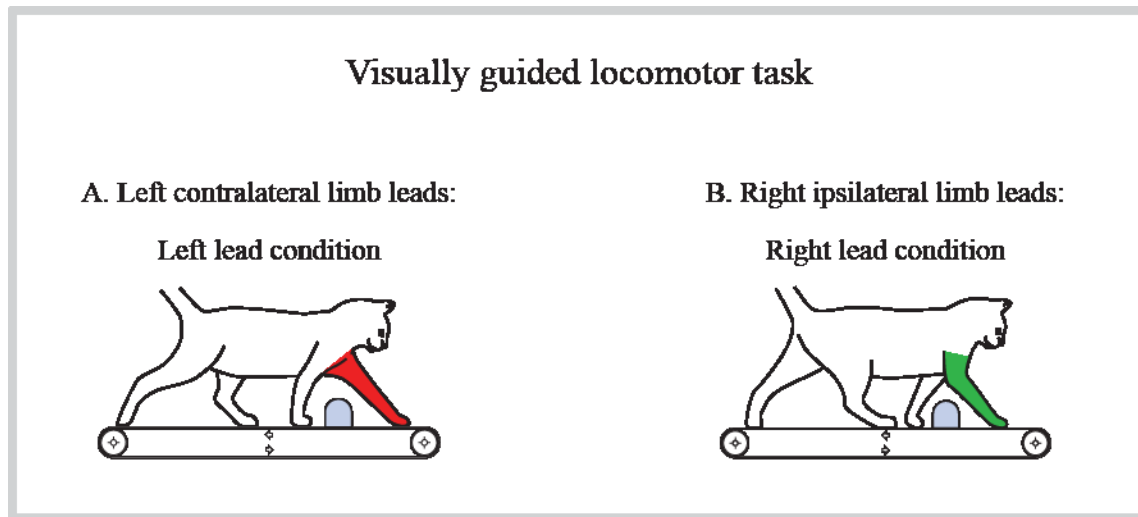


Figure 6. Visually guided locomotor task. Data were collected from the right STN of a cat that was trained to walk without interruption on a treadmill moving at 0.4m/s and to step over moving obstacles attached to a moving belt. When the cat first stepped over the obstacle with the left limb, contralateral to the recording site, we called this the left lead condition (A). When the cat stepped over first with the right limb, ipsilateral to the recording site, we called this the right lead condition (B).

Selected forelimb, hindlimb and neck muscles were implanted (see Table 1) with pairs of Teflon-insulated braided stainless steel wires that were sewn into the muscles and led subcutaneously to connectors cemented to the skull (Drew 1993, Drew et al 1986).

A craniotomy was performed over the right hemisphere to allow access to the stereotaxic coordinates of the right subthalamic nucleus (STN) and a recording chamber (12 x 15mm) was placed over the cranial aperture. A connector for a pre-amplifier was placed on the cranium and fixed in place with dental acrylic (Drew 1993). Stainless steel screws inserted in the skull ensured a firm fixation of the implant. Meloxicam (0.2mg/kg) was given at the end of the surgery as an analgesic as well as to control inflammation and fever and was administered along with Buprenorphine (0.005mg/kg) for 2-3 days after the surgery. Cats were allowed to recover for 1–2 weeks before beginning experiments. All surgical procedures followed the

recommendations of the Canadian Council for the Protection of Animals and protocols were approved by the local animal ethics committee.

Protocol

Experiments occurred 3-5 times a week and generally lasted about 3 hours. During each experimental session, a custom-made microdrive was attached to the recording chamber, allowing us to advance a conventional glass-insulated tungsten microelectrode (impedance of 0.6–1.2 MΩ) into the brain at specific coordinates. Coordinates were changed for each experiment allowing us to cover the extent of the right STN in a grid pattern with 0.5 mm resolution in both the anteroposterior and mediolateral planes.

The localization of the STN and surrounding structures within the recording chamber was achieved using multiple methods. In initial experiments, we targeted the magnocellular part

Tableau I. Abbreviations and muscles used in this study.

Name	Abbreviation	Function
Acromiotrapezius	AcT	Arm abduction
Brachialis	Br	Flexion of the elbow
Cleidobrachialis	CIB	Protraction of the shoulder and flexion of the elbow
Palmaris longus	PaL	Plantarflexion of the wrist and digits
Spinodeltoideus	SpD	Flexes the shoulder and rotates the humerus
Teres major	TrM	Retraction of the shoulder
Triceps brachii Long, head	Tri	Extension of the elbow, extensor humerus
Triceps brachii, lateral head	TriL	Extension of the elbow
Sartorius	Srt	Flexor thigh and shank
Semitendinosus	St	Extensor thigh, flexor shank
Vastus Lateralis	VL	Extensor shank
Biventer Cervicis	BvC	Extension head

of the red nucleus (RN) as this nucleus can be readily identified by the presence of large, close-packed cells discharging during the swing period of locomotion and brisk twitch responses in the limbs to trains of low intensity microstimulation (11 pulses at 33Hz, 0.2 ms duration pulses, current intensity < 25uA). Confirmation of the location of the RN was also provided by the presence of eye movements to stimulation of the oculomotor nerve, which lies ventral to the RN. The localization of the RN allowed us to estimate the relative location of the STN within the chamber coordinate system and facilitated the localization of the STN, which is a relatively small structure. Once we had determined the relative position of the STN, we more firmly identified its location by carefully determining the presence of different nuclei and axon bundles as we descended the electrode. In particular, the identification of the ventral parts of the thalamus and of the Fields of Forel was important in determining depth. When passing through the thalamus, we identified a subsequent layer of axons, a small layer of cells (either the Fields of Forel or the nucleus of the zona incerta) and then another axon layer before encountering a second cell layer that we identified as the STN.

All isolated neurons recorded within the targeted structure were recorded during locomotion for several minutes. During this time, the cat would alternate voluntary gait modification as it stepped over the obstacles and unobstructed locomotion when walking between obstacles (control activity). When the cat had performed ~ 10 steps over each obstacle in both left lead and right lead conditions, the treadmill was stopped and we determined the receptive field of the cell. The entire body was first explored to see whether the neuron discharged to the light touch of the fur or skin. In the absence of a cutaneous field, we passively manipulated the limbs to determine whether the cells could be activated by proprioceptive inputs. Once we had determined a receptive field, the electrode was moved to isolate another cell.

EMG activity was amplified, filtered, and sampled off-line at a frequency of 1 kHz. Unit activity was sampled at 100 kHz. DVD recordings were made of all experiments and synchronized to the EMG and unit data by recording a digital time code on both the DVD and the digitized data file. This allowed us to inspect the recordings off-line to ensure that only

periods of stable walking were included for analysis. Small electrolytic lesions (50 μ A) were made in selected penetrations to aid in histological reconstruction.

Histology

At the end of the series of experiments, the cats were deeply anesthetized with an intraperitoneal injection of Ketamine (11 mg/kg) followed by pentobarbital sodium (Somnotol, 40 mg/kg) and perfused per cardia with saline then with a formaldehyde solution. The fixed brain was removed, photographed and preserved in formol. It was later sectioned in the parasagittal plane (40 μ m) and stained with cresyl violet. Histological reconstruction of recording penetrations was made using the gliosis that formed around the penetrations and the electrolytic lesions that were made as a guide.

Data analysis

Neurons were selected for detailed analysis if on-line inspection suggested either rhythmical activity in relation to locomotion or modified activity during the step over the obstacle, and if the amplitude of the recorded action potential and the pattern of locomotion were both stable. An offline sorterTM (Plexon) was used to isolate and discriminate neural spikes of the recorded cell from background noise. The recorded data were then processed similarly to those described in previous studies from this laboratory (Andujar et al 2010, Drew 1993, Lavoie & Drew 2002). The data were first displayed on a monitor and a custom program was used to mark the onset and offset of the locomotor activity of selected muscles and to identify selected series of step cycles during the voluntary gait modifications. Specifically, for each sequence of locomotion, we identified whether the left (contralateral to the recording site) or the right (ipsilateral) forelimb was the first to step over the obstacle (left and right lead condition, respectively) (Fig.6). In addition, we separately identified steps over the smaller and larger of the two obstacles. Steps over the obstacle were therefore classified into four groups with respect to two criteria; (1) left or right lead conditions and (2) large or small obstacle. We also separately identified each of the steps preceding the step over the obstacle as well as the step following the gait modification.

The EMG and cell activity for each group of step cycles were then averaged. EMG activity in each step cycle was normalized prior to averaging by resampling the activity into

512 equal bins. Cell discharge activity was converted into instantaneous frequency (1000/interspike interval in ms) and also normalized into 512 bins prior to averaging by using the method described by Udo and colleagues (1982). Averages, presented as peri-event histograms (PEH) were always synchronized to the onset of activity of either the contralateral CIB or the Br muscle, each of which discharges at the onset of the swing phase of locomotion (Drew 1993). Raster plots, synchronized on the onset of activity of the two same muscles, were constructed to visualize the temporal relationships between periods of cell discharge and the correlated muscle activity. Rasters were always rank-ordered according to the duration of the activity of the muscle on which the neural activity was synchronized (CIB or Br).

To determine whether a cell was phasically modulated during unobstructed locomotion, we used the Rayleigh test for directionality ($P < 0.01$) (Batschelet 1981, Drew & Doucet 1991). In brief, once the PEH has been constructed, the data was treated as a circular event where the step cycle begins at phase 0 which corresponds to the onset of a selected muscle and continues in a clockwise direction until the onset of the next step (phase 1.0). The test provides an objective indication as to whether a cell has a significant tendency to discharge in a particular direction (i.e in relationship to a particular phase of the step cycle) over any other (modulated) or whether there is no directionality (tonic discharge). The period or phase of activity of a cell during control locomotion was calculated by using the method described in Lavoie and Drew (2002). In brief, the onset and offset of the period of activity in modulated cells was identified as the point at which the histogram of cell discharge frequency respectively crossed and then recrossed the mean level of the discharge calculated from all trials (Fig.9).

To determine whether cell discharge was modified during the visually-guided gait modification, the discharge frequency of the cell during steps over an obstacle was compared with that during control locomotion. This latter variable was calculated from the averaged discharge activity occurring 2-3 steps before the obstacle (Drew 1993). Cell discharge activity in a given condition was considered to be significantly different from control when it deviated from the interval of confidence ($P < 0.01$) of the standard error (SE) of the control activity for 10% of the 512 bins comprising each cycle (~ 51 consecutive bins). The period of modified activity was defined as the period during which the discharge activity significantly differed

from the interval of confidence, defined as the SE activity of the control task (Andujar et al 2010). The phase and magnitude of the peak discharge frequency were calculated from averaged traces low-pass filtered at 25 Hz (digital dual-pass Butterworth filter, fourth-order). After an initial analysis showed that the size of the obstacle did not influence activity during the modified step we combined data obtained with the small and large obstacle. Cells were classified into groups using definitions similar to those in previous studies from this lab examining the discharge characteristics of neurons in the posterior parietal cortex (PPC) (Andujar et al 2010). Cells in which discharge activity deviated significantly from control less than 200 ms before the onset of activity in the CIB or Br (swing onset) were classified as step-related cells. Cells in which discharge activity differed significantly from control earlier than this were classified as step-advanced cells. Further, when discharge activity was similar regardless of which limb was the first to step over the obstacle, we refer to this as a limb-independent cell (Andujar et al 2010). In contrast, if cell activity was always related to the same limb (always the contralateral left limb in this study) in both the lead and trail conditions, we referred to this as a limb-specific cell.

III. Results

Database

The results in this section are presented from 1 of the 2 cats used in this study as data from the other cat has not yet been fully analyzed. From the first cat, a total of 133 cells were recorded from 23 electrode penetrations in the right STN during locomotion. All of these penetrations were histologically verified to lie within the boundaries of the STN and were concentrated in the lateral half of the nucleus. Histological reconstructions of some of these penetrations are shown for different lateralities in Fig.7.

In this thesis, we report on the activity of 52 neurons recorded from 18 of those tracks. These cells were selected based on an initial online inspection of discharge activity. Cells were analyzed when their cellular discharge was phasically related to limb movement, either during unobstructed locomotion and/or in relation to the obstacle. The remaining cells were not analyzed since they discharged either tonically, irregularly, or in relationship to saccadic eye movements according to online analysis.

Subthalamic activity during normal locomotion

Cellular activity during normal (unobstructed) locomotion was analyzed using the cell discharge occurring either 2 or 3 steps before the modified step (step over the obstacle) as detailed in the Methods. Of the 52 analyzed cells, the discharge activity of 40/52 was either time-locked to the activity of forelimb muscles during unobstructed locomotion and/or was modified when the forelimb stepped over an obstacle. Such cells were identified as forelimb-related cells (FL-related), regardless of whether the cell discharged in relation to the right forelimb (ipsilateral to the recording side) or left forelimb (contralateral to the recording side). The other cells were either hindlimb-related (6/52) or had ambiguous activity (6/52) (see Fig. 8).

By using the Rayleigh test for directionality (see Methods), we determined that most of the FL-related neurons that we analyzed showed a non-uniform pattern of discharge activity during unobstructed locomotion and were identified as modulated cells (30/40, 75%).

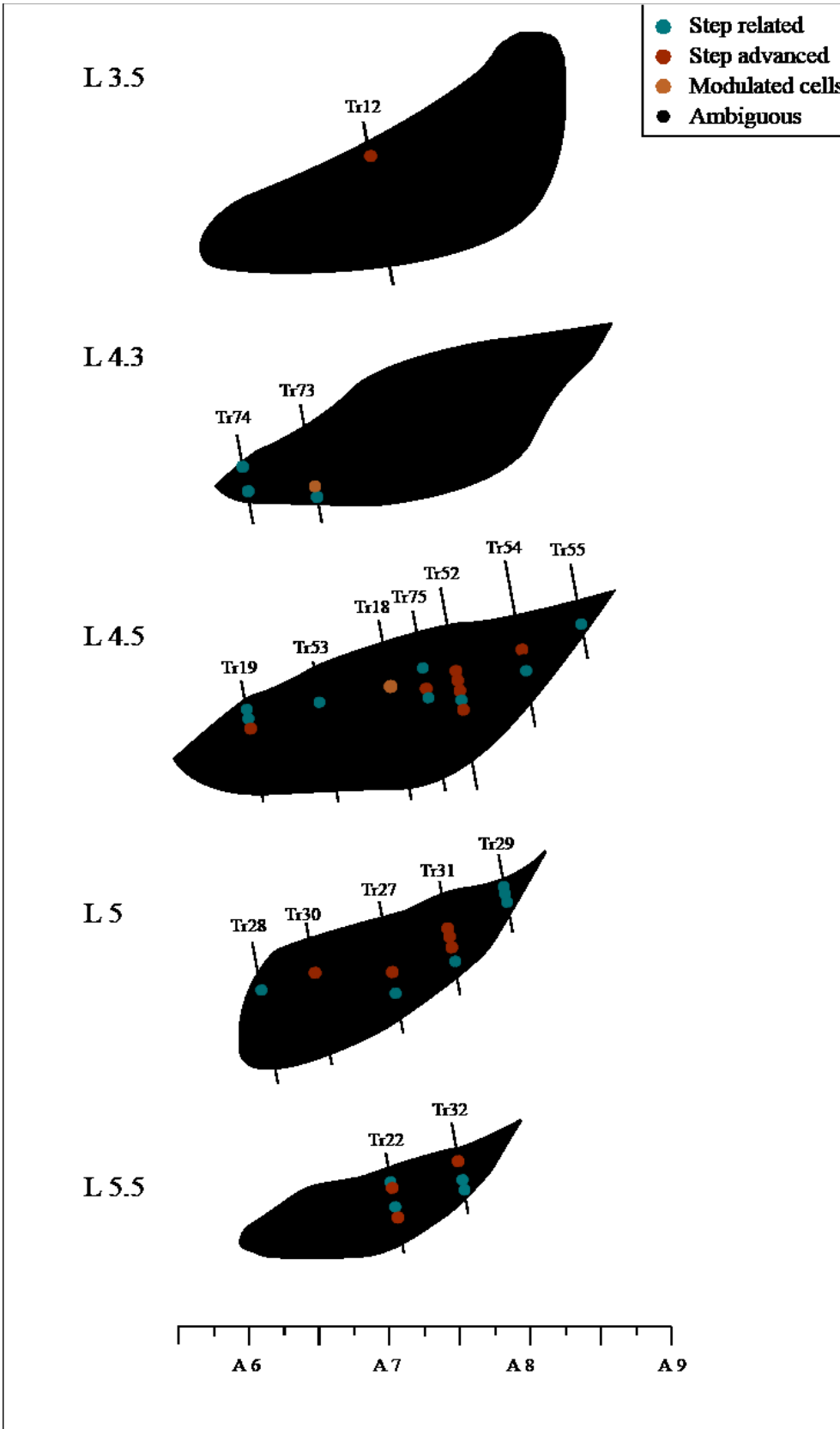


Figure 7. Schematic representation of histological reconstruction of recording tracks in the STN. Tracing of parasagittal sections of the STN (grey areas) at different lateralities (L) with the representation of electrode penetrations (black lines) and all recorded cells that showed movement-related activity, represented by circles. Blue circles represent step-related cells (N=21), red circles represent step-advanced cells (N=16), orange circles show cells that showed phasic activity during control but did not modify their discharge in relation to the obstacle (modulated cells, N=2). Black circles represent cells that showed movement-related activity that was ambiguous. A, Anteriority according to the stereotaxic frame; L, laterality in mm according to the stereotaxic frame. Tr, recording track.

Within these cells, two subgroups were identified: cells that discharged maximally during the swing phase and cells that discharged maximally during the stance phase. An example cell from each group is presented in Fig.9. The first example in Fig.9A showed significant discharge (defined in Methods) from phase -0.06 to phase 0.35 of the step cycle, which roughly corresponds to the duration of the swing phase, defined by the period of activity of the contralateral CIB (coCIB) (Drew 1993). The cellular discharge reached its maximum (19Hz) at phase 0.23 of the step cycle. The second example cell in Fig.9B showed a significant discharge from phase 0.46 to phase 0.9, which corresponds to the stance phase identified as the period of activity of extensor muscles such as the coTriL. The cell discharged maximally at phase 0.7 at a frequency of 35.5Hz. The graphs on the right show a vectorial representation of the discharge of each example cell where the step cycle is represented as a circle and the arrow indicates the average direction (phase) of the cell discharge.

The period of significant discharge and the phase of peak activity of the 30 FL-related modulated cells are plotted as a function of the phase of the step cycle in Fig.10A. The figure illustrates the two groups of modulated cells previously mentioned; cells that discharged maximally during swing phase (23/30, 77%) between phase 0 and phase 0.37 of the step cycle, and cells that discharged maximally during the stance phase (7/30, 23%) between phase 0.47 and phase 1. The distribution of phases of maximum discharge is illustrated in Fig.10B. The figure shows that the majority of cells discharged maximally during the swing phase, between phase 0.2 and 0.3 of the step cycle. The distribution of the maximum discharge frequencies of the same 30 cells during normal locomotion is shown in Fig.10C. As for the 10/40 non-

modulated cells, they were either silent or showed tonic activity during control, except for one cell that showed multiple peaks of activity per step cycle.

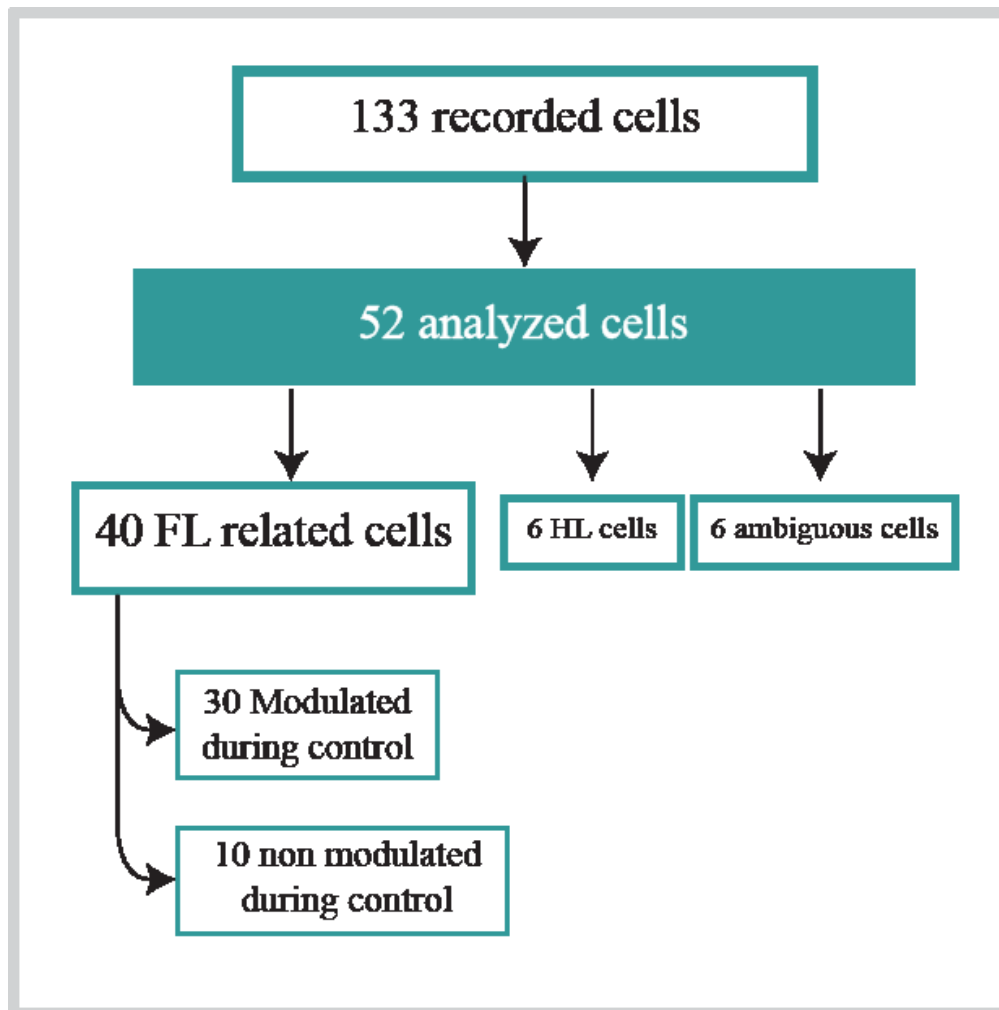


Figure 8. Summary of the database. We recorded 133 cells, out of which 52 neurons showed limb related activity according to offline analysis and were quantitatively analyzed. 40/52 cells were found to display forelimb-related (FL) activity during either unobstructed locomotion or voluntary gait modifications. Hindlimb-related (HL) cells and cells that showed an ambiguous relationship to limb movement were excluded from subsequent analysis and will not be discussed. Modulated cells showed significant phasic discharge during unobstructed locomotion according to the Rayleigh test of directionality.

STN activity during voluntary gait modifications

During unobstructed locomotion, 30/40 FL-related cells showed limb-related phasic activity, out of which 29/30 changed their discharge frequency when the cat had to plan and execute a voluntary gait modification to step over an obstacle. Most of these cells were step-related (19/29), and in lesser proportion, step-advanced (10/29). Cells that were not modulated but changed their discharge in relation to the obstacle were mostly step-advanced (N=6), and in smaller number step-related cells (N=2).

Overall, out of the 37 FL-related cells that showed a change of activity in relation to voluntary gait modification, 21 cells showed step-related activity while 16 cells showed step-advanced activity. These changes were generally expressed in terms of change of firing rate, although changes in the phase of the activity were also observed. However, these were less prominent and will not be discussed. Some cells in both groups significantly changed their activity in relation to the obstacle more than once, with one change of activity being substantially larger than the other. In all figures, we will refer to the larger change as the “main burst”, while the smaller change of activity will be referred to as the “secondary burst”. Only main bursts of cellular activity will be considered for all of the histograms and scatter plots. Patterns of each type of activity and function will be discussed in the next sections.

Step-related activity

Step-related activity in relationship to gait modification in the left lead condition was expressed in a change of discharge frequency, where most cells increased their discharge (12/21), a few showed a decrease of activity (3/21) and others showed an initial decrease followed by an increase of activity (6/21). Moreover, step-related discharge was mostly limb-specific (19/21) and limb-independent activity was only found in 2/21 cells. Two examples of step-related cells are presented in Fig.11 where neural activity is synchronized to the EMG activity of the flexor muscle, coBr.

The first example in Fig.11A shows a cell that displays limb-dependent activity in that cell discharge occurs during the period of activity of the coBr during both the left lead and the right lead conditions. In the left lead condition, the cell increased its discharge throughout the swing phase from 16.5 Hz during control to 34.5 Hz.

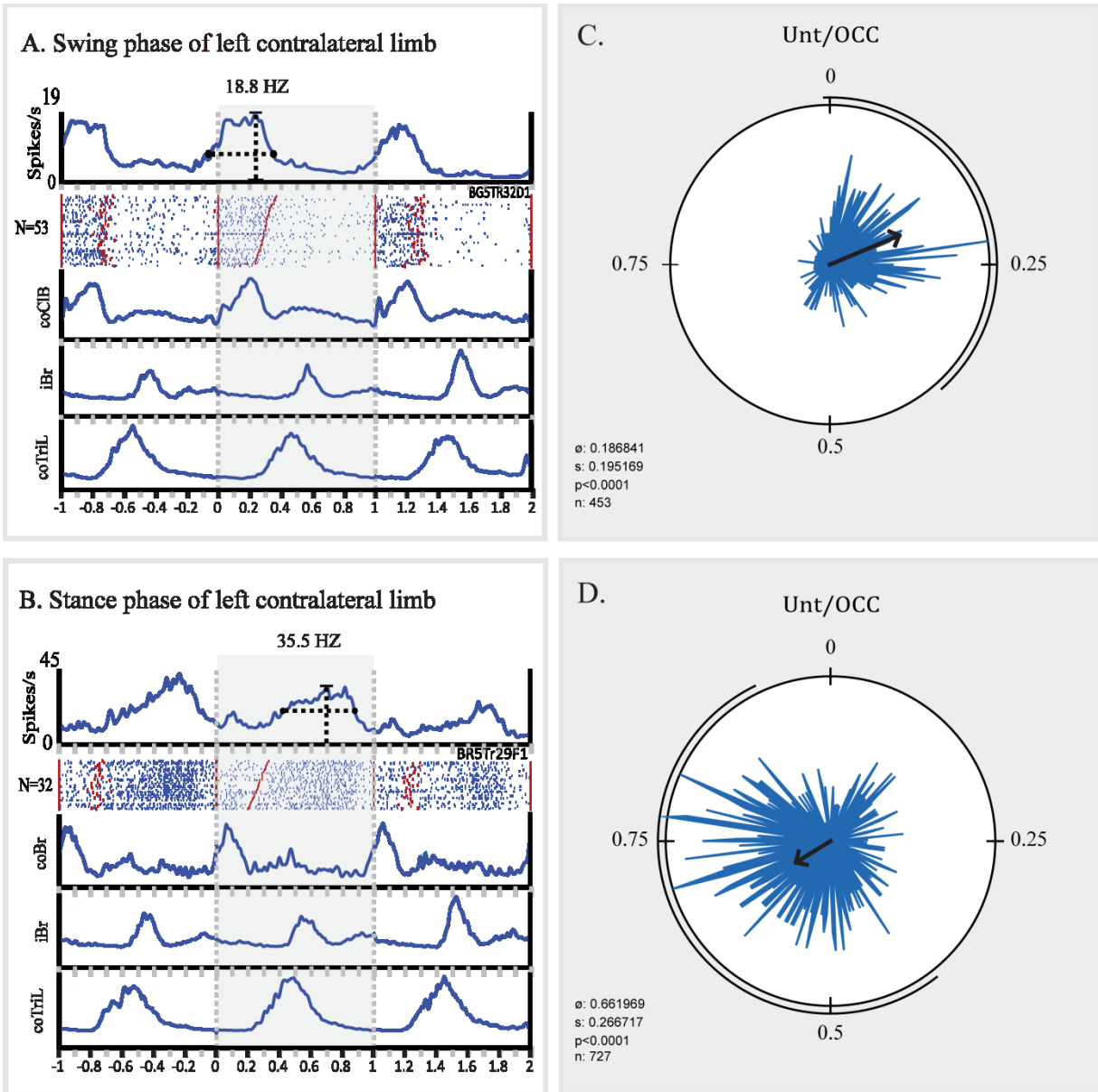


Figure 9. Neuronal activity recorded in the STN during unobstructed locomotion.

A and B: Peri-event histograms (PEHs) and raster displays of 2 examples of neurons phasically modulated during unobstructed locomotion, together with recordings from selected muscles of the contralateral and ipsilateral forelimbs. The cell in A discharged maximally during the swing phase of the left contralateral forelimb, while the cell in B discharged maximally during the stance phase of the same limb. Data are synchronized to the onset of the left contralateral cleidobrachialis (coCIB) for cell A and contralateral brachialis (coBr) for cell B, and each cycle is repeated 3 times to emphasize the rhythmic nature of the discharge activity. Horizontal black dotted lines on the unit trace in the middle step cycle (shaded gray area) indicate average activity of the neuron during the step cycle, the two points mark the period of activity of the cell (defined in methods) and the vertical black dotted line indicates the phase of maximum activity. N indicates

the number of step cycles in the average. **C** and **D**: Vectorial representation of the discharge of the two cells; the black vector shows the mean phase direction of cellular discharge (θ). The curved black line outside the circle indicates the angular deviation (s). n , number of spikes; p , Probability that the cell discharges uniformly throughout the step cycle; Tril, triceps brachii, lateral head.

In the right lead condition, when the left contralateral limb is the second to pass over the obstacle, the cell started to increase its discharge before the gait modification but shows decreased activity during the swing phase in comparison to control activity (blue trace). The change in discharge activity during the step over the obstacle in the left and right lead was therefore reciprocal in this example. As mentioned above, this pattern of activity was observed in 12/21 step-related cells, 4 of which showed modified activity before the period of coBr activity in the right lead condition.

A second example of a step-related cell is illustrated in Fig.11B. In the left lead condition, the cell showed an initial decrease of activity at the beginning of the swing phase, followed by a strong increase of discharge throughout the second half of the swing phase (18.8Hz during control to 48.6Hz), followed by a maintained, but smaller, increase of activity throughout the stance phase. In the right lead condition, illustrated in the right panel, there was no significant change of activity during the step over the obstacle. A similar pattern of limb-specific activity was found in 5 other step related cells.

Altogether, step-related cells recorded in the STN showed mainly limb-specific activity where the cell either changed its activity only in left lead condition or changed its activity in both conditions, where the change of firing frequency was always smaller in the right lead condition. In the lead condition, the change of activity was mainly restricted to the swing phase, although the change of activity continued onto the stance phase in some cells.

A summary of the period of significantly modified activity of all step related cells and the phase of their peak modification of discharge in the left lead condition are illustrated in Fig. 12A. The maximum modification of discharge activity (increase and/or decrease) of almost all of the cells (20/21) occurred during the swing phase of the left forelimb (also

illustrated in Fig.12B). Only 1/21 cell changed its discharge maximally during the stance phase of the left

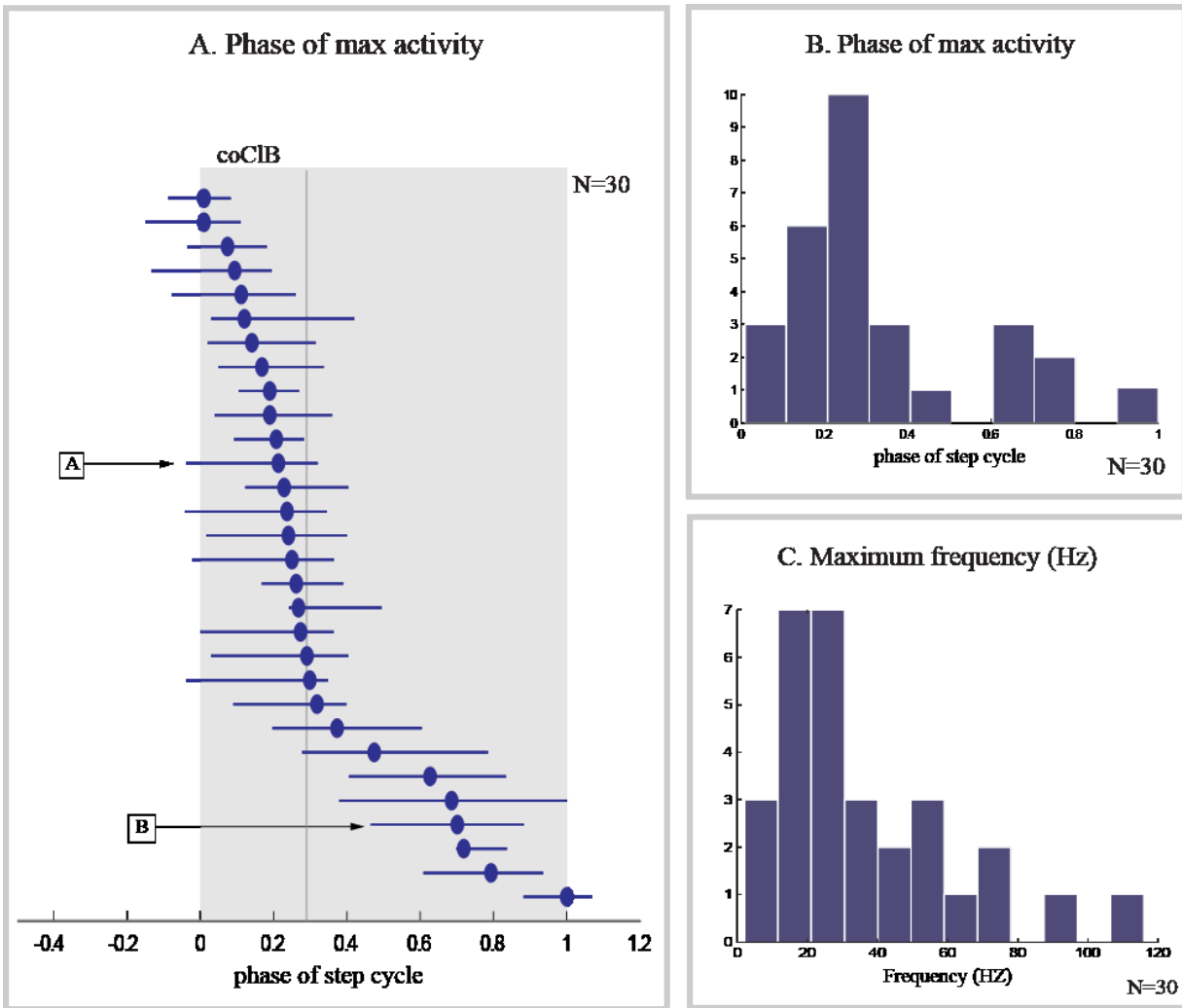


Figure 10. Summary of neural activity during unobstructed locomotion. A: The phase of peak discharge (circles) and the period of activity (horizontal lines), calculated in the same manner as illustrated in Fig.9, for all 30 cells that showed a significant, phasic discharge during unobstructed locomotion according to the Rayleigh test for directionality ($P < 0.01$). The traces are rank-ordered based on the phase of the peak discharge. The shaded area indicates the duration of one step cycle and the vertical continuous line indicates the average offset phase of the coClB (phase 0.25). The 2 cells shown in Fig.9A and Fig.9B are indicated with arrows. **B:** Histogram showing the distribution of the phase of the maximum activity for the 30 cells illustrated in A. **C:** Histogram showing the distribution of the maximum frequency discharge during control for the 30 cells illustrated in A.

lead condition, although 4/7 of cells that discharged maximally during the stance phase in control locomotion were step related. As illustrated in Fig. 12A, 6/21 cells showed a small decrease in activity (secondary burst) before the main step-related increase of discharge (main burst).

Maximum changes of activity in comparison to control activity for step-related cells are illustrated in Fig.13. For cells that increased their discharge or that showed both a decrease and an increase of discharge, the maximum change of activity was presented. For cells that showed a decrease, minimum activity was presented. The histogram in Fig.13A presents the distribution of maximum changes of activity during voluntary gait modification in the left lead condition with an average of 47 ± 28.22 Hz in comparison to the activity of modulated cells during control 35 ± 30 Hz (19/21). Fig.13B illustrates the activity of each cell during gait modification in comparison to the maximum discharge of the same cell during control locomotion.

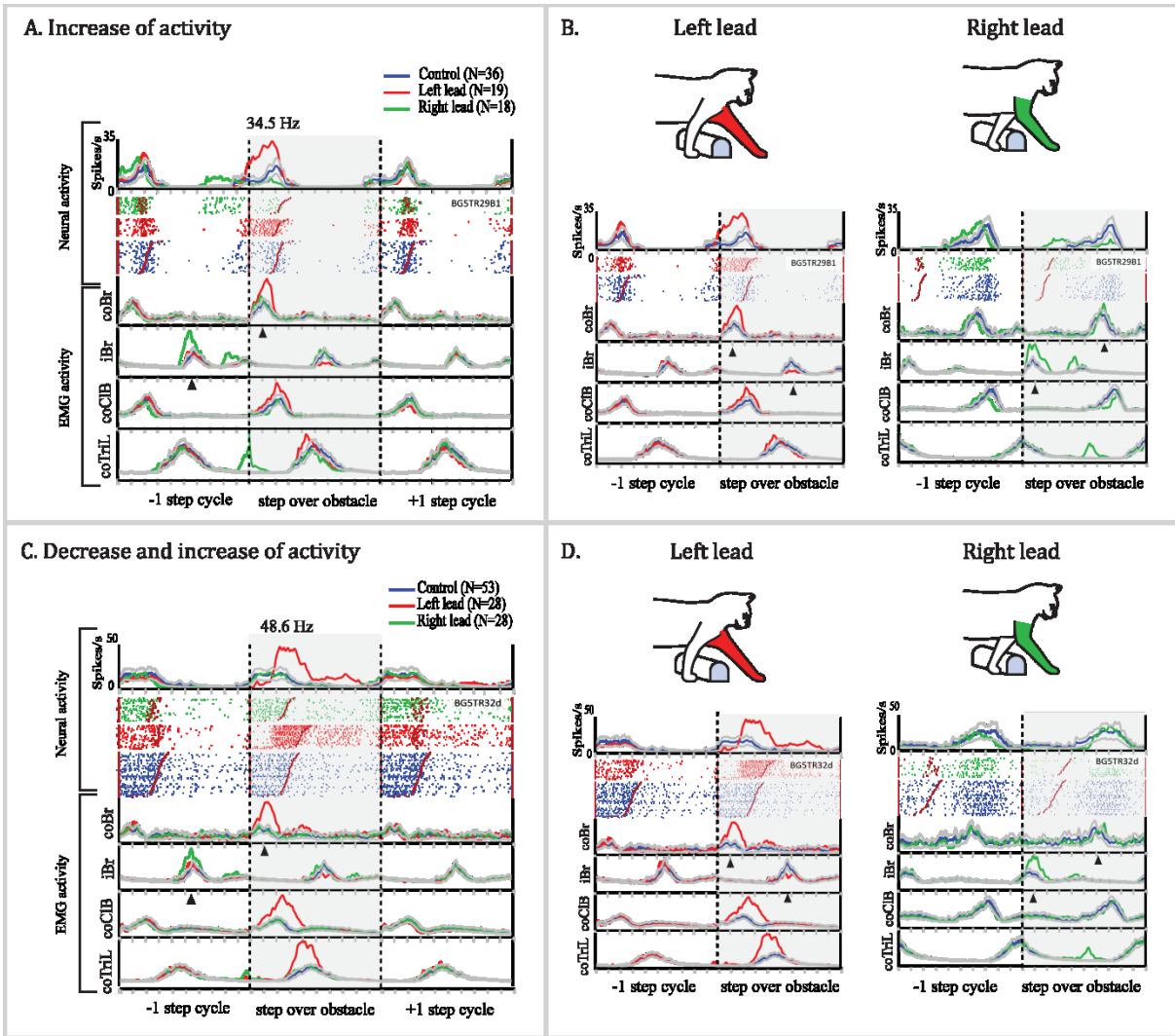


Figure 11. Step-related, limb-dependent activity recorded from 2 cells in the STN during gait modification. A-C: Peri-event histograms (PEHs) and raster displays of two example cells (A,B and C,D) displaying step-related activity in relation to the step over the obstacle (shaded area). Black vertical dashed lines on each side indicate the end of each step cycle. Small black triangles indicate the electromyographic (EMG) activity when the cat steps over the obstacle. Red traces represent activity during the left lead condition, green traces represent activity during the right lead condition, the blue traces are the control activity and the grey traces indicate the interval of confidence of the standard error (SE, $p < 0.01$) of the mean control activity. Note that A and C show the step before and the step after the modified step, while B and D show one step before the cat steps over the obstacle. Note also that in A and C, neural activity for the left and right lead conditions (red and green traces) is synchronized on the coBr, while in B and D, activity is synchronized on coBr in the left lead condition and on the iBr in the right lead condition. Both cells show swing-related activity during the period of activity of the coBr during control (blue trace). During steps over the obstacle in left lead condition (red trace), the cell in A increased its discharge in the swing phase and reached a maximum

of 34.5 Hz. The discharge was also increased during the swing phase in the right lead condition (green trace). **C:** In the left lead condition, (red trace) this cell exhibited an initial decrease of activity at the beginning of the swing phase of the left limb followed by an increase of activity during the latter part of swing and into the stance phase, reaching a maximum discharge of 48.6 Hz. During the right lead condition (green trace in D), neural activity was identical to control.

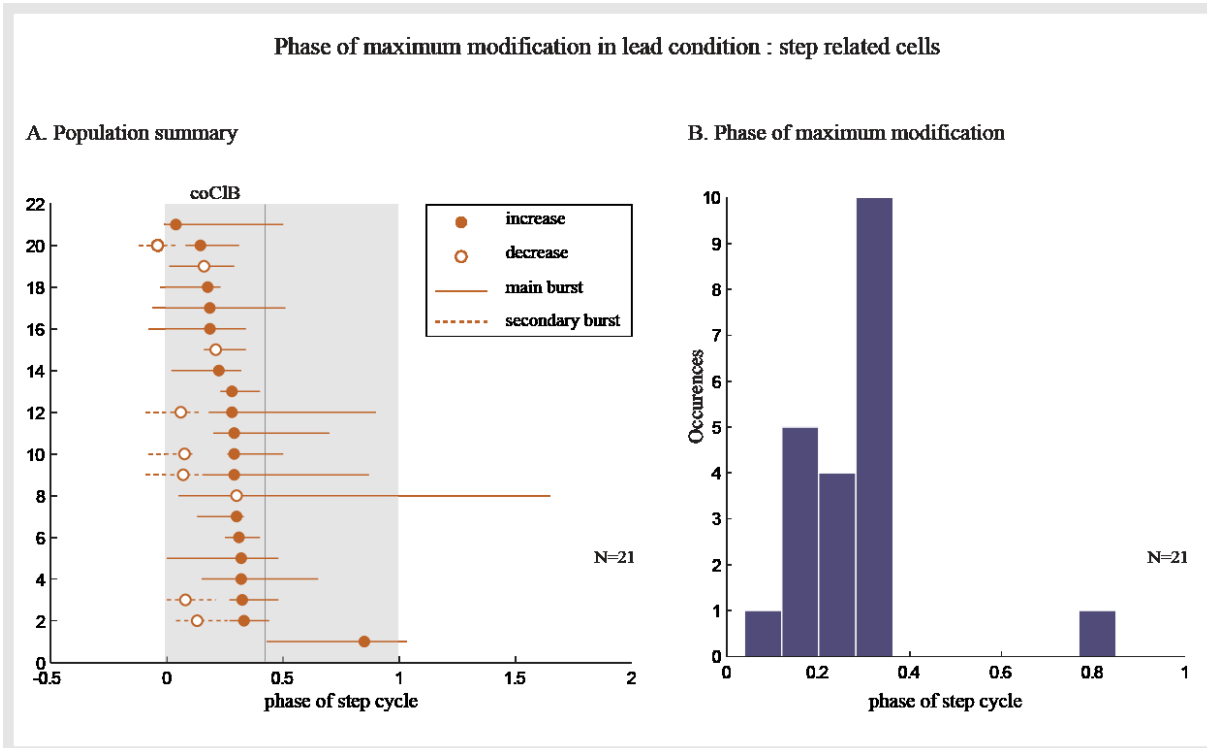


Figure 12. Phase of maximum modification of activity in step-related cells. A: Phase of peak discharge (circles) and the period of mean discharge (horizontal lines) for all 21 step-related cells in the left lead condition. The traces are rank-ordered based on the phase of the peak discharge. The shaded area indicates the modified step, the vertical continuous line indicates the average phase of offset of the coCIB (phase 4.7). Full circles indicate increased activity, open circles indicate decreased activity, solid horizontal lines indicate the main burst of discharge of the cell and dashed horizontal lines indicate secondary bursts of discharge. **B:** Histogram showing the distribution of the phase of the maximum increase and decrease of activity for the 21 cells illustrated in A.

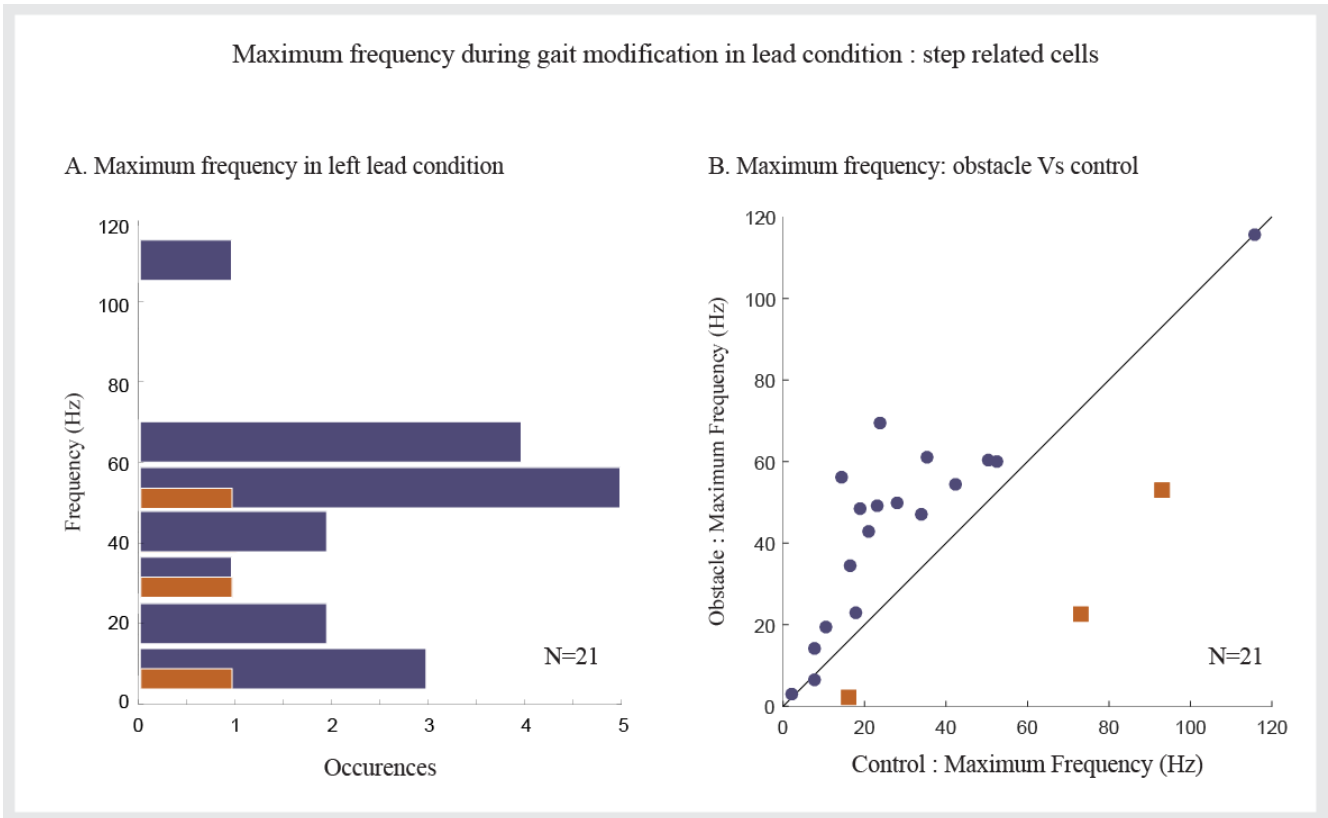


Figure 13. Maximum change of frequency discharge of step related cells during gait modification. **A:** Histogram showing the distribution of the maximum change of frequency of step related cells during voluntary gait modification. Purple bars represent the frequency of cells that increased their discharge, orange bars cells that decreased their discharge in relation to the step cycle. **B:** Maximum discharge frequency during the voluntary gait modification as a function of the discharge activity during control locomotion. The diagonal line indicates equal discharge activity in each condition. Blue circles indicate cells that showed an increase of discharge, orange squares indicate cells that showed a decrease in discharge during gait modification. N, number of step related cells in both graphs.

Step-advanced activity

Cells that were characterized as having a step-advanced activity (N= 16) significantly changed their discharge frequency more than 200ms before the onset of the swing phase of the modified step. Step advanced activity was mostly expressed as an increased activity (15/16), although 1/16 cell showed a decrease in activity.

Most of these cells (14/16) showed limb-independent activity in relation to the obstacle, although the amplitude of the modified activity in the left and right lead conditions was not always equal. The other 2/16 cells showed limb-dependent activity as one cell did not show a significant change of activity during right lead condition, and the other cell did not discharge at all. Moreover, the change of discharge in left lead condition was mostly larger or equal to the one in right lead condition, although some cells showed a larger increase of discharge in right lead condition and occasionally a change in the pattern of discharge.

Two examples of step-advanced activity are presented in Fig. 14. The first example in Fig.14A shows that, in the left lead condition, the cell showed a “ramp” increase of activity two steps before the obstacle, and reached a maximum just before the onset of the gait modification, at which point the cell stopped discharging. In the right lead condition, the cell discharged with a similar pattern, increasing its activity two steps before the step over the obstacle with the right limb and stopping just before the gait modification, although the amplitude of increase was smaller than in the left lead condition. The second cell illustrated in Fig.14B increased its discharge half a step cycle before the step over the obstacle but continued to discharge into the swing phase and stopped discharging at the end of the swing phase of the modified step. In the right lead condition, the cells displayed a similar pattern of discharge in relation to the right forelimb. Another type of step-advanced activity (not shown) was characterized by phasic activity during control locomotion which increased in frequency in both the left lead and right lead conditions (6/16). Moreover, this group usually showed an increase of discharge early during the step before the obstacle that reached a maximum during the swing phase of the modified step (although one cell showed a maximum increase during stance).

A summary of the phases at which all the step advanced cells maximally modified their discharge as well as the periods of significant change of activity are presented in Fig.15A.

Most cells started changing their discharge between phases -1 and -0.5 (7/16), meaning during the first half of the step before the obstacle, 6/16 cells started changing their discharge in the second half of the step before the obstacle (between phases -0.5 and 1), and only 3/16 cells changed their discharge two steps before the obstacle. Time of maximum discharge also varied between cells; 7/16 cells changed their discharged maximally during the step before the

obstacle, 5/16 right before the modified step, and 4/16 during the swing phase of the modified step. The modified activity stopped before the gait modification in some cases (3/16), during or at the end of the swing phase in most cells (12/16) and later during the stance phase in 1/16 cell.

The maximum discharge frequency of all step-advanced cells is illustrated in Fig.16A. As shown by the distribution of the bars, step-advanced cells showed a large range of maximum discharge in relation to voluntary gait modification.

The scatter plot in Fig.16B shows the relative increase of each cell in comparison to their discharge frequency during control locomotion. As illustrated in the plot, most step advanced cells (15/16) increased their discharge compared to their activity during control, while 1/16 cell decreased its activity in relation to the obstacle. Amongst these, 10/16 were modulated during control locomotion, while 6/16 were non-modulated and either discharged tonically or did not discharge at all during the unobstructed steps.

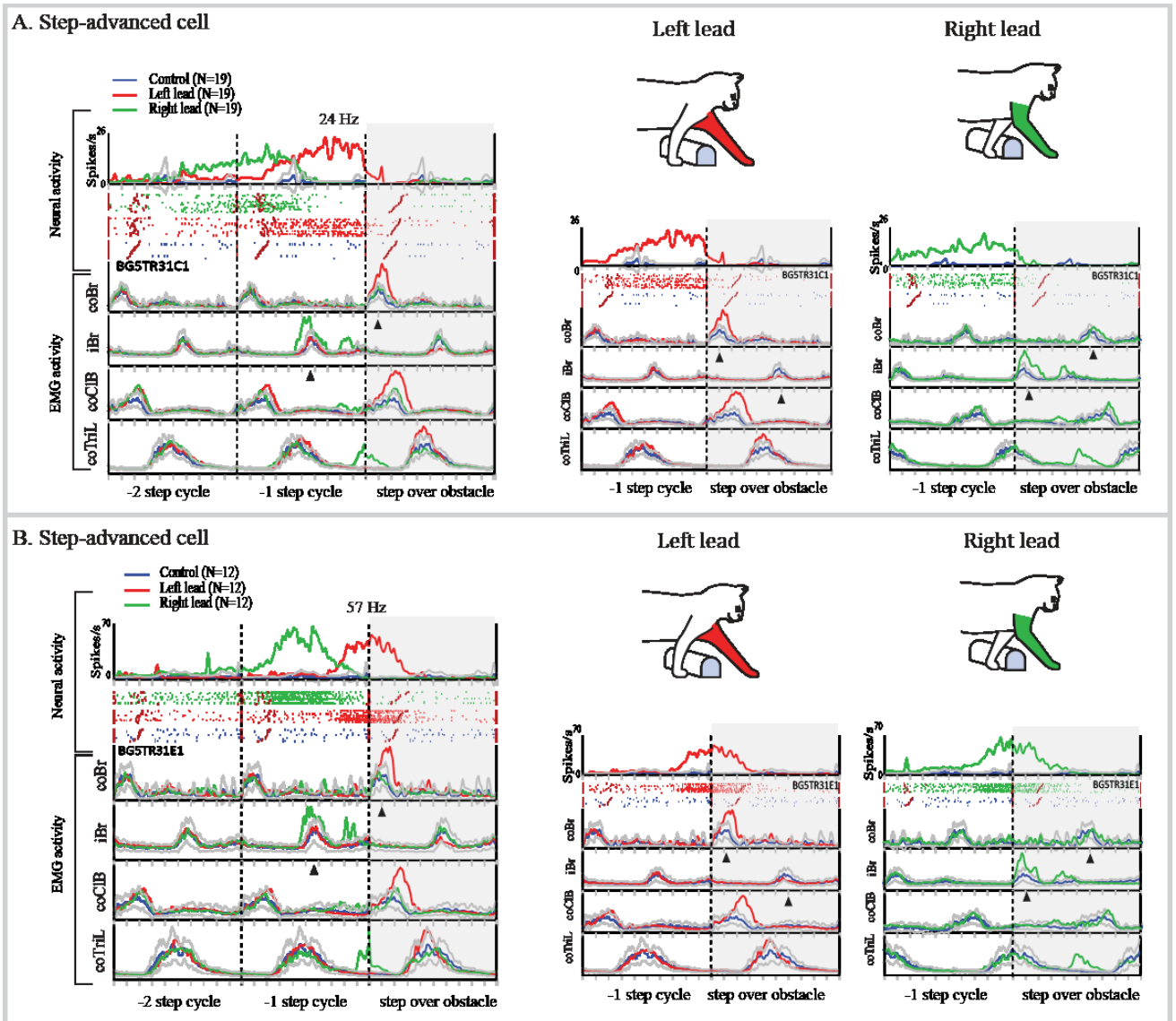


Figure 14. Step-advanced, limb-independent activity recorded from 2 cells in the STN during gait modification. A and B: PEHs and raster displays of two examples of the discharge activity of step-advanced cells during the step over the obstacle. Same conventions as in Fig.11, except for figures on the left that show two steps before the obstacle. **A:** Neural activity is triggered on the coBr. Cell in which activity in the left lead condition (red trace) increased one step cycle before the step over the obstacle, reached a maximum firing rate of 24 Hz and ended at the beginning of the modified step. Similar activity is observed in right lead condition (green trace). **B:** Cell in which activity also began prior to the step over the obstacle, which reached a maximum firing rate of 57 Hz, but which continued throughout the swing phase in both left lead and right lead conditions. The middle and right plots emphasize the limb-independent nature of the activity by synchronizing the activity either to the left coBr (left lead) or the right iBr (right lead).

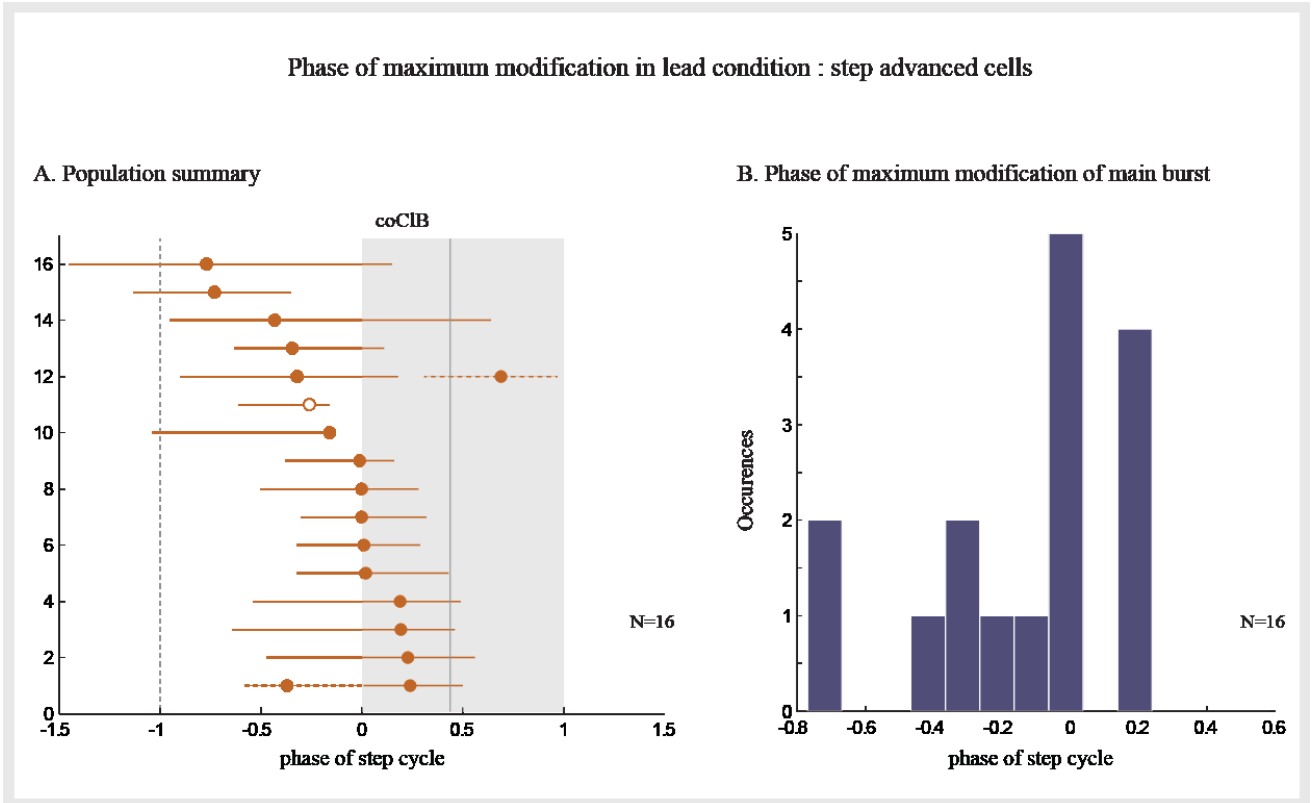


Figure 15. Phase of maximum modification of activity in step advanced cells. A: The figure is arranged as in Fig. 12A. Phase of peak discharge (circles) and the period of changed discharge (horizontal lines) for all 16 step-advanced cells that showed a significant deviation from the control activity (SE, $P < 0.01$) during the gait modification. The vertical dashed line indicates the beginning of the step before the obstacle (phase -1). **B:** Histogram showing the distribution of the phase of the maximum modification for the 16 cells illustrated in A.

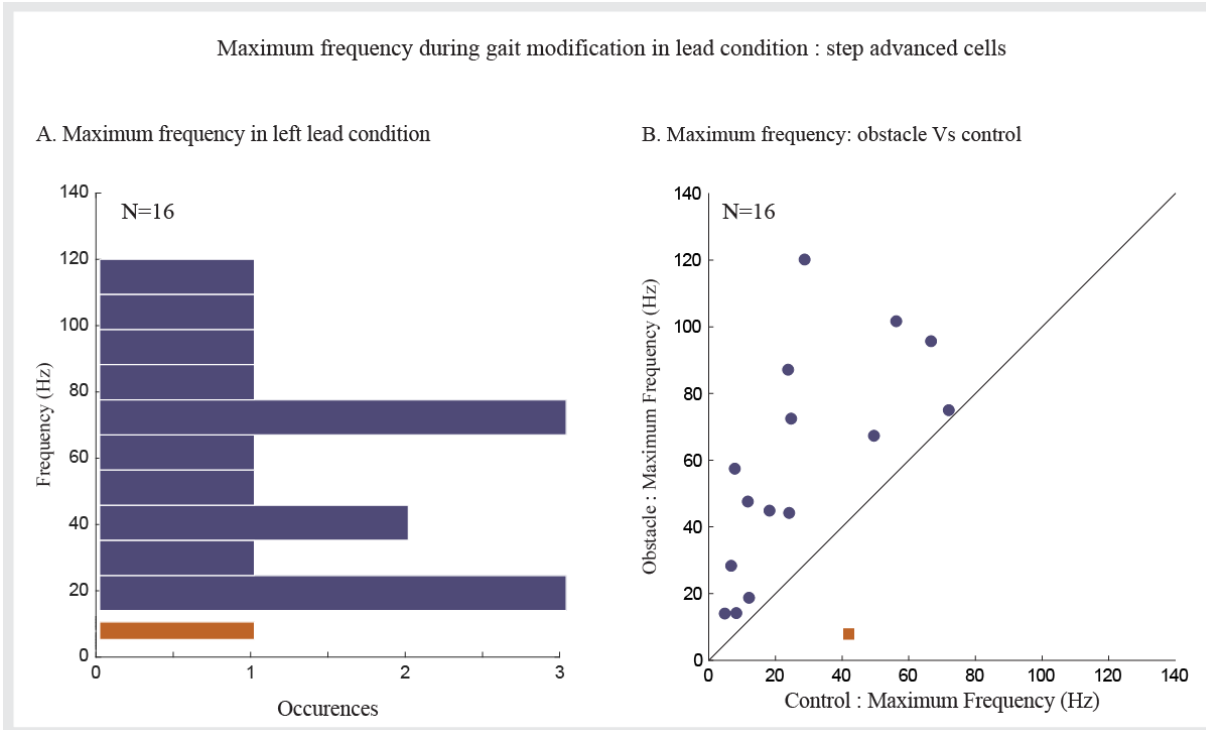


Figure 16. Maximum change of frequency discharge of step advanced cells during gait modification. **A:** Histogram showing the distribution of the maximum frequency of discharge of the step advanced cells during the gait modification. **B:** Peak discharge frequency during the step over the obstacle as a function of the discharge activity during control locomotion. Same conventions as in Fig.13.

IV. Discussion

The results of this study show that neurons in the STN display movement-related activity during both unobstructed treadmill locomotion and voluntary gait modification. During unobstructed locomotion, a population of subthalamic neurons was found to discharge in relation to different phases of the step cycle. During voluntary modification of gait, cells were found to change their firing rate either before the gait modification (step-advanced cells) or during the step over the obstacle (step-related cells). Such cells could contribute, respectively, to the planning and execution of the gait modification.

Unobstructed locomotion

Cells chosen for analysis (N=52) were selected based on initial on-line inspection of discharge activity that showed phasic activity related to limb movement either during unobstructed locomotion and/or in relation to gait modification. The remaining 81 cells were not analyzed, as online analysis showed either tonic, irregular discharge patterns or discharged in relation to saccadic eye movements. From our analysis, we found that 30/52 cells showed significant, unimodal distribution of their discharge in relation to forelimb movement during unobstructed locomotion. This modulated activity was characterized by a phasic increase of firing rate that reached its maximum either during the swing or the stance phase of the step cycle. These results extend those of previous studies showing a limb-related increase of subthalamic activity during unobstructed locomotion in the rat (Shi et al 2004) by revealing step-by-step changes in cell discharge in relation to different phases of the step cycle.

Given that a major input to the STN comes from the motor cortex and that the major output of the basal ganglia is directed towards the motor areas of the cortex, one might also usefully compare these results to those previously obtained in the motor cortex. On a general level, the results were similar in that both structures show a phasic increase of discharge frequency during unobstructed locomotion, which starts with the beginning of the step cycle and reaches its maximum mainly during the swing phase (Drew 1993). Moreover, in both structures, the majority of cells show increases of activity related to the swing phase of locomotion. However, the M1 contains multiple subpopulations of cells that display various patterns of activity at different times of the limb movement, which are closely related to the time and amplitude of activity of various muscles, mainly physiological flexors (Drew 1993). In contrast, the discharge in the STN was more homogenous in that cells discharged during the entire swing or stance phase of the step cycle instead of showing a more fractionated pattern of activity. This suggests that the STN might contribute more to the control of more global parameters of the ongoing limb movement such as direction, movement speed, movement direction and movement amplitude, rather than specifying the patterns of muscle activity.

Voluntary gait modification

This study is the first to examine subthalamic activity during voluntary gait modification. Our results show that a group of subthalamic cells, including some cells that did not show movement related activity during unobstructed locomotion, changed their firing rate in relationship to gait modification (N=37). Moreover, we identified two groups of cells with distinct times of discharge in relation to the obstacle: cells that showed step-related activity; and cells that showed step-advanced activity. In the following section, we will discuss the possible functions of each type of cellular activity.

Step related activity

Neurons displaying step-related activity constitute the majority of cells that modified their discharge in relation to voluntary gait modification (21/37). Most of these cells showed increases of discharge frequency during gait modification and virtually all of them (20/21) reached maximum activity during the swing phase of the step over the obstacle. This is unlike the activity of these cells during unobstructed locomotion where, out of the 19/21 cells that showed phasic activity during control locomotion, 15/19 cells discharged during swing and (4/19) discharged during stance phase. In other words, 3 step-related cells that discharged maximally during the stance phase in control locomotion, changed their discharge maximally during the swing phase during gait modification. This could be due to a higher need for supraspinal control when the cat negotiates the obstacle, and less so during the stance phase when the limb is in contact with the treadmill. The decrease of activity followed by an increase in some of the cells could be due to a change of phase of activity, where the cell would increase its discharge later than it would during control. This shift of phase could be due to the increased inhibitory effect of the GPe on the STN during movement, which would make the STN less excitable and delay the excitatory effect of the cortex.

The general features of subthalamic cellular discharge are similar to the neural activity observed in pyramidal tract neurons in M1 (Drew 1993). Indeed, most neurons in the primary motor cortex (63%) show step-related activity in relation to voluntary gait modification (Drew 1993). Moreover, similar to subthalamic activity, changes in activity were mainly expressed as an increase of firing rate that was maximum during the swing phase of the modified step, when the change of flexor activity was also maximum (Drew 1993).

However, subgroups of cells in M1 showed a pattern of fractionation in which different subpopulations of neurons were active in relation to specific groups of synergistic muscles (Drew 1993). On the contrary, subthalamic cells showed a pattern of discharge that was more generally related to the entire swing phase locomotion. As the STN receives a major input from the motor cortex, this suggests that subthalamic cells integrate activity from neurons with diverse patterns of activity to produce a more global signal containing information on the extent of the movement rather than information on the specific changes in muscle activity required to execute the gait modification. This interpretation is compatible with preliminary results of recordings from this laboratory of neuronal activity from other BG nuclei during locomotion, including the striatum and the GP (Leonard et al 2014, Mullié et al 2015), that equally show no indication of activity related to specific patterns in muscle activity.

Step advanced activity

Step-advanced activity was observed in a substantial population of the cells (16/37) showing modified activity in relation to voluntary gait modification. Most cells showed an increase in firing rate that was limb-independent. Cells began to discharge one or several steps before the gait modification and their discharge ended at the same time as/or during the gait modification.

This is similar to what has previously been described for cells in the caudal region (area 5b) of the PPC (Andujar et al 2010). In both the STN and the PPC, changes in discharge activity occurred between one and three steps before the gait modification and continued onto the modified step. Moreover, both displayed preparatory activity that was limb-independent, which suggests neither structure plays a role in specifying movement parameters in the first limb to step over the obstacle. This signal could, however, provide other preparatory information such as the location of the body in relation to an object (Marigold & Drew 2017) or information on the attributes of the obstacle (size, shape etc.). Although no direct projections from the PPC to the STN have been reported, predominant limb-independent activity in step-advanced cells of the STN could be due to an indirect influence from the PPC through the striatum. However, as premotor areas are known to project to the STN, we would expect a proportion of subthalamic step-advanced activity to be limb-specific, as limb-specific activity has been recorded in premotor areas (Nakajima et al 2015).

Similar to the activity in the PPC, step-advanced preparatory cells either ended their increased discharge just before or during the modified step (Andujar et al 2010). Cells that ended their discharge before the gait modification could provide information on the time of gait initiation, while cells that ended their discharge during gait modification could provide additional information on limb trajectory.

These results show that information on the planning of locomotor gait is transmitted to the basal ganglia through the STN. This information could be used by the BG to select the patterns of activity required for the upcoming gait modification. This activity prior to the gait modification is reminiscent of the preparatory activity recorded in the striatum prior to reaching movements (Alexander 1987, Alexander & Crutcher 1990a, Alexander & Crutcher 1990b, Crutcher & Alexander 1990, Schultz & Romo 1992).

Reaching studies

Our results regarding subthalamic activity during locomotion are consistent with previous recording studies of the STN during reaching movements in the cat (Cheruel et al 1996) and in primates (Georgopoulos et al 1983), which have shown strong movement-related activity that correlated to various movement parameters. Moreover, subthalamic cells were found to display movement-related activity during arm movement (average of 127ms before movement onset in the cat and 50ms in primates), and in lesser proportions, a preparatory activity which occurred prior to the movement onset. This movement related modification suggests that the STN plays a crucial role in the control of ongoing movement, likely through the hyperdirect pathway (Cheruel et al 1996, Georgopoulos et al 1983, Wichmann et al 1994a).

Although not reported in this memoir, we also recorded activity from some cells both during the gait modifications and during reaching movements. In almost all cases, we found that cells showed movement-related activity during both activities. This suggests that the subthalamic activity related to planning and execution is not specific to locomotion, but is rather related to the more general control of limb movement.

Implication of subthalamic activity in the role of the basal ganglia

According to current BG models (Alexander & Crutcher 1990, DeLong 1990, Nambu et al 2002), increased activity in the STN results in increased activity in the GPi, which inhibits the motor thalamus and reduces thalamocortical activity. In this model, an increase of subthalamic activity is thought to have a generalized, movement-suppressing effect. When taking this model in consideration, it is hard to make sense of the strong movement related patterns of activity recorded in the STN during locomotion, and the increase of subthalamic activity when the contralateral limb executes the gait modification. A similar consideration holds for the strong increases in activity observed during reach (see preceding paragraph). Therefore, the idea that subthalamic activity suppresses movement has to be reconciled with the results of recording studies showing a strong relationship between subthalamic activity and the executed movement.

One possibility is that the strong movement-related activity could be compatible with the center surround model of BG motor control, according to which the indirect pathway suppresses, not the executed movement, but “competing motor plans“ by inhibiting the BG output (Mink 1996). According to this model, a subthalamic increase of discharge could have a movement suppressing effect that would promote the executed movement by exciting the BG output structures through the indirect pathway.

One element to consider, however, is the projections from the STN to the GPe (Sato et al 2000). BG intrinsic pathways have been typically seen as a one-directional transmission of information from input to output structures, but these “upstream“ connections could allow the STN to have a different effect on the GPi through the GPe. Subthalamic glutamatergic projection to the GPe would increase its inhibitory effect on the Gpi, resulting in a movement promoting effect. However, the resulting outcome of these two opposing effects of subthalamic activity on movement is not yet fully understood.

Future experiments

It goes without saying that additional research is needed to fully understand the contribution of the STN to the control of locomotion. Further insight into this contribution could be achieved through various lines of study.

From an anatomical point of view, few studies have examined subthalamic connections in cats. Although we expect the afferent and efferent connections of the STN to be similar to those described in primates, it is important to confirm the origins of the projections to the STN, especially those coming from different cortical areas. This would allow us to better interpret the patterns of neuronal activity recorded in the STN and to compare them with those obtained from different cortical areas in the same task (Drew 1993, Marigold & Drew 2011, Nakajima et al 2015).

From a behavioral standpoint, examining the effect of STN inactivation on unobstructed and visually guided locomotion, by using pharmacological methods (such as Muscimol) or optogenetic methods would complement the results of this study and provide a better understanding of the role of the STN in gait control. Moreover, studying the effect of the same lesion during reaching movements and comparing the observed motor deficits with those seen during voluntary gait modification would give more insight on the general role of the STN in the control of visually guided movement.

Finally, only a few studies in rats have looked at the effect of dopaminergic depletion on locomotion, and none of these studies have specifically examined how visually guided locomotion is affected. Additionally, information on the effect of STN stimulation on parkinsonian gait is limited to clinical research.

Overall, much remains to be discovered when it comes to the BG and subthalamic contribution in the control of locomotion, particularly visually guided locomotion. A deeper understanding of the fundamental networks that contribute to the production of voluntary gait modification is crucial for the further development of treatments that would grant PD patients a greater and safer mobility, as well as an overall better quality of life.

Conclusion

Overall, the results from this study show that the STN in the cat displays movement related activity in relation to forelimb movement during locomotion. This activity can be phasic during unobstructed locomotion and can occur in different phases of the step cycle. During visually guided locomotion, subthalamic neurons show mainly an increase of activity either before or during voluntary gait modification. Together, these results suggest an

important contribution of the STN to the control of locomotion and particularly to the planning and execution of voluntary gait modifications. However, a deeper understanding of this contribution is needed to fully grasp the role of the STN and the BG in the control of visually guided locomotion.

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