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The subthalamic nucleus: a hub for sensory control via short three-lateral loop connections with the brainstem?

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ABSTRACT

The subthalamic nucleus (STN) is classically subdivided into sensori-motor, associative and limbic regions which is consistent with the involvement of this structure in motor control, but also in cognitive and emotional tasks. However, the function of the sensory inputs to the STN's sensori-motor territory is comparatively less well explored, although sensory responses have been reported in this structure. There is still a paucity of information regarding the characteristics of that subdivision and its potential functional role in the basal ganglia processing and more widely in associated networks. In this Perspective paper, we summarize the type of sensory stimuli that have been reported to activate the STN, describe the complex sensory properties of the STN and its anatomical link to a sensory network involving the brainstem, characterized in our recent work. Analyzing the sensory input to the STN led us to suggest the existence of previously unreported three-lateral subcortical loops between the basal ganglia and the brainstem which do not involve the cortex. Anatomically, these loops closely link the STN, the substantia nigra pars reticulata and various structure from the brainstem such as the superior colliculus and the parabrachial nucleus. We also discuss the potential role of the STN in the control of sensory activity in the brainstem and its possible contribution to favoring sensory habituation or sensitization over brainstem structures to optimize the best selection of action at a given time.

1. THE SUBTHALAMIC NUCLEUS

The subthalamic nucleus (STN) was initially described as a “simple” relay in the indirect pathway between the input and the output structures of the basal ganglia (BG). In recent years, however, evidence has accumulated that it should also be considered as another crucial entry point to this system. It is now widely appreciated that “hyperdirect” cortico-subthalamo-nigral/pallidal connections constitute an important parallel component of the general looped architecture of the BG and those connections have been incorporated into contemporary computational models of the BG [1,2]. The function(s) of those hyperdirect connections however are not clear. The STN has long been thought of as a “motor structure” exclusively with a role in motor control. However, this view has been challenged by the discovery that the STN is strongly involved in regulating motivated behaviour [3-5], reward processing [6-8], emotional processing [9], behavioral interruption and switching between actions [10-15].

Sensori-motor, associative and limbic regions of the cortex form functional loops with the equivalent regions of the BG - the striatum, pallidum and substantia nigra pars reticulata (SNr) [16]. These distinct subdivisions also characterize the STN [17], an anatomical segregation which is consistent with the involvement of the STN in motor control, but also in cognitive and emotional tasks that have been extensively studied in humans and animals (for a review see [18]). However, the function of the sensory inputs to the STN’s sensori-motor territory is comparatively less well explored, although sensory responses have been reported in the STN [e.g. [19)].

2. SUBTHALAMIC NUCLEUS AND SENSORY PROCESSING

While the characterization of sensory responses was not necessarily the primary objective of

many of the earlier experiments performed in the STN, these studies nonetheless reported that STN neurons responded to visual, auditory, noxious and non-noxious somato-sensory stimuli [19-22]. The presentation of somato-sensory stimuli such as electrical stimulation or natural light touch on the head, body, paws and tail of the rat elicit short latency excitation in the STN. These responses are suppressed by the ablation or cooling of the somato-sensory cortex [20]. Subthalamic somato-sensory responses were later confirmed in patients with Parkinson's disease in whom somato-sensory evoked potentials were recorded from the STN through DBS electrodes [23, 24] and were used to optimize the localization of these electrodes within the STN [25]. Neurons in the STN have also been reported to be activated by visual stimulation in an oculomotor task in non-human primates [21] and 30 % (70/226) of STN cells recorded in freely moving rats exhibit short latency / short duration auditory responses to a tone or a white noise [22]. The involvement of the STN in auditory processing has also been demonstrated in patients with Parkinson's disease performing an auditory oddball task [26] or subject to auditory change detection [27]. Finally, nociceptive responses have been documented in the STN (which has clinical implications for the potential control of chronic pain, for example in Parkinson's disease where pain is common [19]. Noxious stimulation can modulate STN activity physiologically [19] and in the parkinsonian brain [19, 28, 29]. Furthermore, nociceptive perception has recently been demonstrated to be modulated by optogenetic manipulation of the STN [30] or STN lesions [19]. These results highlight an important functional role of STN in pain processing, perception and modulation (for review see [31]).

Overall, despite the traditional description of a sensori-motor territory in STN, there is still a paucity of information regarding the characteristics of that territory and its potential functional role in BG processing and more widely in associated networks.

3. CHARACTERIZATION OF STN SENSORY INPUT AND SENSORY RESPONSES.

Our work over the past few years has helped to shed considerable light on the anatomical and physiological organization of the STN and related structures. We discovered additional monosynaptic hyperdirect pathways to the STN, this time from two subcortical brainstem structures rather than from the cortex: the superior colliculus (SC), a multi-sensory structure in the midbrain and the parabrachial nucleus (PBN), a primary nociceptive structure [19, 32] (Figure 1). The initial discovery of the cortical hyperdirect pathway positioned the STN as a critical structure in a network processing information simultaneously from the cortex and the BG [2]. Our demonstration of the hyperdirect connections between the SC / PBN and the STN, in complement to the pedunculo-pontine (PPN) and periaqueductal grey nucleus (PAG) - STN pathways [33, 34], extends this view of the STN as a central node in between the BG, the cortex and the brainstem.

These additional subcortical hyperdirect pathways relay short latency visual and nociceptive sensory information to the STN, from the SC and PBN, respectively [19, 32]. Our preliminary experiments also indicate that the SC is crucial for relaying short latency auditory signals as well (unpublished data). Neurons in the STN have complex sensory properties. We identified subpopulations of cells which increase or decrease their tonic firing rate in the context of nociceptive stimulation (Figure 2). Phasic responses to noxious stimulation are also complex (Figure 3). Short latency phasic responses to noxious stimuli are not constant in amplitude across repetitive stimulus presentations, but instead they vary. Examining the first 60 trials versus the last 60 trials of a 120 set of noxious footshocks, some cells in the STN show a strong phasic response during the first set of stimulations, but not during the second set (Figure 4). In cells responsive to auditory stimulation, phasic responses evolved in a positive or negative linear way with the repetitive presentations.

4. STN SENSORY INPUT - ANATOMICAL ORGANIZATION: THREE-LATERAL SUBCORTICAL LOOPS

An important component of the general architecture of the cortical-BG connectivity, which has been argued to reflect the function of the BG, is the parallel, mainly segregated, closed-loop projections that originate from, and return to, the same neocortical domains [16]. A few years ago, we extended this idea by suggesting that many sensori-motor subcortical structures from the brainstem with the capacity to guide movement also have connections with the BG that may represent a series of parallel, at least partially, closed loops [35]. This implies that the BG are processing information coming from the cortex but also from evolutionarily older brainstem sensory structures to direct behavioral output.

The previous work characterizing the sensory input to the STN led us to another observation regarding the connectivity between the BG and brainstem structures. The organization of these connections is likely to give rise to additional short loops, previously uncharacterized, which do not involve the cortex. This idea is based on work from our group and others concerning connections between the BG and the SC / PBN, but also the PAG and the PPN. As illustrated in figure 5, the SC, PBN, PAG and PPN all receive an afferent input from the SNr [36-39] and send a direct projection to the STN [19, 32-34, 40], which in turn projects to the SNr [41]. We thus suggest that these short three-lateral subcortical links may represent a set of brainstem – STN – SNr parallel loops. This idea is further supported by the recent description of specific populations in SNr projections targeting distinct brainstem areas [42], which suggests that these loops may well be segregated. Whether these connections represent closed loops or not remains to be elucidated. However, our preliminary anatomical data is consistent with at least a partial closure of the loops (Figure 6).

5. STN SENSORY INPUT - FUNCTIONAL IMPLICATIONS

The STN is positioned to integrate sensory modalities coming from the brainstem to

adjust/select adapted behavioral output directly via the SNr (Figure 5). These sensory inputs have implications for the assumed function(s) of the STN. Our data are consistent with the idea that the STN is involved in the interruption of ongoing behavior [13]. The SC has been likened to a novelty detector [43]. Any unexpected event happening in the environment is likely to activate this structure at short latency. The transmission of this information is crucial for STN's role in behavioral interruption as these new events may be of vital adaptive importance and require a change of behavior. The processing of nociceptive information by the STN is also consistent with the role of the STN in behavioral interruption. Pain is a clear indicator that a behavior with negative consequences is taking place and hence needs to cease.

It would not be behaviorally adaptive to be interrupted by stimuli once their salience has lessened, if they appear repeatedly. In such cases, the sensory transmission to STN should somehow shut down to block the behavioral re-orientation. The reduction of the sensory responses we observed in the STN with repeated sensory stimulation indicates that the impact of afferent sensory inputs can be adjusted. Does this reduction of activity in the STN reflect a habituation of brainstem-derived sensory responses, leading to a reduced likelihood of interruption? The mechanism involved in this process remains to be found, but the outcome may be achieved by modulating the output of the SNr. The complex increase and decrease of STN baseline firing rate with noxious stimulation suggests that control of the SNr by the STN is complex, consisting as it does of phasic and tonic components. The SNr represents a structure via which the final command given by internal processing in the BG is transmitted to the thalamus and sensori-motor structures from the brainstem. SNr GABAergic projections serve to inhibit and disinhibit neurons in nuclei such as the SC and the thalamus [44]. They have a spontaneous tonic, high frequency, regular firing rate under normal conditions. Following an extrinsic input to the BG, this firing rate might increase or decrease, and/or the

firing pattern might change, impacting the structure's output. The change in firing rate/pattern from the SNr is thought to control action selection computed by the BG. The modulation of STN responses when a sensory stimulus occurs should increase or decrease SNr firing rate. We can therefore expect a dual behavioral outcome, the blocking or favoring of the selection of an action, respectively.

6. FUNCTIONAL HYPOTHESIS

One of the major unsolved ethological questions in neuroscience is the neurobiological bases of sensory habituation. It is characterized by a progressive decrease in the amplitude or frequency of motor responses to repeated sensory stimulation that is not caused by sensory receptor adaptation or motor fatigue. Habituation plays an important role in attentional process allowing you to turn your attention to new salient stimuli or to slowly ignore uninteresting stimuli. Therefore, the brain's ability to ignore repeating, often redundant, information while enhancing novel information processing is paramount to survival, although the mechanism is not known.

We thus suggest that the control of the brainstem sensory habituation could be effected within the loops linking the brainstem to the STN and SNr. The STN could exert dual red (preventative) and green (permissive) control to regulate the sensory processing in the brainstem via the SNr. Since STN responses to these sensory inputs are universally excitatory (i.e. 19, 22, 32], the phasic activation of the STN would lead to a phasic increase of glutamatergic tone to the SNr, increasing the inhibitory tone of SNr GABAergic neurons over their targets and interrupting the ongoing action. However, the STN also exhibits a modulation of its tonic activity following a sensory stimulation, increasing or decreasing its general firing

rate. Therefore, this would lead to a tonic potentiation or reduction of STN-related glutamatergic tone in the SNr, interrupting or facilitating actions respectively. The anatomical three-lateral subcortical loops may thus represent the subcortical contribution of the BG in action selection for fast control over brainstem activity and behavior. Changes in that relationship over time may subserve sensory habituation and sensitization.

Finally, several lines of evidence suggest that the firing pattern in the STN is driven by the cortico-subthalamic pathway [45, 46]. Chudasama et al. (2003) [47] demonstrated the functional interaction and conjoint importance of the medial prefrontal cortex and the STN in attentional performance. Animals with disconnections between the prefrontal cortex and the STN have profound attentional impairments and a high level of perseveration (absence of habituation?) [47] comparable to those of bilateral STN lesions [3]. This suggests that the involvement of the STN in attentional performance is possibly under the control of the prefrontal - STN projection. We thus suggest that the STN constitutes a hub integrating both sensory information arising from the SC and PBN, and attentional selection driven by the prefrontal cortex to control sensory activity in the brainstem (Figure 7). Whether or not the prefrontal - STN projection contributes to regulate STN activity to favor habituation and/or sensitization of sensory control over the brainstem to optimize the best selection of action at a given time remains to be clarified.

LIST OF ABBREVIATIONS

BG	=	Basal ganglia
PAG	=	Periaqueductal grey nucleus
PBN	=	Parabrachial nucleus

PPN	=	Pedunculo pontine nucleus
SC	=	Superior colliculus
SNr	=	Substantia nigra pars reticulata
STN	=	Subthalamic nucleus

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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FIGURE LEGENDS

Figure 1: Superior colliculus and parabrachial nucleus projections to the subthalamic nucleus. Adapted from Coizet et al., *Journal of Neuroscience*, 2009 and Pautrat et al., *eLife*, 2018.

Top panels (left): Coronal sections illustrating a biotinylated dextran amine (BDA, anterograde tracer) injection site in the lateral deep layers of the SC (a) associated with dense labelling of terminals in the rostral (b) and central (c) STN. A corresponding injection of BDA into the medial SC (d) produced virtually no anterograde labelling at the same rostrocaudal levels of the STN (e and f). In the latter case, neurons of the STN marked with purple dye were retrogradely labeled by an injection of Fluorogold in the SN. Note that the tecto-subthalamic nucleus pathway is regionally specific.

Top panel (right): Collicular neurons retrogradely labeled from the STN are concentrated in the lateral deep layers. Photomicrographs of retrogradely labelled neurons (arrows) in the SC (a) following a cholera toxin (CTb, retrograde tracer) injection site confined to the STN (b).

Bottom panel (left): Sagittal sections illustrating a PHAL (anterograde tracer) injection site (c) associated with labeled terminals in the medial (a) and lateral (b) PBN.

Bottom panel (right) Photomicrographs of coronal sections showing retrogradely labeled neurons in the PBN (a) following an injection of CTB into the STN (b). Scale bars: 20 μ m.

Abbreviations: BDA: biotinylated dextran amine; cp: cerebral peduncle; f: fornix; ic: internal capsule; IPBN: lateral parabrachial nucleus; MG: medial geniculate thalamus; mPBN: medial parabrachial nucleus; mt: mammillothalamic tract; PAG: periaqueductal grey nucleus; SC:

superior colliculus; scp: superior cerebral peduncle; SN: substantia nigra; STN: subthalamic nucleus; ZI: zona incerta.

Figure 2: STN tonic sensory responses. *Adapted from Pautrat et al., eLife, 2018.*

Peristimulus histograms showing individual cases of decreased (left) and increased (right) subthalamic nucleus (STN) baseline firing rate with the introduction of nociceptive stimulation. Histograms of the group mean data (\pm standard error of the mean, SEM) during the sham (dark gray) and nociceptive (light gray) stimulation. The histograms show a significant increase or decrease of the baseline firing rate in the up ($p < 0.001$) and down groups ($p < 0.001$), respectively. Note the higher baseline firing rate of the down cells during the sham stimulation compared to that of the up groups ($p < 0.05$).

Figure 3: Subthalamic nucleus phasic visual and nociceptive sensory responses. *Adapted from Coizet et al., Journal of Neuroscience, 2009 and Pautrat et al., eLife, 2018.*

Top panel: Peristimulus histograms showing individual cases of different types of visually evoked responses in the subthalamic nucleus (STN). The dashed vertical lines indicate the onset of the visual stimulus. The n associated with each histogram indicates the number of cases exhibiting that class of response (total = 13, multi-unit recordings).

Bottom panel: Peristimulus histograms showing individual cases of different types of phasic nociceptive responses in the STN. The dashed vertical lines indicate the onset of the noxious footshock. The n associated with each histogram indicates the number of cases exhibiting the class of responses (total = 98, single unit-recordings).

Figure 4: STN phasic sensory habituation. Peristimulus histograms showing individual cases

of nociceptive evoked responses during the first 60 trials (left) and last 60 last (right) of a 120 trial run to illustrate the effect of the sensory stimulation repetition over time. The red lines indicate the onset of the noxious footshock. Note that these cells in the subthalamic nucleus (STN) showed a strong phasic response during the first set of stimulations, and a reduced amplitude of that response but not during the second set of stimulations.

Figure 5: Subcortical three-lateral loops. Diagram illustrating the connectivity in a triangle between 1. The periaqueductal grey nucleus (PAG) / the parabrachial nucleus (PBN) / the superior colliculus (SC) / the pedunclopontine tegmental nucleus (PPN), 2. The subthalamic nucleus and 3. The substantia nigra reticulata. Note that the PBN and the SC relays nociceptive and visual signals to the subthalamic nucleus, respectively. Preliminary data from our group also suggest the transmission of auditory information through the tecto-subthalamic pathway.

Figure 6: Subcortical three-lateral open or closed loops? We iontophoretically injected an anterograde tracer (Phaseolus vulgaris- leucoagglutinin, PHA-L) in the substantia nigra pars reticulata simultaneously to a retrograde tracer (fluorogold) in the subthalamic nucleus (left diagram). The photomicrographs (right panel; two per structure) centered on the superior colliculus (left), the periaqueductal grey nucleus (center) and the parabrachial nucleus (right) illustrate the proximity of some labelled fibers and boutons from the substantia nigra pars reticulata (brown) and labeled cells bodies projecting to the subthalamic nucleus (grey/black).

Abbreviations: PAG: periaqueductal grey nucleus; PBN: parabrachial nucleus; SC: superior colliculus; SNr: Substantia nigra pars reticulate; STN: Subthalamic nucleus.

Figure 7: The subthalamic nucleus position in between the cortical and brainstem inputs.

Diagram illustrating the anatomical position of the subthalamic nucleus (STN) in between the

hyperdirect projections from the cortex and the brainstem, suggesting that the STN may constitute a hub integrating sensory information arising, at least in part, from the superior colliculus (SC) and parabrachial nucleus (PBN) and attentional selection driven by the prefrontal cortex to control sensory activity in the brainstem.

FIGURES

Figure 1

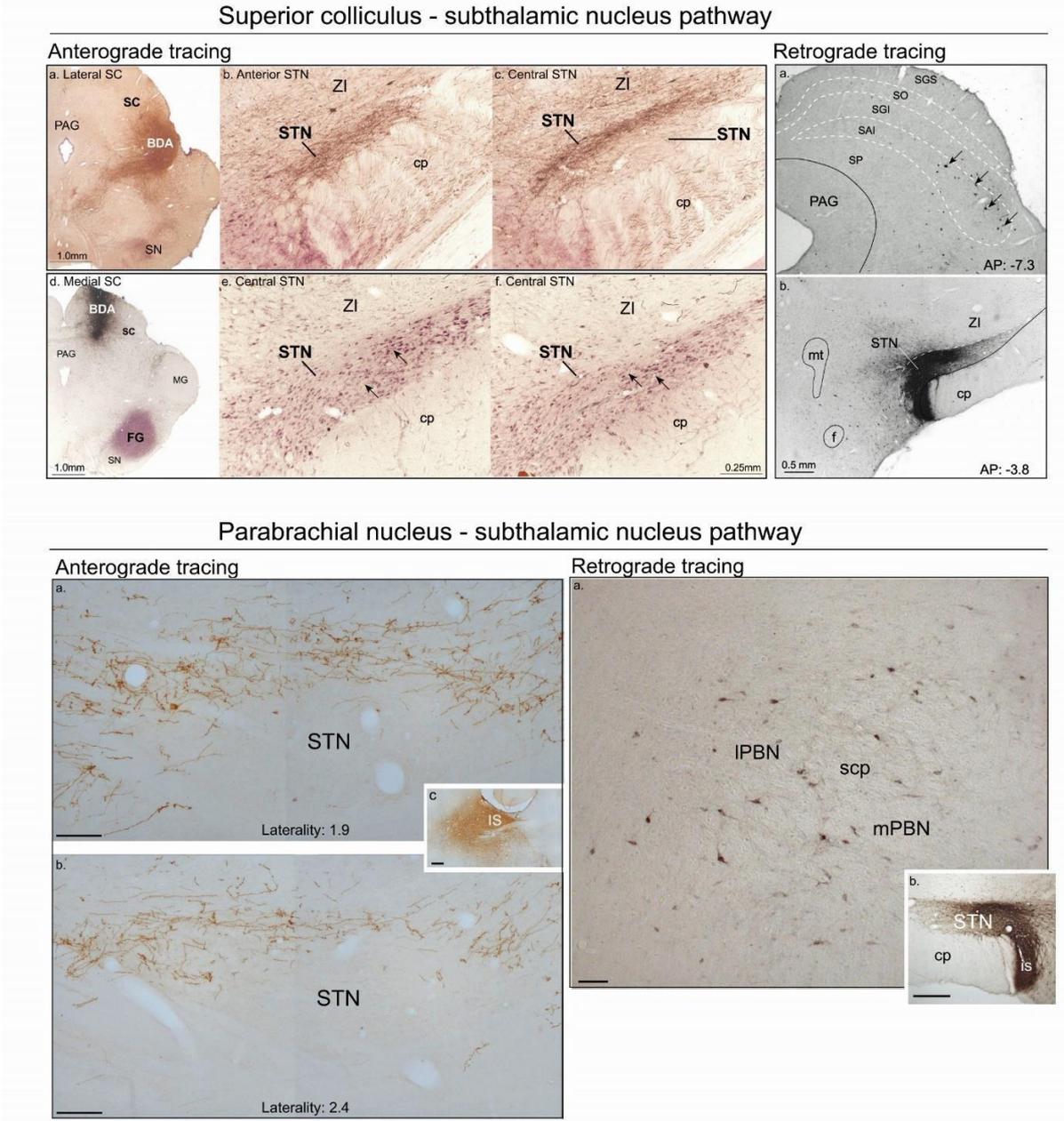


Figure 2:

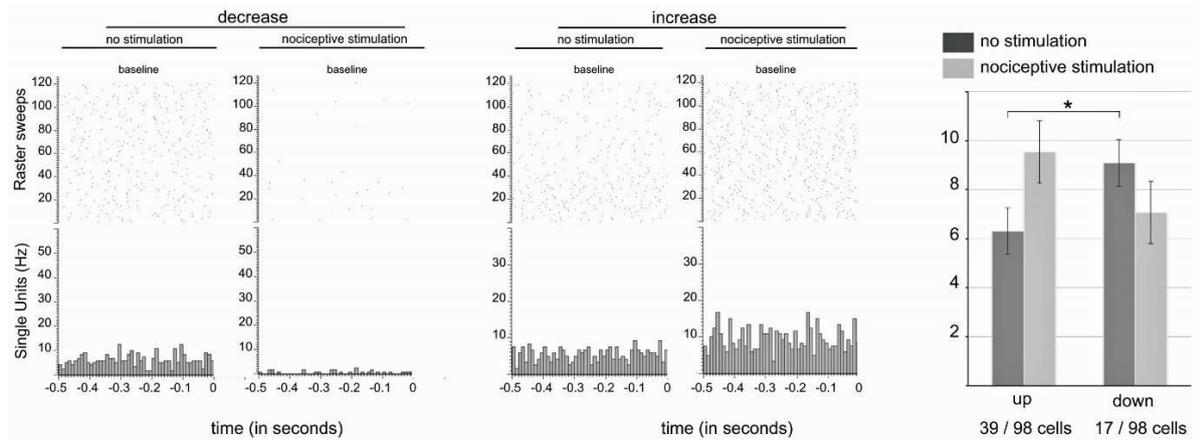
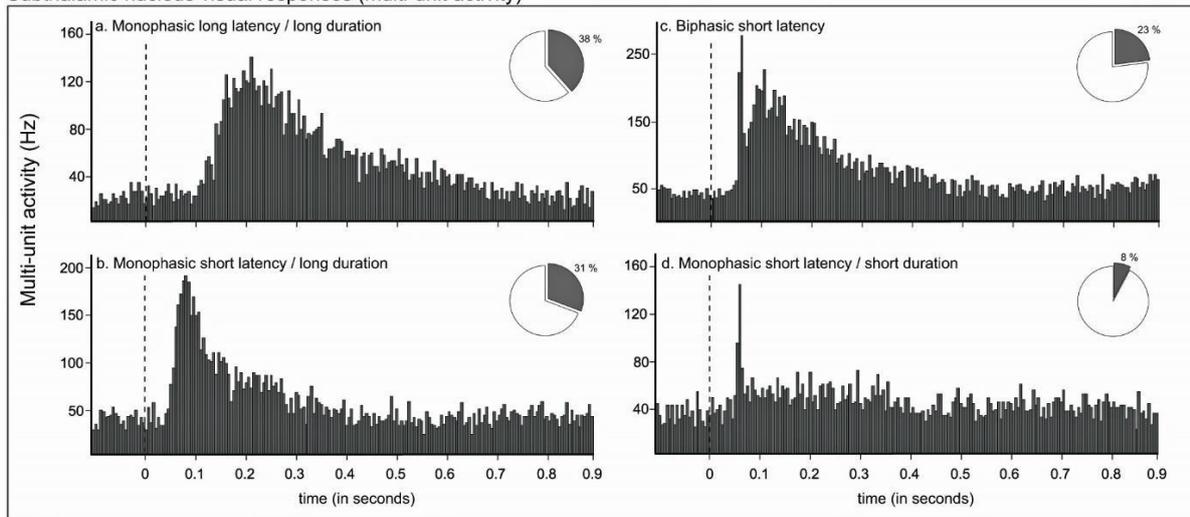


Figure 3:

Subthalamic nucleus visual responses (multi-unit activity)



Subthalamic nucleus nociceptive responses (single-unit activity)

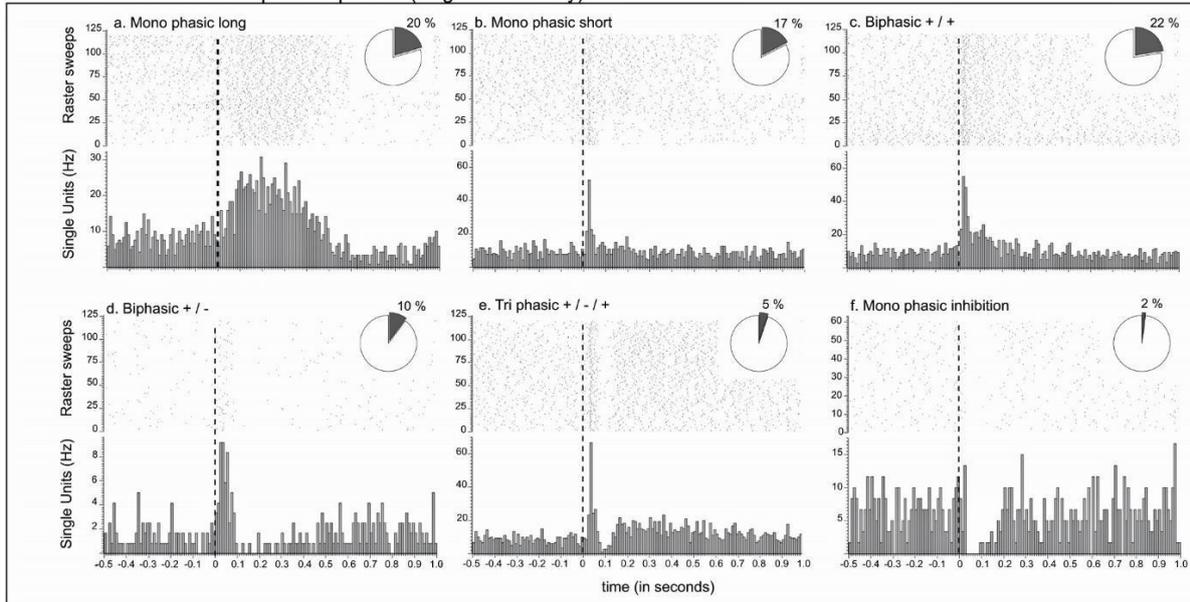


Figure 4:

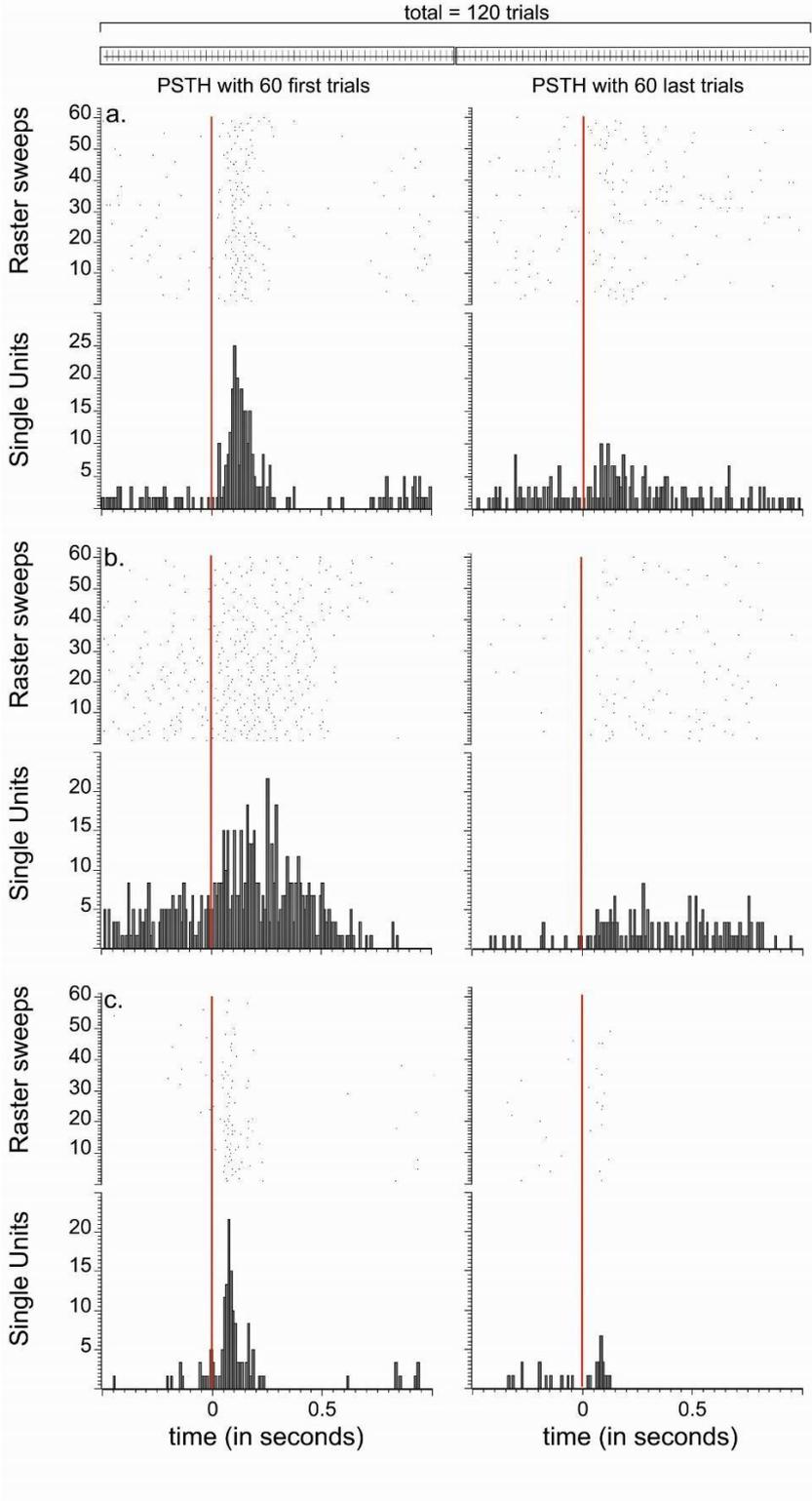


Figure 5:

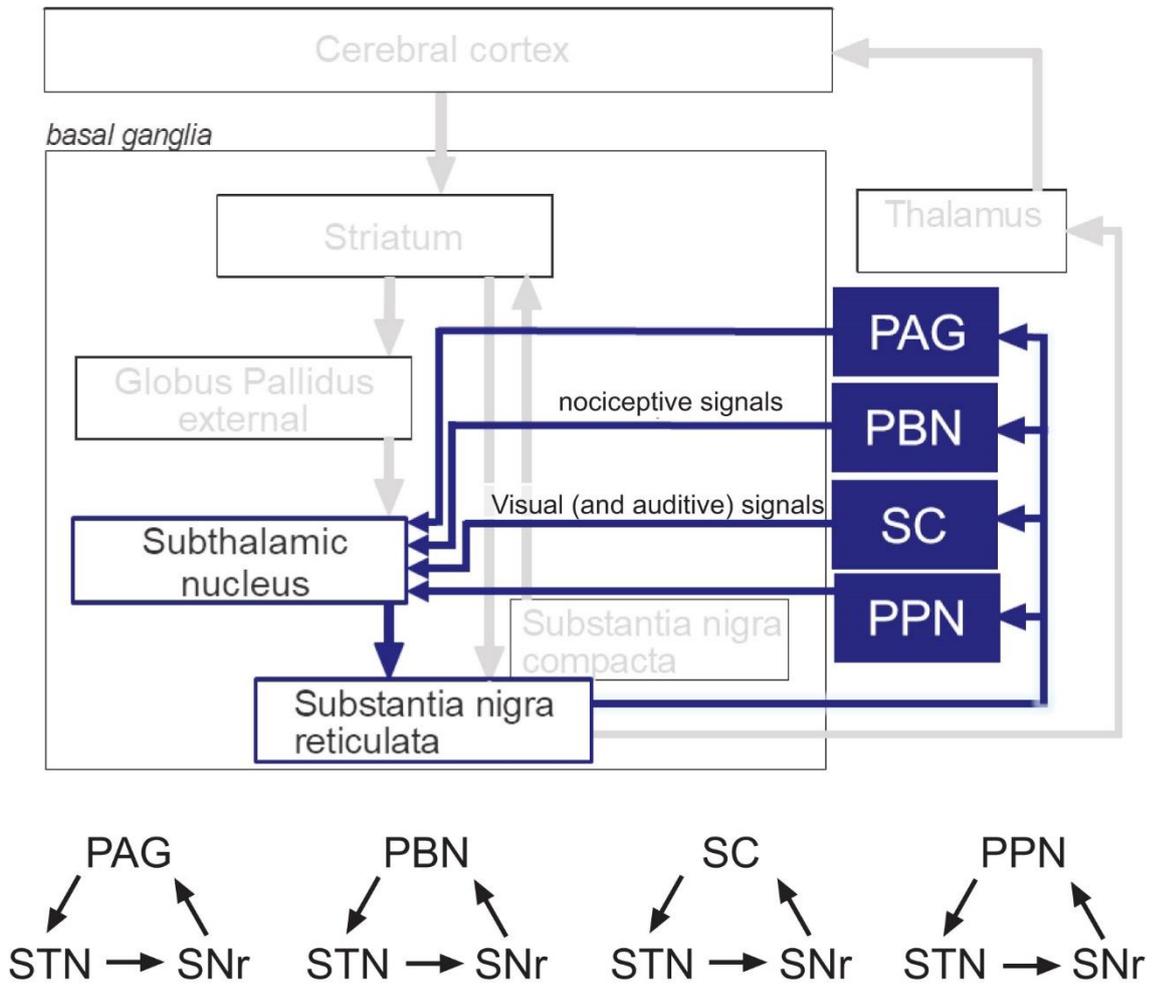


Figure 6:

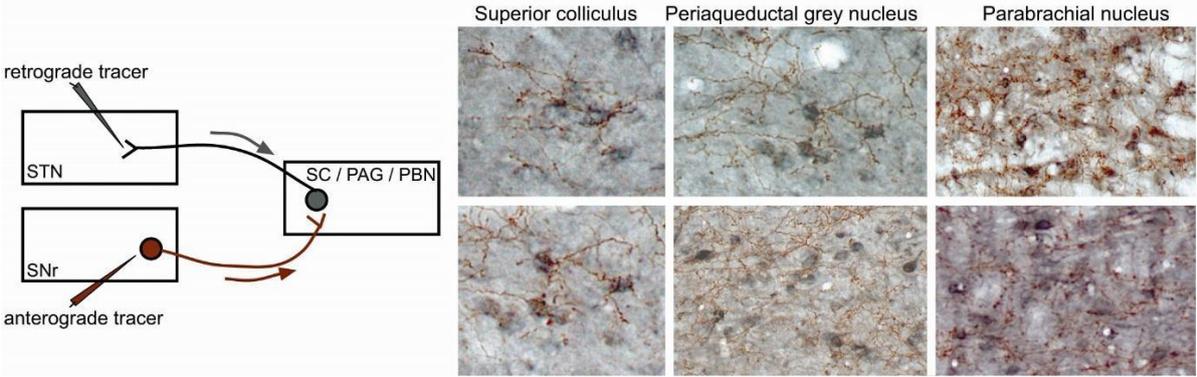


Figure 7:

