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Leading tonically active neurons of the striatum from reward detection to context recognition

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Tonically active neurons (TANs) in the primate striatum, which are presumed to be cholinergic interneurons, carry signals that are traditionally considered to be important for reward-related learning. Recent studies investigating the functional properties of TANs in behaving monkeys have shown that other factors beyond motivation can affect their responsiveness. There is now evidence that TAN responses reflect stimulus detection, movement control and recognition of a specific context, suggesting that these local circuit neurons contribute to different computations used in learning and action functions of the striatum. This is consistent with the view that TAN responses could represent an important component of the processes that are responsible for the ability to select the appropriate behavioral response to environmental events.

Introduction

In the striatum, several neuron types have been described according to their morphological and chemical features [1–3]; the function of striatal circuitry has been interpreted mainly in terms of the relatively large population of GABA-containing medium spiny neurons that are the source of striatal efferent projections. Although most theoretical models of striatal function have emphasized a role for output neurons, the various interneuron types are increasingly considered as key determinants of the information-processing operations performed in the striatum. Therefore, to improve our understanding of how local circuit neurons can affect the functioning of the striatum, it would be extremely helpful to establish clear behavioral relationships between these interneurons. At present, only one class of interneurons can be readily identified during single-neuron recordings in the striatum of monkeys performing behavioral tasks. They are referred to as the tonically active neurons or TANs, the nature of which is probably cholinergic, as has been suggested by *in vivo* intracellular recordings in anesthetized rats [4,5]. The electrophysiological characteristics of TANs are sufficiently distinct to permit recordings to target units belonging to this specific neuron population [6]. Through a better evaluation of the behavioral relationships of TANs, it is hoped that we will gain detailed insights into the role of cholinergic neurotransmission in the processing of

information in the striatum [7,8]. Although the earliest studies argued that TANs might have a key role in detecting motivationally relevant events, a number of observations indicate that these neurons can provide information about the nature of the stimuli present, irrespective of whether they are motivationally salient or not [6]. It appears therefore that the role of TANs in behavior applies to a broader range of functions than was previously assumed. In particular, evidence has recently accumulated suggesting that these neurons might participate in the control of movement and the integration of contextual information within striatal networks. This review aims to emphasize new insights into the role of TANs drawn from findings from single-neuron recording studies in behaving monkeys.

A role for TANs in detecting rewarding stimuli

Kimura *et al.* [9] described for the first time the presence of highly reliable pauses in tonic firing of TANs, in response to stimuli that have acquired an incentive value for the behavior of the animal. Although these activity changes occurred in response to a stimulus that elicits a learned motor reaction towards obtaining reward, they appeared unrelated to movement. Subsequent studies [10–12] have also found evidence suggesting that the response of TANs can reflect the rewarding nature of the stimulus. Aosaki *et al.* [12] described the adaptation of TAN activity during reward-based learning: after repeated pairing of a reward with an initially neutral stimulus, TANs become responsive to this stimulus that predicts the future reward. The response is a transient suppression of tonic firing frequently followed by a rebound activation (Table 1). The stereotyped pause response is a reliable electrophysiological indicator of TAN identity [6]. In some instances, brief excitation occurred immediately before the pause in discharge. It is noteworthy that the same TAN can give qualitatively different response patterns to a given stimulus depending on the behavioral condition, suggesting that distinct classes of TANs cannot be identified on the basis of their response modes [13]. Such neurons also respond to reward in the absence of a task, indicating that TANs are not specialized neurons in detecting stimuli that have acquired a reward-predicting value [13]. Conversely, most responses are the result of conditioned stimuli and not of the reward itself, once the monkeys have learned to associate stimuli and rewards.

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Table 1. Physiological properties of tonically and phasically active striatal neurons and midbrain dopaminergic neurons^a

	Striatal tonically active neurons (TANs)	Striatal phasically active neurons (PANs)	Dopaminergic neurons of the midbrain
Firing properties			
Basal pattern of firing	Tonic irregular (2–10 spikes/sec)	Usually silent or less than 1 spike/sec	Slow irregular (0.5–7.0 spikes/sec)
Characteristics of modulations under behavioral conditions	Transient depression in activity ('pause'), alone or followed by a rebound activation in response to stimuli with motivational value. The response can also include a brief excitation immediately before the pause. A pure activation has been described in relation to movement initiation.	Phasic or sustained activation occurring after, or in anticipation of, sensory-motor, cognitive, and motivational aspects of task performance.	Phasic activation ('burst') following unexpected rewarding events. Phasic depression in activity following omission of expected reward.
Potential functions of the observed behavioral relationships	Modulation of the sensitivity of PANs to different aspects of task performance in a context-dependent manner.	Involvement in a wide range of processes including motor control, cognition and reward-related activities.	Modulation of the sensitivity of PANs in relation to motivation and reward-related learning.

^aBasic activity patterns and spontaneous firing rates are obtained while the monkey is at rest. Striatal TANs and PANs correspond to cholinergic interneurons and GABAergic projection neurons, respectively. All information given in this table are obtained from studies using extracellular recordings in awake monkeys.

This has led to the prevailing view that the network of TANs might carry signals that are important for reward-related learning in the striatum, notably for storing stimulus–reward associations [12,14]. In this regard, it seems that research on the role of midbrain dopamine (DA) neurons in behavior has influenced our thoughts on TAN functioning [15]. In fact, the sensitivity of TANs to task events is similar in some respects to those of DA neurons (Box 1 and Table 1) and it has been demonstrated that the TAN response to rewarding stimuli requires an intact DA input for its expression [16–18]. These results have suggested that changes in DA neuron firing that occur during learning can train TANs to respond to stimuli that become predictors of reward. It is worth noting that the distribution of TAN responses to rewarding stimuli is widespread in the dorsal and middle parts of both the caudate nucleus and putamen. Most studies have emphasized the uniformity of these responses in different striatal regions, that is, the anterior striatum and posterior putamen, which appear to process, respectively, cognitive and motor information [10–13]. On the other hand, no study has yet monitored TAN activity changes in the ventral striatum, including nucleus accumbens, which is specialized for processing of motivational information arising from limbic structures.

Do TANs report an error in the prediction of reward?

Given the suggestion that TANs might receive reward information from the midbrain DA neurons, there has been much interest in the possible contribution of TANs to reinforcement learning. In particular, it is important to know whether TANs might provide signals necessary for associative learning, such as an error in the prediction of a rewarding outcome [19]. By comparing the responsiveness of TANs and DA neurons to conditioned stimuli and primary reward in an instrumental task using various reward probabilities, Morris *et al.* [20] have recently demonstrated that TANs, similarly to DA neurons, show activity changes when a reward is expected but does not occur. The response to reward omission consists of a mild decrease in the tonic firing similar to the typical response

This is in contrast to DA neurons that are activated by unpredicted rewards and depressed by omitted rewards [15,19]. Moreover, unlike DA neurons, TANs do not show different degrees of modulation upon variation of the probability of reward. Hence, it seems that TANs can emit a signal reflecting the absence of an expected reward. However, the finding showing that reward probability is not an important factor for the modulation of their responses clearly highlights the limits of the reward-related information encoded by these neurons. Data from this study do not fit with our findings obtained in a Pavlovian-conditioned task in which TANs fail to encode information concerning the specific time at which a reward is expected [21]. One explanation for this discrepancy might relate to differences in the type of reward-related learning mechanisms specific to the behavioral situations. In the task used by Morris *et al.*, the reward probability is determined by an explicit signal before movement initiation, by contrast, in our experimental context, the predicted reward is passively delivered at the end of an accustomed time interval after a stimulus and is occasionally delayed. It is possible that tasks involving instrumental reactions might introduce in the TAN system additional constraints that are not present in a simple form of associative learning, such as Pavlovian conditioning. The available data are therefore not sufficient to establish a clear relationship of TANs to the coding of the reward prediction error (Box 1).

TANs are not related to exclusively rewarding stimuli

Early investigations of the response properties of TANs have centered upon their sensitivity to rewarding stimuli. More recent studies have extended these findings by showing that these neurons are also concerned with non-rewarding events, including those that are aversive to the animal [22–25]. Interestingly, our experiments have reported that a distinctly different profile of TAN response is produced as a result of aversive and appetitive stimuli. Indeed, although appetitive stimuli induce the typical pause–activation response in most neurons tested, aversive stimuli frequently elicit a triphasic response pattern, consisting in a depression, followed by an activation and further by another phase of depression [22,25]. This

Box 1. Processing characteristics of striatal TANs and midbrain dopaminergic neurons

There is evidence that some of the signals and effects that are seen in TANs can be observed in dopaminergic (DA) neurons. Here, we review similarities and differences between the response properties of the two neuron populations.

Common features

- TANs and DA neurons provide a signal that reports rewarding properties of stimuli, as indicated by their responsiveness to stimuli that are associated with reward through learning and to stimuli that have intrinsic rewarding properties [6,15]. The responses of TANs consist mostly in phasic suppressions of firing, whereas those of DA neurons are phasic activations.
- TANs and DA neurons acquire a response to neutral stimuli during learning of stimulus–reward associations [12,15]. Before learning, both types of neurons only respond to the reward itself, while after learning this response is transferred to reward-predicting stimuli [13,15].
- TANs and DA neurons respond to a rewarding event when its occurrence is unpredictable, either during task performance or outside of a task [13,15,21]. This prediction effect includes not only the occurrence but also the timing of the event: The more predictable the onset time of a stimulus, the less strongly the neuron responds to it [15,21,27].
- TANs and DA neurons respond to novel and intense stimuli [12,15,23]. These responses habituate rapidly with repeated stimulus presentation, suggesting that these neurons are influenced by attentional stimulus components.
- TANs and DA neurons are supposed to show a largely homogeneous response to rewarding stimuli occurring uniformly throughout the striatum and midbrain, respectively [12,13,15,24,25]. However, most previous studies have monitored TAN activity changes in the dorsal striatum mainly.

Distinctive features

- Compared with TANs, DA neurons are less frequently responsive to stimuli having an aversive value [15]. Also, TANs appear to be able to discriminate between motivationally opposing stimuli on the basis of the differential temporal structure of responses [22,25]. This latter point has been called into question by other studies [23,24] and the extent to which a code based on distinct profiles of TAN responses can achieve such a discriminative capacity remains to be further investigated.
- TANs appear to be sensitive to the omission of an expected reward under certain behavioral conditions, but they do not show any relationship to reward predictability [20]. These findings highlight a clear difference with DA neurons, which encode information regarding reward predictability and can signal errors in the prediction of reward [15,19]. However, some conflicting observations exist on the contribution of TANs to the encoding of reward prediction errors [21].
- Changes in TAN activity might relate to the expression of motor acts [33]. Moreover, the response of TANs can be influenced by spatial information about stimulus or movement [34]. Such a property clearly differentiates TANs from DA neurons, which are not involved in the specification of the details of movement [15].
- An important feature of TAN responses is their dependency on contextual factors [10,24,32–34]. Compared with TANs, DA neurons appear less influenced by the context of task performance, although it has been reported that they might be involved in the processing of contextual information about expected reward [39,40].

neuronal behavior has been observed when an initially aversive stimulus is followed by reward delivery in a Pavlovian conditioned task [25]. As illustrated in Figure 1, the precise temporal pattern of the population response of TANs to the stimulus changes over the course

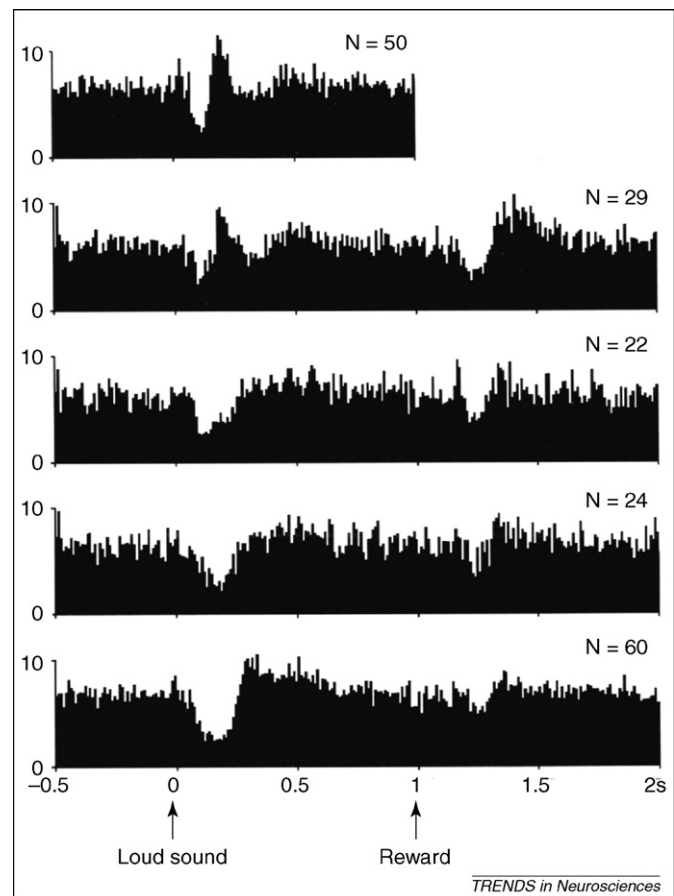


Figure 1. Responses of TANs to motivationally opposing stimuli. Changes of average population activity of TANs when an aversive auditory stimulus is associated through Pavlovian conditioning with reward delivery. All displays show histograms obtained by averaging the activity of all TANs recorded before conditioning and during the successive stages of training, irrespective of the presence or absence of a response. The different periods are shown chronologically from top to bottom. Population histograms are aligned on the presentation of the sound. Vertical scale denotes impulses per second. Before and at the start of conditioning, there is a specific population response profile to the aversive sound, which is composed of depression, activation and, again, depression. This response is gradually modified during associative learning, moving from a triphasic to a primarily biphasic response pattern consisting in a depression followed by activation. Furthermore, the early pause component of TAN responses is shorter for the aversive stimulus than for the appetitive one. The responsiveness of TANs to reward decreased during conditioning. Abbreviation: N, number of neurons included for each histogram. Vertical calibration is in impulses per second. Reproduced, with permission, from Ref. [28].

of repetitive presentations of the stimulus–reward pairing, suggesting that the aversive value is progressively lost when the original stimulus is associated with reward. We interpreted this finding as a possible indication of TANs differentiation between motivationally opposite stimuli. However, contrasting response features for appetitive and aversive conditioned stimuli have not been reported in other studies [23,24] and the possibility that TANs might discriminate the specific motivational value of stimuli remains to be assessed in detail (Box 1).

A body of evidence suggests that TAN responses might be elicited by behaviorally irrelevant stimuli that are effective in attracting and focusing the attention; these responses, however, are generally smaller than those obtained when the stimulus has a rewarding significance. For example, the response to a neutral stimulus is influenced by stimulus novelty, that is, TANs respond more to novel stimuli than they do to familiar ones [23]. Other

studies have indicated that intense stimuli produce stronger responses than mild ones do [12,23], suggesting that TANs are influenced by attentional stimulus components. Although it is difficult to separate motivational and attentional aspects of a behavioral state without carefully designed paradigms, the different response patterns of TANs to appetitive and aversive stimuli we have observed [22,25] appear to reflect differential neuronal coding of motivational value rather than nonspecific changes in attention level [26].

Taken together, the results of these studies contradict traditional views of TAN function, which consider the response properties of this neuronal system as largely determined by the intrinsic or learned motivational properties of environmental events. As we will see, the diversity of findings concerning the response properties of TANs over the last years clearly emphasizes the fact that TAN function does not fit with the prevailing view that these neurons are exclusively involved in motivation and reward-related learning.

TANs are sensitive to the temporal predictability of stimuli

TAN responses are generally absent when the reward is delivered in a predictable manner in both instrumental and Pavlovian learning situations [13]. In a series of experiments, we have shown that TANs can change their responsiveness by factoring the temporal structure of successive task events [21,27]. As illustrated in Figure 2, the responsiveness of TANs is markedly enhanced when the time of reward becomes unpredictable, both inside and outside of task context. The sensitivity of TANs to changes in the temporal predictability of stimuli suggests that these neurons are critically involved in processing temporal attributes of sequential events. This interpretation highlights the significance of TAN responses in its relation to specific learning modes. In particular, the assessment of duration might be implicit in a behavioral situation in which the onset of an event becomes precisely timed when the temporal structure in the sequence of

events is held constant throughout training. We have suggested that TANs participate in a mechanism that mediates the automatic processing of information concerning the temporal relationship between successive task events in conditions involving routine and stereotyped behavioral performance [28]. The tonic discharge of these neurons might be important for the control of automatic behaviors, whereas their typical pause response might promote information processing when behaviors are executed in a less automatic fashion. This interpretation is consistent with the view that the striatum has a key role in the procedural forms of learning, such as habit formation [29–31].

TANs are under the control of contextual factors

A different role has been proposed by Shimo and Hikosaka [32] who have observed, in monkeys performing an oculomotor task, that the sensitivity of TANs for a particular target location in space varies with the reward schedule: their sensitivity is stronger, when only one direction of eye movement is rewarded, than when all directions were rewarded. This demonstrates that TAN responses are not tied to the rewarding properties of the stimulus that initiated the movement, but to the spatial location of this stimulus only in specific rewarding contexts. It thus follows that TAN involvement in stimulus detection could vary with the identification of the context for the movement and the role played by reward information in that movement. Other studies have identified contextual variables as a determinant of TAN responsiveness to task stimuli. Yamada *et al.* [24] showed that TANs respond differentially to a stimulus depending on whether it provides information about a positive or aversive outcome. As expressed by these authors, TANs discriminate ‘motivational contexts for actions’, that is, what type of event (appetitive, aversive or neutral) is expected at trial end. In a Go–NoGo discrimination task, which requires the flexible shifting of behavioral reactions from trial to trial, we showed that the modulation of TAN activity by stimuli is contingent upon the trial type [10]. Lee *et al.* [33] have

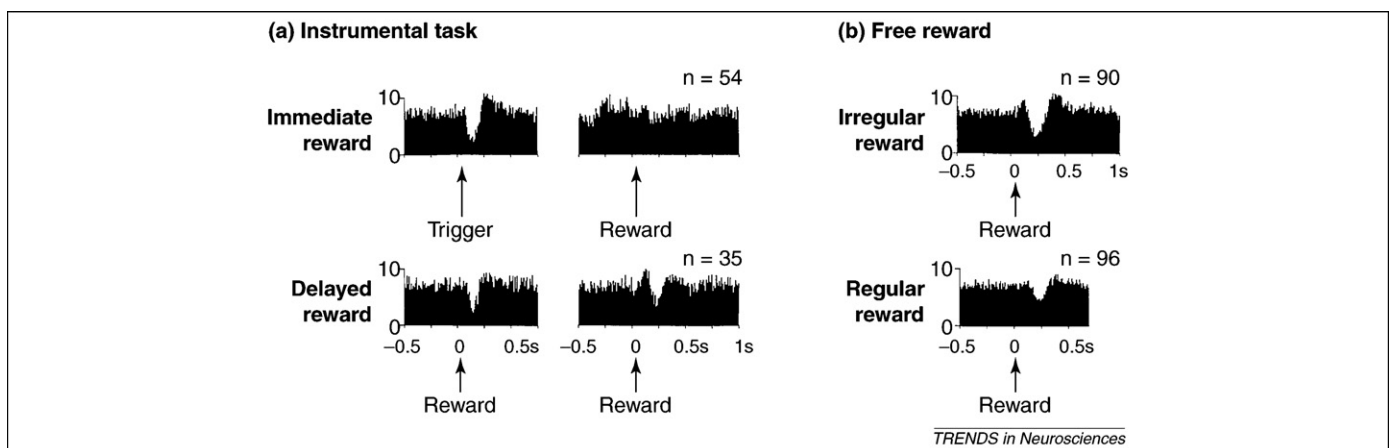


Figure 2. Responses of TANs are influenced by temporal aspects of stimulus prediction. Changes of average population activity of TANs when the timing of reward is made more or less predictable inside and outside the context of a task. All displays show histograms obtained by averaging activity of TANs tested in the two behavioral states indicated: **(a)** in the instrumental task condition, there is a response to the stimulus that triggers a reaching movement toward a target, but absence of response to the subsequent reward when it occurs immediately after target contact, whereas the response to reward is increased when it is delivered after a variable time interval after target contact; **(b)** in the free reward condition, a response occurs to reward delivered at irregular time intervals, whereas it is less prominent with a constant interval of 2 s. Abbreviation: n, number of neurons included for each histogram. Vertical calibration is in impulses per second. Reproduced, with permission, from Ref. [24].

also emphasized the fact that TAN responses are highly dependent on the context in which stimuli are presented. Finally, recent data from our laboratory [34] indicate that TANs can exhibit spatially selective responses that are not linked to stimulus location or movement direction *per se*, but rather to one or the other of these two aspects only under certain circumstances. Altogether, these studies demonstrate that the responsiveness of TANs is contingent upon contextual information concerning the motivational state of the subject, the action planned, the location of targets of movement and the availability of stimuli that have acquired a meaning as a trigger for learned behavioral reactions. Several authors have reported the presence of context-dependent firing properties of phasically active neurons (PANs), which correspond to striatal projection neurons [35–37]. According to the view proposed by Wise *et al.* [35], the basal ganglia would be involved in learning the context for behavior-guiding rules formed in the frontal cortex and the activation of striatal projection neuron would signal the recognition of particular circumstances under which stimuli and appropriate behavioral reactions occur [38]. To back this view, the context dependency in TAN activity is in agreement with the idea that surrounding projection neurons act as context detectors. In addition, it has been reported that changes in the activity of DA neurons are under the control of the context of reward delivery [39,40], suggesting that contextual factors can also affect the responsiveness of DA neurons (Box 1).

Do TANs contribute to the generation of action?

It is generally assumed that TAN responses to conditioned stimuli reflect the motivational value of stimuli rather than their motor significance. However, even if TANs are considered to be relatively isolated from motor processes, there is now evidence that they might contribute to the initiation and control of movement. Blazquez *et al.* [23] have drawn a particular emphasis on the fact that TAN responses to a conditioned stimulus are linked to the

immediate behavioral reaction induced by this stimulus. They have suggested that TANs, as a population, are able to take into account the probability that a given stimulus elicits a specific behavioral response. According to this view, the overall responsiveness of the entire population of TANs is linked to the probability of actions. Other evidence suggests that TANs are able to change their activity during the execution of movement. Lee *et al.* [33] have examined the activity of TANs in relation to arm movements, whether self-initiated or triggered externally. They found that TANs show changes in activity around the time of movement; those changes are independent of somatosensory or proprioceptive information regarding limb state. Although movement-related changes in TAN firing were quantitatively moderate in comparison to those elicited by a stimulus to which the animal has no motion reaction (Figure 3), these findings provide evidence for a relationship between TAN firing and the processes contributing to the initiation of movements, including internal processes specific to movements elicited in the absence of a trigger stimulus. Interestingly, TANs were moderately activated during the initiation of arm movements without expressing the typical pause response component, whereas the response of the same neurons to a reward-predicting stimulus presented in another task condition consisted of the pause followed by a rebound activation (Figure 3). Lee *et al.* have proposed to extend the role of TANs to the initiation and active withholding of movements in the context of conditional motor association involving Go–NoGo responses. Recently, we have examined the processing of spatial information reflected in TAN activity modulations [34]. In monkeys trained to perform visually triggered reaching movements, we found that TANs can exhibit spatially selective responses, as previously noted by other authors [11,32]. In a variant of the task that enabled us to dissociate the spatial features of the movement-triggering stimulus from those of the associated movement, we further showed that the spatial

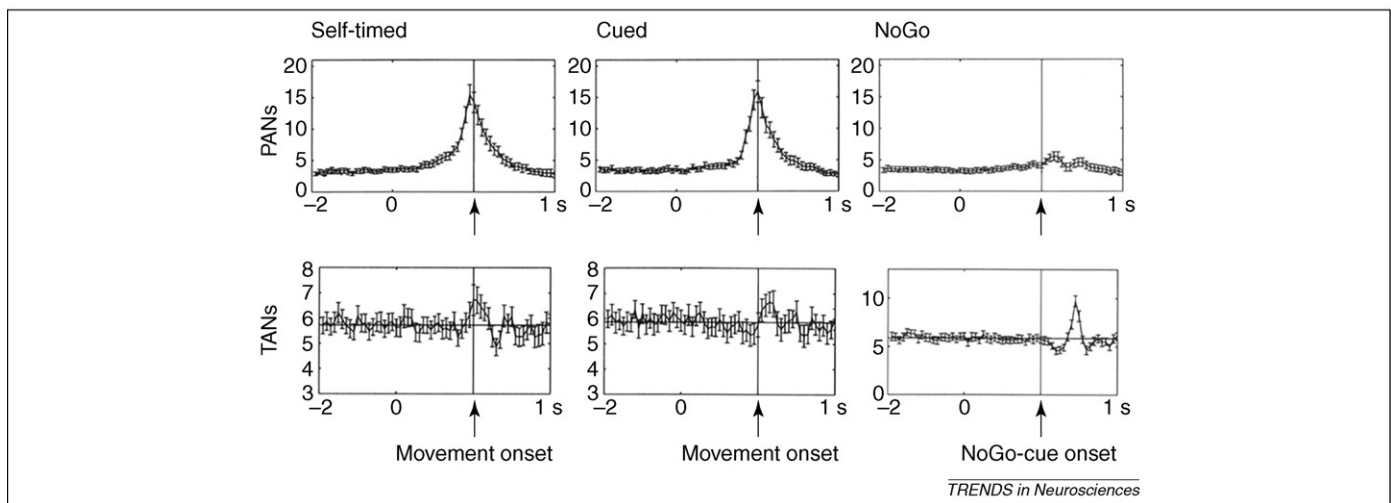


Figure 3. Changes of average population activity of TANs related to the initiation of movement. Neuronal activity was recorded in three conditions involving visually-triggered movements (cued), self-initiated movements (self-timed) and the withholding of movement (NoGo). Population activities of phasically active neurons (PANs), corresponding to striatal projection neurons, are also shown for comparison. Neuronal activity is aligned on movement onset or presentation of the non-triggering signal. The modulation of TAN activity around the time of movement is weak in both movement conditions, compared with the no-movement condition. Conversely, PANs show clear activations around the time of movement, but are less activated in the no-movement condition. The numbers of TANs and PANs tested are 69 and 78, respectively. Vertical calibration is in impulses per second. Adapted, with permission, from Ref. [36].

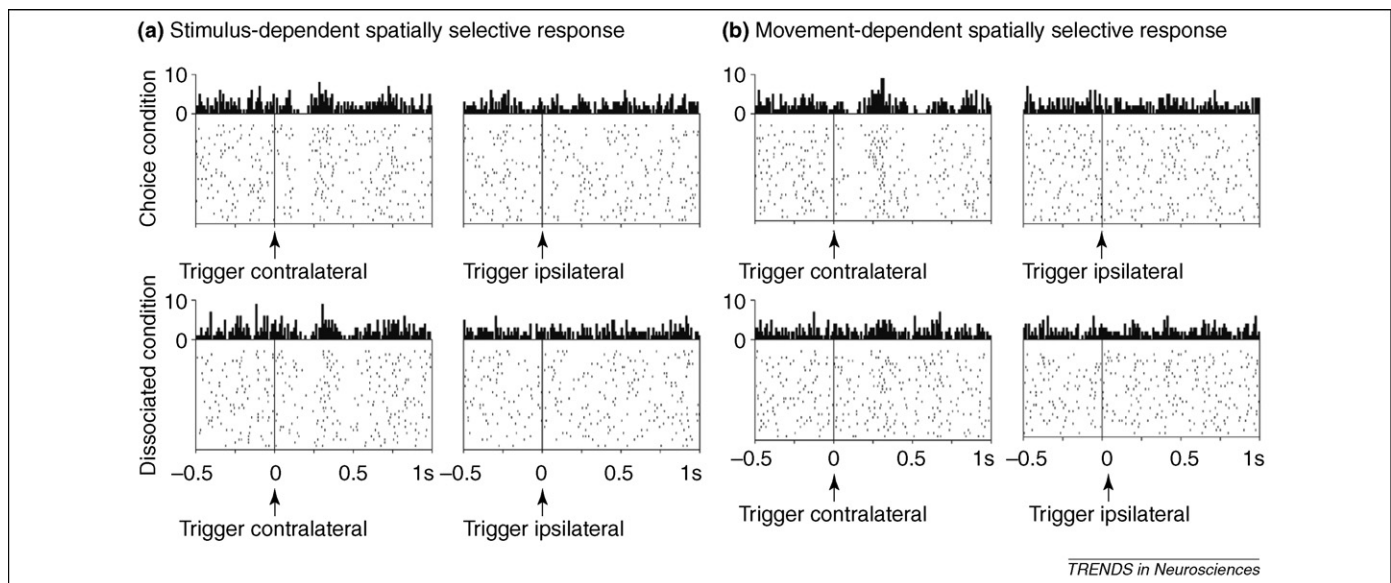


Figure 4. Spatially selective responses of two TANs dependent on stimulus location or direction of movement. Each dot in rasters represents one neuronal impulse, and each line of dots the neuronal activity during one trial. Dot displays and perievent time histograms are aligned on the onset of the trigger stimulus, indicated by vertical lines. In the choice condition, the location of the trigger stimulus corresponds to the side of the movement target and the arm moved toward stimulus location. In the dissociated condition, the movement direction remains constant across trials, regardless of the location of the trigger stimulus, and thus, the arm moved towards stimulus location (trigger ipsilateral) or in a direction opposite to stimulus location (trigger contralateral). In this latter case, stimulus location is dissociated from the direction of movement. In the choice condition, both neurons respond to the trigger stimulus only when it is located contralaterally to the moving arm. The response of the neuron in (a) is maintained in the dissociated condition, whereas the response disappears in the neuron shown in (b). Vertical calibration is in impulses per bin. Bin width for histograms is 10 ms. Reproduced, with permission, from Ref. [37].

selectivity of TAN responses can be dependent on the location of the trigger stimulus or the direction of the movement (Figure 4). All responses consisted of a pause in TAN firing, with or without subsequent rebound activation. Thus, there are now indications that TANs might incorporate parameters of movement into their responsiveness, at least in behavioral situations in which the spatial dimension is relevant. TANs contrast in these properties with DA neurons, which do not show relationships to movement parameters (Box 1).

Conclusion

Although changes in activity of TANs have been most extensively studied in the context of reward processing and associative learning, increasing attention has been paid to the role of these neurons in other aspects of behavior. The responses of TANs to environmental events are far more varied and complex than previously thought, and it becomes apparent that a motivational interpretation of TAN functioning is not sufficient to reveal their contribution to the control of goal-directed behavior. The available data demonstrate that ‘reward signal transmission’ fails to appropriately characterize TANs’ behavioral role, and it is necessary to look at the properties of these neurons from a new perspective. The different relationships of TANs to behavior should reflect distinct neuronal processes in the striatum dealing with stimulus detection, context recognition and the initiation and control of movement. This agrees well with the variety of firing modulations exhibited by striatal projection neurons, which might reflect the processing of different types of information conveyed to the striatum. The TAN system could serve as an interface between the diversity of signals received by the striatal output circuits and might exert

some sort of control over the activity of these circuits according to several factors, such as motivation, movement and context. Although a consensus has yet to be reached regarding the functions attributed to these local circuit neurons, our view is that the various processes in which the processing of contextual information concerning the motivational state of the animal, the action planned, the location of targets of action and stimuli for the selection and triggering of appropriate behavioral reactions to environmental events. It is unclear at this time whether the regional specializations of the striatum, which are largely determined by the distinct connections with motor, associative and limbic areas of the cerebral cortex, could influence the response properties of TANs [24,25,33,34]. Moreover, we need to understand how brief changes in TAN firing impact on the striatal output circuits underlying motivational, motor and cognitive aspects of behavior. Resolving this question rests on an improved understanding of how cholinergic signals are integrated with the processing of information in the striatal circuitry [41]. Striatal interneurons other than TANs are also involved in shaping the activity of surrounding projection neurons (Figure 5). Consequently, there is considerable interest in the properties of GABAergic interneurons described as fast-spiking, which are considered as key regulators of striatal output circuitry [42–45]. An important goal for future studies will be to examine how these interneurons modulate their firing in behavioral conditions to incorporate further data on interactions between distinct neuron types in the striatum. This review has attempted to present a new interpretation of the properties of the network of TANs. It becomes evident that the particular circumstances under which sensory or motor

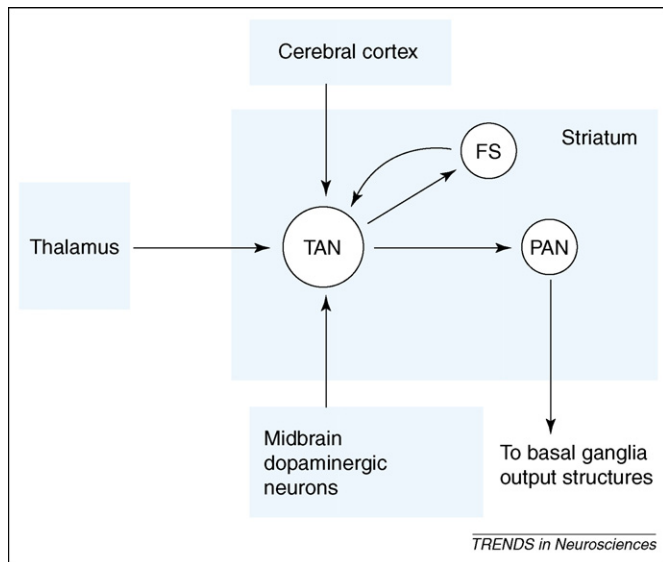


Figure 5. A schematic diagram of the main extrinsic and intrinsic connections of TANs. TANs receive afferents from the cerebral cortex, thalamus and ascending midbrain dopaminergic projections. Within the striatum, they are contacted preferentially by the collaterals of projection neurons (PAN) and inputs from GABAergic interneurons known as fast-spiking neurons (FS). Not all connections are shown in this diagram. In particular, the PANs receive extrinsic afferent fibers in the same way as TANs. This scheme is intended to suggest that TANs are ideally located to integrate different information and modulate projection neurons. The output of TANs could provide a signal required to translate a given context into an appropriate behavioral response to environmental events.

events occur are a crucial determinant of the involvement of TANs in the processing of information. The issue of the context dependency of TAN responses might yield valuable new insights into the role of these local circuit neurons in striatal function.

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References

- 1 Kawaguchi, Y. *et al.* (1995) Striatal interneurons: chemical, physiological and morphological characterization. *Trends Neurosci.* 18, 527–535
- 2 Cicchetti, F. *et al.* (2000) Chemical anatomy of striatal interneurons in normal individuals and in patients with Huntington's disease. *Brain Res. Brain Res. Rev.* 34, 80–101
- 3 Tepper, J.M. and Bolam, J.P. (2004) Functional diversity and specificity of neostriatal interneurons. *Curr. Opin. Neurobiol.* 14, 685–692
- 4 Wilson, C.J. *et al.* (1990) Firing patterns and synaptic potentials of identified giant aspiny interneurons in the rat neostriatum. *J. Neurosci.* 10, 508–519
- 5 Reynolds, J.N.J. *et al.* (2004) Modulation of an afterhyperpolarization by the substantia nigra induces pauses in the tonic firing of striatal cholinergic interneurons. *J. Neurosci.* 24, 9870–9877
- 6 Apicella, P. (2002) Tonicly active neurons in the primate striatum and their role in the processing of information about motivationally relevant events. *Eur. J. Neurosci.* 16, 2017–2026
- 7 Calabresi, P. *et al.* (2000) Acetylcholine-mediated modulation of striatal functions. *Trends Neurosci.* 23, 120–126
- 8 Zhou, F.M. *et al.* (2002) Cholinergic interneurons and nicotinic properties in the striatum. *J. Neurobiol.* 53, 590–605
- 9 Kimura, M. *et al.* (1984) Tonicly discharging putamen neurons exhibit set dependent responses. *Proc. Natl. Acad. Sci. U. S. A.* 81, 4998–5001

- 10 Apicella, P. *et al.* (1991) Tonicly discharging neurons of monkey striatum respond to preparatory and rewarding stimuli. *Exp. Brain Res.* 84, 672–675
- 11 Kimura, M. (1992) Behavioral modulation of sensory responses of primate putamen neurons. *Brain Res.* 578, 204–214
- 12 Aosaki, T. *et al.* (1994) Responses of tonicly active neurons in the primate's striatum undergo systematic changes during behavioral sensorimotor conditioning. *J. Neurosci.* 14, 3969–3984
- 13 Apicella, P. *et al.* (1997) Responses of tonicly discharging neurons in the monkey striatum to primary rewards delivered during different behavioral states. *Exp. Brain Res.* 116, 456–466
- 14 Graybiel, A.M. *et al.* (1994) The basal ganglia and adaptive motor control. *Science* 265, 1826–1831
- 15 Schultz, W. (1998) Predictive reward signal of dopamine neurons. *J. Neurophysiol.* 80, 1–27
- 16 Aosaki, T. *et al.* (1994) Effect of the nigrostriatal dopamine system on acquired neural responses in the striatum of behaving monkeys. *Science* 265, 412–415
- 17 Raz, A. *et al.* (1996) Neuronal synchronization of tonicly active neurons in the striatum of normal and parkinsonian primates. *J. Neurophysiol.* 76, 2083–2088
- 18 Watanabe, K. and Kimura, M. (1998) Dopamine receptor-mediated mechanisms involved in the expression of learned activity of primate striatal neurons. *J. Neurophysiol.* 79, 2568–2580
- 19 Schultz, W. and Dickinson, A. (2000) Neuronal coding of prediction errors. *Annu. Rev. Neurosci.* 23, 473–500
- 20 Morris, G. *et al.* (2004) Coincident but distinct messages of midbrain dopamine and striatal tonicly active neurons. *Neuron* 43, 133–143
- 21 Ravel, S. *et al.* (2001) Reward unpredictability inside and outside of a task context as a determinant of the responses of tonicly active neurons in the monkey striatum. *J. Neurosci.* 21, 5730–5739
- 22 Ravel, S. *et al.* (1999) Tonicly active neurons in the monkey striatum do not preferentially respond to appetitive stimuli. *Exp. Brain Res.* 128, 531–534
- 23 Blazquez, P.M. *et al.* (2002) A network representation of response probability in the striatum. *Neuron* 33, 973–982
- 24 Yamada, H. *et al.* (2004) Tonicly active neurons in the primate caudate nucleus and putamen differentially encode instructed motivational outcomes of action. *J. Neurosci.* 24, 3500–3510
- 25 Ravel, S. *et al.* (2003) Responses of tonicly active neurons in the monkey striatum discriminate between motivationally opposing stimuli. *J. Neurosci.* 23, 8489–8497
- 26 Tobler, P.N. *et al.* (2003) Coding of predicted reward omission by dopamine neurons in a conditioned inhibition paradigm. *J. Neurosci.* 23, 10403–10410
- 27 Sardo, P. *et al.* (2000) Influence of the predicted time of stimuli eliciting movements on responses of tonicly active neurons in the monkey striatum. *Eur. J. Neurosci.* 12, 1801–1816
- 28 Apicella, P. *et al.* (2007) A possible role for tonicly active neurons of the primate striatum in learning about temporal relationships among salient stimuli. In *Recent Breakthroughs in Basal Ganglia Research* (Bezard, E., ed.), pp. 55–63, New York, Nova Science Publishers
- 29 Graybiel, A.M. (1995) Building action repertoires: memory and learning functions of the basal ganglia. *Curr. Opin. Neurobiol.* 5, 733–741
- 30 Packard, M.G. and Knowlton, B.J. (2002) Learning and memory functions of the basal ganglia. *Annu. Rev. Neurosci.* 25, 563–593
- 31 Yin, H.H. and Knowlton, B.J. (2006) The role of the basal ganglia in habit formation. *Nat. Rev. Neurosci.* 7, 464–476
- 32 Shimo, Y. and Hikosaka, O. (2001) Role of tonicly active neurons in primate caudate in reward-oriented saccadic eye movement. *J. Neurosci.* 21, 7804–7814
- 33 Lee, I.H. *et al.* (2006) Activity of tonicly active neurons in the monkey putamen during initiation and withholding of movement. *J. Neurophysiol.* 95, 2391–2403
- 34 Ravel, S. *et al.* (2006) Influence of spatial information on responses of tonicly active neurons in the monkey striatum. *J. Neurophysiol.* 95, 2975–2986
- 35 Wise, S.P. *et al.* (1996) The frontal cortex-basal ganglia system in primates. *Crit. Rev. Neurobiol.* 10, 317–356
- 36 Mink, J.W. (1996) The basal ganglia: focused selection and inhibition of competing motor programs. *Prog. Neurobiol.* 50, 381–425

- 37 Saint-Cyr, J.A. (2003) Frontal-striatal circuit functions: context, sequence, and consequence. *J. Int. Neuropsychol. Soc.* 9, 103–127
- 38 Houk, J.C. and Wise, S.P. (1995) Distributed modular architectures linking basal ganglia, cerebellum, and cerebral cortex: their role in planning and controlling action. *Cereb. Cortex* 2, 95–110
- 39 Nakahara, H. *et al.* (2004) Dopamine neurons can represent context-dependent prediction error. *Neuron* 41, 269–280
- 40 Ravel, S. and Richmond, B.J. (2006) Dopamine neuronal responses in monkeys performing visually cued reward schedules. *Eur. J. Neurosci.* 24, 277–290
- 41 Cragg, S.J. (2006) Meaningful silences: how does dopamine listens to the ACh pause. *Trends Neurosci.* 29, 125–131
- 42 Koos, T. and Tepper, J.M. (2002) Dual cholinergic control of fast-spiking interneurons in the neostriatum. *J. Neurosci.* 22, 529–535
- 43 Berke, J.D. *et al.* (2004) Oscillatory entrainment of striatal neurons in freely moving rats. *Neuron* 43, 883–896
- 44 Tepper, J.M. *et al.* (2004) GABAergic microcircuits in the neostriatum. *Trends Neurosci.* 27, 662–669
- 45 Mallet, N. *et al.* (2005) Feedforward inhibition of projection neurons by fast-spiking GABA interneurons in the rat striatum *in vivo*. *J. Neurosci.* 25, 3857–3869