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► **To cite this version:**

Paul Apicella. THE ROLE OF THE INTRINSIC CHOLINERGIC SYSTEM OF THE STRIATUM: WHAT HAVE WE LEARNED FROM TAN RECORDINGS IN BEHAVING ANIMALS?. *Neuroscience*, 2017, 360, pp.81-94. 10.1016/j.neuroscience.2017.07.060 . hal-02329069

HAL Id: hal-02329069

<https://hal.science/hal-02329069>

Submitted on 24 Oct 2019

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The role of the intrinsic cholinergic system of the striatum: What have we learned from TAN recordings in behaving animals ?

Paul Apicella

Institut de Neurosciences de la Timone UMR 7289, Aix Marseille Université, CNRS
13385, Marseille, France

Corresponding author: Paul Apicella
Institut de Neurosciences de la Timone UMR7289
CNRS, Aix Marseille Université
13385, Marseille
FRANCE
Fax: 00 33 491324056
paul.apicella@univ-amu.fr

Number of pages 31
Number of figures 6
Number of tables 0

Number of words in the Abstract 246

Acknowledgements. Research in my laboratory mentioned in this article was supported by Association France Parkinson, Association Française du Syndrome de Gilles de la Tourette, and by Centre National de la Recherche Scientifique. I thank two anonymous referees for their constructive comments.

Abstract

Cholinergic interneurons provide rich local innervation of the striatum and play an important role in controlling behavior, as evidenced by the variety of movement and psychiatric disorders linked to disrupted striatal cholinergic transmission. Much progress has been made in recent years regarding our understanding of how these interneurons contribute to the processing of information in the striatum. In particular, investigation of the activity of presumed striatal cholinergic interneurons, identified as tonically active neurons or TANs in behaving animals, has pointed to their role in the signaling and learning of the motivational relevance of environmental stimuli. Although the bulk of this work has been conducted in monkeys, several studies have also been carried out in behaving rats, but information remains rather disparate across studies and it is still questionable whether rodent TANs correspond to TANs described in monkeys. Consequently, our current understanding of the function of cholinergic transmission in the striatum is challenged by the rapidly growing, but often confusing literature on the relationship between TAN activity and specific behaviors. As regards the precise nature of the information conveyed by the cholinergic TANs, a recent influential view emphasized that these local circuit neurons may play a special role in the processing of contextual information that is important for reinforcement learning and selection of appropriate actions. This review provides a summary of recent progress in TAN physiology from which it is proposed that striatal cholinergic interneurons are crucial elements for flexible switching of behaviors under changing environmental conditions.

Introduction

The striatum, the major input structure of the basal ganglia, is composed largely of projection neurons and small groups of interneurons, predominantly GABAergic, subdivided into neurochemically diverse classes. A special feature of the striatum is the presence of scattered large-sized cholinergic interneurons which predominantly contribute to provide this structure with one of the highest contents of acetylcholine in the brain (Butcher and Butcher 1974; Woolf and Butcher, 1981; Calabresi et al., 2000; Zhou et al., 2002). Even though the number of these local circuit neurons is very low, they exert powerful modulatory effects on excitability of the vast majority of neurons which form the output of the striatum (Pisani et al., 2007; Bonsi et al., 2011). Cholinergic interneurons also play a key role in controlling multiple forms of striatal synaptic plasticity (Kreitzer and Malenka, 2008; DiFillipo et al., 2009; Fino and Venance, 2010) and the interactions between dopaminergic and cholinergic systems within the striatum are crucial for adaptive behavior (Cragg, 2006; Threlfell et al., 2012; Cachope et al., 2012; Cachope and Cheer, 2014). Understanding the integration of cholinergic interneurons into the striatal circuitry will provide insights into the pathophysiology of movement disorders, such as Parkinson's disease, dystonia, and Tourette syndrome (Pisani et al., 2007; Deffains and Bergman, 2015), as well as psychiatric disorders, including drug addiction (Williams and Adinoff, 2008), mood disorders (Warner-Schmidt et al., 2012), Alzheimer's disease (Parent et al., 1984; Oyanagi et al., 1987; Lehericy et al., 1989; Selden et al., 1994), and schizophrenia (Holt et al., 2005).

Striatal cholinergic interneurons have received considerable interest when it was realized that it is possible to identify them during extracellular recording studies performed in awake animals, mostly monkeys. This has allowed to provide neurophysiological correlates for the involvement of these interneurons in specific behavioral processes. It is now widely accepted that striatal cholinergic interneurons correspond to an electrophysiologically distinct group of neurons, termed the tonically active neurons or TANs, that are involved in signaling the occurrence and motivational relevance of stimuli. However, the diversity of findings concerning the functional properties of these presumed interneurons over the last years, not only in primates but also in rodents, has expanded this view by demonstrating that TAN signaling cannot be attributed exclusively to motivation and reward processing. In particular, an influential view implicates the striatal cholinergic transmission in the representation of contexts for adaptation to a changing environment. This review sets out recent advances in understanding the function of the cholinergic TAN system in the striatum, with emphasis on recordings of single neurons in behaving animals. A special focus is devoted to

inconsistencies associated with the identification of TANs and characterization of their behavior-related changes in activity in rats and monkeys.

Basic response properties of TANs in the striatum of monkeys

Initial single-neuron recording studies in behaving monkeys have allowed to distinguish between two striatal neuron firing patterns which were considered as indicators of two electrophysiologically distinct neuronal populations (Crutcher and DeLong, 1984; Kimura et al., 1984; Alexander and DeLong, 1985). The first type, referred to as PANs (for phasically active neurons), are usually silent and become active in relation to specific aspects of task performance, such as movement initiation and execution, preparation of movement and expectation about upcoming events, including reward. The firing pattern of PANs has long been recognized as typical of the striatal output neurons also called medium-spiny projection neurons (Wilson and Groves, 1981). The second group of neurons corresponds to the TANs, thought to be cholinergic interneurons, which fire continuously at relatively slow rates (~5 Hz) and display brief changes in activity after the detection of motivationally relevant events. These two populations are also readily distinguished on the basis of waveform shapes, TANs having longer spike duration than PANs (Apicella, 2002). Despite the relatively small population size of cholinergic interneurons in the striatum, neurons identified as TANs are encountered quite frequently in extracellular recordings performed in behaving monkeys. In addition, recordings from TANs provide better spike sorting quality compared to PANs (Joshua et al., 2008), which make them the most easily recorded neurons in the monkey striatum.

The first description of the characteristic behavior-related modulation of TAN activity was in a study by Kimura et al. (1984) in which monkeys experienced a tone that signaled the delivery of reward. The majority of TANs exhibited a phasic decrease in firing in response to the reward-predicting tone independently of whether it occurred after a learned motor reaction or automatically once every 6 seconds. Since this initial description, the so-called « pause » response has been repeatedly observed under a variety of behavioral conditions and is considered a reliable indicator of the TAN identity (Aosaki et al., 1994; Apicella et al., 1997; Morris et al., 2004; Yamada et al., 2004; Lee et al., 2006). An example of responsive TAN is shown in Figure 1A with a prominent pause clearly coupled to the movement-triggering stimulus. This pause is often followed by a transient increase, designated as the rebound activation, and preceded only very occasionally by a brief activation (Apicella, 2002). The combination of these three components can vary from neuron to neuron or, for the same

neuron, according to the condition of event occurrence. Several mechanisms have been considered to explain the multiphasic response of the TANs (Schulz and Reynolds, 2013). In particular, the pause and the ensuing rebound activation have been assumed to depend on inputs from the intralaminar nuclei of the thalamus, namely the centromedian-parafascicular (CM-Pf) complex (Matsumoto et al., 2001). Dopaminergic inputs derived from the midbrain have also been demonstrated to be involved in the generation of the TAN pause-rebound response (Aosaki et al., 1994). By contrast, the brief activation that precedes the pause remains unaltered following suppression of dopaminergic or thalamic afferents to the striatum, suggesting that this early, and often difficult to discern, component may be driven by other excitatory inputs.

Some evidence indicates that the pause and rebound components of the TAN response carry distinguishable information (Goldberg and Reynolds, 2011). It has been suggested that the pause conveys attention-related signals, possibly contributing to the interruption of ongoing behavior when a stimulus eliciting an orienting reaction is detected (Ding et al. 2010). This attentional shift is thought to rely upon intralaminar thalamic signals sent to the striatal TAN system (Matsumoto et al., 2001). On the other hand, as discussed in further detail later, the rebound activation after the pause has been shown to be sensitive to factors that are related to reward availability, possibly reflecting reward prediction error coding (Apicella et al., 2009; 2011).

Are TANs cholinergic interneurons?

Although the combination of distinctive firing properties, waveform characteristics, and task-related changes in activity, provides good evidence that TANs form a single group of electrophysiologically identifiable neurons in the monkey striatum, it should be reminded that it is not possible to make definitive statements about their cellular identity. Accordingly, identification of specific cell types remains a critical issue and the following section recalls the arguments in favor of the presumptive cholinergic nature of extracellularly recorded TANs.

Electrophysiological recordings in acute slices of rodent striatum have demonstrated that neurons immunopositive for choline acetyltransferase (ChAT), the synthetic enzyme for acetylcholine, exhibit tonic firing patterns almost identical to those of TANs recorded in behaving monkeys (Bennett and Wilson, 1999). These firing properties are similar to those of giant aspiny neurons morphologically identified after intracellular recording and staining in anesthetized rats (Wilson et al., 1990; Reynolds et al., 2004). These data have provided

evidence that giant striatal cholinergic interneurons share similarities with monkey TANs. Subsequent studies combining extracellular recordings and juxtacellular labeling in anesthetized rats confirmed that ChAT-positive striatal neurons displayed firing properties similar to those of TANs in monkeys (Inokawa et al., 2010; Schulz et al., 2011; Sharott et al., 2012). This method has proven to be successful in the awake rat to establish the identity of striatal neurons after recording and juxtacellularly labeling them and sacrificing the animal (Isomura et al., 2013). For obvious practical and ethical reasons, it is not feasible to use this approach in monkeys.

The recent advances in genetic targeting are a promising avenue to allow on-line identification of recorded neurons by combining optogenetics with electrophysiological recordings to validate grouping of cell types in behaving animals. This approach has been used in freely moving genetically modified animals (i.e., transgenic ChAT-Cre mice) to allow targeted manipulation of striatal cholinergic interneurons (Witten et al., 2010; English et al., 2012). It has been shown that neurons identified optogenetically as cholinergic interneurons in ChAT-Cre mice have firing properties resembling those of TANs identified by electrophysiological criteria in rats (Atallah et al., 2014). Although there are still obstacles to apply cell-type specific tagging methods for extracellular recording in behaving non-transgenic animals, we can expect advances in this direction in coming years.

At the moment, the cholinergic identity of TANs recorded extracellularly in behavioral work, both in rats and monkeys, remains uncertain in the absence of an unambiguous confirmatory evidence. Moreover, given the variety of GABAergic interneurons which have been characterized in recent years in the rodent striatum (Tepper et al., 2010; Silberberg and Bolam, 2015), some of them discharging spontaneously in a tonic manner (Beatty et al., 2012), it cannot be excluded that the group identified as TANs may contain some non-cholinergic neurons.

Diversity of putative cholinergic interneurons in the striatum of rodents

Following the initial work of Kimura et al. (1984), single-neuron recording studies primarily conducted in monkeys have contributed to insights into the role of TANs in the processing of reward information. It is only recently that investigators have scrutinized electrophysiological features of neurons recorded in the striatum of freely moving rodents in order to reveal a population that could be similar to monkey TANs. However, TAN identification based on spontaneous firing rate, spike width, and task-related changes in activity (i.e., the characteristic pause in tonic firing in response to rewarding events) widely used in monkey

studies appears more problematic in behaving rodent experiments. Somewhat unexpectedly, the classification of striatal neurons via firing rate and spike width in rats allowed to separate two main classes, namely medium-spiny projection neurons and fast-spiking interneurons (FSIs), thought to be parvalbumin-expressing GABAergic interneurons (Berke, 2011), while a third class corresponding to TANs is virtually undetectable or only represents a very small sample of the striatal neurons, far below what can be recorded in primates. In the rat striatum, there are concerns that identification of TANs which relies on the electrophysiological criteria set out in monkeys are less reliable (Atallah et al., 2014; Thorn and Graybiel, 2014; Stalnaker et al., 2016). Several investigators have therefore considered that quantification of the firing pattern (e.g., interspike intervals, autocorrelograms, coefficients of variation of the interspike interval) is a more valid criterion to distinguish TANs from other striatal neuron types (Sharott et al., 2009; Thorn and Graybiel, 2014; Stalnaker et al., 2016). Also, as further discussed below, the pause in TAN firing in monkeys is far from being systematically reported in rodent studies and this contributes to problems in establishing a similarity between TAN populations recorded in the two species.

As mentioned above, TANs are not frequently encountered during recording experiments in behaving rodents, with proportions ranging from 2 to 6% (Schmitzer-Torbert and Redish, 2008; Atallah et al., 2014; Thorn and Graybiel, 2014; Stalnaker et al., 2016). For other investigators, the scarcity of recorded TANs in the rodent striatum is such that it precludes any valuable analysis (Berke et al., 2004; Gage et al., 2010; Lansink et al., 2010). However, a noticeable exception comes from the work of Cohen and colleagues who found that more than half striatal neurons (52-68%) can be classified as TANs (Yarom and Cohen, 2011; Benhamou et al., 2014). A possible reason for explaining why TANs are difficult to target for extracellular recordings in rodents compared to primates refers to the electrode types used. It is common to use tetrodes in striatal recordings in behaving rodents, whereas metal electrodes are used in monkey studies. It has been reported in anesthetized rats that tungsten electrodes are well suited to identifying distinct types of striatal neuron, including TANs (Sharott et al., 2009). Also, as mentioned above, a sizeable fraction of TANs has been recorded by Cohen group with tungsten wires in freely moving rats (Yarom and Cohen, 2011; Benhamou et al., 2014), that goes well beyond the tiny fractions obtained with tetrode recordings (Thorn and Graybiel, 2014; Atallah et al., 2014). However, TAN sampling with tungsten electrodes seems more difficult in mice (Yamin et al., 2013) compared to rats. This suggests that variation exists between these two rodent species in the ease with which recordings from TANs can be obtained, which has probably nothing to do with the type of

electrode.

Notwithstanding the difficulty of detecting TANs in rodent striatum, several studies have recently examined the activity of neurons that resemble monkey TANs in different regions of the striatum. In rats trained to perform instrumental tasks, however, the TAN responses to rewarding events appear less stereotyped compared to those seen in monkeys. Indeed, rodent TANs appear to be less easily categorized into a single group based on the pause response criterion which is applied when identifying TANs in monkeys. Undoubtedly, the homogeneous responses of monkey TANs, which consistently involve a pause in firing, contrasted with the variety of modulation types observed in the group of neurons identified as TANs in the rat striatum. However, before addressing the variety of TAN response patterns observed in rats, it should be noted that some evidence also exists in monkeys that TANs may display increases in activity in response to task events in the absence of accompanying pause in firing (Yamada et al., 2004; Lee et al., 2006; Nougaret and Ravel, 2015).

Recent studies in behaving rats have shown that modulations of TAN activity may have opposite polarity at different moments of task performance. For example, in the dorsolateral striatum of rats that learned a T-maze task, TANs showed a phasic decrease in activity after the onset of the instruction cue and at the time of goal reaching, whereas a phasic increase in activity occurred after the presentation of the signal delivered at the start of trial (Thorn and Graybiel, 2014). Variations of TAN response patterns have also been reported in the dorsolateral striatum and ventral striatum in rats performing a simple instrumental task (Benhamou et al., 2014). It was observed that TANs in both regions can either decrease or increase their firing following the stimulus that triggers the instrumental response (lever pressing) (Figure 1C), but TANs that decreased their activity were more frequent than TANs that increased their activity. The same study showed that TANs could also display brief changes in activity in response to the delivery of reward consisting predominantly of a decrease in firing quite comparable to the TAN pause response observed in monkeys. Finally, the authors found a pattern of opposite changes in TAN firing (i.e., increase-type responses) mostly at the start of trial and when reward was delivered at an unexpected time (Benhamou et al., 2014). In a previous study by the same group, it was reported that TANs displayed increases in activity during movement performed in a task that requires a choice between response options (Yarom and Cohen, 2011). It is possible that this excitatory TAN response may arise from differences in task demands and processing requirements when a phase of decision making is added to the behavioral paradigm. It has also been found, in behaving rats, that TAN responses in the ventral striatum appear to

respond in a more homogeneous fashion compared to TAN responses in the dorsal striatum. Attalah et al. (2014) reported that the vast majority of TANs recorded in the ventromedial striatum displayed a strong sensitivity to changes in reward contingencies during T-maze performance with excitatory responses to the delivery of reward occurring selectively during the acquisition phase of the task. As the authors emphasized, there is an obvious contrast between the increase in TAN activity in response to reward and the pause in TAN firing in response to rewarding stimuli commonly described in monkeys. This obvious contrast between rodents and primates in the polarity of the TAN modulation at the time of reward raise questions about the identity of the two neuronal populations. However, it is important to point out that monkey studies have provided an extensive characterization of modulation types observed among TANs only in the dorsal regions of the striatum. Consequently, there is as yet no information on the response pattern of TANs recorded in the ventral striatum in the primate.

Until now, there is no consensus about the reasons that account for the variety of behavior-related TAN firing observed in rodent studies. It has been suggested that the dissimilarity of the behavioral conditions available for comparison may contribute to observed differences in TAN responses across rodent and monkey studies (Benhamou et al., 2014). In addition, it cannot be excluded that the TAN group may contain non-cholinergic types of neurons that meet electrophysiological criteria used to identify TANs (Beatty et al., 2012). In this regard, it would be of particular interest to compare in more detail the firing properties and waveform parameters of TANs exhibiting decreased activity to those showing increased activity in behaving rodents.

In summary, interspecies differences in the properties of TANs do not promote clarification of their functions. It remains questionable whether TANs identified in rodents and primates correspond to the same class of striatal neurons. In the primate, a coherent set of data has demonstrated that TANs can be easily recognized based on firing properties, spike shape, and functional characterization, and there is broad acceptance that they are cholinergic interneurons. On the other hand, the review of the rodent literature indicates that identification of TANs is sometimes limited to a subset of the electrophysiological features currently used in monkeys. In addition, the diversity of behavior-related changes in TAN activity, including the polarity of these changes, is in striking contrast with the homogeneity in expression of TAN modulations which has been reported in monkeys. My view is that the variety of modulation types observed in rodent TANs can be explained from sampling different populations of neurons even if they fulfil the electrophysiological criteria to be identified as

TANs. In this regard, it should be considered that distinct groups of TANs in this species may exhibit different functional properties that potentially relate to their precise nature (i.e., cholinergic or non-cholinergic). Although advanced methods for the identification of extracellularly recorded neurons are still difficult to implement in behaving rats, it becomes essential to assess cellular phenotypes of recorded TANs.

Species difference in the morphology of cholinergic interneurons

Given the apparent ease with which TANs are sampled in monkeys compared with rodents, one could postulate that differences in striatal cholinergic interneuron densities exist between species. However, anatomical studies using ChAT immunohistochemistry have estimated that cholinergic interneurons account for about 1-3% of striatal neurons (Bolam et al., 1984; Phelps et al., 1985), this proportion being apparently similar in both rodents and primates. On the other hand, species differences in the morphology of striatal cholinergic interneurons might be particularly relevant in explaining why TAN activity is preferentially detected with extracellular recordings in monkeys rather than in rodents. In their study with the Golgi method, Yelnik et al. (1991) classified the neurons of the monkey striatum into morphologically distinct types, among which the cholinergic giant neurons have a somatodendritic configuration that is quite unique. It has been pointed out that this group of cells, referred to as spidery neurons, do not have the same morphological features than the cholinergic giant neurons found in the rat striatum (Yelnik et al., 1993; Gonzales and Smith, 2015). In rodents, cholinergic interneurons are characterized by an elongated cell body that gives rise to a small number of long and sparsely ramified dendrites, whereas, in primates, they display a globular cell body with numerous, highly ramified, and varicose dendritic processes which curve back toward the soma, giving them the appearance of a spider (Figure 2). This indicates a species distinction in the morphological features of cholinergic interneurons in the primate striatum that not only could underlie distinct information processing capabilities (Yelnik et al., 1993; Gonzales and Smith, 2015) but also, as we suggested before, could create a sampling bias towards neurons with large soma size and dendritic field (Apicella, 2002).

Role of TANs in signaling reward prediction errors

The well-known role of TANs in the signaling and learning of the motivational significance of environmental stimuli (Aosaki et al., 1994; Apicella et al., 1997; Shimo and Hikosaka, 2001; Ravel et al., 2003; Morris et al., 2004) has prompted studies on the information

encoding capacity of these neurons in relation to the expected value of stimuli. In particular, the question was raised whether TANs can detect if rewards occur differently than predicted, thus potentially reflecting reward prediction error coding which is critical for guiding learning of relationships between stimuli, actions and outcomes (Rescorla and Wagner, 1972; Sutton and Barto, 1981). In a first study aimed to investigate the sensitivity of TANs to changes in the availability of reward in an instrumental task, Morris et al. (2004) found no evidence for an influence of reward probability on TAN responses. However, in a Pavlovian conditioning task, the same group showed that responses of these neurons are stronger with decreasing reward probability (Joshua et al., 2008). Our own lab's studies (Apicella et al., 2009; 2011) have subsequently confirmed that TANs modulate their responsiveness to reward in a manner reflecting discrepancies between actual and predicted rewards (Figure 3A). Interestingly, the influence of reward probability was much less obvious in an instrumental task compared to a Pavlovian protocol (Figure 3B), suggesting that the particular reinforcement learning context may be at stake in the TAN expression of reward prediction error signals. As was mentioned before, we have demonstrated that distinct components of the TAN response were differentially modulated by reward probability (Apicella et al., 2009; 2011). In particular, outcome encoding was less prominent in the pause than in the ensuing rebound activation, suggesting that the late excitatory component of the TAN response is preferentially involved in reward prediction error coding. It was also found that TANs encode both reward delivery and omission (Joshua et al., 2008) with some TANs responding to reward and no reward with decreases and increases in firing, respectively, potentially reflecting the encoding of positive and negative errors in prediction of reward (Apicella et al., 2009). Taken together, these findings suggest that the striatal TAN system is a possible neuronal substrate for reward-driven behavior, working in concert with dopamine inputs from the midbrain (Schultz, 1986) in providing striatal circuitry with an error signal for the prediction of reward.

Recent findings in behaving rats also support the notion that TANs may signal discrepancies between expected and obtained rewards. Atallah et al. (2014) have reported that a large majority of TANs show changes in activity that varied according to whether or not the expected reward was obtained during maze task performance. Namely, TANs increase their activity for reward delivery during learning and decrease their activity for reward omission (Figure 3C). An important aspect of this study is that TAN recordings were performed in the ventromedial striatum, suggesting that the bidirectional outcome signaling could be restricted to ventral striatal circuits. It remains unclear whether TANs of dorsal regions of the rodent striatum may also contribute to the encoding of reward prediction errors, as has been shown in

monkeys (Joshua et al., 2008; Apicella et al. 2009; 2011). A finding which needs clarification in behaving rats is the sensitivity of ventral TANs to omission of an expected reward (Atallah et al., 2014) which has not been confirmed by another study (Benhamou et al., 2014) possibly as a consequence of variations in task design. As outlined in the following section, it is becoming increasingly clear that the different circumstances under which the same event occurs may exert a strong influence on the responsiveness of TANs to this event.

Context dependency of TAN activity in monkeys

Although the cholinergic TAN system is considered as a system mostly involved in detecting the motivational significance of environmental stimuli, a number of data has expanded this view by demonstrating that TAN involvement in stimulus detection could vary with the identification of the context. As mentioned before, TANs manifest stronger sensitivity to reward prediction errors in Pavlovian rather than in instrumental conditioning tasks (Morris et al., 2004; Joshua et al., 2008; Apicella et al., 2009; 2011), suggesting that the information encoding capacity of TANs depends on the specific learning situation in which stimulus-outcome relationships are established. Many observations have led to consider that contextual factors are crucial determinants of TAN responses.

Studies from our laboratory have provided evidence that temporal relationships between task events influence the responsiveness of TANs, namely the more predictable the time of occurrence of a rewarding event, the less strongly TANs respond to it (Sardo et al., 2000; Ravel et al., 2001). A representative example of such a modulation of TAN responsiveness is illustrated in Figure 4. This responsive TAN was recorded in a Pavlovian procedure in which a monkey was given a reward at the end of a 1 s interval after the onset of a visual stimulus. The TAN displayed a clear pause-rebound response to the stimulus that was predictive of reward, but failed to respond to the reward itself. In the following block of trials, the length of the stimulus-reward interval was changed by delivering reward 0.3 s after the stimulus onset, then eliciting a response to reward at that new time. Thereafter, the reward response disappeared when the 1 s interval was reinstated and came back when the interval was prolonged to 2 s. All these manipulations did not affect the TAN response to the preceding stimulus. The marked plasticity in TAN responsiveness to reward is compatible with the idea that changes in temporal regularities between events determines their efficacy in eliciting TAN responses.

Other studies have emphasized that TAN involvement in stimulus detection could vary with the environment in which actions are generated. Shimo and Hikosaka (2001) have

reported findings suggesting that TANs may act to gate movement initiation in a context-dependent fashion. In monkeys performing an oculomotor task, they showed that TAN responses to visual stimuli indicating the spatial location of a saccade target were stronger when only one direction of eye movement is rewarded than when all directions are rewarded (Figure 5). It therefore appears that TAN responses are not tied to the reward value of the stimulus that initiated the movement, but to the particular rewarding context in which this stimulus was presented. A number of studies using a variety of behavioral tasks in monkeys have also provided evidence that the responsiveness of TANs is dependent on the context of performance (Yamada et al., 2004; Lee et al., 2006; Ravel et al., 2006).

It is noteworthy that the impact of context on the responsiveness of TANs extends beyond the motivational aspect. For example, we have reported an effect of spatial features on the selectivity of TAN responses in monkeys trained to perform a reaching task (Deffains et al., 2010). In this study, a cue given at the start of trial served as a predictor of the onset time of a movement-triggering stimulus whose locations varied from trial to trial according to a repeating sequence or a random order. The overall responsiveness of TANs to either the cue or the trigger stimulus remained approximately the same, regardless of the order of stimulus presentations (see inset in Figure 6A). However, individual TANs could change their responsiveness when the animal switched from the repeating to the random sequence. As shown in Figure 6A, illustrating the locations of TANs recorded in dorsal striatal regions, some TANs responding selectively in the repeated condition changed or lost their selectivity when tested in the random sequence, while others that were unresponsive started to respond in a selective or non-selective manner. The figure also shows that the response properties did not depend on the exact location of TANs in the caudate nucleus or putamen. It therefore appears that the maintenance of the responsiveness of TANs when spatial features of context are modified relies on a reconfiguration of the sensitivity of individual neurons to task stimuli.

Another kind of contextual influence was demonstrated in the same reaching task by keeping spatial context stable (i.e., same repeating sequence of movements) and varying the temporal context by lengthening the duration of the interval between trials. Figure 6B shows two examples of TANs recorded when a monkey first experienced trials with short intertrial interval duration and then shifted to a longer duration. Both neurons showed stronger responsiveness to task stimuli when trials are separated by long durations, despite the fact that the cue-trigger interval remained constant. It therefore appears that temporal and spatial features of the task, which are key elements of the performance context, may affect the responsiveness of TANs.

Role of rodent TANs in behavioral flexibility in the face of context change

There has been renewed interest in the influence of context on TAN activity with behavioral studies carried out in rats demonstrating that the striatal cholinergic system plays a key role in the identification of particular situations in which learning takes place. Bradfield et al. (2013) have reported that disruption of cholinergic activity in the striatum impairs the rats' ability to adjust to new instrumental contingencies for obtaining reward. In this study, impaired cholinergic transmission was caused by lesion of input from the parafascicular nucleus, a major component of the intralaminar nuclei of the thalamus, which is known to target directly cholinergic interneurons (Lapper and Bolam, 1992; Doig et al., 2014). More specifically, the lesioned rats seemed to be unable to adapt what has been learned from one context to another, thus resulting in interferences in distinct learning contexts when response-outcome contingency changed. It therefore appears that the circuitry linking the thalamus and striatal cholinergic interneurons may be involved in the detection of the context in which the association between stimulus, action, and outcome has been learned.

Other pharmacological and lesion studies in rats have provided evidence that striatal cholinergic deficiency causes impaired flexible behavior when instrumental contingencies change. Ragozzino and colleagues were among the first to outline the contribution of cholinergic transmission in the striatum to the flexible shifting of instrumental responses based on change in task contingencies (Ragozzino, 2003; Ragozzino et al., 2009; Brown et al., 2010). Recent reports on the effect of selective immunotoxin lesions of striatal cholinergic interneurons on performance of tasks that require flexible switching of behaviors have confirmed the role of these interneurons (Okada et al., 2014; Aoki et al., 2015). All of these behavioral studies concluded that alteration in cholinergic transmission, specifically within the dorsomedial striatum, led to substantial changes in the animals' capacity to adapt to a changing environment.

This is in line with the widely accepted notion that information processing required when reinforcement contingencies change occurs in a specific part of the striatum. Indeed, distinct striatal regions are thought to differentially contribute to learning, with the dorsomedial striatum subserving actions that are flexible and guided by their consequences, and the dorsolateral striatum mediating actions that become automatic with extensive practice and are not outcome-driven (Balleine et al., 2009). It is still uncertain whether such regional specialization of learning functions is paralleled by differences in functional properties of local circuit neurons in the striatum. In particular, if cholinergic interneurons in the

dorsomedial striatum are selectively involved into a context detection process, it remains to be clarified whether those located in the dorsolateral striatum play some alternative role. Region-specific differences in the response properties of TANs have been reported in behaving rats, with TANs more responsive to the cue in the dorsolateral striatum than in the dorsomedial striatum (Thorn and Graybiel, 2014). As previously mentioned, ventral striatal TANs in rats are able to emit signals that reflect the difference between received and expected reward (Atallah et al., 2014).

The challenge now is to search for the neuronal correlates of hypothesized context representations in the activity of TANs. Electrophysiological recordings in rats performing a choice task have recently provided evidence that TANs located in the dorsomedial striatum, but not in the dorsolateral striatum, display changes in activity related to the encoding of a particular state of the environment (Stalnaker et al., 2016). The authors also reported that the pathway linking the orbitofrontal cortex with striatal cholinergic interneurons is involved in the processing of information about different environmental states. Thus, the TAN population is probably driven by different afferents from specific cortical and thalamic regions that integrate information about stimuli, actions and motivational state. However, the precise nature of the resulting information conveyed by TANs is still a matter of debate and further research is required to ascertain that TAN firing contains information which is required to form representations of the context.

Another issue is how contextual information carried by cholinergic TANs can have an impact on striatal output pathways involved in action selection. In this regard, there is increased emphasis on nicotinic acetylcholine receptor-mediated activation of specialized classes of striatal GABAergic interneurons which, in turn, provide an inhibitory regulation of striatal efferent pathways. Recent studies have shown that at least two types of GABAergic interneurons, called neuropeptide-Y-expressing neurogliaform interneurons (English et al., 2012) and fast-adapting interneurons (Faust et al., 2015), are activated by cholinergic inputs. An indirect effect of acetylcholine on striatal output neurons can therefore be mediated by nicotinic receptors that are localized on these specialized inhibitory local circuits. This may provide a mechanism by which transient changes in TAN firing can modify striatal output when the environment undergoes a change in context.

Relation to attentional control

There is a long-standing problem related to distinguishing TAN responses to motivationally relevant events from those related to the accompanying shifts of attention elicited by these

events. Indeed, TANs have been reported to respond to stimuli that are novel or perceptually salient (Aosaki et al., 1994; Blazquez et al., 2002; Ravel et al., 2003) and consideration must be given to the possibility that they may carry potential attentional signals. Bradfield et al. (2013) have argued that deficits in behavioral flexibility seen in rats with striatal cholinergic deficiency reflect an inability to separate different contexts in which learning takes place rather than deficits in attention when the initial action-outcome contingency was varied. They pointed out that lesioned rats were able to learn the initial action-outcome association at a rate comparable to that of normal control rats, suggesting intact attentional control necessary for the acquisition of the learned behavior. However, we cannot fully rule out that there might be special forms of attention closely tied to some features of the environment that are modulated as a result of changes in reward contingencies. Additional verifications are therefore needed to convincingly establish that the amount of attention paid to particular task features in a given context is not the exclusive determinant of TAN responses. It can be expected that progress in designing experiments which distinguish changes in attention from changes in circumstances under which behaviors are generated can reveal how TAN activity relates to context representations or fluctuations in attentional control. It is important to note that two major inputs to the striatum (i.e., midbrain dopamine neurons and thalamic CM/Pf neurons) may act in the control of attention to the environment. Apart from dopamine neurons showing discriminative responses to appetitive and aversive stimuli by an increase and a decrease in firing, respectively, other dopamine neurons are found to be uniformly excited by both stimuli (Matsumoto and Hikosaka, 2009). These non-discriminative responses appear to reflect the encoding of stimulus salience rather than its motivational value. In addition, neurons in the thalamic CM-Pf complex are highly sensitive to salient events that produce an orienting reaction (Matsumoto et al., 2001; Minamimoto and Kimura, 2002). We have already underlined the fact that dopamine and thalamic inputs play a crucial role in determining TAN responses to rewarding stimuli.

Conclusion

It is now recognized that the TAN population is not exclusively linked to motivational functions and stimulus-response learning reinforced by reward. By highlighting the diversity of TAN response properties in both rats and monkeys, the findings reported currently focus on the assumption that the intrinsic striatal cholinergic system seems to do something rather different than simply signaling motivationally salient events. Several studies have now emphasized that an important feature of TAN responses is their dependency on contextual

factors. In a previous comprehensive review on the TAN functions, I stated that « 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 » (Apicella, 2007). It seems that this view has gained ground in recent years as evidence has accumulated for the involvement of local cholinergic transmission in the integration of contextual information within the striatal circuitry. We are now moving towards the notion that the intrinsic striatal cholinergic system may serve as an interface between a representation of the context and appropriate action selection which is essential for flexible control of behavior. This is a promising avenue for future investigation of TAN physiology that should be extended using appropriate behavioral testing procedures designed to tackle the issue of the link between context representation and TAN activity. Recordings from behaving rats have just started to validate the hypothesis that TANs may contain information about behavioral context and this needs to be complemented by studies in monkeys.

Recent modeling studies have attempted to integrate cholinergic TANs into functional circuits in the striatum to refine hypotheses concerning their specific computational role (Stocco, 2012; Franklin and Frank, 2015; Crossley et al., 2016). Models of striatal function may prompt new experiments for understanding how the cholinergic TAN system may control information processing in striatal circuits. This may allow further characterization of the properties of TAN signals in order to gain insights into the contribution of this neuronal system to flexible behaviors.

In this review, I have emphasized that the data gathered in rodents are not always in agreement with those collected in monkeys, partly as a consequence of problems associated with the electrophysiological characterization of TANs. It is clear that accurate identification of TANs remains a critical issue. These differences in response properties of TANs between rodents and primates do not promote clarification of their functions. A next important step will be to use genetic tools with which to target specific cell types for objectively identifying striatal cholinergic interneurons with extracellular recording methods in behaving animals.

Understanding the information encoded by the TAN system represents a challenge for answering questions like how impaired cholinergic transmission in the striatum causes difficulties adjusting behavior to new conditions of the environment. This may provide insights into the pathophysiology of various neurological and psychiatric disorders in humans in which cholinergic mechanisms in the striatum are altered.

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Figure Legends

Figure 1. Modulations of TAN activity in behaving monkeys and rats.

A. Response of a single TAN to a reward-predicting stimulus. The monkey was trained to perform an arm reaching movement after the presentation of a visual stimulus. Each dot indicates the time of a neuronal impulse and each line of dots the neuronal activity occurring during a single trial. Dot displays and perievent time histograms are aligned on the onset of the stimulus (top) and movement (bottom) which are marked by thick vertical lines, and trials were ordered off-line according to the latency of movement. Movement onsets are indicated by heavy dots in raster displays. The neuron's response consisted of a decrease in activity followed by an increase, termed pause and rebound, respectively. Note that the latency of the TAN's pause response to the stimulus was independent of the timing of the subsequent movement, indicating that the response was precisely aligned to stimulus onset and did not reflect movement per se. Bin width of the histogram is 10 ms and vertical calibration is in spikes per bin. B. The multiphasic TAN response. Response of a single TAN (top) and a population of TANs (bottom) to a reward-predicting stimulus. The sample (n=85) included both responsive and unresponsive TANs. The three components of the TAN response (initial activation, pause, and rebound) are apparent in the population-average response. Vertical calibration is in spikes per 10-ms bin for the individual neuron and in spikes per second for

the population average. C. Examples of four responsive TANs recorded in the striatum of behaving rats. Rats were trained to perform a nose-poke response after the presentation of an auditory stimulus (GO signal) to obtain reward. The activities are aligned on the onset of the stimulus which is marked by vertical green lines. Same conventions as in A. Brown markers in raster displays indicate the beginning of the waiting period prior to trigger onset. Both dorsolateral and ventral striatal TANs responded to the trigger stimulus by decreasing (top) or increasing (bottom) their firing rate. The right part of the figure illustrates the population activity of TANs with decreasing or increasing activity in response to the trigger stimulus. Histogram scales are in spikes per second for example neurons and activity is normalized by the baseline firing rate for the population average (modified from Benhamou et al. 2014).

Figure 2. Morphological features of giant aspiny striatal neuron in primates and rodents.

Reconstruction of a striatal giant aspiny neuron of the monkey (baboon), as revealed by Golgi staining (left), and of the rat after *in vivo* intracellular staining (right). The observed morphological features allow to identify these neurons as cholinergic interneurons in both monkeys and rats. Contrasting to neurons in rats, the soma size and dendritic arborization of neurons in monkeys are considerably larger (left part, from Yelnik et al. 1991; right part, from Wilson et al. 1990).

Figure 3. Reward-prediction error signaling by TANs.

A. Modulation by reward probability of population responses of monkey TANs. Animals performed an instrumental task in which probabilistic rewarding outcomes were contingent on a visually-triggered arm movement in block-design experiments. Populations activities at different levels of reward probability ($p=1.0$ to 0.25) are superposed and separately aligned on stimulus onset and reward delivery. Only rewarded trials are included. The average TAN response to reward was stronger as the probability of reward decreased, whereas there were no detectable effects on responses to the stimulus that triggered the movement. B. Comparison of magnitudes of two distinct components of TAN responses (pause and rebound) in relation to reward probability levels in two learning task situations. The modulation of TAN responses to reward by probability was relatively weak in the instrumental task, particularly for the pause component, compared with that observed in the classically conditioning task. Dots represent means \pm SEM. (modified from Apicella et al. 2011). C. Sensitivity of rodent TANs to the delivery or omission of reward. Examples of three responsive TANs recorded in distinct phases of training. Rats consecutively learned two

versions of a T-maze task with cues indicating the availability of reward at the left or right arm of the maze (Goal). They were first trained with auditory cues instructing the location of reward and then with tactile cues, thus allowing comparison of TAN activity during successive training periods. TAN responses to reward delivery, consisting of an increase in firing, occurred selectively during each acquisition phase of the two task versions (auditory and tactile), whereas TAN responses to reward omission, expressed as a decrease in firing, were observed at all phases of training. The bottom part of the figure shows population activity of all TANs modulating their activity in relation to goal-reaching during each training period, separately for rewarded (blue) and unrewarded (red) trials. Same conventions as in Fig. 1A (modified from Atallah et al. 2014).

Figure 4. Influence of changing the timing of reward during performance of a Pavlovian task. Response of the same TAN to reward delivered at various times after a predictive stimulus. The monkey was trained on a classically conditioned task in which a visual stimulus and reward were separated by a constant time interval (1 s). On some occasions, the duration was shortened (0.3 s) or prolonged (2.0 s), the time of reward being changed across blocks without explicit indication as to which time interval will be used. The dot displays corresponding to each trial block are shown in order of occurrence from top to bottom. The reward response emerged when the event occurred earlier or later than the usual time, without affecting the response to the preceding stimulus. Same conventions as in Fig. 1A, except that the sequence of trials is shown chronologically from *top* to *bottom* in each dot display.

Figure 5. Spatial selectivity of TAN responses dependent on reward schedule.

Population activities of TANs modulating their activity in relation to the onset of a visual stimulus (Cue) presented on the side contralateral or ipsilateral to the hemisphere from which recordings were made. In this task, the cue was presented at one spatial location and the monkey was subsequently required to make a saccadic eye movement to this previously cued location. In the one-direction rewarded condition (1DR), only one stimulus location was followed by reward, whereas in the all-directions-rewarded condition (ADR), all stimulus locations were followed by reward. The pause response of the TAN population to the contralateral cue was stronger in 1DR than in ADR, indicating that the spatial selectivity of TAN responses was dependent on the context of reward availability (modified from Shimo and Hikosaka 2001).

Figure 6. Modulation of TAN responses by changes in spatial or temporal features of task context.

A. Influence of the serial order of stimulus presentations on TAN responses. Locations of recorded TANs ($n=79$) are indicated by symbols on coronal sections of the striatum (from 1 mm anterior to 7 mm posterior to the anterior commissure (AC). TANs were classified into four types depending on their responsiveness and the selectivity of their responses. The behavioral task consisted of a presentation of a first visual stimulus serving as a preparatory signal (cue) for an upcoming reaching movement triggered by a second visual stimulus (trigger) whose spatial location varied from trial to trial. The cue only indicated the timing of the impending trigger stimulus without providing information about its location. Target stimuli were presented in two spatial contexts according to their sequential order: (1) the repeated condition, in which the monkey produced the same sequence of three movements; (2) the random condition, in which the order of movements was randomly generated. The two conditions were similar in overall trial timing and were run in separate blocks. Although percentages of TANs responding to visual stimuli in the repeated and random conditions remain approximately the same (inset), a number of TANs changed their response selectivity or acquired responses to visual stimuli when passing from the repeated to the random conditions. The figure illustrates the locations of all TANs studied in the two conditions in two monkeys. It can be seen that neurons were sampled from the full rostro-caudal extent of the dorsal striatum, both in the caudate nucleus and putamen, without extension on the ventral striatum. Neurons displaying changing response characteristics were evenly distributed over the striatal areas from which we recorded. This suggests that the stimulus selective tuning functions of TANs are dynamic and may be expressed differentially according to the context established by the sequential organization of stimuli and movements. Put, putamen; Cd, caudate nucleus (modified from Deffains et al. 2010).

B. Influence of changing trial duration on TAN responses. The upper part shows the timing of stimulus presentation. The task used the fixed sequence of movements (repeated condition) and a constant cue-trigger interval (1.5 s), and the overall trial duration was shifted from 4 s to 7 s in separate blocks. The lower part shows two examples of TANs with enhanced responses to visual stimuli by lengthening trial duration. Same conventions as in Fig. 1A except that trials are shown in chronological order from top to bottom and gray markers in raster displays indicate movement onsets (Deffains and Apicella, unpublished observations).

Figure 1

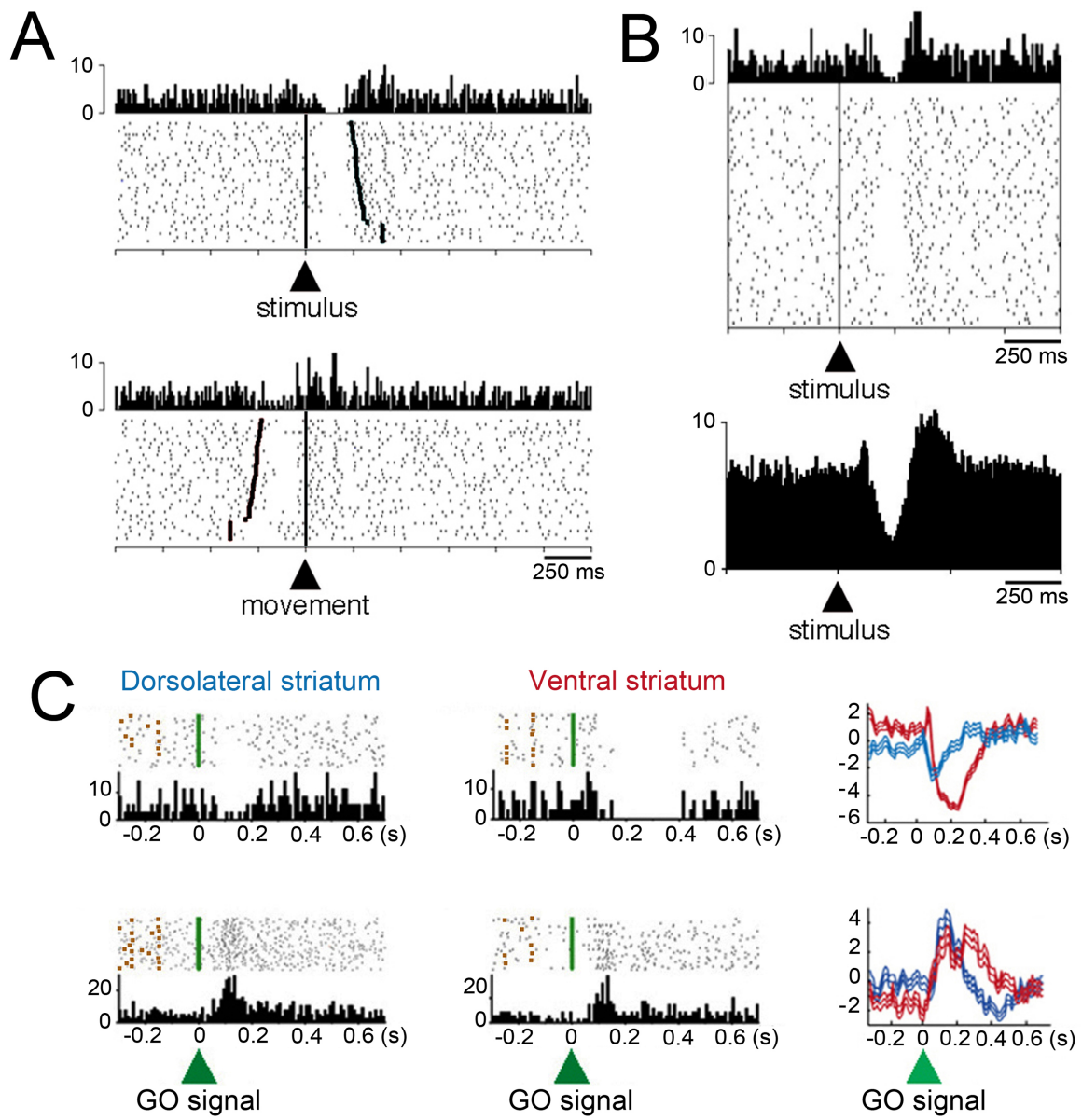


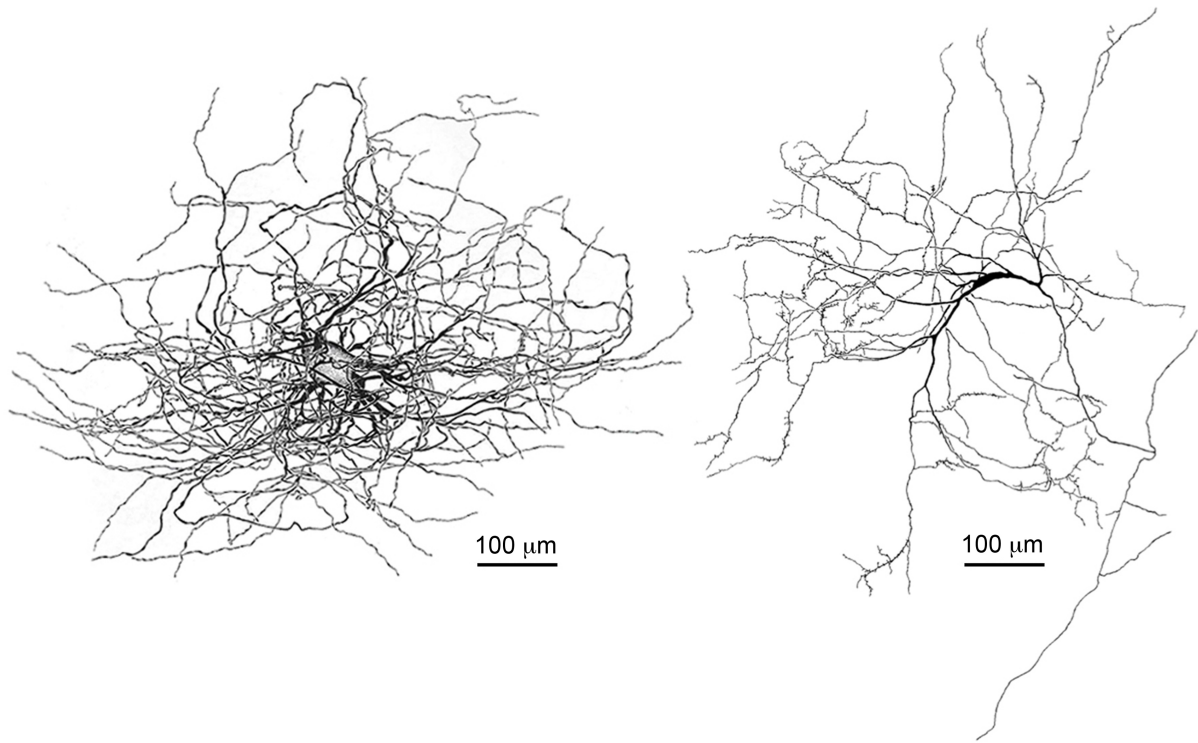
Figure 2

Figure 3

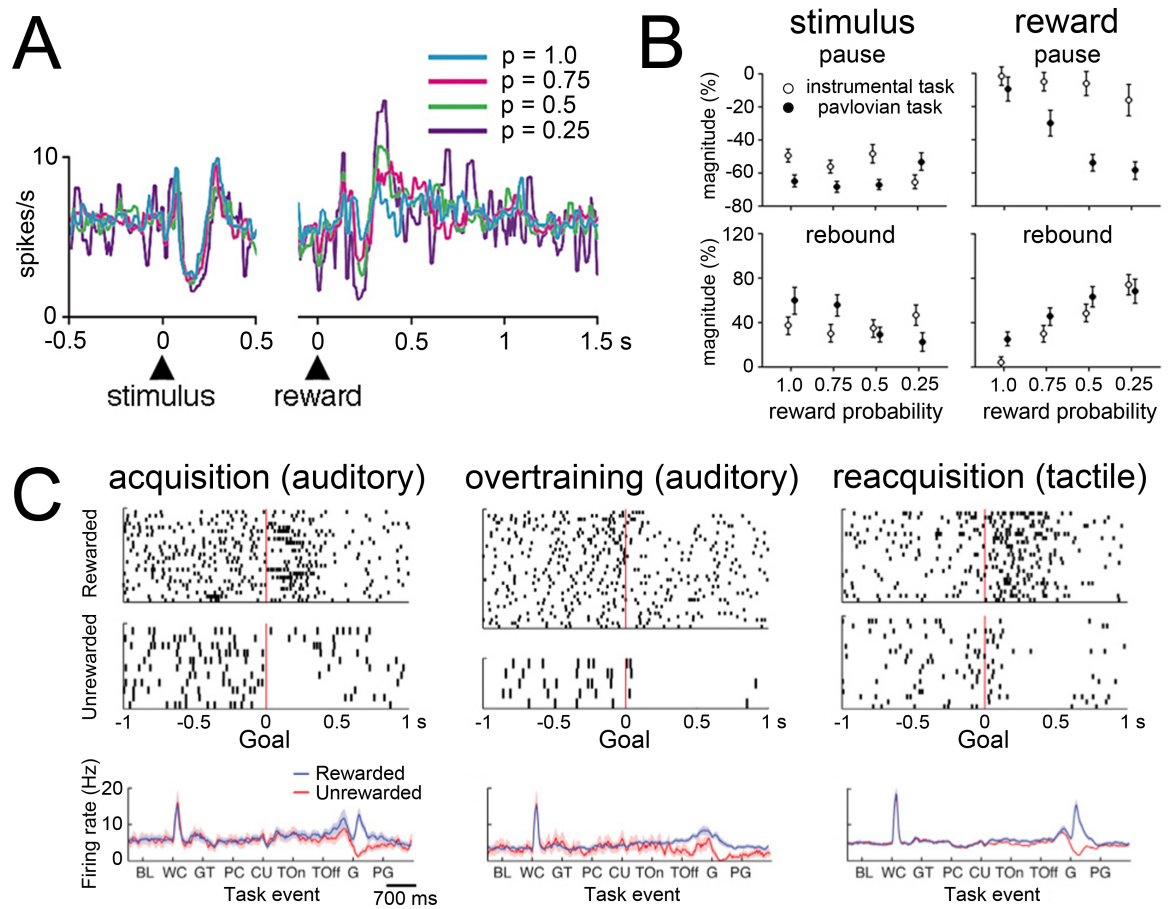


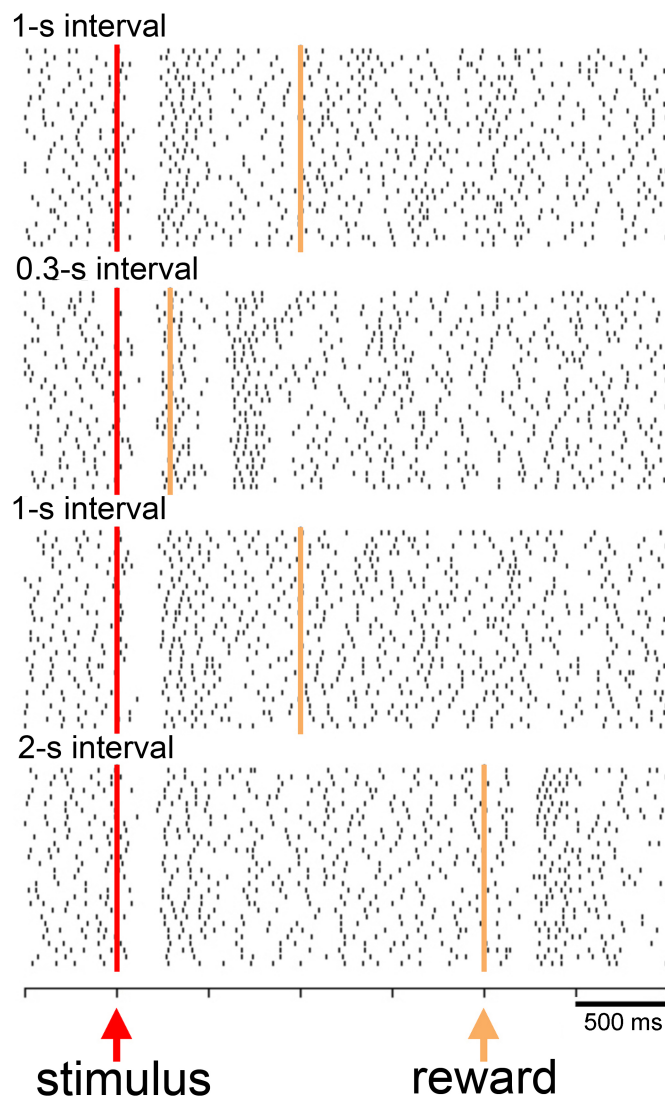
Figure 4

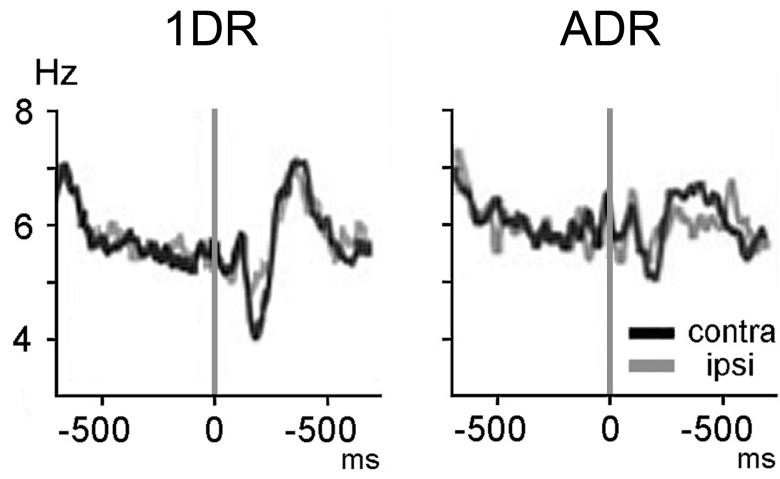
Figure 5

Figure 6

