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Activity of fast-spiking interneurons in the monkey striatum during reaching movements guided by external cues or by a free choice

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List of abbreviations :

FSI: fast-spiking interneuron

PAN: phasically active neuron

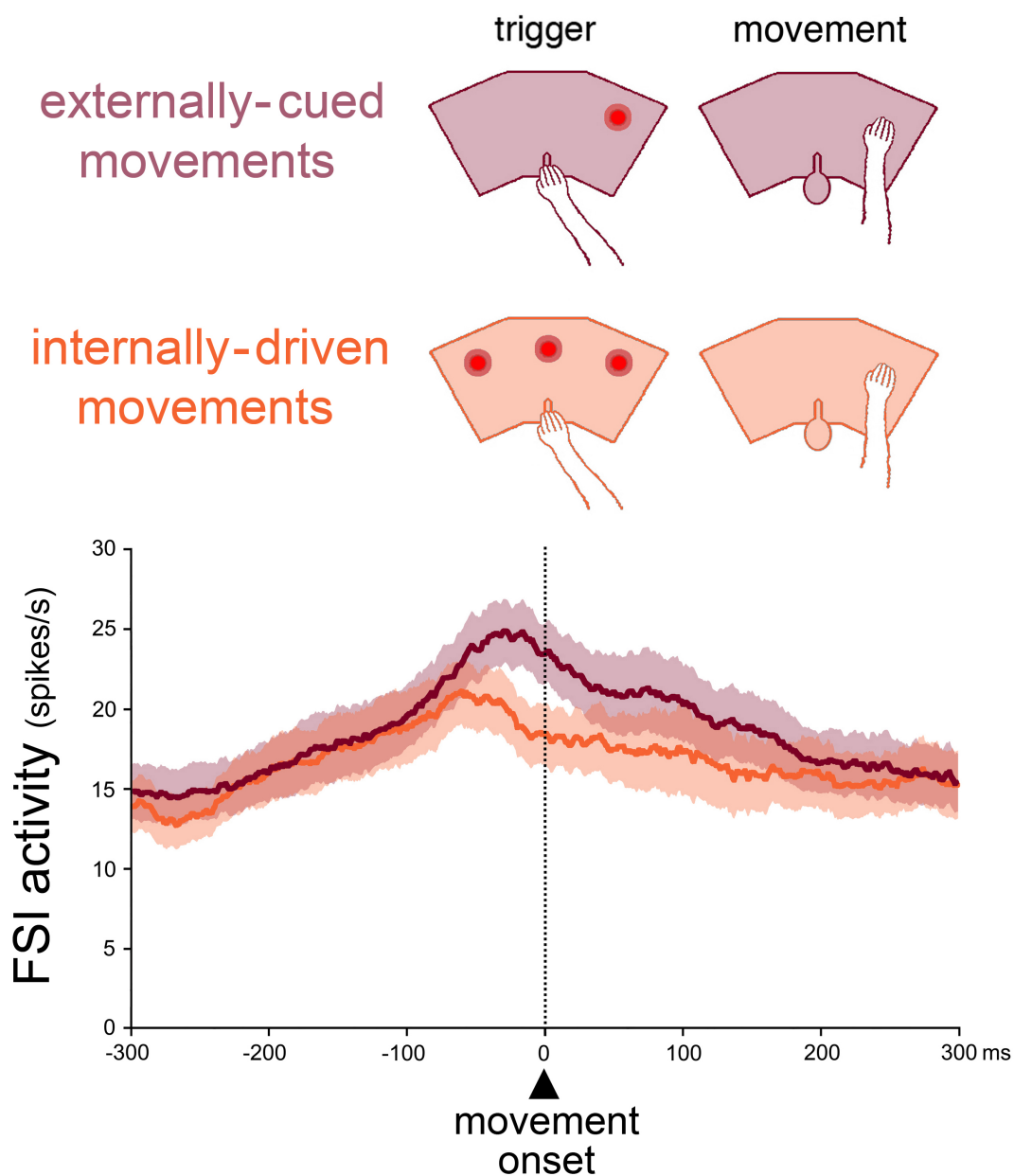
PV: parvalbumin

MT: movement time

RT: reaction time

TAN: tonically active neuron

Graphical Abstract



We recorded activity of fast-spiking interneurons (FSIs) in the striatum, presumed parvalbumin-containing GABAergic interneurons, in monkeys performing reaching movements based either on external cues or internal choice. By comparing modulations of FSI activity around movement onset, we report that stronger activation occurred with externally-cued than internally-driven movements, suggesting a dependence on movement selection mode which appeared predominant in the motor striatum. We propose that changes in FSI activity carry information that is scaled by constraints on movement initiation.

Abstract

Parvalbumine-containing GABAergic interneurons in the striatum, electrophysiologically identified as fast-spiking interneurons (FSIs), exert inhibitory control over striatal output to drive appropriate behavior. While a number of studies have emphasized their importance in motor control, it is unknown how these putative interneurons adapt their functional properties to different modes of movement selection. Here, we tested whether FSIs are sensitive to externally vs. internally selected movements by recording their activity while two male rhesus monkeys performed reaching movements to visual targets. Two variants were used: an *external* condition, in which movements were instructed via external cues, and an *internal* condition, in which movements were guided by an internal representation of the target location. These conditions allowed to contrast the FSI activity associated with either externally-cued or internally-driven movement selection. After extensive training, reaching performance was only marginally affected by the type of movement, albeit with some differences between the monkeys. Over two thirds of the FSIs were modulated around movement onset, regardless of the condition, consisting mostly of increased activity. We found that a subset of FSIs showed stronger activation related to the initiation of movements in the external condition than in the internal condition, suggesting a dependence on movement selection mode. Moreover, this difference in the strength of FSI activation was predominant in the motor striatum. These data indicate that changes in FSI activity carry information that is scaled by constraints on action selection reflecting the involvement of local striatal inhibitory circuits in adaptation of behavior according to task demands.

Introduction

Different subgroups of GABAergic interneurons that have been electrophysiologically and morphologically characterized are involved in regulating activity of the striatum (Tepper *et al.*, 2010; Silberberg & Bolam, 2015). Among them, the presumed fast-spiking interneurons (FSIs), thought to correspond to the parvalbumin (PV)-containing GABAergic interneurons (Kawaguchi, 1993; Mallet *et al.*, 2005; Sharott *et al.*, 2012), are the predominant source of feedforward inhibition onto striatal output pathways which is thought to be critically important for motor control (Gittis *et al.*, 2010; Koos & Tepper, 1999; Planert *et al.*, 2010; Szydlowski *et al.*, 2013). Indeed, dysfunction of striatal FSIs in humans has been reported in neuropsychiatric diseases characterized by involuntary generated movements, such as Tourette syndrome (Kataoka *et al.*, 2010) and Huntington's disease (Reiner *et al.*, 2013). Further evidence comes from animal experiments indicating that striatal FSI deficiency is associated with movement abnormalities, including dystonias (Gernert *et al.*, 2000; Gittis *et al.*, 2011), spontaneous repetitive behaviors (Burguière *et al.*, 2013), and motor stereotypies at least under acute stress (Xu *et al.*, 2016). In addition, recording studies in behaving rodents have pointed to the potential role of FSIs in motor control and action selection (Bakhurin *et al.*, 2016; Gage *et al.*, 2010; Kim *et al.*, 2014; Kim *et al.*, 2019; Kulik *et al.*, 2017; Roberts *et al.*, 2020; Schmitzer-Torbert & Redish, 2008). Although few in number, studies in monkeys also provide evidence linking FSI activity to the initiation and execution of movement (Marche & Apicella, 2017; Yamada *et al.*, 2016).

While the role of local GABAergic circuits of the striatum has been mainly considered in the field of motor control, recent inactivation studies in rodents indicate that striatal FSIs can have a role in the acquisition of stimulus-reward associations (Lee *et al.*, 2017), the learning of behavioral responses to stimuli (Owen *et al.*, 2018), and the expression of operant responding that becomes automatic with extensive practice (O'Hare *et al.*, 2017). These data support the

notion that the FSI system may serve a broad range of functions that go beyond the more strictly motor aspects of behavior. Further work is therefore required to better understand the functional significance of changes in FSI activity and its impact on behavior.

In this regard, it has long been recognized that the basal ganglia are preferentially involved in performing internally-generated movements such as those guided by memory (Jueptner & Weiller, 1998). For example, patients suffering from Parkinson's disease display deficits in internally generated movements that are improved with the use of external cues (Brown & Marsden, 1988; Canavan et al., 1990; Glickstein & Stein, 1991). Recordings of striatal output neurons in monkeys (Kimura *et al.*, 1992; Schultz & Romo, 1992) and neuroimaging studies in humans (Jahanshahi *et al.*, 1995; Jenkins *et al.*, 2000) have shown that there are differences in striatal activity when actions are externally- or internally-specified. However, it remains unclear whether the inhibitory interneuron circuit in the striatum is sensitive to the mode of movement selection.

To address this question, we used in monkeys a task that allows for comparing the ways in which arm movements towards targets are selected. In one condition, the monkey was externally-instructed where to make a movement, while in the other condition, the monkey had to select the movement direction on its own, based on an internal representation. We investigated whether the modulation of FSI activity around movement onset showed a dependence to the mode of movement selection. We found that most FSIs were activated by both types of movements, but the activation of a subset of these neurons was greater for externally-guided movements than for internally-guided movements, indicating that these presumed GABAergic inhibitory interneurons carry information that is scaled by constraints on movement selection.

Materials and methods

Behavioral paradigm

Experiments were conducted according to the protocol approved by the Comité d'éthique en Neurosciences INT-Marseille (Protocol A2-10-12) and in accordance with the Council Directive 2010/63EU of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes. We used two adult male rhesus monkeys (*Macaca mulatta*), F and T, that were previously trained to make arm reaching movements to visual targets to obtain a liquid reward (Marche & Apicella, 2017). Animals sat in front of a panel ~30 cm away equipped with three two-color (red and green) light-emitting diodes (LEDs) aligned horizontally, at the monkey's eye level, and separated from each other by 10 cm. Three metal knobs of 10-mm diameter, one below each LED, served as movement targets. A metal bar located on the lower part of the panel, at the monkey's waist level, served as the starting point for the movement. A tube positioned directly in front of the monkey's mouth dispensed small amounts of fruit juice (0.3 ml) as a reward. We used two task conditions with two modes of movement selection:

(1) *Reaching task with externally-guided movement selection*. The first task variant, called the *external* condition, is characterized by a stimulus–response association involving single target stimuli. The trial structure is illustrated in Figure 1A (upper part). At the beginning of each trial, the monkey kept the hand on the bar. After 1 s, the onset of a green light (duration: 0.5 s) pseudorandomly presented either to the left or to the right served as a cue for a trigger stimulus which came on 1.5 second later at the same location. In response to that stimulus, the monkey had to initiate a movement toward the corresponding target to get a reward. The trigger stimulus remained on until a target contact or an upper time limit of 1 s. After each target contact, the animal brought the hand back on the bar and the next trial could not begin until the total duration of the current trial (6 s) had elapsed.

(2) *Reaching task with internally-guided movement selection.* For the second task variant, called the *internal* condition, the trigger stimulus did not define the reach target explicitly. The sequence and timing of events was identical to the previous condition, but there were three simultaneous visual stimuli instead of one. As illustrated in Figure 1A (lower part), the onset of three green lights (duration: 0.5 s) was followed after 1.5 second later by the presentation of three red lights serving as a trigger stimulus. At the start of a trial block, the three choice options were assigned a reward probability and the monkey identified the more frequently rewarded of the three targets, after which its choice remained stable for the rest of the block. In the present study, we used mostly a low level of uncertainty on which a target yielded reward with probability of 0.70 whereas the two others yielded reward with a probability of 0.15, the location of the best rewarded target being chosen pseudorandomly across trial blocks. This reward schedule allowed monkeys to make the right choice quickly.

Behavioral testing comprised of interleaved blocks of stimulus-guided trials, in which both the timing and direction of movement are specified by external cues, and internally-guided trials, in which only the timing of movement is specified by external cues, the direction of movement being selected by retrieving a memory representation of the target location. The two conditions were presented in blocks of 30-50 trials therefore allowing to contrast the task performance associated with either externally cued or internally driven movement selection. It was assumed that conditions switched unpredictably between blocks so that the monkey never knew in advance the condition on any given block. In general, each neuron was tested in both conditions, the order being counterbalanced across sessions, unless the correct isolation of individual neurons could not be ensured. When recordings were stable enough, the internal condition occasionally included transitions to different probabilities of reward, so that the previous chosen target has to be replaced by a new one for another series of 30-50 trials.

Task performance was assessed in terms of reaction time (RT) and movement time (MT) which were the time taken to release the bar in response to trigger onset and to move from the bar to a target, respectively. If the monkey released its hand from the bar before trigger onset or after 1s, it was not rewarded, and the trial was repeated. We also excluded trials on which RTs were less than 100 ms (< 1% of all trials in both conditions) considered as premature responses arising from the anticipated initiation of the movement. In the internal condition, we restricted our analysis to trials that immediately followed a rewarded trial, including the first few trials in each trial block during which monkeys' choice stabilized. In this way, the comparison between the two conditions can be considered to be for trials performed in a similar motivational state (i.e., after rewarded trials in both external and internal conditions).

Electrophysiological recording

After the monkeys were fully trained on the two task conditions, they underwent aseptic surgery to implant a head holder and a recording chamber to the skull under general gas anesthesia (isoflurane 2.5%) and sterile surgical conditions. The chamber was stereotaxically positioned above the left hemisphere to record neuronal activity in the striatum, its center being aimed at the anterior commissure. Both animals were required to use the right arm (contralateral to recording side) to perform the reaching task.

Standard electrophysiological techniques for extracellular single neuron recording were used. To record from the striatum, a stainless steel guide tube (0.6 mm outer diameter) was lowered below the surface of the dura matter. A glass-insulated tungsten microelectrode (2 to 3 M Ω) was passed inside the guide and was advanced using a manual hydraulic microdrive (MO-95; Narishige, Tokyo, Japan). Neuronal signals were bandpass filtered between 0.3 and 1.5 KHz, amplified 5000-fold, and monitored with oscilloscopes. Spike sorting was performed online using a window discriminator (Neurolog, Digitimer, Hertfordshire, UK). Throughout the recording session, stability of spike isolation was monitored on a digital oscilloscope to check

the good-quality single-neuron isolation. Only the neurons that maintained stable spike isolation throughout the recording session were included in the analysis.

Electrode penetrations were directed toward striatal regions rostral and caudal to the anterior commissure, mainly to the putamen. A few penetrations were continued through the dorsal precommissural striatum until the ventral region. In agreement with previous studies, including our own, we classified each neuron as belonging to one of the three recognized types of extracellularly recorded neuron found in the striatum of awake monkeys, namely phasically active neurons (PANs), tonically active neurons (TANs), and FSIs (Adler *et al.*, 2013; Marche & Apicella, 2017; Yamada *et al.*, 2016).

Neuronal data analysis

In the present study, we focused on modulation in FSI activity occurring just before and during reaching toward the target. The time period used to examine FSI activity, referred to as the *perimovement period* (300 ms before and after the onset of the movement), was chosen based on the data obtained from a previous experiment indicating that peak activations of FSIs related to movement onset mainly occurred during this period (Marche & Apicella, 2017). A test window of 50 ms was moved in 10 ms steps within 600 ms starting 300 ms before movement onset (perimovement period). For each time step, we calculated the averaged firing rate within the test window across all trials and we compared it with the baseline firing rate calculated during the 0.5 s period immediately preceding the presentation of the cue (i.e., control period). The onset of a modulation was taken to be the beginning of the first of at least 5 consecutive steps showing a significant difference as against the baseline activity. Statistical comparisons were performed with a cluster-based permutation test ($P < 0.05$) with 2000 permutations that intrinsically corrects for multiple comparisons (Maris & Oostenveld, 2007). The offset of a modulation was defined in the same manner by the first of at least 5 consecutive steps with activity back to control. We adopted this sliding time window procedure based on the results

of preliminary analyses using different window lengths and step numbers indicating that it is a good compromise between temporal resolution and reliability.

In addition to the analysis of individual neurons, we pooled activities across neurons tested in both conditions to examine their activity at the level of population average. In this analysis, a 50-ms sliding window moved in 1 ms steps to identify (i) when the population changed its activity compared with control period, and (ii) when the level of population activity between conditions differed, again using cluster-based permutation test to assess statistical differences ($P < 0.05$).

The temporal relation between changes in FSI activity and movement parameters (i.e., RT and MT) were assessed by a correlation analysis on a trial-by-trial basis (Pearson's correlation). We also defined each neuron's sensitivity to the target location and/or direction of the movement by comparing the spike counts in a predefined time window (specified in the Results section). The selectivity of the FSI activity for a particular location was judged to be present if the magnitudes of the activity were significantly different between the left and right target locations (Wilcoxon signed-rank test, $p < 0.05$). For proportions, chi-squared (χ^2) test was used to compare groups between time periods or task conditions. Data were analyzed using custom-written MATLAB (version R2019b, Natick, MA) scripts and all statistical analyses were performed using JMP software (version 11, Chicago, IL).

Recording sites

The recording sites were reconstructed based on small electrolytic marking lesions (20 μ A for 15-20 s, cathodal current) in the striatum and globus pallidus as reference points. The monkeys were sacrificed with an overdose of pentobarbital and perfused transcardially with 0.9% saline followed by a fixative (4% paraformaldehyde, pH 7.4 phosphate buffer). A block of tissue containing the striatum was cut into frontal sections of 40- μ m thickness on a freezing microtome, and every section was stained with cresyl violet. Marking lesions were then

identified and electrode penetrations were reconstructed in serial sections through the striatum. Based on the location of recording sites identified histologically in each animal, we confirmed that most FSIs were recorded in the putamen, between 4 mm anterior and 6 mm posterior to the anterior commissure, and over the entire lateral to medial extent of the nucleus, including some penetrations in the most ventral portion of the precommissural striatum. According to previous studies (Parent, 1990), the primate striatum is divided into three regions corresponding to the postcommissural part of the dorsal putamen (motor striatum), dorsal portion of the precommissural part of the caudate nucleus and putamen (associative striatum), and ventral portions of the caudate nucleus and putamen rostral to the anterior commissure (limbic striatum).

Results

Behavior

Figure 1B shows distributions of RTs and MTs from the two task conditions, separately for each monkey. A significant effect of condition was observed on RTs in monkey T ($t = 8.71$, degree of freedom (d.f.) = 627, $P < 0.0001$ two-sided paired t-test) with *internal* trials being associated with shorter RTs compared to *external* trials, but not in monkey F ($t = 0.19$, d.f. = 1024, $P = 0.0843$). There was no significant effect of condition on MTs in monkey T ($t = 0.38$, d.f. = 695, $P = 0.697$) and monkey F ($t = 1.66$, d.f. = 859, $P = 0.096$). Thus, behavioral evidence suggests that one animal initiated movements faster in the internal condition than in the external condition, while the other maintained a comparable level of RT performance regardless of the condition. On the other hand, the speed of movement from the resting bar to target was not affected by the task condition in both animals. We quantified performance in the internal condition by calculating, for each block, the percentage of trials in which the animal chose the best rewarded target. Both monkeys reached a performance of >80% of best choices ($n=51$ and

56 trial blocks in monkeys F and T, respectively). Monkeys' choice stabilized within the first few trials of a new block (6.3 ± 5.2 and 6.5 ± 6.0 (mean \pm SD) trials in monkeys F and T, respectively) and remained consistent for the rest of the block.

Neurons

Neuronal data used for examination of spike waveforms and baseline discharge rates were obtained from all neurons sampled for each site of recording where at least one presumed FSI was recorded. We collected 250 neurons in total across 30 and 26 recording sessions in monkeys F and T, respectively. We identified neurons as putative PANs (n=88), TANs (n=89), or FSIs (n=73) according to the electrophysiological classification criteria defined in previous extracellular recording studies in behaving monkeys (Adler *et al.*, 2013; Yamada *et al.*, 2016; Marche & Apicella, 2017). The FSIs had a mean baseline firing rate of 12.6 ± 8.5 (mean \pm SD) spikes/s (n=73), which is higher than that of the TANs (5.6 ± 2.2 , n=89) or PANs (1.5 ± 1.9 , n=88). Their duration of spikes, defined as the time interval between the first negative and second positive peaks of the spike (i.e., peak-to-peak duration) was shorter (429 ± 71 μ s, n=72) than that of the TANs (906 ± 178 μ s, n=93) and PANs (759 ± 79 μ s, n=88) (Wilcoxon's rank sum test, $P < 0.01$). These characteristics of FSIs were in accordance with previous reports (Adler *et al.*, 2013; Yamada *et al.*, 2016; Marche & Apicella, 2017) and clearly differentiate them from other types of striatal neurons. As detailed later, histological reconstruction showed that recording sites in the two monkeys were localized predominantly to the putamen, both rostral and caudal to the anterior commissure, with some extending to the ventral portion of the striatum.

A total of 63 FSIs (32 and 31 in monkeys F and T, respectively) were recorded in the external condition. Using our sliding time window analysis (see Materials and Methods), we found that 49 of these 63 neurons (78%) showed statistically significant changes in activity during the perimovement period (cluster-based permutation test, $P < 0.05$). Figure 2A shows

the temporal profile of changes in perimovement activity for each of the modulated neurons in the two conditions. The predominant modulation was an increase in activity (37 of 49 neurons, 76%), the other neurons displaying a decrease in activity (12 of 49 neurons, 24%). We also recorded the activity of 61 FSIs in the internal condition (31 and 30 in monkeys F and T, respectively). As shown in Figure 2B, 48 neurons (79%) significantly modulated their activity during the perimovement period with an increase (32 of 48 neurons, 67%) or decrease (16 of 48 neurons, 33%) in activity. The proportions of modulated neurons did not differ significantly between the two conditions ($\chi^2 = 0.015$, degree of freedom (d.f.) = 1, $P = 0.902$). Also, the proportions of FSIs displaying increases or decreases in activity were not significantly different ($\chi^2 = 1.847$, d.f. = 3, $P = 0.604$) when comparing the external and internal conditions.

We focused on 44 FSIs tested in both the external and internal conditions. Among these neurons, 29 showed significant increased firing compared to the control baseline in the external condition, most of them ($n=21$) maintaining their activation when tested in the internal condition, whereas the remaining lost their activation, four of them becoming inhibited and four being no longer modulated. It therefore appears that the switch from one condition to the other may affect the expression and polarity of FSI modulations to the onset of movement, indicating that at least some of the changes in FSI firing were not exclusively related to the requirement for movement initiation but might be influenced by task demands.

Two examples of FSI modulated around the time at which the monkey initiated movements are shown in Figure 3. In neuron A, an increase in activity occurred immediately before movement onset and was maintained during reaching toward the target, this neuron being activated in a similar manner in the two conditions. The increase in activity occurred earlier in neuron B and was stronger in the external condition compared to the internal condition. The FSI activation during movement was changed in inhibition when passing from the external to the internal conditions. In this latter condition, an unsignaled block switch

occurred during the test, the location of the best rewarded target being replaced by a new location and the monkey's choice being adjusted accordingly. As can be seen, the shift in target choice had no influence on FSI activity, suggesting that modulation did not depend on the visuo-motor contingencies of choice.

We then examined changes in FSI activity at the population level. Figure 4A illustrates the ensemble average activity during the perimovement period for the 44 FSIs tested in both conditions. The mean population firing rate aligned with movement onset shows a rise in activity peaking just before the onset of movement and the magnitude of this activation appears to be somewhat more pronounced in the external condition compared to the internal condition. To test this impression, we compared the magnitude of population activity between the two conditions using a sliding 50-ms time window shifting by 1 ms during the perimovement period (see Materials and Methods), but differences between the external and internal conditions failed to reach statistical significance (cluster-based permutation test, $P > 0.05$). To further assess a possible influence of task condition, we performed the same analysis by including only those neurons activated in the external condition ($n=29$). As indicated in Figure 4B, the comparison between conditions for this subset of neurons revealed that the activation was significantly higher in the external condition than in the internal condition during a period from 45 ms before to 21 ms after movement onset (cluster-based permutation test, $P < 0.05$). The latencies of peak activity of the population were -30 ms and -61 ms before the movement onset in the external and internal conditions, respectively. Restricting the analysis to the sample of 24 FSIs that were activated in the internal condition (Fig. 4C), we only showed a trend toward stronger activation in the external condition but it failed to reach statistical significance (cluster-based permutation test, $P > 0.05$). In sum, it was only a particular subset of FSIs that were activated in the external condition that showed significantly stronger activation around movement onset when monkeys were externally cued about which movement to make, as compared to internally driven

movements. Our results indicate that within the FSIs there are discrete subtypes activated around movement onset, one type being particularly sensitive to movement selection mode, while other FSIs showed a similar trend but did not attain significance. Additionally, we analyzed the subset of FSIs showing a decreased activity in the external condition (n=11) and found that the magnitude of the decreasing activity was not significantly different between the two conditions (Fig. 4D).

To assess whether FSIs were sensitive to target location or movement direction, we quantified firing rates for the 49 FSIs modulated in the external condition by using the same window analysis as previously defined and then compared the spike counts between leftward and rightward movements for each neuron. The results of this analysis are shown in Figure 5. Of the 49 neurons, 9 (18%) showed activity that differed significantly between the two target locations (Wilcoxon's rank-sum test, $P < 0.05$), of which 5 showed stronger activity when the target was ipsilateral to the moving arm (i.e., contralateral to the side of recording) and 4 when the target was contralateral. The same analysis was conducted with 16 neurons recorded in the internal condition whose activity could be tested using the left and right locations of the best rewarded target. Of these, 5 (31%) showed statistically significant effects for target location (1 and 4 with stronger activity for ipsilateral and contralateral target locations, respectively). The proportion of neurons with spatial preference was not significantly different between the two conditions ($\chi^2 = 1.185$, $df = 1$, $P = 0.276$) suggesting that FSI activity was not markedly influenced by the spatial stimulus-response correspondence, irrespective of the task condition.

FSI activity during the delay period

To assess a possible influence of the expectation of trigger stimuli and/or the preparation of movements, we examined FSI activity during the delay period in which the monkey held its hand steady and awaited the signal for the reaching movement. Data were analyzed in the same manner as for activity around movement onset, using our sliding window procedure. Overall,

we found that 49 % (31 of 63) and 44 % (27 of 61) of the FSIs recorded in the external and internal conditions, respectively, showed statistically significant changes in activity during the delay periods (cluster-based permutation test, $P < 0.05$). The temporal profile of these changes in activity for individual neurons is illustrated in Figure 6A separately for the two conditions. The group of FSIs modulated prior to trigger onset was heterogeneous in terms of the timing of changes in activity and the direction of these changes (i.e. increased or decreased in firing rates), and four FSIs recorded in the external condition displayed modulations that combined increases and decreases. The fractions of neurons modulated during the delay period were not significantly different between the external and internal conditions ($\chi^2 = 0.304$, d.f. = 1, $P = 0.581$), in terms of increases ($\chi^2 = 1.048$, d.f. = 1, $P = 0.305$) or decreases in firing ($\chi^2 = 0.511$, d.f. = 1, $P = 0.476$). To compare the proportion of modulated FSIs further, we divided the delay period into four successive intervals of 250 ms and found that the proportion of modulated FSIs was significantly enhanced in the external condition, compared to the internal condition, only in the 500-750 ms window after cue offset ($\chi^2 = 4.254$, d.f. = 1, $P = 0.039$) (Fig.6A, inset bar graphs).

Overall, it appears that the latencies of changes in FSI activity were not statistically different between the two conditions (median latencies relative to cue offset: 390 ms and 520 ms for external and internal conditions, respectively; Wilcoxon signed-rank test: $z = 1.068$, $P = 0.285$), indicating that the task condition did not affect the timing of these modulations. In most FSIs, a significant change in activity was rarely maintained for more than 0.5 s. This occurred in 5 and 2 neurons in the external and internal conditions, respectively, some of which persisting beyond the onset of the trigger stimulus (3 and 2 neurons in the external and internal conditions, respectively).

We plotted the population-average activity in the delay period for the sample of 29 neurons recorded in both conditions and superimposed them (Figure 6B). As it can be seen,

FSIs showed a slightly higher level of firing during the delay period in the external condition, as compared with the internal condition, but this difference did not reach significance (cluster-based permutation test, $P > 0.05$). Overall, there were no marked differences in the temporal evolution of the population activity between the two conditions, population activities increasing immediately after trigger onset, and reaching a maximum level during movement. It therefore appears that the effect of condition had relatively little influence on FSI activity at the population level during the delay period.

Interindividual differences in FSI activity

Our behavioral findings have shown that monkey T initiated movements faster in the internal condition than in the external condition, whereas monkey F maintained its reaching performance at a constant level in both conditions. We therefore investigated whether these individual differences in task performance may be associated with differences in FSI activity. To do this, we re-examined the population activity of the same subset of 29 neurons analyzed before separately for each monkey (Figure 7A). The magnitude of the activation tended to be greater in the external condition than that in the internal condition in both monkeys, but did not reach statistical significance (cluster-based permutation test, $P > 0.05$). The latencies of peak activity were -10 ms and -32 ms (monkey F) and -38 ms and -61 ms (monkey T) before the movement onset in the external and internal conditions, respectively.

We then examined at the single-neuron level for each monkey how many FSIs exhibited differential activity between conditions. We did this by computing the spike counts of each neuron in the previously defined time period during which the population activity in the external condition significantly diverged from that in the internal condition (i.e., 45 ms before to 21 ms after movement onset) and we compared activity between conditions. Of the 29 neurons, 10 were significantly more activated in the external condition than in the internal condition (5 neurons in each monkey) and 3 were significantly less activated in the external condition (1 and

2 neurons in monkeys F and T, respectively) (Figure 7B). We also tested, for each neuron in our sample, the sensitivity of FSIs to the monkey's level of task performance, in terms of latency and duration of the reaching movement (i.e., RT and MT). We used a trial-by-trial correlation (Pearson's r) between movements parameters and averaged spike counts in the same time period as before. Across the sample of studied neurons, 24% (7 of 29 neurons) and 10% (3 of 29 neurons) were sensitive to the RT in the external and internal conditions, respectively, and 10% (3 of 29 neurons) and 7% (2 of 29 neurons) were sensitive to the MT in the external and internal conditions (Figure 7C), significant correlations being either in the same or opposite direction (i.e., the FSI activity increased or decreased as RT or MT increased). It therefore appears that the relationship between FSI activity and speed of movement initiation (i.e., RT) was more prominent than speed of movement execution (i.e., MT) and the proportion of FSIs sensitive to the motor performance was not markedly affected by the condition. It is noteworthy that these effects were almost exclusively observed in monkey T.

FSI activity in distinct striatal regions

Finally, we investigated whether FSI activity may vary depending on the striatal region. The recording sites identified histologically for the two monkeys were distributed between 4 mm anterior and 6 mm posterior to the anterior commissure, mostly in the putamen. As illustrated in Figure 8A, they were scattered over the whole part of the striatum explored. We evaluated whether there were differences in FSI activity depending on the location of recorded neurons. As defined in Materials and Methods, the striatum was divided into motor, associative, and limbic regions. among 63 neurons recorded in the external condition, 27 were located within the motor striatum (15 and 12 in monkeys F and T, respectively), 22 within the associative striatum (13 and 9 in monkeys F and T, respectively), and 14 within the limbic striatum (4 and 10 in monkeys F and T, respectively). The frequency of modulated FSIs did not vary significantly between the three regions of the striatum explored ($\chi^2 = 3.97$, d.f. = 2, $p = 0.136$).

We plotted the average activity for the subset of 29 neurons on which we have focused our analyses, separately for each striatal region and each condition (Figure 8B). An enhanced level of population activity that reached a peak close to movement onset was observed in each group of FSIs, with slight differences in magnitude between conditions in the motor and associative striatum, but not in the limbic striatum. This trend achieved significance only in the motor striatum during a period of 44 ms before to 35 ms after movement onset (cluster-based permutation test, $P < 0.05$), suggesting that the condition effect might be predominant on the activity of the FSIs localized in this particular striatal region. It also appears that increase in FSI activity in the motor and associative striatum showed a tendency to occur later than it did in the limbic striatum (timing of peak activity relative to movement onset: limbic striatum: -38 ms and -87 ms, associative striatum: 60 ms and 119 ms, motor striatum: -10 ms and -43 ms, in the external and internal conditions, respectively). This may indicate that there were differences in the time course of changes in population activity, with FSIs in the limbic striatum being modulated earlier than FSIs in other striatal regions, but this needs to be confirmed on a larger sample of neurons.

Discussion

In the experiments reported here, we examined the extent to which striatal FSIs, believed to be PV-containing GABAergic interneurons, are influenced by the mode of movement selection. To this end, we compared FSI activity when monkeys were switched from a condition in which movement was specified by external stimuli to one in which movement was selected on the basis of choice that requires the use of stored representations of movements. These two conditions allowed to contrast the FSI activity associated with either externally-cued and internally-driven movements. We obtained two key results: (1) although the proportion of FSIs modulated around the time of movement initiation was similar in the two conditions, the

magnitude of changes in population activity in a subset of FSIs was greater for externally-guided movements than for internally-guided movements; (2) the tendency for FSIs to fire more strongly around the onset of an externally-guided movement was most evident in the posterior putamen, namely the region of the striatum that is more closely tied to the motor aspects of behavior. This is the first account in the primate striatum of differential modulation of FSI activity that is dependent on the condition in which the movement is initiated. Our findings suggest that the FSI system, particularly in the motor striatum, is most prominently involved in sensory-cued movements rather than free-selected movements, indicating that the role of this local striatal inhibitory circuit in behavior applies to a broader range of functions than was previously assumed.

In the present study, we used a free-choice task that included a probabilistic reward schedule in which monkeys were required to maintain information about the location of a best rewarded target in working memory to choose a movement accordingly. We originally designed this task for studying the sensitivity of striatal output neurons to the relative value of available options according to the probability of reward associated with each option. To minimize the influence of reward probability and to make the choice easier, we mainly used here a reward schedule that includes large differences between probabilities (i.e., one target was rewarded 70% of the trials and the two others 15% of the trials) so that monkeys quickly resolved which action to choose among the possible alternatives. We then compared this condition in which movements are selected based on an internal representation of the target with a condition in which movements are selected based on external stimuli. We reasoned that such comparison would allow us to examine the influence of the way in which movements are selected, namely, in the presence or absence of an explicit cue as to which target to reach.

Across the sample of studied FSIs, approximately 78% were modulated around the time at which the monkeys initiated movements. This is in line with our previous work showing a

preferential change in the activity of FSI s just before or during movements (Marche & Apicella, 2017). Rodent studies have also reported increases in FSI activity during the initiation and execution of motor behaviors in a variety of tasks (Gage et al., 2010; Schmitzer-Torbert & Redish, 2008). Altogether, these findings lend support to the idea that FSI s are primarily involved in processes of movement initiation and control. The present study provides new data indicating that a subset of FSI s changed the magnitude of their movement-related activation when performance in the task involves sensory-cued or free-selected movements, suggesting that modulation of FSI activity is not exclusively tied to motor output, but may be influenced by the way in which movements are generated (i.e., with external or internal guidance). The fact that FSI activation around movement onset was stronger for externally-guided movements than for internally-guided movements may indicate that the FSI system is preferentially involved in external control of movements.

Previous studies have indicated that the basal ganglia are prominently engaged in generating behaviors that require the use of stored representations of movements. This idea is supported in particular by clinical data showing that patients with Parkinson's disease exhibit greater initiation deficits for internally-guided movements than for externally-guided movements (Brown & Marsden, 1988; Canavan et al., 1990; Glickstein & Stein, 1991). Contrary to this notion, we found that a subset of FSI s exhibited an enhanced activation when movements were externally-guided. Although the FSI system is considered to be a powerful inhibitory mechanism for regulating striatal network activity, we still lack an understanding of how it acts on neighboring output neurons to modulate their activity in behaving animals. Recording studies in monkeys have shown that discrete groups of striatal output neurons can be activated during movements that are either externally- or internally-guided (Kimura et al., 1992; Schultz & Romo, 1992), without evidence of a preferential relationship with the latter type of movement. On the other hand, a strong link with movement selection guided by internal

representations has been reported at the level of the substantia nigra *pars reticulata*, a downstream region of the basal ganglia directly connected to thalamic and brainstem circuits that control movement (Hikosaka & Wurtz, 1983; Lintz & Felsen, 2016).

Following the rodent literature, the FSIs recorded from the monkey striatum have been suggested to correspond to the PV-containing group of GABAergic interneurons that are the source of an inhibitory influence on striatal output pathways (Koos & Tepper, 1999; Szydlowski et al., 2013; Owen et al., 2018). However, given the description of novel GABAergic interneuron classes in the striatum (Assous et al., 2018; Faust et al., 2015; Garas et al., 2016), it cannot be ruled out that other GABAergic interneuron types have contributed at least in part to electrophysiologically defined FSIs. Since these presumed interneurons are thought to provide inhibition of striatal output pathways controlling movements, their stronger activation in the external condition might be related to an enhanced inhibitory level necessary for selecting what action to perform when the condition required to map spatial location of the stimulus to the appropriate direction of movement on each trial. Conversely, the internal condition allowed the monkey to repeatedly move in the same direction throughout a series of trials, thus requiring less FSI inhibition. The higher level of FSI activation observed in the external condition might therefore arise from frequent switches between left and rightward movements which involve the suppression of unwanted motor commands that may interfere with the selection of appropriate actions. This is in agreement with the prevailing idea that the FSI system plays a prominent role in shaping striatal output according to task demands for movement initiation and execution.

Previous studies in animals (Gernert et al., 2000; Gittis et al., 2011; Burguière et al., 2013; Xu et al., 2016) and humans (Kataoka et al., 2010; Reiner et al., 2013) have indicated that defects in striatal PV-GABAergic interneurons are linked to abnormalities in selecting appropriate motor behaviors. In this view, reduced inhibition in striatal output neurons is

believed to trigger “excess” motor behavior, in the form of dyskinesia and uncontrolled movements described as compulsive.

Modulation of FSI activity depending on the mode of movement selection is likely to have consequences for the mechanisms by which local inhibition regulates output from the striatum and resulting behavior. In the present study, only monkey T showed significant differences in task performance, consisting of slower RTs when the movement was externally-guided. This suggests a possible link, at least in this animal, between the increase in population-level FSI activity and reaching performance. Interestingly, it was almost exclusively in this same animal that we found changes in FSI activity that were correlated with how quickly the monkey responds to the trigger stimulus. This further suggests that modulation of FSI activity may reflect a mechanism for shaping striatal output during the initiation and execution of movement.

Given the known synaptic organization of basal ganglia circuits, an increase in FSI activity may lead to increasing inhibition of striatal output neurons that are responsible for sending motor commands, making them less inhibitory on target structures that are parts of the so-called direct and indirect pathways. These two pathways are assumed to exert opposing effects on motor behavior, the direct pathway facilitating movements while the indirect pathway terminates or suppresses movements. It is an open question as to how the inhibitory influence provided by the FSI system may affect the dynamic balance between the two pathways that underlies the correct expression of behavior.

Our study also showed that a small fraction of the FSIs sampled reduced their activity around movement onset, leading to disinhibition of striatal output pathways. Because a decrease in FSI firing may result in an enhanced striatal output signal, it is important to consider the functional impact of these opposing changes in FSI activity. In contrast to increases in FSI

activity, we found that the magnitude of decreases in FSI activity did not appear to be scaled with the mode of movement selection.

Our findings have highlighted a new feature of the functional properties of striatal FSIs, namely that the activity of some of these presumed inhibitory interneurons was influenced by constraints on movement selection. However, additional research is clearly required to understand which aspects of task performance are determinant in modulating their activity. Beyond the distinction between external and internal control of movements, the interpretation of the observed changes in FSI activity suffers from some limitations due to the current task design in which several processes might overlap in reaching performance.

Firstly, one can argue that the differential FSI activity may reflect a particular form of learning that underlies reaching performance. We considered it possible that the monkey's task performance under the external condition relies on automatic stimulus-response mapping after prolonged training, while in the internal condition the action choice is implemented by retrieving a memory representation of the target location which may impose an increase in online control demands. Although it needs to be clarified if distinct learning processes are an issue in our experiments, there is evidence in rodents that a disruption of the striatal FSI system can produce an impairment of mechanisms whereby behavior becomes automatic with extensive practice (O'Hare et al., 2017). However, in the only monkey showing a condition effect on reaching performance (monkey T), movement initiation was not faster in the external condition than in the internal condition, which does not fit well with the idea of a higher degree of automaticity in the former condition.

Alternatively, the dependence on the action selection mode may reflect an attentional component of the task. Recently, a study in the monkey reported that striatal FSIs modulate their activity during an oculomotor task according to the amount of attention allocated to stimuli (Banaie Boroujeni et al., 2020). In our experiment, it is conceivable that attention is higher in

the external condition in which monkeys were required to allocate attention to detect and report the location of the trigger stimulus presented pseudorandomly in one of two locations and this difference may bring about an increased level of FSI activity. As in our previous study (Marche & Apicella, 2017), we find that FSIs rarely displayed sustained changes in activity during the period in which the monkey held its hand steady and awaited the trigger stimulus, a period during which attention was presumably allocated to a particular target location. It has been shown that PV-expressing GABAergic interneurons of the striatum receive synaptic inputs from intralaminar thalamus (Assous et al., 2017; Sciamanna et al., 2015; Sidibé & Smith 1999) and a recent study has also revealed that the thalamic reticular nucleus sends a projection to striatum that preferentially targets FSIs (Klug et al., 2018). It is therefore possible that attention-related signals are conveyed directly from thalamus to local GABAergic circuits in the striatum. These results underline the need to examine more closely the FSI activity in tasks that allow to dissociate attentional and motor aspects of performance.

Finally, we also considered the possibility that changes in the frequency of reward may contribute to differential modulation of FSIs. Under our experimental conditions, monkeys did not select equally valuable actions: sensory-cued movements are always followed by reward, while free-selected movements have, at best, a 70% probability of reward. It is worth noting that evaluation of the action selected based on its outcome is a key factor in influencing the activity of striatal output neurons (Ding & Gold, 2010; Lau & Glimcher, 2008; Samejima et al., 2005; Seo et al., 2012) and these neurons can also be involved in mediating the influence of the uncertainty of reward on movement selection (Ding & Gold, 2013; White & Monosov, 2016; Yanike & Ferrera, 2014). However, if the external condition was supposed to be more motivating, then RTs on these trials would be expected to be shorter than those on internal trials. In fact, as mentioned before, we observed just the opposite in monkey T, suggesting that action value did not impact task performance possibly as a consequence of overtraining.

Are FSIs influenced by action selection mode irrespective of the striatal region ?

Considering that interneurons as well as output neurons receive information from different cortical areas which confers functional specialization within the striatum, it is conceivable that FSI processing may vary among different striatal regions. So far differences in behavior-related changes in FSI activity among distinct striatal regions have not been reported in the monkey (Adler et al., 2013; Marche & Apicella, 2017; Yamada et al., 2015). In the present study, we show for the first time that distinct functional properties of FSIs can be (related to) their localization in the primate striatum. Our data indicate that FSIs sensitive to action selection mode were present predominantly in the dorsal putamen, caudal to the anterior commissure, which receives motor and premotor cortical inputs and corresponds to the motor striatum (Parent, 1990). Evidence from neuronal recording experiments in rodents suggests that FSIs in the dorsolateral striatum, which is anatomically homologous to the motor striatum in primates, are related to the processing of motor information (Bakhurin *et al.*, 2016; Gage *et al.*, 2010; Kim *et al.*, 2014; Kim *et al.*, 2019; Kulik *et al.*, 2017; Roberts *et al.*, 2020; Schmitzer-Torbert & Redish, 2008). FSIs localized in the motor striatum have been implicated in mediating stimulus-response associations that appear in well-trained rodents (O'Hare *et al.*, 2017), whereas those in dorsomedial and ventral striatum may be more concerned with outcome processing (Atallah et al., 2014; Lansink et al., 2010; Stalnaker et al., 2012). Our analysis showing that the condition effect was stronger in the motor striatum than in other striatal regions indicates that FSIs localized in this particular region may be more specifically involved in adaptation of behavior according to task demands.

In summary, our results extend the existing literature on functional properties of FSIs in the primate striatum. Based on our electrophysiological findings, it is conceivable that these presumed inhibitory interneurons are influenced by the ways movements are generated. These findings give new insights into how abnormal local GABAergic signaling in the striatum, due

to FSI network dysfunction, can lead to an inability to suppress unwanted repetitive behaviors. Further experiments will be needed to elucidate the role of this interneuron circuit in regulating striatal activity and associated behavior to better understand the relationship of striatal FSI pathology to compulsive-like behaviors that occur in neuropsychiatric diseases.

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Conflict of interest

The authors declare no competing interests

Authors contributions

P.A. designed the experiments. K.M. and P.A. collected the recording data, analyzed the data, and wrote the manuscript.

The datasets used for this study are available on request to the corresponding author.

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Figure Legends

Figure 1. Sequence of events and reaching performance in the two conditions. A. At the start of each trial, the monkey kept the hand on a bar. After a 1-s delay following cue offset, a trigger stimulus was presented, in response to which the monkey had to make a reaching movement toward a target. In the *external* condition, a single cue was presented either to the left or to the right in the same location where the trigger stimulus will subsequently appear, the movement being selected based on the location of the trigger stimulus. In the *internal* condition, three cues displayed simultaneously were followed by three visual stimuli serving as a trigger stimulus. In this case three target options were assigned a reward probability and the movement was

selected based on an internal representation of the most frequently rewarded target. The two conditions were tested in separate blocks of trials. B. Frequency distribution histograms of latencies and durations of movement during performance in each condition. Medians are indicated for each distribution. The asterisk indicates a significant difference between conditions (paired t -test, $P < 0.05$).

Figure 2. Temporal profiles of changes in FSI activity around the time of movement initiation in the two conditions. Changes in activity detected between -300 and 300 ms from movement onset are indicated by lines (red for increased firing and blue for decreased firing). Lines are sorted by onset time of the modulation and referenced to movement onset (dashed vertical line). n , number of modulated neurons. Arrows correspond to the two example neurons illustrated in Figure 3.

Figure 3. Influence of the movement selection mode on FSI activity around the time of movement initiation. Activity of two example FSIs tested in both the external and internal conditions. Top, raster plots, Bottom, perievent time histograms. Each row is one trial and each dot is one spike. Dot displays and histograms are aligned on the onset of movement. Trials were shown in chronological order from top to bottom. Green markers in dot displays indicate target contact for each trial. Bin width for histograms is 20 ms. For the neuron B, the horizontal dashed line in the internal condition indicates a transition to a new location of the best rewarded target. Insets show examples of spike waveforms of each neuron (vertical bar 250 μ V; horizontal 400 μ s).

Figure 4. Population average activities of FSIs tested in both conditions. Data are pooled for the two monkeys. Colored curves depict mean activity of samples of FSIs separately for

external and internal conditions, aligned to the movement onset marked by the vertical dashed line. Shading indicates SEM. A. Activity of all FSIs tested in both conditions, regardless of the presence or absence of modulation around movement onset. B. Activity of a subset of FSIs showing an increase in activity around movement onset in the external condition. C. Activity of a subset of FSIs showing an increase in activity around movement onset in the internal condition. D. Activity of a subset of FSIs showing a decrease in activity around movement onset in the external condition. The blue horizontal line above the curves indicates the time period of significant difference between the external and internal conditions (cluster-based permutation test, $P < 0.05$). n, number of neurons.

Figure 5. Changes in FSI activity as a function of target location. Black lines indicate FSIs whose activity was significantly different between the left and right target locations. Neurons from both monkeys are included. n, number of neurons.

Figure 6. Changes in FSI activity during the delay period. A. Temporal profiles of changes in FSI activity during the time interval between cue offset and trigger onset in the two conditions. Same conventions as in Fig. 2, except that the activity is aligned on the cue offset. The inset bar graphs show the proportions of modulated neurons, either increases or decreases in firing, during four successive 250-ms windows starting from the cue offset in each condition. B. Population average activities during the delay period for the sample of FSIs recorded in both conditions. Same conventions as in Fig. 4.

Figure 7. Modulation of FSI activity in each monkey. A. Population average FSI activities. Conventions are the same as in Fig. 4. B. Changes in the activity of single FSIs tested in both conditions. Activations shown individually for neurons. Black lines indicate neurons with a

significant difference between the external and internal conditions ($P < 0.05$; Wilcoxon rank-sum test). C. Sensitivity of FSI activity to task performance. Correlation coefficients between neuronal activity and movement parameters (reaction time, RT; movement time MT) were computed separately from a constant windows in both task conditions. Significant correlations ($P < 0.05$; Pearson's r) are indicated by black dots.

Figure 8. Modulation of FSI activity in different striatal regions. A. Positions of FSIs recorded in the external condition in the two monkeys. Neurons modulated (either increases or decreases) or unmodulated during the perimovement period are indicated by empty circles and horizontal lines, respectively. Standard coronal sections are labeled in rostrocaudal stereotaxic planes according to distances from the interaural line (A12 to A22). Coordinates were taken from the stereotaxic atlas of Paxinos et al. (2008). The anterior commissure (A18) was used as a landmark to separate the associative and limbic striatum (dorsal and ventral parts of the precommissural caudate nucleus and putamen, respectively) from the motor striatum (dorsal part of the postcommissural putamen). Cd, caudate nucleus; Put, putamen; gray area denotes the approximate extent of the limbic striatum. B. Population FSI activities for each of the three striatal regions. We subdivided the subset of 29 neurons tested in both conditions into motor, associative, and limbic striatal subgroups. The blue horizontal line indicates bins with significant difference between the two conditions (cluster-based permutation test, $P < 0.05$). n, number of neurons that was recorded in each striatal region. Same conventions as in Fig. 4, except that curves are smoothed with a cubic spline function.

Figure 1

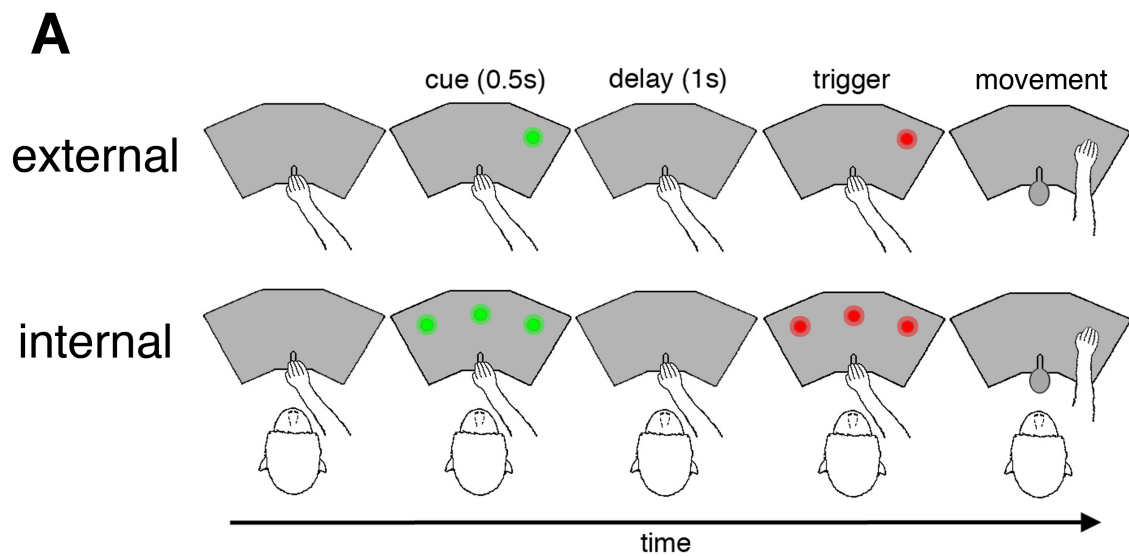
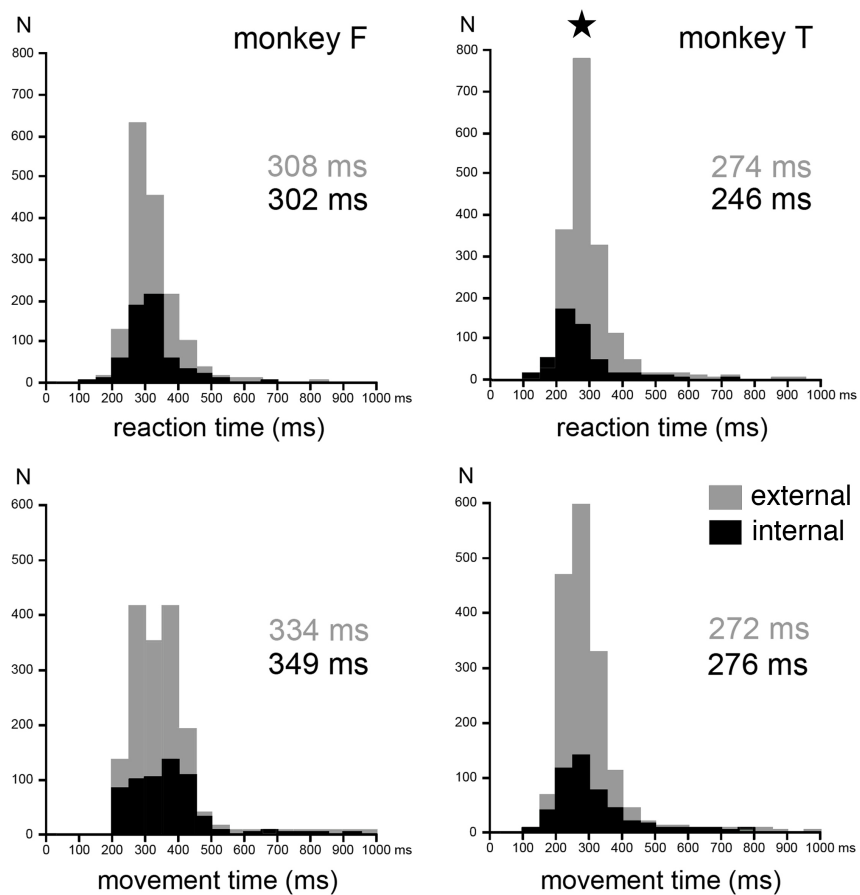
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Figure 2

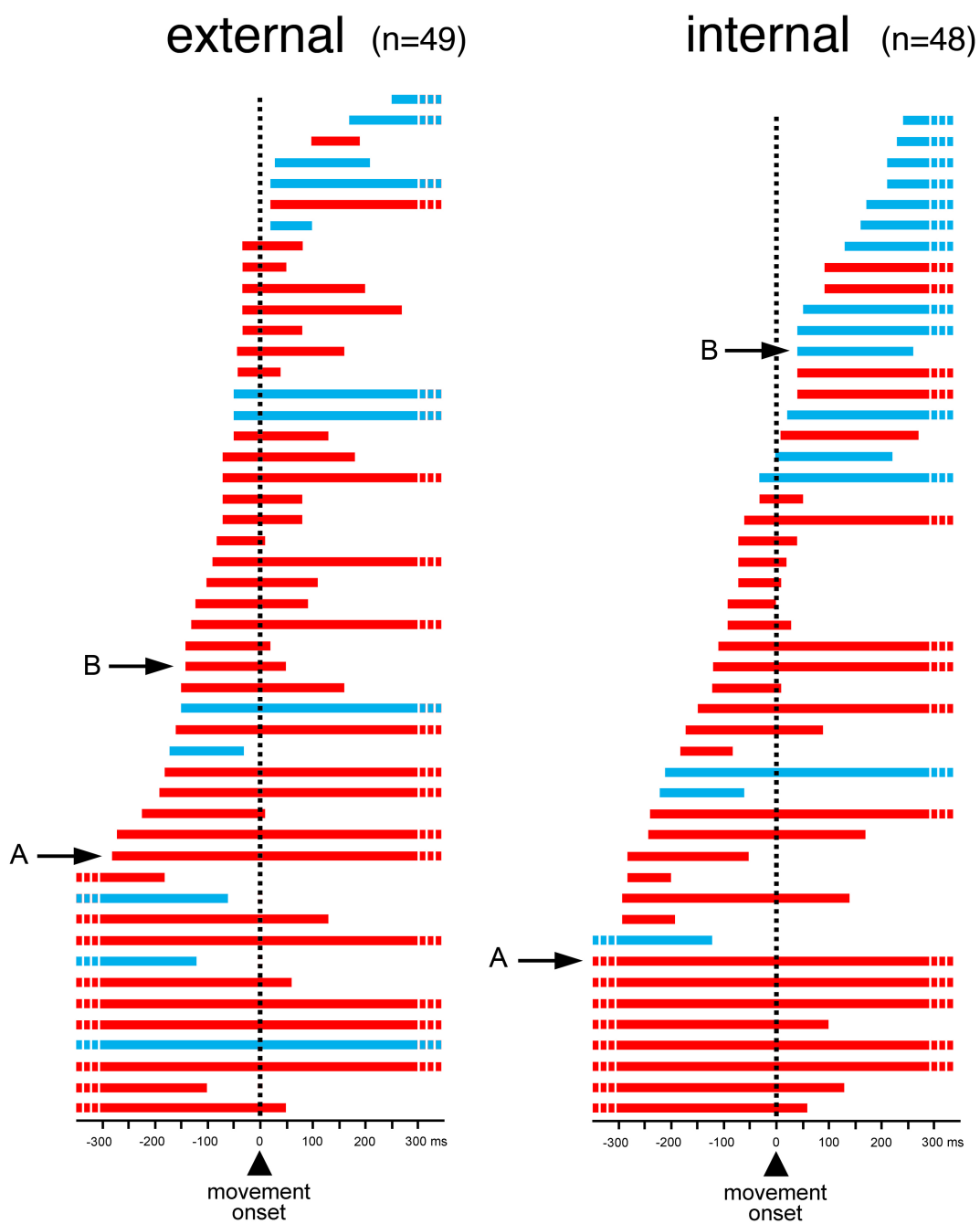


Figure 3

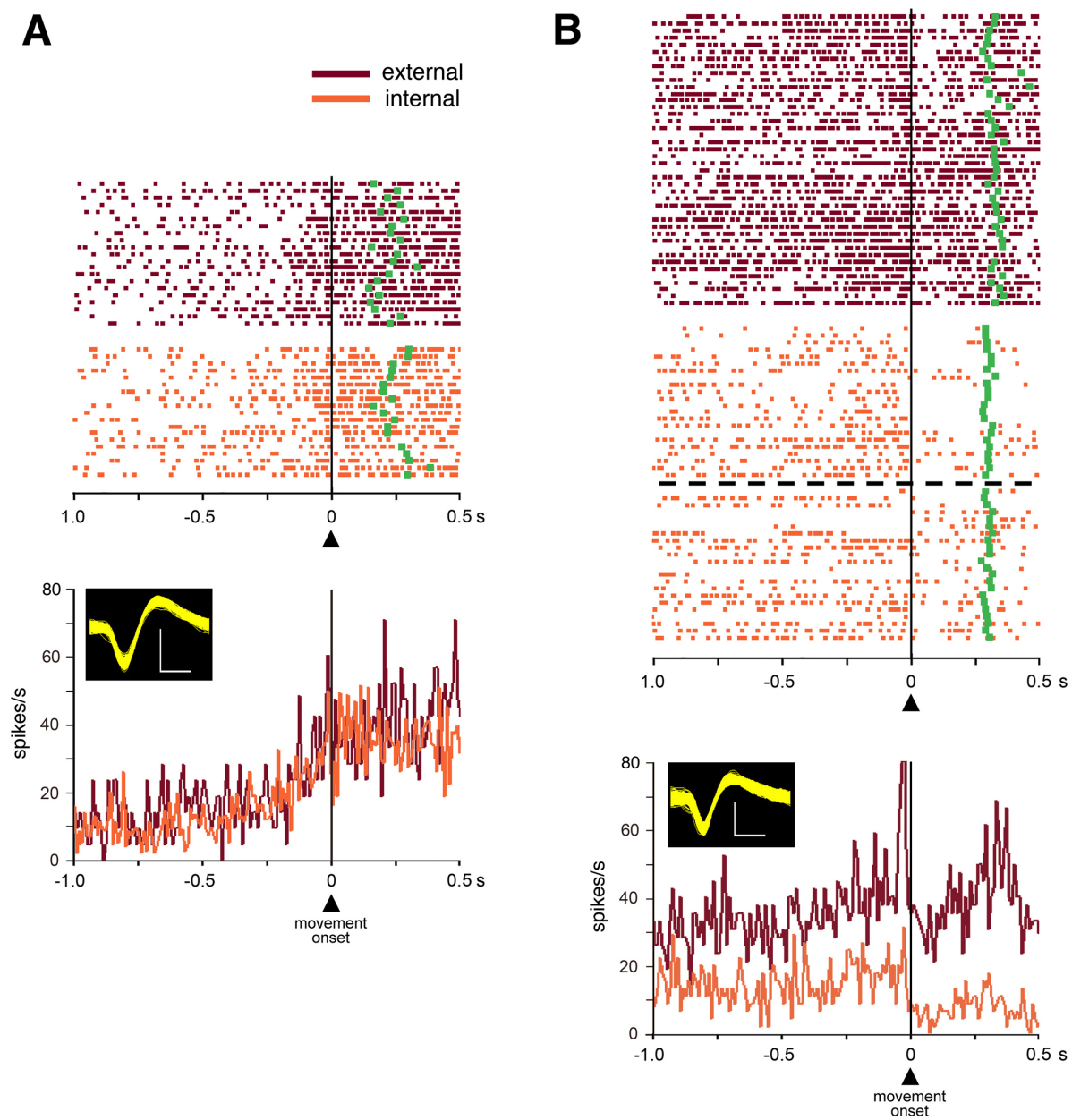


Figure 4

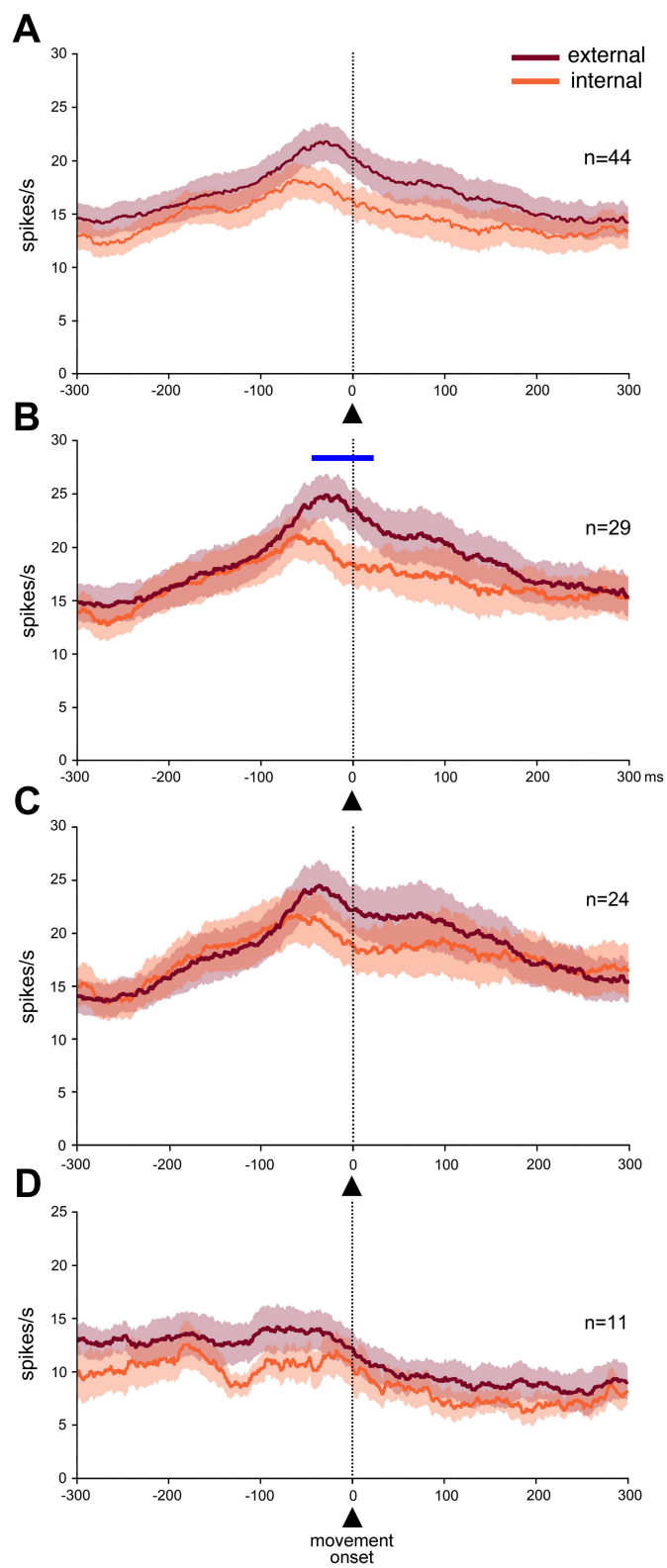


Figure 5

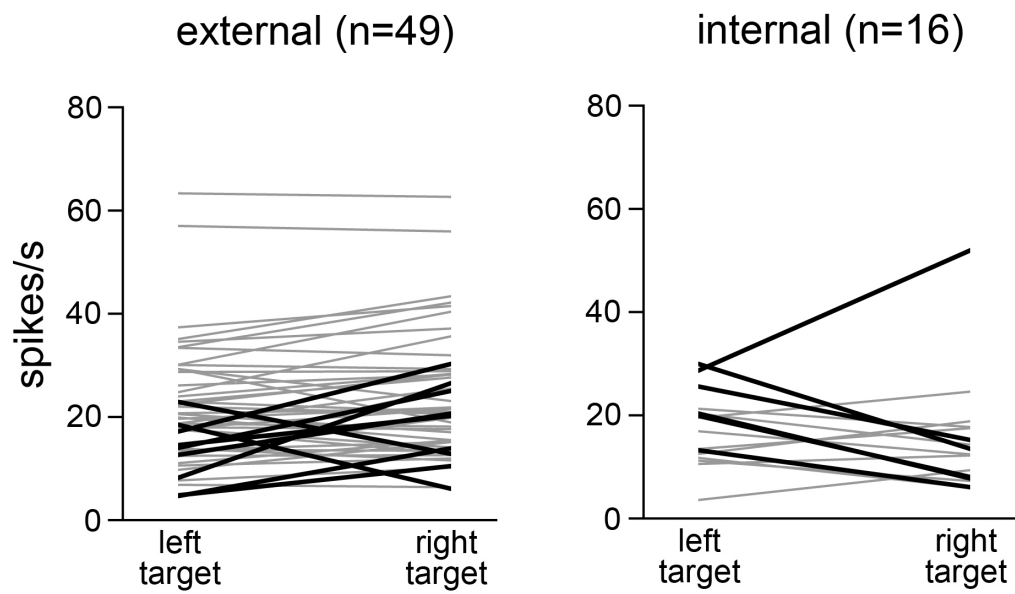


Figure 6

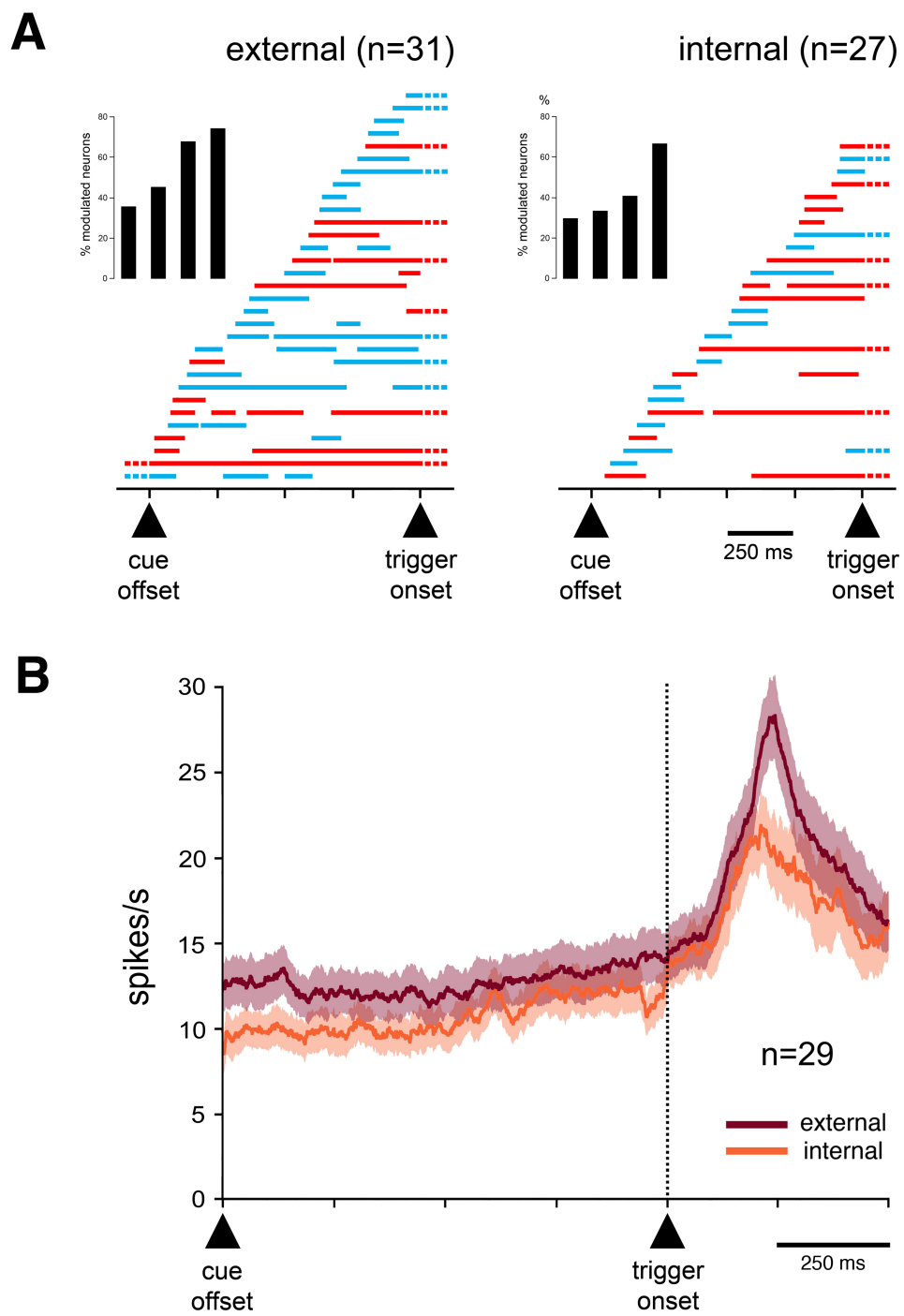


Figure 7

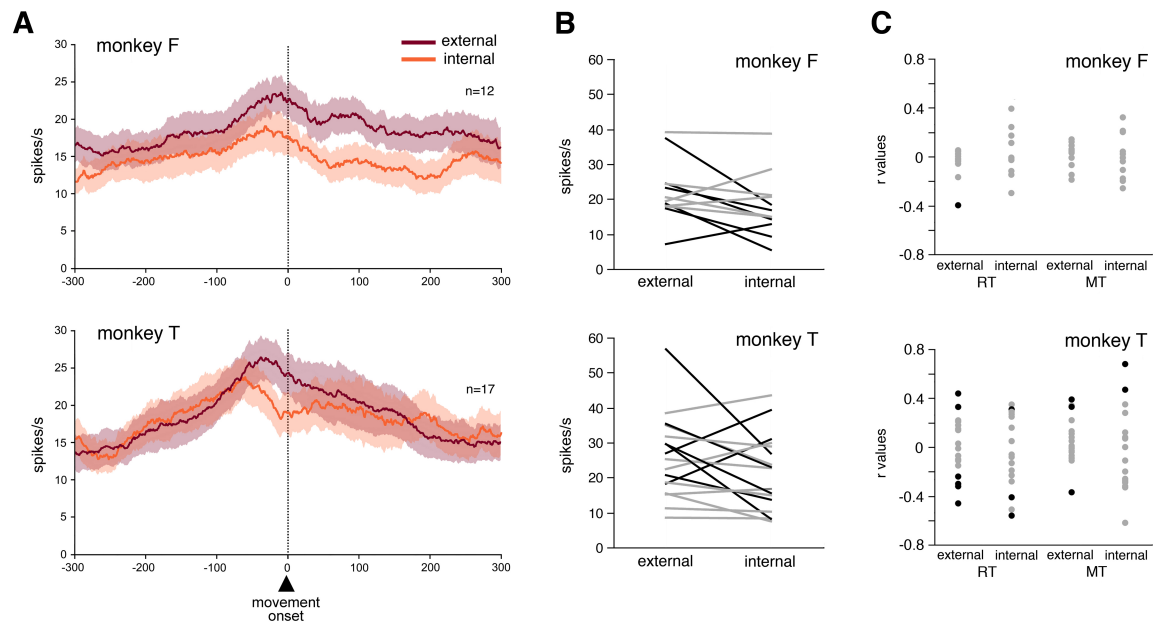


Figure 8

