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**Embodied Time Estimation
and the Contribution of the Dorsal Striatum**

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Abstract

How animals adapt their behavior to take advantage of temporal regularities in their environment is a puzzling question, particularly in the suprasecond timescale. It has been proposed that time estimation is internally-driven, using either a central neuronal clock or emergent self-sustained dynamics across ensembles of neurons. Alternatively, animals could use embodied strategies, such as a motor routine, the execution of which takes the same duration as the interval they need to estimate. The implementation of both timing mechanisms in the brain is still a matter of debate. Many brain regions are implicated, one of which, the dorsal striatum (DS), is of special interest. DS neurons reportedly represent elapsed time and perturbation of DS activity affects temporal perception. On the other hand, the DS is a known motor area, thought to be involved in the selection/repression of purposive actions, driving their execution on a moment-to-moment basis, or modulating their speed. Here, we used a task in which rats freely moving on a powered treadmill could obtain a reward if they approached it after a fixed interval. Most animals took advantage of the treadmill length, speed, and moving direction, and by trial and error developed a wait-and-run motor routine whose execution resulted in the precise timing of their reward approaches. We then addressed two questions: whether animals are able to time their behavior without resorting to this motor routine; and how the DS contributes to the performance of this motor routine.

To address the first question, we trained naïve animals in modified versions of the task, specifically designed to hamper the development of this motor strategy. Compared to rats trained under the normal protocol, these animals never reached a comparable level of timing accuracy. We conclude that motor timing critically depends on the ability of animals to develop motor routines adapted to the structure of their environment.

Secondly, the exact contribution of the DS to the execution of such motor routines remains unclear. Unexpectedly, following DS lesions, the performance of the motor routine was spared, but altered in peculiar ways: animals reduced their running speed

and waiting period of their routine. Complementary experiments demonstrated that DS lesions did not affect animals' motivation, their ability to perform motor routines, and to control their running speed. We conclude that lesions of the DS increased the sensitivity to energy expenditure. Thus, we propose that the DS computes an effort signal that modulates the kinematics of purposive actions.

Résumé

Comment les animaux adaptent leur comportement pour tirer profit des régularités temporelles de leur environnement est une question difficile, en particulier pour ce qui est des intervalles de l'ordre de quelques secondes. Il a été proposé que l'estimation du temps est mesurée de manière interne, en utilisant soit une horloge neuronale, soit la dynamique émergente et auto-entretenue des ensembles de neurones. Les animaux pourraient également utiliser des stratégies incarnées ('embodied'), telles que des routines motrices, dont l'exécution prend la même durée que l'intervalle qu'ils doivent estimer. La validité relative de ces deux mécanismes n'est toujours pas établie. De nombreuses régions du cerveau sont impliquées dans l'estimation du temps, dont l'une, le striatum dorsal (DS), présente un intérêt particulier. En effet, les neurones du DS représenteraient le temps écoulé et la perturbation de l'activité du DS affecterait la perception temporelle. D'autre part, le DS est une zone motrice connue, dont la fonction est également débattue (sélection/répression d'actions, génération des mouvements ou modulation de leur vitesse). Ici, nous avons utilisé une tâche dans laquelle des rats se déplaçant librement sur un tapis roulant motorisé pouvaient obtenir une récompense s'ils s'approchaient de l'avant du tapis après un intervalle de temps fixe. La plupart des animaux profitait de la longueur, de la vitesse et de la direction du tapis roulant et, par tâtonnement, développait une routine dont l'exécution permet de respecter la règle spatio-temporelle et d'obtenir une récompense. Nous avons ensuite abordé deux questions : Les animaux sont-ils capables de s'adapter à la règle spatio-temporelle sans avoir recours à cette routine motrice ? Comment la DS contribue-t-il à la performance de cette routine motrice.

Pour répondre à la première question, nous avons entraîné des animaux dans des versions modifiées du test original, spécialement conçues pour empêcher le développement de leur routine motrice. Par rapport aux rats entraînés selon le protocole original, ces animaux n'ont jamais atteint un niveau comparable de précision temporelle. Nous

en concluons que l'adaptation précise à une contrainte temporelle est facilité par la capacité des animaux à développer des routines motrices adaptées à la structure de leur environnement.

Pour répondre à la deuxième question nous avons réalisé des lésions du DS. De manière inattendue, à la suite de lésions du DS, l'exécution de la routine motrice a été épargnée, mais modifiée de manière particulière : les animaux ont réduit leur vitesse de course et la période d'attente de leur routine. Des expériences complémentaires ont démontré que les lésions du DS n'affectaient pas la motivation des animaux ni leur capacité à effectuer des routines motrices ou à contrôler leur vitesse de course. En nous appuyant sur des modélisations du comportement, nous concluons que les lésions du DS augmentent la sensibilité des animaux à la dépense énergétique. Ainsi, nous proposons que le DS calcule un signal d'effort qui module la cinématique des actions intentionnelles.

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To my parents

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Chapter 1

Introduction

For humans and other animals, in any context, adaptive behavior is defined as executing an action that would maximize immediate or future rewards, while minimizing energy expenditure. For example, consider any solitary hunter that would wait for the right time to attack: when the prey is most distracted or vulnerable. However, in some situations, the appearance of a sensory cue will not only indicate which action should be performed, but also how long, after the appearance of the cue, this action must be initiated [1, 2]. For instance, athletes performing sprint races learn by experience that the *go* command, signaling them to start running, will be given in two seconds after the *set* command. False starts, i.e., beginning to run just before the *go* command, demonstrate that athletes estimated the 2 second interval between the *set* and *go* commands. More generally, the ability of animals to exploit temporal regularities in nature is crucial for survival: the appearance of a sensory cue at a given time can predict food availability, predator attack, or mating opportunity [3, 4].

In this chapter, first I introduce the taxonomy used in the timing literature to establish a reference for this manuscript. Then I discuss two possible mechanisms that could give rise to the perception of elapsed time. Next, I will review some evidence of how either mechanism is thought to be implemented in the brain, focusing on the

role of a certain brain structure of interest. Finally, I will lay out the question and the hypothesis underlying this work and the structure of the following chapters.

1.1 Time Taxonomy

It is important to point out different categories of tasks used to study timing.ⁱ Appropriate classification of a phenomenon, alone, could lead to scientific advances. First step toward a taxonomy of time is to define what could be considered a timing task. Not every task with a temporal dependency is regarded as a time estimation task. A timing task requires an understanding of a given duration, i.e., one would need a clock to solve the task. For example, judging which of any two sensory stimuli occurred first does not require a timing device to be solved and hence, it is not a timing task. On the other hand, judging which of those stimuli were longer, indeed is a timing task, since it cannot be solved without any reference for time.

It is not perfectly clear, but there is some consensus over principal dimensions of the taxonomy of time.

Subsecond vs. Suprasecond Timing. There is ample evidence that timing relies on different mechanisms for short and long timescales [see 5]. Although the boundary is not definite, for timescales relevant to this work, short intervals are several tens of milliseconds (50–100 ms), and long intervals include several hundred milliseconds to several seconds.

Interval vs. Pattern Timing. It has been suggested that different neural mechanisms are at play for simple timing tasks (such as reproducing a duration) as opposed to tasks where the global temporal structure of the stimulus is determinant (such as recognizing the tempo of a song) [6].

ⁱThis section follows the arguments presented by Paton and Buonomano in [5].

Sensory vs. Motor Timing. This dimension of time taxonomy, not unlike the other two, is a continuum. In sensory tasks the subject analyzes the temporal information in the external world and reports their decision, such as in an interval discrimination task. Motor timing tasks, on the other hand, require a timely motor response, with no sensory cue, such as delayed blinking in response to a conditioned stimulus. While some tasks can be considered exclusively motor, or sensory, most tasks possess both sensory and motor components, namely, reproducing a temporal pattern, e.g., a Morse code.

1.2 Internal Time Estimation

Understanding how animals adapt their behavior to time intervals of various durations is challenging, because unlike sensory modalities (vision, olfaction, audition), time is not a material entity and animals are not equipped with a sense organ for time perception. Time perception in the timescale of a few seconds (compared to, say, 100 ms) seems to be even more puzzling, since it is much longer than intrinsic properties of neural function [7].

One influential idea in the field of systems neuroscience, hereafter referred to as the **internal clock**, posits that complex nervous systems have acquired the ability to estimate elapsed time and use this representation to determine if the duration of a given time interval is similar to (or different from) a previously learned interval [8–11]. Irrespective of its exact neural implementation, which will be discussed later, the internal clock works according to the following principle. Once a cue appears to signal the beginning of a time interval (e.g., the *set* command in sprint races), the neuronal time quanta begin to accumulate. Time interval estimation consists in comparing the magnitude of this ongoing accumulatory process with a stored value determined through experience (e.g., multiple exposures to time intervals between *set* and *go* commands in

sprint races) [12]. Errors in counting neuronal time quanta will accumulate with time too. Consequently, such a mechanism predicts that time estimation accuracy should degrade proportionally to the duration of the time interval, which has been verified in humans and animals [8, 13–19]. This is a feature of timing, generally referred to as the **scalar property**, and resembles the Weber’s law in sensory perception.ⁱⁱ

Another proposal suggests that time estimation ultimately relies on task-specific emergent properties of interacting neuronal networks, rather than a pure time-dedicated internal clock [5]. Such an **emergent** clock also has the assumption that the origin of time perception is internal, i.e, organisms infer the elapsed time purely from their neuronal dynamics.

1.2.1 Central Clock

It has been long proposed that a central clock provides temporal information for organisms [20, 21]. The **pacemaker-accumulator** model is the most prominent computational account of such a central clock. In essence, this model postulates: a pacemaker, which generates periodic pulses at intervals shorter than those being estimated; a switch, that following training, gates pulses through for a certain duration; an accumulator, downstream of the switch, that records the number of pulses in working memory; a reference memory, that holds the number of pulses that previously have been reinforced; a comparator, which determines whether the accumulated value is close enough to the reference value to warrant a response or not [20]. This model explains the scalar property by introducing sources of variability to its components. The pacemaker-accumulator model has many advantages: it is very straightforward, intuitive, and biologically feasible; it has clear separation of memory and decision-making systems, which could map

ⁱⁱ“Formulated by Ernst Weber in 1831 to explain the relationship between the physical intensity of a stimulus and the sensory experience that it causes. Weber’s Law states that the increase in a stimulus needed to produce a just-noticeable difference is constant. Later, Gustav Fechner (1801-1887) generalized Weber’s law by proposing that sensation increases as the logarithm of stimulus intensity: $S = k \log I$, where S = subjective experience, I = physical intensity, and k = constant.” [7]

to neural structures; and it is extremely successful in predicting behavioral data, given its simplicity [7].

Other internally-driven models of temporal processing have been proposed as well. The **Beat-frequency model** is another dedicated model for interval timing [9]. In this model, different intervals could be decoded from a bank of oscillators with different frequencies, since subgroups of such oscillators may be in the same phase at intervals much greater than those of individual oscillators. For example, three oscillators with periods of 5, 8, and 11 s are in the same phase every 440 s.ⁱⁱⁱ Hence, by choosing various subgroups and detecting the time at which they are phase-locked, one could generate a wide range of intervals. This model is also biologically feasible, as each oscillator could be as simple as a single neuron with a constant firing rate. Consider a series of these *oscillatory* neurons being reset with the stimulus (at the beginning of the interval). At any point in time, their spiking could be observed by a downstream structure. A subset of these neurons that fire at the time of reinforcement (i.e., the end of the interval) could represent a neural code for this particular interval [22]. Similarly, other subsets could encode different intervals. Among others, Miall simulated the beat-frequency model with 500 units oscillating at 5 to 15 Hz [9]. One output unit received single synapses from every oscillatory unit and the strength of each synapse followed a simplified Hebbian rule. This model managed to learn to encode intervals ranging from 200 ms to 10 s.

Finally, another class of models are based on ramping activity of neurons. These models propose that a linear metric of elapsed time is encoded in decreasing/increasing firing rate of neurons [5]. Crucially, the slope of the ramping must correlate negatively with the duration of the interval, since the maximum possible firing rate is relatively constant [23]. Moreover, neurons have timescales of tens of milliseconds, thus, for these model to account for time estimation in behaviorally-relevant timescales, i.e.,

ⁱⁱⁱMathematically, for any number of oscillators, it will be their *least common multiple*.

several hundreds of milliseconds to seconds, there must be a feedback mechanism. Simulations by Gavornik and others demonstrate that recurrent excitatory synapses could provide such a feedback signal [24]. In this network, the activity of each neuron, if isolated, would decay after stimulus presentation. However, by introducing recurrent connections, lateral propagation of activity in the network decreases decay rate of each neuron's activity in response to a stimulus. In other words, the network modifies the temporal properties of the response of individual neurons, which could translate to elapsed time representation.

1.2.2 Emergent Clock

A different class of models postulate that representations of time emerge from distributed dynamics of neural networks. These models differ from those discussed in section 1.2.1 in that these models are not localized, i.e., they could involve different brain areas however, they similarly assume time estimation is internally driven. These models assume that sensory, motor, and cognitive systems that are not specifically dedicated to timing might form networks that (after training) act as interval timers [11].

One type of such models, namely state-dependent networks, proposes that neural networks inherently contain temporal information as a result of their complexity. In a seminal work, Karmarkar and Buonomano simulated a network of 400 excitatory and 100 inhibitory neurons, recurrently connected and exhibiting synaptic plasticity [25]. This network was then exposed to two identical events, 100 ms apart (e.g., two auditory tones). Due to complex synaptic processes, the state of the network at any point in time after the presentation of the first stimulus was unique. Thus, the population response to the second stimulus inherently encoded the duration between the two stimuli. In this fashion, various intervals could be decoded from dynamics of ever more complex networks. Indeed, in a more recent work, Pérez and Merchant simulated a recurrent network of 800 excitatory and 200 inhibitory neurons [26]. The neurons

were randomly connected and received two membrane currents induced by the stimulus (one inhibitory, one excitatory). In addition, each neuron in the network also received two recurrent inputs. All of the synaptic currents followed time-varying dynamics. These temporal synaptic properties (such as time constant of neurotransmitter release, inhibitory input current dynamics, ...) allowed an optimal Bayesian decoder to produce interval-selective responses, in the range of several hundred milliseconds. This network, given parameter values within physiological range, could demonstrate scalar property as well.

This, by no means, is a comprehensive review of all the literature on timing models and that is not the focus of this manuscript. There are numerous articles proposing different neurocomputational models (using ramping activity, drift diffusion, synfire chain, coincidence detector, ...) to account for psychophysical evidence of timing behavior in humans and other animals. It is worthwhile to point out that what these models have in common is an assumption that a clock-like mechanism provides the organism with a measure of time, one that is internally-generated and disembodied.

1.3 Embodiment

Je pense, donc je suis (I think, therefore I am).

René Descartes, *Discours de la Méthode*

I am not invoking Descartes just because I am in France, there is a point too! This quote implies a duality between the brain and the body: the reason one exists is one's mind, not the body. Although the intricacies of the *mind-body problem* are not the focus of this work, a simple reading suggests that the brain is the ruler of the body. This simple unidirectional approach has been vastly used in fields such as robotics, by designing agents with a central processing unit that commands the actuators. This simplicity, however, comes at a cost. The most unremarkable actions that animals perform with

little cognitive load, such as grasping an object or locomotion on uneven terrains, have proved to be painstakingly difficult to implement in robots [27]. For decades now, an alternative approach has been proposed that has improved the performance of robotic agents [28]. Embodiment,^{iv} has enabled engineering of more robust and adaptable robots, inspired from biological organisms. Pfeifer and others present insect locomotion as a very convincing example of taking advantage of embodiment principles in robotics [30]. Insects demonstrate coordinated walking and running, which given their six legs, pose a challenging problem with dozens of degrees of freedom, in particular on uneven terrains. It is plausible to assume they do not solve the kinematic problem for all their joints at every moment, which was the classic approach in robotics and required enormous computational resources. However, by taking embodiment into account, pushing back a single leg, which could be detected by angle sensors in the joint, could command all the other joints to move in the ‘correct’ direction. This way, a low level communication between the legs could be exploited to achieve leg coordination without any central controller in the nervous system [30].

In the animal kingdom, embodiment enables both cognition—even the most abstract processes, like mathematical reasoning [31]—and action. In this framework, behavior is not reduced to internal computations, rather it is the manifestation of intricate brain-body-environment interactions. Perception of the external world relies upon how the information is channeled through different parts of the body and differences in the shape of body parts alter the incoming and outgoing signals [29]. The body also shapes the way we interact with our environment. Gomez-Marin and Ghazanfar discuss the interesting case of the well-coordinated stepping behavior in human infants [29]. When held upright, newborns show coordinated step-like movements. This phenomenon disappears after around 2 months. While it was long assumed that this is due to the

^{iv}According to the Oxford dictionary, embodiment is defined as: “A tangible or visible form of an idea, quality, or feeling”. Here, embodiment refers to the fact that “the brain has a body”, and the body is not a mere placeholder for the brain [29].

developing nervous system, Thelen and others showed that loss of stepping behavior is due to weight gain of the legs and it can be recovered by submerging the legs in water (which would decrease their mass) [32]. Thus, embodiment, through brain-body-environment interactions subjects us to the laws of physics—having to deal with gravity, friction, and inertia [27].

1.3.1 Embodied Clock

Time by itself does not exist...It must not be claimed that anyone can sense time apart from the movement of things.

Lucretius, Book 1

Principles of embodiment could be applied to the time-estimation problem as well. All the sensorimotor processes that comprise embodiment (and indeed everything else!) unfold in time. Especially, movement has long been associated with time estimation, so far as one study stating that “timing is inexorably tied to movement” [33].^v

As early as 1948, it has been reported that periodic reward delivery leads to ‘superstitious’ behavior, i.e., performing stereotypical actions between consecutive deliveries of the reinforcer [35]. For example, once submitted to a fixed interval schedule (i.e., reward deliveries every 15 s, irrespective of the animal’s behavior), one pigeon started to turn counter-clockwise in the cage two or three times between successive reward deliveries. Each pigeon in this study developed such a unique behavior [35]. Similar phenomenon has been reported in many other species as well. Wilson and Keller trained rats to press a lever after progressively longer intervals (from 15 s to 30 s) to get a food pellet [36]. Rats slowly adjusted their lever presses to the scheduled interval however, during the interval, they also engaged in a recognizable chain of behaviors that the authors called ‘collateral’. These behaviors were unique to each animal too.

^vIt is noteworthy that the devices we use to measure time mostly do so by moving objects in space. Also, we extensively use metaphors containing movement and space references when speaking of time (*holidays are approaching, time flies*) [34].

Interestingly, with increasing the interval between reward deliveries, more links were added to the chain of collateral behaviors [36]. Both studies mentioned above explain these behaviors as being accidentally reinforced by the reward delivery, which would make them more probable to occur later, which in turn would strengthen their association with the reward [21]. Such a mechanism explains why these behaviors are unique to individual subjects. Developing accidentally-reinforced behaviors could bring about repercussions. Falk, in a very enlightening article, discusses ‘adjunctive’ behavior in food-deprived rats without any water deprivation [37]. When exposed to intermittent food delivery during their daily test session (3 hr long), animals followed each food pellet intake with consumption of excessive amounts of water (up to half their body weight) until the next food delivery, while almost no water was consumed during the rest of the day, despite being available ad libitum. This form of adjunctive behavior persisted even after water consumption during the session was discouraged by punishment [37].^{vi}

Modern technology has enabled synchronized video tracking of behaving animals. In tasks in which reinforcement is contingent upon respecting time intervals, animals do not stay still, but they take advantage of the structure of their environment to develop stereotyped motor routines whose duration amounts to the temporal constraint of the task. In one study, rats and pigeons, trained to discriminate a 12 s stimulus from a 6 s one, developed ‘collateral’ behaviors. Rats, during the stimulus, engaged in sniffing, rearing, grooming, and moving from one lever to another. Similarly, birds displayed pecking, bobbing,^{vii} wing flapping, and moving between the keys in their cage. Quantifying these behaviors better predicted their temporal judgment than the passage of time [38].

^{vi}He then discusses that even though this behavior seems absurd (“heating a large quantity of room-temperature water to body heat and expelling it as copious urine is wasteful for an animal already pressed for energy stores by food deprivation”), in certain ecological settings, it might provide an adaptive response even with evolutionary advantages.

In another study with precise monitoring of behavior, Gouvêa and others trained rats (and one mouse) to categorize an interval as shorter or longer than 1.5 s by pressing a lever, correspondingly. Animals demonstrated highly stereotyped and idiosyncratic behavior during the interval. Critically, their perceptual report was best predicted based on their behavior, even from early in the trial [39]. Similar idiosyncratic embodied strategies were also used by rats trained to reproduce a 700 ms interval by waiting between successive lever presses. Kawai and others reported that animals developed very specific and reproducible limb movements to fill the required interval [40]. Earlier work from our group also reported stereotypical use of embodied strategies, adapted to a dynamic environment, in a task in which rats learned to wait 7 s before approaching the reward delivery port [41].

Humans, too, seem to resort to motor activity to estimate time. Naturally, people tend to develop rhythmical movements of body parts (e.g., tapping fingers or feet, moving arms, and nodding heads) to perceive elapsed time [42]. Around 97% of adults default to counting as a time estimation strategy, and interestingly, in research, different sorts of measures has been employed to prevent use of counting in favor of a more *pure* time estimation strategy [see 43]. Similarly, children as young as 7 years old, estimate suprasecond time intervals by counting [14, 44]. Although counting could be in their heads (i.e., not out loud), it is difficult to separate it from the repeated experiences of counting the passing seconds aloud in everyday life, which is a motor activity: a sequence of coordinated movements across respiratory, laryngeal and supraglottal articulatory systems. Indeed, it has also been proposed that explicit perception of time may be constructed implicitly by associating the duration of an interval with its sensorimotor content [45]. For instance, 1 s is the time one takes to rock their head with a certain speed, or the time it takes to say 1001, 1002, ... in cardiac resuscitation. Instruct-

^{vii}For those unfamiliar with bird behavior (such as myself), *bobbing* refers to the two-phase movement of the head in birds, most commonly seen during walking when they hold their head while moving the body forward and then thrust their head faster than their body. Watching YouTube clips is advised!

ing human subjects to not use motor strategies or interfering with overt movements, lowers performance in a variety of time estimation tasks [14, 33, 46–49].

1.3.2 Cost of Embodiment

Being subject to the laws of physics is a major implication of embodiment. An animal with a physical body in the real world needs to obtain the rewards (for survival or gratification) as soon as possible (due to competition, uncertainty,...) while minimizing the energy expenditure (since resources are limited). Foraging is a relevant example. A honeybee harvests the nectar of a flower for a certain *duration*. At some point, perhaps following a diminishing rate of supply, it decides to leave the flower in order to find another one and flies off with a certain *speed*. These behaviors are well-predicted by theories such as **optimal foraging** in a diverse group of species, from worms to humans [50]. Optimal foraging proposes a kind of ‘currency’ with evolutionary advantages to behave in a way that it become maximized [51, 52]. This currency is the **capture rate** and in principle, it is defined as the sum of the acquired rewards,^{viii} minus costs of action, divided by total elapsed time [51].

Maximizing the capture rate is also an arguably intuitive policy in the case of the time estimation problem, since animals naturally use motor strategies to fill the interval that they need to estimate. Thus, time estimation transforms to performing a motor routine with the following properties:

- It is of appropriate duration and reproducible to generate reliable well-timed responses;
- It is the least costly.

Although the capture rate ostensibly depends on three parameters, in practice those parameters are not mutually independent. For instance, the cost of action mostly trans-

^{viii}Reward itself could be considered as a function of economic utility, and the certainty with which the action yields the reward. Shadmehr and others defined *economic utility* as “a measure of how much one values a particular good”, i.e., the subjective value of outcome [51].

lates to the metabolic cost, which is directly related to the speed of movement. The faster the speed, the higher the metabolic cost, and therefore the lower the capture rate. However, faster movements finish earlier, i.e., shorter elapsed time, and therefore higher capture rates! So, one way by which defining parameters of the capture rate become interdependent is the passage of time itself.

Cost of Time

The passage of time inevitably incurs a cost to the subjective value of the reward. For example, young adults prefer a small amount of money immediately, rather than a larger sum in a year. This common attitude is referred to as **temporal discounting**. Children are known to discount rewards more quickly and the elderly, more slowly. The rate with which one discounts future rewards varies among individuals and is used as a measure of impulsivity, i.e., higher rate of discount means more impulsive behavior [53]. The discounting of the reward value is usually characterized via a hyperbolic function of time.

Strikingly, in humans and other animals and across a wide range of tasks, there is a correlation between discounting of reward and control of movements [53–57]. Individuals with naturally faster movements discount future rewards more steeply [53]. Moreover, animals move faster when the prospect of a greater amount of reward exists. For instance, in an environment with a higher reward rate, monkeys in a decision-making task, chose the target with shorter deliberation times and faster saccade velocities [58]. This phenomenon is remarkable since it bridges between the fields of decision-making and motor control. It has been hypothesized that, in principle, the purpose of any goal-directed movement is transitioning to a more rewarding state, then, due to temporal discounting of rewards, the duration of movement per se incurs a cost by postponing the reward acquisition [54]. This is called the cost of time (CoT) hypothesis.

The concept of CoT has been applied for understanding why we don't move slower [57]. Indeed, humans are extremely reluctant to move their arms slowly [55], even though moving fast is constrained by energetic demand [59] and speed/accuracy trade-off [60]. Optimal control framework has been utilized to infer the shape of the CoT as a function of movement time. Consistent with the empirical data, CoT displays a sigmoidal shape over relevant time durations [57]. Moreover, CoT also accounts for inter-individual differences in **vigor**.^{ix} Berret and others show that in a single-joint self-paced arm reaching task, up to 89% of inter-individual variability of vigor is explained by parameters of the CoT function, e.g., the value of reward [55]. Similarly, delaying the reward, and thus decreasing its value, is associated with decreased saccade vigor [54]. Moreover, when human subjects are presented with two options with different values, the relative saccade vigor to each option reflected the subjective evaluation of the value of that option [63]. These results suggest that the expected reward upon action completion is an important determinant of the vigor with which the action is executed [see 51, for a review].

Different strategies of time estimation were discussed so far at a high-level. Next logical step is to think about how either one could be implemented in the nervous system. In the next section, I review a number of theories regarding the implementation, with a focus on a single structure of interest.

1.4 Implementation

The renowned neuroscientist, David Marr (1945–1980), proposed three levels of analysis to understand a complex system. First, the **computational level**, describes the task and the goal that need be achieved. Second, the **algorithmic level**, specifies the procedures

^{ix}Vigor is a key parameter of any movement. It is often correlated with several measurements of movement kinematics, such as speed and amplitude [61]. Movement vigor is generally considered as those aspects of movement kinematics which are subject to motivational state, e.g., implicit motivation [62]. Vigor will be covered in [section 1.4.3](#).

for manipulating the information associated with the computation. Third, the **implementation level**, characterizes how to physically realize the algorithm [64]. Krakauer and others in a perspective article that greatly influenced this work, present the following example [65]. Understanding a flying bird could be achieved at three levels: A bird attempts to *fly* (level 1: computation) by *flapping* its wings (level 2: algorithm) which is plausible due to aerodynamic properties of the *feathers* (level 3: implementation). They then argue that the explanatory power of studying feathers alone is fundamentally restricted, evident by some birds that fly without feathers and some types of flight that does not require flapping. As it pertains to the link between brain and behavior, it may be much more difficult to infer the algorithms used by the brain from studying the nervous system, compared to understanding them at a computational level [see also 66].

Thus far, I portrayed the case for behavioral importance of time estimation (level 1), and different possible strategies to estimate an interval (dedicated, emergent, and embodied clock, level 2). In this section, I will address how those strategies could be implemented in the brain (level 3). Of all the brain regions that have been suggested to be involved in time perception,^x across a wide range of tasks and scales, the basal ganglia (BG) is of special interest. For decades, the BG have been the focus of many timing studies [see 5], as well as motor studies [see 67]. Therefore, it could be considered as an ideal candidate structure to mediate well-timed behavior through either sensorimotor or disembodied internally-driven mechanisms.

1.4.1 The Basal Ganglia

The BG are implicated in both timing and the control of action. In this section, I introduce their general anatomy and review some of the evidence with regards to

^xSo many brain structures have been found implicated in time estimation that prompted Wittmann to state: “one may be inclined to state that researchers are actually clueless concerning the question of how the brain processes time.” [11]

their function. The BG are a set of interconnected subcortical nuclei. Their neural organization, cell types, and neurochemical markers are highly conserved in vertebrates for over 500 million years, ranging from the lamprey to the primates [68]. The BG may be viewed as a two-input two-output system. The striatum and the subthalamic nucleus (STN) are the input structures receiving excitatory afferents from virtually the entire cerebral cortex and thalamus. In rats, compared to STN, the striatum contains more than two-hundred times more neurons and thus is regarded as the main input to the BG [69].

The output nuclei are the internal segment of the globus pallidus, i.e., globus pallidus internus (GPi), and the substantia nigra pars reticulata (SNr). They are exclusively composed of GABAergic projection neurons with high baseline firing rates. GPi and SNr hold the targeted premotor centers in the brainstem and thalamus under tonic inhibition [70]. There are no direct connections from the BG efferents to motor neurons of the brainstem or spinal cord [71].

Other than the input and output nuclei, the BG also include the external segment of the globus pallidus, i.e., globus pallidus externus (GPe), which is innervated by the striatum and the STN. Most neurons in the GPe provide GABAergic projection to the STN, GPi, and SNr [72]. STN in turn innervates the GPe and the output nuclei. STN efferents form the only intrinsic excitatory connections in the BG, an otherwise inhibition-dominated structure. The other nuclei of the BG are the dopamine (DA)-containing centers of the midbrain, namely ventral tegmental area, and substantia nigra pars compacta (SNC). Ventral tegmental area preferentially targets the ventral striatum and SNC, projects to the dorsal striatum (DS) [73]. These nuclei innervate striatal neurons in a dense and rather uniform manner, however, they also target structures external to the BG, like several cortical and limbic regions. [Figure 1.1](#) summarizes the anatomy of the BG.

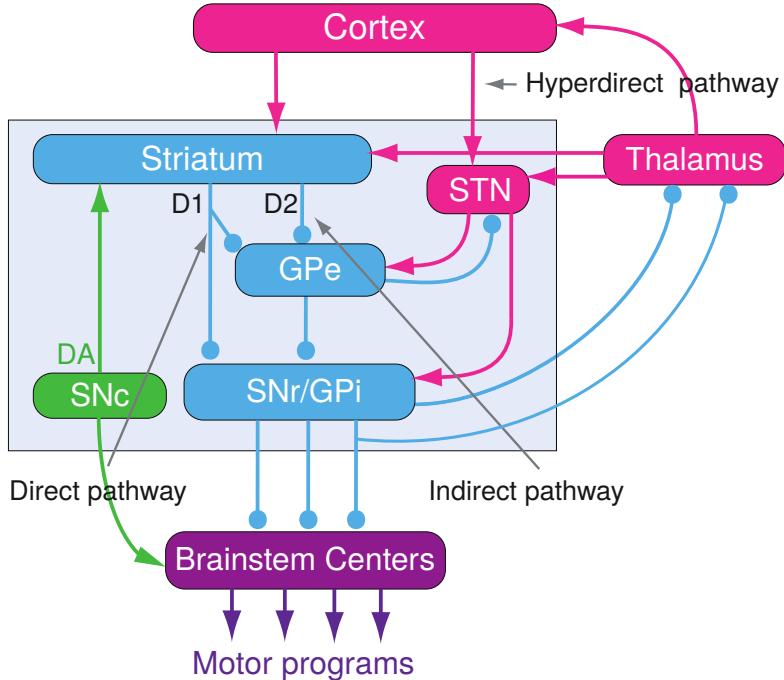


Figure 1.1: Anatomy of the basal ganglia. The gray highlighted rectangle depicts the BG nuclei. Arrows show anatomical connections (red: glutamatergic; blue: GABAergic; green: DAergic). STN: subthalamic nucleus; GPe: globus pallidus externus; SNC: substantia nigra pars compacta; SNr: substantia nigra pars reticulata; GPi: globus pallidus internus; DA: Dopamine. Figure slightly modified from [68].

Striatum

The striatum is the main input nucleus of the BG and one of the largest undivided structures in the rodent brain atlas [74, 75]. Despite having several cell types, GABAergic medium spiny neurons (MSNs) constitute 90–95% of its neural population. Their name stems from their morphological appearance, their size and the abundance of their dendritic processes [76]. MSNs receive glutamatergic inputs from the entire cortex, thalamus, and amygdala. These excitatory afferents make up 80% of all the synapses in the striatum [77]. Several other inputs modulate the responsiveness of the MSNs to massive excitatory synapses, namely DA afferents, inhibitory input from GABAergic interneurons (and from MSN collaterals), and input from cholinergic interneurons [72]. Consequently, MSNs are mostly quiescent, except during motor activity or in response to sensory stimuli [78].

Based on morphological and neurochemical identification, there are two major types of interneurons within the striatum, which make up 5–10% of striatal neural population: the medium aspiny GABAergic interneurons, and the large aspiny cholinergic interneurons. The most abundant type of GABAergic interneurons express parvalbumin. Parvalbumin-positive interneurons are physiologically characterized by their hyperpolarized resting potential and fast spiking activity. Thus, they are usually referred to as the fast spiking interneurons (FSIs) [72]. They target MSNs at the soma level by gap junctions and provide powerful GABAergic synapses to several hundreds of surrounding MSNs [68, 79]. Although they are scarce, with higher firing rate compared to MSNs, they are capable of delaying action potentials in the neighboring MSNs [77].

Large cholinergic interneurons are the other type of striatal interneurons. Their soma could be as large as 40 μm in diameter, with expansive arborization and an axon that extends over 2 mm [72]. They have tonic discharge patterns, and in primate, are called *tonically active neurons*. FSIs and cholinergic interneurons are not noticeable in number, nonetheless, they are believed to strongly contribute to the dominance of inhibition in the striatum [79]. In addition to these two, several other types of interneurons within the striatum are described as well [see 68, 72].

Organization of Cortical Inputs The striatum receives massive input from almost the entire cortex. It has been long known that corticostriatal projections are topographical, roughly following the rostro-caudal and latero-medial organization of the cerebral cortex. For instance, frontal cortices project to rostral areas, sensorimotor cortex provides input to DS, and parietal cortex to more caudal areas [72]. Such topographical organization suggests parallel circuits for limbic, cognitive, and sensorimotor processes via cortico-BG-thalamo-cortical loops [80]. In this framework, the sensorimotor loop consists of the dorsolateral striatum (DLS), ventrolateral thalamus, and sensorimotor cortices. Similarly, the limbic (emotional) loop includes the ventral striatum, dorsome-

dial thalamus, and limbic areas (amygdala, limbic cortices, and hippocampus). Finally, the cognitive (associative) loop comprises the dorsomedial striatum (DMS), anterior ventral thalamus, and frontal cortices [81]. However, reduced number of neurons from cortex to BG outputs by a factor of more than one million, implies integration of information from different loops to shape the appropriate behavior [82].

In the DS, loose somatotopic organization has also been long reported [see 71, as an early review]. In 1991, Carelli and West recorded from hundreds of neurons during movement and somatosensory stimulation. They found that more than 70% of recorded neurons in the DLS responded to movement, passive manipulation or cutaneous stimulation. Moreover, neurons selective for an individual body part (e.g., the forelimb, neck, snout,...) were generally located in close proximity, generating a somatotopic map [83]. Such an anatomical mapping from sensorimotor cortices to the DLS has recently been quantitatively scrutinized in mice too [74, 75]. These studies, using multiple injections of anterograde tracers, constructed a comprehensive excitatory input map of the DS. Figure 1.2 shows an example of different cortical regions projecting to the DLS in a somatotopic manner. Interestingly, cluster analysis of cortical regions projecting to arbitrarily-defined striatal voxels revealed dorsal striatal subregions which relatively agreed with parallel circuits for limbic, cognitive, and sensorimotor processes. With the strictest clustering criteria, Hunnicutt and others identified two areas, which map roughly to the DLS and DMS^{xi} [75]. Of note, DMS and DLS have been suggested as functionally distinct areas as well, contributing to goal-directed and habitual behaviors, respectively [84]. Another noteworthy result concerns the extent of these areas. The identified DLS receives inputs from the motor cortex, somatosensory cortex, but also frontal association cortex, amygdala, and prelimbic cortex. Importantly, the DLS expands medially much larger than what has been traditionally regarded as the DLS,

^{xi}DLS and DMS correspond to the putamen and caudate nuclei, respectively. In primates, the internal capsule divides the striatum in two halves, thus the use of caudate-putamen nucleus instead of the striatum is more common.

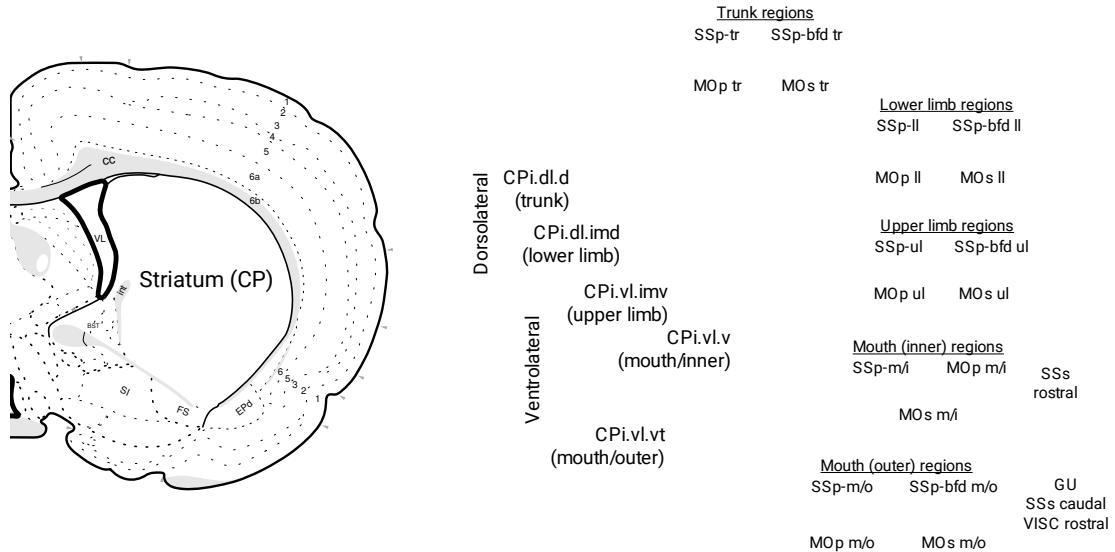


Figure 1.2: Somatotopic map of cortical inputs to the DLS. *Left:* striatum (CP) in the rat brain atlas. *Right:* inputs from somatosensory cortices form a topographic map in the DLS. CPi: the intermediate portion of the striatum along the rostrocaudal axis (other abbreviations are defined in the original reference and are not important here). Figure adopted from [74].

suggesting that areas that has been considered as the DMS in the literature, partially includes the DLS too. It has since been suggested that the sensorimotor information in the DS is more prevalent than classically considered and it should be taken into account in studies concerning the function of the striatum [85].

Direct/Indirect Pathways MSNs are the majority of the neuronal population of the striatum. They are homogeneously distributed in a way that the striatum lacks any architectural organization when all the neurons are stained in a histologic slice [72]. Nonetheless, MSNs are divided into two major categories, based on their neurochemistry and connectivity. One class expresses D1 dopamine receptor (D1) and projects directly to GPi/SNr neurons, hence they form the so-called **direct pathway**. The second kind expresses D2 dopamine receptor (D2) and projects to the GPe. This pathway, in turn, leads to the output nuclei through two routes: monosynaptic GPe→output, or bisynaptic GPe→STN→output projections [76]. These MSNs form the **indirect path-**

way (Figure 1.1). D1-expressing neurons and D2-expressing neurons exist in rather equal numbers and are intermingled and spread rather uniformly throughout the striatum [72]. The net effect of the direct pathway activity is to inhibit the GPi/SNr nuclei, thus releasing the target areas of the BG from inhibition (i.e., disinhibition). On the contrary, indirect pathway activity, through GPe and STN, disinhibits the output nuclei and in turn causes further inhibition of BG targets. This bidirectional control of the BG output by the direct and indirect pathways is believed to substantially influence the behavior, either by gating movements [86], or by selecting the appropriate actions and repressing others [87].

DA significantly modulates neuronal activity in the striatum [88]. Parkinson's disease (PD), with many behavioral and cognitive ramifications, is characterized by the degeneration of SNC neurons and DA depletion in the striatum [see 89, for a comprehensive review]. Axons from SNC neurons arborize widely in the striatum. They primarily synapse with principle neurons (MSNs) targeting the narrow necks connecting the spines to dendritic shafts, whereas cortical inputs mostly terminate on dendritic shafts. This particular arrangement may be a mechanism by which DA release modulates the cortical input to the MSNs [76]. This mechanism is of extra importance since D1-expressing neurons are excited by DA, whereas D2 neurons are inhibited. Thus, DA signals can up-regulate or down-regulate the excitability of the direct and indirect pathways.

The physiology and anatomy of the BG give this structure the potential to have a wide range of functions, from providing a central clock by implementing models such as the ramping activity, to controlling actions through different mechanisms, and even providing an essential node in the decision-making network. Following section reviews the evidence in support of each of these possibilities.

1.4.2 Basal Ganglia as a Clock

Many brain structures have been proposed to contribute to time estimation. Among them, the BG are especially of interest, since they are directly involved in motor processes as well [78]. Moreover, the BG are also involved in reinforcement learning—selecting actions in an uncertain world in a way that maximizes reward in the long term [90]. Such learning necessitates an understanding of temporal contingencies in order to maximize future rewards. Behavioral data supports that animals build probabilistic models for timing of the reward and even adjust their models in response to modified reward delays [91].

The BG are often implicated in timescales of several hundreds of milliseconds to several seconds [5]. Evidence of involvement of the BG in timing stems from a variety of sources, including pathologies such as PD, lesion studies, and pharmacological and genetic manipulations. Following the taxonomy discussed in section 1.1, there is evidence of involvement of the BG in sensory timing. Rao and others reported encoding of time intervals in the human striatum in a task in which subjects reported whether an interval was shorter or longer than a standard interval of 1200 ms.^{xii} They also observed a dynamic network of cortical activity in inferior parietal, premotor, and dorsolateral prefrontal cortex. These nodes in the network were attributed to different components of temporal processing, respectively, attention, memory, and interval comparison. They ultimately concluded the implication of “striatal dopaminergic neurotransmission in hypothetical internal timekeeping mechanisms” [92]. Moreover, Pouthas and others investigated interval categorization for two durations (450 ms and 1300 ms). They observed ramping striatal activity during both intervals. They concluded a direct role of the basal ganglia in duration estimation, and that the caudate nucleus “may support a clock mechanism” [93]. Similar evidence exists in other species as well. Gouvêa and others trained rats in a sensory categorization task to judge whether an interval

^{xii}This paradigm is commonly referred to as “interval categorization task”.

is shorter or longer than 1.5 s. They decoded animals' choice and elapsed time from ensembles of striatal neuronal activity, whereas apparent behavior in an overhead video failed to do so. Transient inactivation of the DS did impair performance, however, it did not cause a systematic under- or over-estimation [10].

Furthermore, the BG are also well studied for their role in motor timing. Matell and others trained rats to receive a reward in a fixed interval reinforcement schedule.^{xiii} The interval alternated between 10 s (25% of trials) and 40 s (75% of trials). After learning, animals increased their lever press rate around the reinforced intervals. Electrophysiological recordings from the striatum showed neurons with tuned firing rate only around 10 s interval, but not 40 s, while apparent behavior of the animals was similar. The authors then suggested that a population of duration-coding cells, each tuned to different values, could accurately represent the elapsed time [94]. Mello and others also used a similar task for intervals ranging between 12 s to 60 s [95]. They found striatal cells that rescaled their activity when intervals changed. As rats adjusted to the new interval, time estimations decoded from population dynamics predicted animals' timing performance. In another study, Bakhurin and others used an operant conditioning paradigm in which the conditioned stimulus was followed by a delayed reward delivery (2.5 s after cue onset) and they monitored anticipatory licking of mice as a behavioral readout of temporal perception [96]. After training, animals started licking ~1.5 s after the conditioned stimulus. Simultaneously recorded neurons in the striatum and orbitofrontal cortex displayed sequential activity during the interval. A machine learning algorithm was then trained to decode the elapsed time from the stimulus onset. They showed that both striatal and cortical networks "encoded time, but the striatal network outperformed the orbitofrontal cortex". Interestingly, removing the neurons modulated by licking activity from the decoder significantly reduced its performance, however, it still remained higher than the chance level [96].

^{xiii}In operant conditioning, fixed interval reinforcement schedule refers to a type of conditioning whereby a response is reinforced only if a certain period of time has elapsed.

A source of impact in the basal ganglia is the neuromodulatory effect of DA. Dopamine's role in reward processing and circuit dynamics of the striatum is discussed in section 1.4.1 and section 1.4.3. DA is also believed to be involved in timing [5]. In a peak interval procedure,^{xiv} De Corte and others found that D2 blockade delayed start and stop times for an interval of 6 s. Whereas, blockade of D1s delayed stop times only. Then they stressed the role of the DS in timing, with DA “being particularly critical for the temporal control of action” [97]. Dopamine neurons encode reward prediction errors which requires accurate reward predictions [see 98]. Takahashi and others recorded from DA neurons of rats while they performed a task with uncertainty in reward timing and reward number. Neuronal activity showed error signals in response to both types of prediction error, however, after ventral striatal lesions, neurons only responded to changes in reward number, and not reward timing. These results suggested that time-dependent component of reward prediction of DA neurons might rely on the ventral striatum [99]. In an interesting study, Soares and others measured and manipulated the activity of DA neurons in a 1.5 s interval categorization task [100]. DAergic activity predicted animal’s time estimates. Transient activation (*inhibition*) of DA neurons caused under- (*over-*) estimation of the interval. Hence, the authors concluded that “DA neurons, which are so central to reward processing, exert control over time estimation”, although these results reflect DA function in general, not specifically in the BG. Similar to scaling of spiking activity in the striatum [95], DA concentration in the DS is also scalable to time intervals in several second time range [101]. However, Howard and others then conducted a series of experiments and concluded that the DA signal in the DS does not reflect interval timing per se, rather it is specific to behavioral choice of action [101].

^{xiv}Peak interval procedure is a common task used to study timing. Similar to fixed interval schedules, a cue indicates that a response will be reinforced only after a certain period of time has elapsed. The profile of the response around the interval is then studied.

Deficits in temporal perception occur in many disorders. Since pathologies usually affect multiple brain structures or manifest in several behavioral domains, it is unclear whether timing deficits are responsible for dysfunctions, or they are merely the result of other malfunctioning systems. Schizophrenia, for example, is a complex psychiatric disorder with a wide range of symptoms, including: delusions, hallucinations, speech poverty, and timing deficits. Time perception impairment is reported in sensory and motor timing tasks and is associated with increased DA levels in the striatum, as well as abnormal activity in the dorsolateral prefrontal cortex and supplementary motor area [see 102]. Furthermore, it has been reported that individuals with attention deficit/hyperactivity disorder did not benefit from the temporal predictability in an oculomotor task that displayed a target after a random delay [103]. Additionally, timing deficiency has also been reported in Huntington's disease. Patients demonstrated lower sensitivity to temporal regularities and overall, poorer performance in different types of sensory timing tasks. Their performance negatively correlated with the progression of Huntington's disease as well [104]. Finally, PD also affects timing performance. Lower timing performance has been reported in multiple tasks. Harrington and others showed that PD patients were impaired in sensory timing, in which "duration perception" was weaker compared to the control group. Also, in a motor task, whereby subjects performed finger-tapping synchronized with a series of tones (in the subsecond range), PD participants were significantly more variable [105]. Interestingly, it has been proposed that frequent exposure to temporally-structured tones might alleviate motor symptoms of PD, especially gait and stride length [106].

1.4.3 Basal Ganglia as a Motor System

Why do we and other animals have brains?... You may reason that we have one to perceive the world or to think, and that is completely wrong... We have a brain for one reason and one reason only, and that is to produce adaptable and complex movements.

Daniel Wolpert, TED talk

Regardless of whether one agrees with Daniel Wolpert's strong words above or not, the importance of volitional movements is trivial. The striatum, in particular, is reported to be involved in different aspects of voluntary action. Among those, its role in motor control^{xv} is well-studied.

Action Selection and Chunking

The BG are postulated to control voluntary actions through direct/indirect pathways. Mink and others proposed the action selection model, according to which the two pathways may work in concert to support the desired actions (direct pathway) and suppress the unwanted competing ones (indirect pathway) [71]. Cell-type specific techniques allowed investigating such a dissection *in-vivo*. For example, by stimulating BG pathways, locomotive activity was bidirectionally controlled [86]. Moreover, calcium transients recorded from D1 and D2 striatal neurons demonstrated concurrent activity in both cell types during movement [87, 107]. Interestingly, MSN ensembles that were active during specific actions were generally spatially closer together and more correlated between similar actions [108]. These studies, however, found similar patterns in both D1 and D2 neurons. Therefore, they proposed a revised action selection model in which the indirect pathway might not inhibit all the competing actions, rather exert a more specific control over particular aspects of an action [108]. Accordingly, during the execution of a learned lever pressing sequence, some neurons displayed sustained

^{xv}By "motor control", I refer to the performance/execution of movements or actions. Those actions are already part of the subject's motor repertoire, i.e., they have been learned earlier.

activity during the sequence in both direct and indirect pathways, while some favored the start and stop of the sequence [109].

Related to the action selection hypothesis is chunking patterns observed predominantly in the DLS. Striatal neurons, in a wide variety of tasks, have preferential firing around the boundaries of a learned motor sequence. For instance, Barnes and others showed that MSNs in the DLS fired sharply at the start and end of an overlearned run bout in a T-maze [110]. This chunking of a behavioral sequence was then proposed to mediate the process of acquiring motor habits. In another study, mice were trained to press a lever 8 times to receive a reward (fixed-ratio schedule) [111]. After training, mice pressed the lever in close succession. Next, authors recorded the spiking activity of DLS neurons and reported that the firing of many neurons peaked just before the first press or around the last one. This pattern grew stronger with learning [111]. Moreover, Martiros and others trained rats to each perform a unique lever pressing sequence (first rat: lever 1→1→2; second rat: lever 2→1→2) [112]. After learning, similar “sequence-bracketing” activity was recorded in the DLS, but only for the reinforced sequence of each animal, and not for the non-reinforced sequences which were rewarded for other subjects.

Further experiments indicated that the activity profile of MSNs during movement is more complex. There is now evidence indicating that the striatal activity may form a continuous space, and functional clusters may reflect instantaneous movement information, rather than discrete start and stop signals [113, 114]. Markowitz and others decoded subsecond syllables of ongoing behavior using both the D1 and D2 activity [114]. Sales-Carbonell and others trained head-fixed mice to run uninterruptedly for 100 cm on a wheel and then remain immobile to allow the next trial to start [113]. Recording from striatal MSNs in proficient animals showed that neuronal activity is modulated during the entire running phase, including the start and stop points. Statistical analysis of neuronal activity indicated a continuous representation of the run phase in the stria-

tum. Finally, authors suggested that the over-representation of the start/stop of the run phase may be due to the altered sensorimotor state that occurred at those points, such as licking the reward or changing the locomotion speed [113].

Kinematics and Urgency

Control of movements has been associated with the BG for a long time. This link dates back to the first descriptions of the behavioral deficits of PD patients by James Parkinson in 1817. Tetriakoff, in 1919, performed postmortem analysis of the brains of patients diagnosed with PD, and first reported loss of dark-pigmented nigral neurons. Ever since, motor dysfunctions of PD are believed to be due to DA depletion in the striatum [70, 88, 89, 115].

Although symptoms differ from patient to patient, three behavioral deficits are typical for PD: resting tremor, which is the most apparent; rigidity and stiffness of muscles; and bradykinesia, i.e., reduced movement vigor. Reduced vigor in PD has been investigated to distinguish between the speed/accuracy trade-off and energetic cost as two possible determinants of movement speed. Mazzoni and others asked PD patients and age-matched control subjects to make self-paced arm movements as accurate as possible toward a target with a speed within an explicitly requested range [116]. After 20 successful trials, the required speed range and/or target distance changed to the next experimental condition. Both groups of subjects, across all conditions (3 target distances, 4 speed ranges) achieved similar peak velocities and maintained the same level of accuracy. However, patients needed significantly more trials to reach the criterion to advance to the next condition. Analysis of those extra trials performed by the PD patients demonstrated that they used a higher proportion of slower movements while retaining the speed range the same as control subjects. Moreover, authors showed that the number of trials required to reach the criterion, as a measure of task difficulty, strongly correlated with subjects' average acceleration. This linear contribution (de-

noted as S_N) was steeper for control subjects. In other words, for any given difficulty of the task, PD patients *chose* a lower level of acceleration. Similar linear relationship existed between number of trials to criterion and accuracy as well, but it was the same for control subjects and patient. Thus, lower S_N in PD was not caused by a different speed/accuracy trade-off, rather by another component of task difficulty related to the acceleration. Authors then argue that acceleration also represents movement energy cost, and that PD patients are more sensitive to energy expenditure. These results suggest that SNC innervation of the striatum carries a “motor motivation” signal and lack thereof in PD leads to a propensity for slow movements [116]. Similar results have been reported from patients with pallidal and striatopallidal lesions. They could generate normal grip force when explicitly instructed, however once left to their own, they failed to squeeze harder to earn more monetary compensation [117].

Available methods in animal research provide an opportunity to further dissect the BG circuit. For instance, infusion of the GABA_A agonist, muscimol, transiently inactivates the surrounding neurons, allowing the researcher to study the functional relevance of the targeted structure.^{xvi} Desmurget and Turner took advantage of this technique to acutely inactivate the sensorimotor territory of the GPi in monkeys [118]. Monkeys were trained to move a cursor using a joystick to a peripheral target and then move it back to its original position. The two experimental conditions differed in the degree to which successive target positions were predictable: random positioning of the target in each trial; or a fixed repetitive sequence of four target positions. GPi inactivation after overlearning the sequence did not prevent its execution, thus failing to support a role for the BG in “storage or execution of well learned motor habits”. The main impairment observed post-injection was reduced movement speed and amplitude in both conditions, i.e., random sequences and the overlearned sequence. Thus, they concluded that the motor circuit of the BG contributes to the kinematics of motor execu-

tion but not its production nor storage of learned sequences [118]. In general, reduced vigor is the most common phenomenon in conditions of perturbed BG activity [41, 120–125]. Importantly, in many types of tasks, including the two mentioned above, reduced vigor could also be regarded as an overestimation of the cost action, i.e., a conservative policy in energy expenditure.

Decision making is another front where cost evaluation is essential. Many decisions are based on partial information that has been gathered over time, like deciding whether the approaching animal is a predator or a prey, or choosing the *best* restaurant for dinner [126]. In such cases, one faces a dilemma analogous to the speed/accuracy trade-off in motor control: waiting longer to accumulate information makes for better decisions at the cost of diminishing reward, increasing danger, and the passage of time. The BG are implicated in controlling this trade-off in decision-making. In an interesting paper, Thura and Cisek used a task that allowed dissociating different aspects of decision-making and movement control [127]. They extensively trained monkeys to guess which of the two potential targets would receive the majority of the tokens that jumped from a central point to one of the possible targets every 200 ms. Crucially, after the subject reached the target, the rest of the tokens jumped more quickly, thus presenting the monkey with a trade-off to either make confident decisions or guess earlier and receive potential rewards sooner. How much faster the tokens jumped after the decision (every 150 ms, or every 50 ms), compared to their normal pace (every 200 ms) determined different speed/accuracy trade-off policies—the faster they jumped, the more hasty decisions were justified. They performed electrophysiological recordings in behaving animals from the motor and premotor areas as well as the GPi and GPe. They showed that during deliberation, information about selecting a target existed in

^{xvi}This technical approach is not free from skepticism. Otchy and others present convincing evidence that acute circuit manipulations, such as inactivation, have unintended consequences. In a complex dynamical system such as the brain, by transiently changing the activity of the area of interest, off-target downstream structures are driven into an unnatural state that could have behavioral implications of its own [119].

the motor areas, but it was much weaker in the BG output. They observed ramping activity in the GPi that “invigorate[s] the decision-making process by providing an urgency signal”. This urgency signal grew over time and was adjusted to different speed/accuracy trade-off policies, but did not reflect the amount of evidence or the target chosen by the animal [127]. In the condition wherein tokens jumped the fastest post-decision, unsurprisingly, the ratio of hasty decisions increased. Moreover, the animals made faster movements too [58]. Therefore, the urgency signal may act as a determinant of the timing of decisions and the vigor with which those decisions are implemented into actions in pursuit of maximal reward [52].

Neural activity in the striatum has been shown to encode kinematics of ongoing behavior too. Single DLS neurons of rats encode locomotion speed and acceleration [41]. In addition, D1 and D2 population activity was correlated with locomotion speed in mice [107]. Moreover, simultaneous recording of calcium activity and mouse 3-D exploratory behavior showed that direct (*indirect*) pathway activity correlated (*anti-correlated*) with movement velocity. Nonetheless, ongoing kinematics was best decoded from the activity of both pathways, suggesting that they contain non-redundant information [114].

Contrary to the classic model of the BG, in which the direct pathway activity is prokinetic and the indirect pathway activity inhibits movement [86], and to the action selection model of the BG that proposes that the direct pathway promotes the selected action while the indirect pathway concurrently suppresses the competing actions [87], a novel behavioral paradigm revealed that control of movement velocity might be the underlying mechanism implemented by the BG. Yttri and Dudman in an article that is one of my all-time favorites, trained head-fixed mice to perform self-paced fore-limb movements to obtain a delayed water reward [128]. While all movements bigger than an easy-to-reach threshold were rewarded, the fastest ones were detected early after initiation and the fastest third of the movements triggered a photo-stimulation

of either D1 or D2 neurons in the DMS. Brief stimulation of direct pathway MSNs produced a significant increase in movement velocity that sustained for multiple trials after cessation of stimulation. On the contrary, indirect pathway stimulation reduced the movement vigor. Interestingly, stimulating the slowest, rather than the fastest, third of trials generated the opposite effect: D1 activation reduced and D2 activation increased the velocity. In all cases, other movement parameters, such as amplitude, duration and tortuosity remained unchanged. Thus, activating the MSNs was sufficient to produce bidirectional control of movement velocity. The authors then argued that reinforcement learning models of the BG could not readily act on a continuous kinematic parameter of movement and they proposed an algorithmic learning rule in which a signed pathway-specific signal determines the mean velocity of movement while a homeostatic component opposes the learned changes in velocity. Such a learning rule explained the empirical data and was conceptually predicted by a history-dependant gain (HDG) model of the BG [61, 128]. The HDG model describes movement vigor as a function of both descending motor commands from the cortex and the BG output. The BG in this model applies a causal gain to the kinematics of behavior [61]. This gain is determined by the relative strengths of cortical synapses onto D1 and D2 neurons. Synaptic strengths depend on the plasticity mediated by prior activity and the DA, which in turn represents a recent history of reward. Thus, the bidirectional control of vigor by either pathway is due to the altered relative synaptic weights of D1/D2 neurons upon stimulation [128]. The HDG model predicts that stimulating random trials, stimulating every trial, and suppressing DA-mediated plasticity should abolish control of vigor. All of these predictions were empirically verified [128].

Related to the HDG model discussed above, Dunovan and Verstynen proposed a model in which the BG encode action uncertainty through direct-indirect pathway competition [129]. This competition implements a commitment to action algorithm by comparing the activity of the direct pathway to the indirect pathway. Due to the

heavily inhibited default state of the BG, the commitment to action only happens if the direct pathway provides enough evidence, otherwise no action is executed. Sensory and contextual evidence is provided by the weighted corticostriatal inputs that modulate direct/indirect pathway activity [129]. The ratio of D1/D2 activity determines the outcome of the competition, the time point at which the action is committed, and possibly, the vigor with which it is executed.

1.5 Motivation, Question and the Organization of the Thesis

The work presented in this thesis has two fronts that might seem unrelated, but in this chapter I tried to present them on a conceptual continuum. The first part is concerned with the question of how animals often act as though they have a sense of time. Enormous body of experimental and theoretical research implicates plenty of brain areas as providers of a time signal. Although such an internal mechanism could be affected by external factors (e.g., reward rate and motivation), however, it is usually assumed to be the means by which well-timed actions are generated. This is what I call “internal time estimation”, not that the world exterior to the brain is irrelevant, but meaning that the brain has a sense of time on its own that underlies behavior. This mechanism is appealingly simple, predictive of many behavioral phenomena, and backed by neurophysiological data. Alternatively, we hypothesized that there is no sense of time per se, and that time is perceived through interactions with the environment. In other words, the duration of an interval is displaced by its sensorimotor content. Since movement generation is among the most basic functions of the nervous system and inevitably, it takes a certain duration to execute any action, elapsed time could just be inferred from actions (or similarly, sensory processes). Such an “embodied time estimation” provides a much more parsimonious explanation, and is in alignment with the long-reported and

replicated observation across many species that animals produce stereotyped motor sequences under temporal constraints. Nonetheless, this hypothesis has not been very popular! Perhaps partly due to technological limitations to monitor a wide range of animal behavior (in rodents, from locomotion to whisking and sniffing), especially in standard experimental paradigms inside Skinner boxes; and in my opinion, partly due to a general brain-centric view where the brain is the puppeteer of the body.

To test the embodied timing hypothesis, I used a novel behavioral paradigm developed by Rueda-Orozco and Robbe [41] that is a powered treadmill with a reward contingent on timing of appetitive approaches (details are discussed in [section 2.1](#)). This task allows monitoring the location of the animals and kinematics of their locomotion. Powered treadmill enabled us to manipulate dynamics of the environment in order to facilitate or hinder exploitation of the stereotyped motor sequences that we hypothesized are essential for solving the task. We assumed if timing was internally-driven, animals should be able to perform the task without resorting to the stereotyped motor strategies. Results from these experiments are presented in [chapter 3](#).

The second facet of this work deals with the problem of implementation, i.e., how the brain generates the motor sequence it presumably uses to keep track of time. Classic models of the BG implicate the DMS in early phases of learning, and the DLS in executing the learned sequences, or controlling their kinematics. Results from an earlier work in our group suggest that the overall behavior of the animals following transient inactivation of the DLS remains intact, although more variable [41]. Therefore, in this work, using a similar approach, we aimed to specify the function of the striatum in development and execution of this behavior. In particular, I evaluated the role of the striatum, the main input to the BG, in learning and controlling the kinematics of a motor sequence, by permanently lesioning its subareas (details are discussed in [section 2.2](#)) in both naïve and trained animals. Results from these experiments are presented in [chapter 4](#).

Finally, I synthesize an overview of my Ph.D. project and discuss its meaning and implications, as well as some shortcomings and directions for future works in [chapter 5](#). It should be noted that I tried to write each chapter such that it would make sense regardless of the rest of the manuscript.

Chapter 2

Methods

Time perception is convoluted with motor functions. As discussed in the [first chapter](#), disentangling the two has proven to be difficult, and sometimes, overlooked. Using original behavioral tasks, designed with the above concern in mind, might shed new light on this matter. In this chapter, I present a novel behavioral paradigm that allowed monitoring the locomotive activity of the animals as well as their timing performance. I also provide technical details about different variants of this paradigm used in this work. I also present all the experimental and analytical methods used in this project.

2.1 Experimental Tools

In this section, all the different conditions and tasks used in this works are described.

2.1.1 Subjects

Subjects were male Long-Evans rats. They were 12 weeks old at the beginning of the experiments, housed in groups of 4 rats in temperature-controlled ventilated racks and kept under 12 h–12 h light/dark cycle. All the experiments were performed during the light cycle. Food was available *ad libitum* in their homecage. Rats had access to

water everyday for 30 min after their experimental session, while their body weight was regularly measured. No animal was excluded from further analysis. All experimental procedures were conducted in accordance with standard ethical guidelines (European Communities Directive 86/60-EEC) and were approved by the relevant national ethics committee (Ministère de l'enseignement supérieur et de la recherche, France).

2.1.2 Task Apparatus

Four identical treadmills were used for the experiments. Each treadmill was placed inside a ventilated sound-attenuating box ([Figure 2.1a](#)). Treadmills were 90 cm long and 14 cm wide, surrounded by plexiglass walls such that the animals were completely confined on top of the treadmill belt. Treadmill belt covered the entire floor surface and was driven by a brushless digital motor (BGB 44 SI, Dunkermotoren). A reward delivery port, connected to a solenoid valve, was installed on the front (relative to the turning direction of the belt) wall of the treadmill and released a ~80 μ L drop of 10% sucrose water solution in case of a full reward. An infrared beam was placed 10 cm from the reward port. The first interruption of the beam was registered as entrance time (ET). A loudspeaker, placed outside the treadmill, was used to play an auditory noise (1.5 kHz, 65 db) to signal error trials. Two strips of LED lights were mounted on the ceiling along the treadmill to provide visible and infrared lighting during trials and intertrials, respectively. The animals' position was tracked via an overhead camera (Basler scout, 25 fps). A custom-made algorithm detected the white coating of the rats and recorded its centroid as animals' position. The entire setup was fully automated by a custom-made program (LabVIEW, National Instruments). Experimenter was never present in the behavioral laboratory during the experiments.

2.1.3 Habituation

Animals were handled 30 min per day for 3 days, then habituated to the treadmill for 3 to 5 daily sessions of 30 min, while the treadmill's motor remained turned off and a drop of reward was delivered every minute. Habituation sessions resulted in systematic consumption of the reward upon delivery.

2.1.4 Treadmill Task

Training started after handling and habituation sessions. Each animal was trained once a day, 5 times a week (no training on weekends). Each of the daily sessions lasted for 55 min and contained ~130 trials. Each trial started by turning the treadmill motor on at a fixed speed of 10 cm/s. One second before motor onset, the ambient light was turned on (to warn the animals of the imminence of the belt movement). The conveyor belt moved toward the rear of the treadmill ([Figure 2.1a](#)). Three types of trials were defined based on the time the animal first interrupted the infrared beam, i.e., the ET, relative to the goal time (GT). Trials in which animals entered the reward area after the GT were classified as **correct** ($7 \leq ET < 15$, [Figure 2.1b](#)). Trials in which animals entered the reward area before the GT were classified as **error** ($1.5 \leq ET < 7$, [Figure 2.1c](#)). In case no infrared beam interruptions were registered in 15 s, the trial ended and was classified as **omission** ([Figure 2.1d](#)). The infrared beam was inactive during the first 1.5 s ($ET < 1.5$) to give the opportunity to the animals to leave (passively or actively) the reward area at the beginning of each trial. Additionally, the exact value of the ET determined a reward/punishment ratio. The reward was a drop of sucrose solution and the punishment was a period of extra running. The running penalty started when the animals erroneously crossed the infrared detector before GT (error trial) and its duration varied between 10 s and 1 s, according to the error magnitude ([Figure 2.1c, inset](#)). Thus, to maximize reward collection and minimize running time, animals should cross the infrared beam just after the GT.

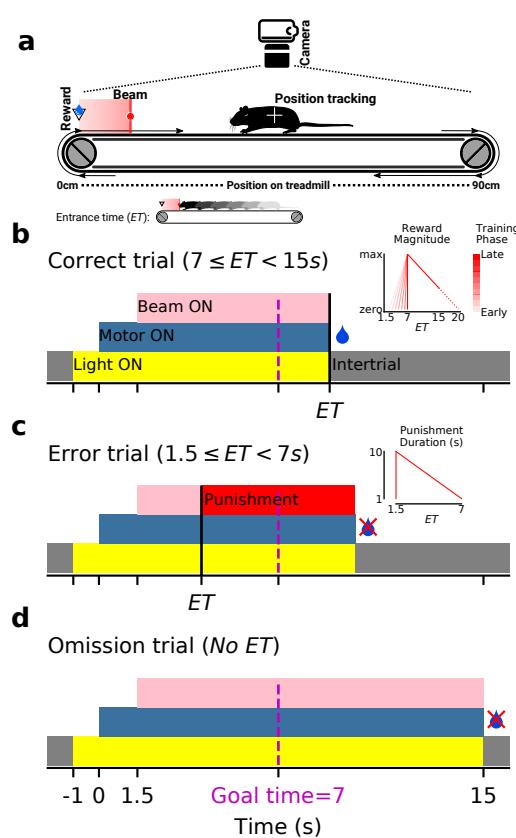


Figure 2.1: Treadmill task and trial types.

a) Rats were enclosed on a powered treadmill. The infrared beam marked the reward area (red shaded area). During each trial, the belt pushed the animals away from the reward area and the first infrared beam interruption defined the ET. During trials and intertrials, the animal's position was tracked via a overhead video camera.

b) Schematic description of a rewarded correct trial. *Inset:* the magnitude of the delivered reward dropped linearly as ET increased (maximum reward at goal time). In early stages of training, smaller rewards were delivered for trials with $ET < 7$ s. The smallest ET value that triggered reward delivery was progressively raised during learning.

c) Schematic description of an error trial. Early ET triggered an extra running penalty and an audio noise. *Inset:* the duration of the penalty was 10 s for the shortest ETs and fell linearly to 1 s for ETs approaching 7 s.

d) Schematic description of an omission trial (no beam crossing between 1.5 s and 15 s). **b-d)** Note that ETs started to be detected 1.5 s after the motor start.

Reward Profile

The magnitude of the reward was a function of the ET and animal's performance in previous sessions. Reward was maximal at $ET = GT$ and dropped linearly to a minimum (i.e., ~38% of the maximum) for ETs approaching 15 s (maximum trial duration). Moreover, in the beginning of the training, partial reward was also delivered for error trials with $ET > ET_0$, where ET_0 denotes the minimum threshold for getting a reward. The magnitude of this additional reward increased linearly from zero for $ET = ET_0$, to its maximum volume for $ET = GT$. In the first session of training, $ET_0 = 1.5$ s and for every following session, it was updated to the maximum value of median ETs of the past sessions. Once ET_0 reached the GT, it was not updated anymore (late training reward profile in Figure 2.1b, inset).

2.1.5 Alternative Task Conditions

In addition to the ‘normal’ treadmill task described above, several modified versions of the task were also designed to investigate the embodiment hypothesis. In each of these conditions, a specific parameter of the task was altered, allowing us to study its effect on animals’ performance.

Variable Speed Condition

In this condition, for each trial, the treadmill speed was pseudo-randomly drawn from a uniform distribution between 5 and 30 cm/s. During any given trial, the speed remained constant. We used 5 cm/s as the lowest treadmill speed, because lower speeds generated choppy movements of the conveyor belt. Also, velocities higher than 30 cm/s were not used, to avoid any physical harm to the animals.

No-timeout Condition

In the control condition, the infrared beam was not active during the first 1.5 s of the trials. This **timeout** period was sufficient to let the animals be carried out of the reward area by the treadmill, provided they did not move forward. In the “no-timeout” condition, the infrared beam was activated as soon as the trial started. Thus, in this condition, error trials corresponded to ETs between 0 and 7 s. Consequently, animals were penalized if they were in the reward area when the trial started (i.e., ET = 0 s).

Short Goal Time Condition

In this condition, the GT was set to 3.5 s, half its value for the control condition. The reward profile in this condition followed the same rules as for the control condition, except that reward was maximal at ET = GT = 3.5 s. Two different groups of animals were trained in this condition, one with treadmill speed set to the normal value of 10 cm/s, and another with the treadmill running twice as fast. In the short goal time

condition, we also examined if the increased variability in ET could be attenuated when the penalty associated with early ETs was increased and when reward magnitude was decreased for late ETs. This was implemented by doubling the treadmill speed during the penalty period (from 10 cm/s to 20 cm/s), and delivering the reward for a narrower window of ETs (maximal reward at $ET = GT = 3.5$ s, and no reward after $ET = 4.5$ s). For proper comparison, we also examined the behavior of rats trained with $GT = 7$ s when the running penalty was increased and the reward was decreased for late ETs (maximal reward at $ET = GT = 7$ s, and no reward after $ET = 9$ s).

Immobile Condition

In this condition, the treadmill motor was never turned on. The ambient light was turned on during the trials and turned off during the intertrials. Error trials were penalized by an audio noise and extended exposure to the ambient light.

2.1.6 Reverse Treadmill Task

This task differed from the normal treadmill task ([section 2.1.4](#)) in three critical properties:

- the treadmill moving direction was reversed, i.e., the conveyor belt moved toward the reward port;
- the treadmill speed was set at 8 cm/s (instead of 10 cm/s) to ensure that starting the trial in the back and remaining still (an reverse routine trial) would be rewarded, i.e., $ET \geq 7$.
- the intertrial duration was 20 s, instead of 15 s, to allow sufficient time for the animals to move to the back of the treadmill while the motor was still off.

The other task parameters were identical to the normal treadmill task.

2.1.7 Locomotion Task

A group of animals with a striatal lesion ($n = 7$ DLS, $n = 2$ DMS, and $n = 3$ DS), and another group of non-lesioned animals ($n = 12$) were used in this test to assess their general locomotor abilities (Figure 4.4A-B). Prior to this task, animals had full access to water and food for at least 3 days. Then, they were placed on an unfamiliar treadmill, with a different structure (slanted walls and covered reward port) compared to the treadmill in which they were trained, while their position was being recorded using a side-mounted high-speed camera (200 fps). During the first 10 min, the ambient light was turned off and the treadmill remained immobile. Their exploratory locomotor activity, i.e., how much they moved along the treadmill, during this period is presented in Figure 4.4A. Then, in a free running task, they ran in trials of 30 s while the treadmill speed progressively increased across trials (5 trials at 0 cm/s, 2 trials at 10 cm/s, 3 trials at 15 cm/s and 5 trials at 20, 25, 30, 35, and 40 cm/s, total of 30 trials, data shown in Figure 4.4B). Each trial was followed by an intertrial of similar duration, while the ambient light and the treadmill motor were turned off. The running speed reported is the average running speed of animals during the trials of any given treadmill speed.

2.2 Technical Tools

In this section, I specify the details of the techniques used in experiments and data processing.

2.2.1 Striatal Lesion

Anesthesia was induced with an intraperitoneal (IP) injection of a mixture of 100 mg/kg ketamine and 10 mg/kg xylazine and was maintained during the surgery with inhalant isoflurane gas (less than 3%). After shaving and cleaning the scalp, the animal was placed in the stereotaxic frame (Kopf instruments) and a local analgesic (lidocaine)

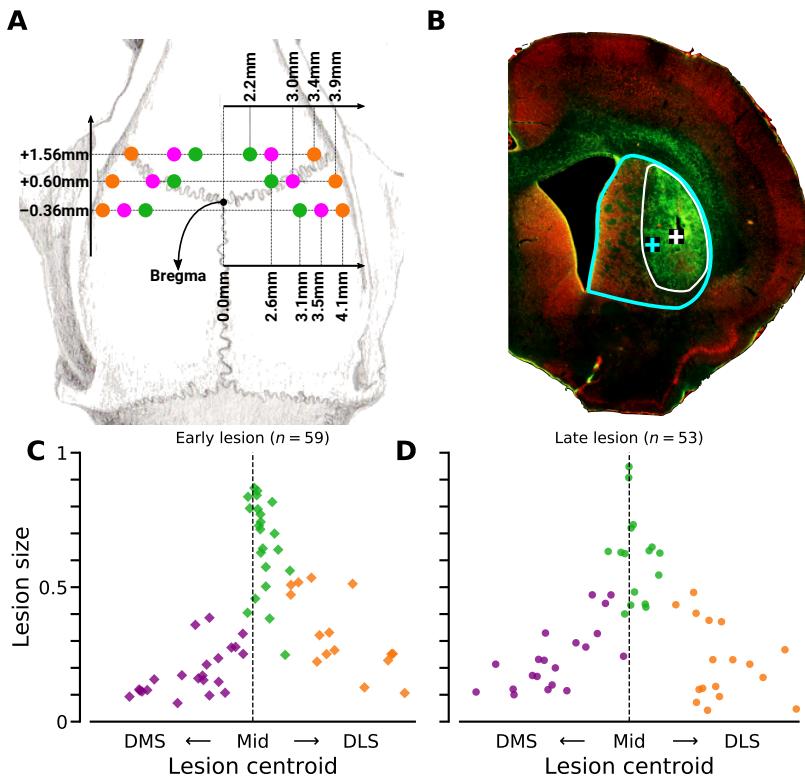


Figure 2.2: Dorsal striatum lesion coordinates and quantification. **A)** Schematic of lesion sites. **B)** Illustration of the quantification of the lesion size. For each coronal slide and hemisphere, the contour of the lesion was manually outlined using the GFAP staining. The relative size of the lesion (compared to the full striatum, manually outlined on the NeuN staining) and the coordinates of the lesion/striatum centroid was calculated. For each animal, the size and location were obtained by averaging data along the anteroposterior axis, for both left and right hemispheres. **C, D)** Lesion size vs. location for animals that underwent lesion before (**C**: early) and after (**D**: late) extensive practice. Lesion quantification was performed blindly relative to the behavior. In four animals with a striatal lesion performed after learning the task (late lesion), the lesion size quantification could not be properly performed. These animals were classified according to their injection coordinates in the surgery (3 DLS, and 1 DMS), however they were excluded from any analysis that required the lesion size (hence the difference between the number of 'late lesion' animals in this figure, $n = 53$, and the total number of animals in Figure 4.1, $n = 57$).

was injected under the scalp. Then, an incision along the midline of the skull was made, followed by cleaning the exposed skull and drilling the craniotomies above the targeted areas. To perform fiber-sparing lesion of the dorsal striatum (DS), ibotenic acid (1% in 0.1 M NaOH, Fisher Scientific) was infused (Pump 11 Elite Nanomite, Harvard Apparatus, using a 10 μ L WPI Nanofil syringe) in 6 specular sites bilaterally, at a rate

of 90 nL/min. The needle remained in-place for 10 min following the injection to allow for the diffusion of the excitotoxic drug. Then, the needle was retracted slowly to avoid backflow of the drug. Once all the injections were performed, craniotomies were filled with bone wax, the skull was disinfected, and the skin was sutured. Animals were allowed to recover for two weeks before resuming behavioral training. After surgery, animals were housed alone for 3 days, to avoid getting hurt by the cagemates, and were force-fed if needed. Injection coordinates (in mm, with reference to Bregma, according to Paxinos) are shown in [Figure 2.2A](#) (each injection at -5.6 mm dorsoventral). The infused volume in each site was 200 nL for DLS and DMS lesions, and 400 nL for DS lesions.

2.2.2 Immunohistochemistry

At the end of the experiments, animals were euthanized with an overdose IP injection of ~2 mL pentobarbital. Then, they were perfused with 4% paraformaldehyde and their brains were harvested for histological analysis of the lesion size and location. Brains were coronally sliced on a vibratome at 60 μm thickness. For each animal, six sections spanning the DS along the rostrocaudal axis were selected (usually the following slice numbers: 5, 15, 25, 35, 45, and 55 for consistency) and submerged in 0.1 M PBS. Then, PBS was replaced with citrate buffer (10 mM) for 10 min at room temperature. Next, slices were submerged in a blocking solution, consisting of PBS with 0.3% triton and 15% normal goat serum for 120 min at room temperature. Then, the solution was replaced with another consisting of 2 μL mouse anti-NeuN antibody (Merks Millipore, MAB377) and 0.5 μL of rabbit anti-GFAP antibody (Agilent, Z033429-2) diluted in 200 μL of the blocking solution, kept overnight at 4 °C. Sections were then rinsed twice in PBS, 10 min each, at room temperature, before being submerged again in 1 μL of donkey anti-mouse antibody (Al555, red), 1 μL of donkey anti-rabbit antibody (Al488, green)

diluted in 400 μ L of PBS for 120 min at room temperature. Finally, they were washed twice in PBS, for 10 min each time, and mounted for microscopy.

2.2.3 Lesion Quantification

Whole slices were imaged using an Apotome microscope (Zeiss, 28126), and stitched together in the processing software (Zeiss Zen). Then for each slice, the ventricule, the striatum, and the lesioned area were manually outlined ([Figure 2.2B](#)) bilaterally in the image processing software (ImageJ, Fiji). The size and the centroid coordinates were automatically computed for all of the above-mentioned areas. Next, the anteroposterior location of each slice was also approximated according to the rat brain atlas (Paxinos).

The lesion size reported in this paper is the ratio of the lesion volume over the volume of the striatum. Both regions of interest (lesion and striatum) were approximated as a truncated cone between any two consecutive sections, and the volume was accordingly calculated and summed up. [Figure 2.2C-D](#) show the lesion coordinates of all the animals trained in the normal treadmill task. The type of the lesion (dorsolateral striatum (DLS), dorsomedial striatum (DMS) or DS) was determined visually and confirmed by comparing the centroid location of the lesion to that of the entire striatum. Animals with a DLS lesion in one hemisphere and a DMS in another ($n = 7$) were excluded from this manuscript. Four rat brains were imaged improperly, they are automatically removed from any analysis that required the lesion size.

2.2.4 Statistics

All statistical comparisons were performed using resampling methods (permutation test and bootstrapping). These non-parametric methods alleviate many concerns in traditional statistical hypothesis tests, such as distribution assumptions (e.g., normality assumption under analysis of variance), error inflation due to multiple comparisons, and sensitivity to unbalanced group size.

We used the permutation test to compare the performance of two groups of animals during training on a session-by-session basis, such as in [Figure 3.2b](#), and [Figure 4.5A](#). To simplify the description [see [130](#), for the complete description], let's assume, as in [Figure 3.2b](#), we have $\mathbf{X} = [X_1, X_2, \dots, X_n]$, where X_i is the set of ETs of all the animals in session i . Similarly, we have \mathbf{Y} that contains ETs from another experimental condition. Here, the null hypothesis states that the assignment of each data point in X_i and Y_i to either \mathbf{X} or \mathbf{Y} is random, hence there is no difference between \mathbf{X} and \mathbf{Y} .

In short, the test statistic was defined as the difference between smoothed (using Gaussian kernel with $\sigma = 0.05$) average of \mathbf{X} and \mathbf{Y} for each session i : $D_0(i)$. I then generated one set of surrogate data by assigning ET of each animal in session i to either X_i or Y_i , randomly. For each set of surrogate data, the test statistic was similarly calculated, i.e., $D_m(i)$. This process was repeated 10,000 times for all the statistical comparisons in this manuscript, obtaining: $D_1(i), \dots, D_{10000}(i)$.

At this step, two-tailed pointwise p-values could be directly calculated for each i , from the $D_m(i)$ quantiles [\[130\]](#). Moreover, to compensate for the issue of multiple comparisons, we defined global bands of significant differences along the session index dimension. From 10,000 sets of surrogate data, a band of the largest α -percentile was constructed, such that less than 5% of $D_m(i)$ s broke the band at any given session i . This band (denoted as the *global band*) represents the threshold for significance, and any break-point by $D_0(i)$ at any i is a point of significant difference between \mathbf{X} and \mathbf{Y} .

A similar permutation test was also used when comparing only two sets of *unpaired* data points (such as in [Figure 3.4e](#), comparing control vs. short GT groups). The same algorithm was employed, having only one value for index i . If none of the $D_m(i)$ s exceeded $D_0(i)$, the value $p < 0.0001$ was reported (i.e., less than one chance in 10,000).

For paired comparisons (such as in [Figure 3.2f](#) and in [Figure 4.3C](#)), I generated the bootstrap distribution of mean differences ($n = 10000$ with replacement). Significance was reported if 95% confidence interval (CI) of the pairwise differences differed from

zero (i.e., zero was not within the CI) [131]. For example, in [Figure 3.2f, right](#), the 95% CI of pairwise differences is (19, 27). Since this interval does not contain zero, it is reported significant, whereas in [Figure 3.4e](#), the CI of the comparison between normal and sharp short GT is (-0.17, +0.01) which includes zero, and hence is reported non-significant.

Exceptionally, for the comparison in [Figure 3.4h](#), even though it is not paired, I used bootstrapping, because I did not have enough data points to perform the permutation test. In this case, the resampled distribution ($n = 10000$ with replacement) for each group was calculated, and it was reported significant, since the distributions did not overlap at 95% CI.

Finally, in [Figure 3.5f](#), I used repeated measures correlation implemented in the Pingouin package [132]. This technique relaxes the assumption of independent data points, since each animal contributes more than one to the analysis.

2.3 Data Analysis

Data from each behavioral session was stored in separate text files, including position information, entrance times, treadmill speeds, and all the task parameters. Position information was then smoothed (Gaussian kernel, $\sigma = 0.3$ s). The entire data processing pipeline was implemented in python, using open-source libraries and custom-made scripts. We used a series of Jupyter Notebooks to process, quantify, and visualize every aspect of behavior and to generate all the figures in this manuscript. All the Jupyter Notebooks, as well as the raw data necessary for full replication of the figures (alongside other complementary information) is publicly available via the Open Science Foundation. The links to the respective repositories could be found from [133, 134].

2.3.1 Behavioral Measures

In this sections, different behavioral indices used in this manuscript are defined.

Motor Routine Definition A trial was considered **routine**, if all the following three conditions were met:

- the animal started the trial in the front (initial position < 30 cm);
- the animal reached the rear portion of the treadmill during the trial (maximum trial position > 50 cm);
- the animal completed the trial (i.e., it crossed the infrared beam).

Then, we quantified the percentage of trials in which animals performed the above motor routine in each session (such as in [Figure 4.1C](#)).

Reverse Routine Definition A trial was considered **reverse routine** if the following conditions were met:

- the animal started the trial in the back of the treadmill (initial position > 60 cm);
- the animal completed the trial (i.e., it crossed the infrared beam).

Percentage of reverse routine trials is analogous to the percentage of routine trials, only in the reverse treadmill.

Speed Calculation Unless otherwise stated, speed in this manuscript refers to the velocity with which animals outran the treadmill toward the reward port. For every trial, it was calculated based on the time the animal took to run from 60 cm to 40 cm along the treadmill. Speed for each training session is the average speed across its trials ([Figure 4.1J](#)). Furthermore, in [Figure 4.6B](#), we categorized the animals based on whether they had an effect on their running speed after the striatal lesion (black), or not (gray). Animals were assigned to the black group (Δ Speed< 0) if the average speed of 5 consecutive stable sessions after the lesion (i.e., session +8 to +13) were lower than that of 5 consecutive sessions before the surgery (i.e., sessions -5 to -1).

Definition of Frontal Trials Frontal trials are defined as trials in which the animal remained in the frontal portion of the treadmill (i.e., position < 30 cm) for the entire first 5 s after trial onset.

Speed Modulation Analysis In [Figure 4.4C-D](#), we split the trajectories that strictly followed the wait-and-run routine (see the definition of the Max. Pos.) into trials with the maximum position between 40 and 60 cm (Mid) and those between 70 and 90 cm (Back). The data was pooled from the last 5 sessions before ([Figure 4.4D, left](#)) and after ([Figure 4.4D, right](#)) the lesion. To improve the reliability, animals were discarded if they did not have at least 10 trials in the Mid and 10 trials in the Back condition (trials that strictly followed the wait-and-run routine, their maximum position was within the range, and for which the speed could have been defined). Fewer number of animals in the [Figure 4.4D, left](#) panel was due to the fact that most animals performed the wait-and-run routine by going all the way to the rear portion of the treadmill, thus not enough Mid trials existed.

Definition of Max. Pos. The maximum position an animal reached along the treadmill before initiating the run bout toward the reward in the wait-and-run routine was quantified as Max. Pos. in [Figure 4.6D](#). Therefore, Max. Pos. was only calculated for trials that strictly followed the wait-and-run routine, i.e., total immobility followed by continuous running until reaching the infrared beam. A trial was qualified if the following conditions were met:

- the animal started the trial in the front (initial position < 30 cm);
- the animal moved at least 10 cm backward (maximum position ≥ 40 cm);
- the animal remained still while being pushed backward by the treadmill (movements shorter than 0.1 s and slower than 5 cm/s were ignored to correct for jitter in position detection);

- the animal performed an uninterrupted running epoch (staying immobile or moving backward shorter than 0.1 s was ignored to correct for jitter in position detection);
- the animal completed the trial (i.e., it crossed the infrared beam).

Notice that compared to the definition of the routine trials, the threshold for maximum position in the second criterion is relaxed (40 cm, compared to 50 cm) to allow detection of trials with a reduced maximum position. To increase the reliability, any session with fewer than 10 trials for which Max. Pos. could be defined was excluded from further analysis. The reported value of Max. Pos. for each session is the average value across its trials ([Figure 4.6D](#)).

Normalizing Speed and Max. Pos. In [Figure 4.6B, D](#), to normalize each animal's performance according to its own behavior prior to the lesion, behavioral measures (speed and Max. Pos.) of individual animals during the illustrated sessions were subtracted from the median value of the respective measure during the pre-lesion sessions. Animals were included only if the behavioral measure could be defined in at least half of the illustrated sessions. Different n in panel D compared to B, and in panel B compared to the total number of animals ([Figure 4.1H](#)) is due to this criterion.

Chapter 3

Embodied Timing

To investigate how animals adapt their behavior to temporal regularities in their environment, we challenged Long-Evans rats in a treadmill-based behavioral assay that required them to wait for 7 s before approaching a “reward area”.ⁱ The treadmill belt was surrounded by long walls. The front wall was equipped with a device delivering rewards (a drop of sucrose solution) and an infrared beam, located 10 cm from this device, which defined the limit of the reward area (see [Figure 2.1a](#)). Animals were first familiarized with the apparatus and were trained to lick drops of the sucrose solution delivered every minute while the treadmill was immobile (see [section 2.1.3](#) for more details). Then, rats were trained once a day (Mondays to Fridays) for 55 minutes in the proper treadmill waiting task. Each daily session contained ~130 trials interleaved with resting periods of 15 s (intertrials, while motor was off). Each trial started by turning the treadmill motor on at a fixed speed of 10 cm/s. The conveyor belt moved toward the rear of the treadmill ([Figure 2.1a](#)). The **entrance time (ET)** of the animals in the reward area, detected by the first interruption of the infrared beam in each trial, relative to a **goal time (GT)** (7 s after motor onset) defined 3 types of trials:

ⁱThe materials related to time experiments in this document were largely borrowed from [\[133\]](#).

- Trials in which animals entered the reward area after the GT were classified as correct ($7 \leq ET < 15$, [Figure 2.1b](#));
- Trials in which animals entered the reward area before the GT were classified as error ($1.5 \leq ET < 7$, [Figure 2.1c](#));
- Trials in which in 15 s since trial onset, the animal failed to interrupt the infrared beam, the trial ended and was classified as omission ([Figure 2.1d](#)).

Interruptions that occurred during the first 1.5 s ($ET < 1.5$) were ignored (in other words, the infrared beam was not active during the first 1.5 s of trials) to allow the animals to leave (either passively or actively) the reward area at the beginning of each trial. Moreover, the exact value of the ET determined the reward/punishment ratio (see [section 2.1.4](#)). A punishment period of extra running started when the animals erroneously crossed the infrared beam before the GT ($1.5 \leq ET < 7$). The punishment duration varied between 10 s and 1 s, according to the error magnitude ([Figure 2.1c, inset](#)). In addition, to progressively encourage the animals to enter the reward area just after the GT, the smallest ET value that triggered reward delivery was raised across sessions, according to each animal's performance, until it reached the GT ([Figure 2.1b, inset](#) and see [section 2.1.4](#) for details). Thus, to maximize reward collection and minimize running time, animals should approach the reward just after the GT.

3.1 Treadmill Task

During the first training sessions, animals started most trials in the front of the treadmill, mostly ran in the reward area and interrupted the infrared beam before the GT ([Figure 3.1a, top, c, left](#)). Progressively, across training sessions, animals waited longer and after ~15 sessions, they reliably entered the reward area just after the GT ([Figure 3.1b](#)). Interestingly, for a large majority of animals, precisely waiting 7 s before entering the reward area was associated with the performance of a stereotyped motor sequence on

the treadmill ([Figure 3.1a, bottom, c, right](#)). This motor sequence (or routine) consists of the following steps:

- I. Animals began each trial in the reward area, i.e., they stayed in the reward area during the intertrials;
- II. When the trial started, they remained largely still while being pushed away from the reward area until they reached the rear wall;
- III. After reaching the rear wall, they ran across the treadmill, without pause, and crossed the infrared beam.

The percentage of trials for which animals used this motor routine increased during learning ([Figure 3.1d](#)). Even though a strong preference for the reward area was observed for both correct and error trials, the probability to start a trial in the front portion of the treadmill was higher for correct trials compared to error trials ([Figure 3.1e](#)), a tendency that developed progressively during training ([Figure A.1](#)).

In addition, if an animal started a trial in the front portion of the treadmill, the probability of reaching the back of the treadmill was higher in correct trials than in error trials ([Figure 3.1f](#)), further confirming that correct trials were mostly those in which the animals followed the wait-and-run routine and effectively reached the back of the treadmill before running forward toward the reward area. However, a significant fraction of the animals (14 out of 54) did not develop such a strategy ([Figure 3.1c, right](#), and [Figure A.2a](#)). Compared to these animals, those regularly following the wait-and-run routine entered the reward area later, demonstrated reduced variability, and an increased percentage of correct trials ([Figure A.2b-d](#)). Note that one cannot exclude the possibility that animals categorized as *other* in [Figure A.2](#) also used a more subtle stereotyped motor routine not captured by tracking the average body position along the treadmill length. Anyway, the above results suggest that following a front-back-front trajectory through the “wait-and-run” routine is the most reliable strategy to accurately respect the 7 s-rule of the task.

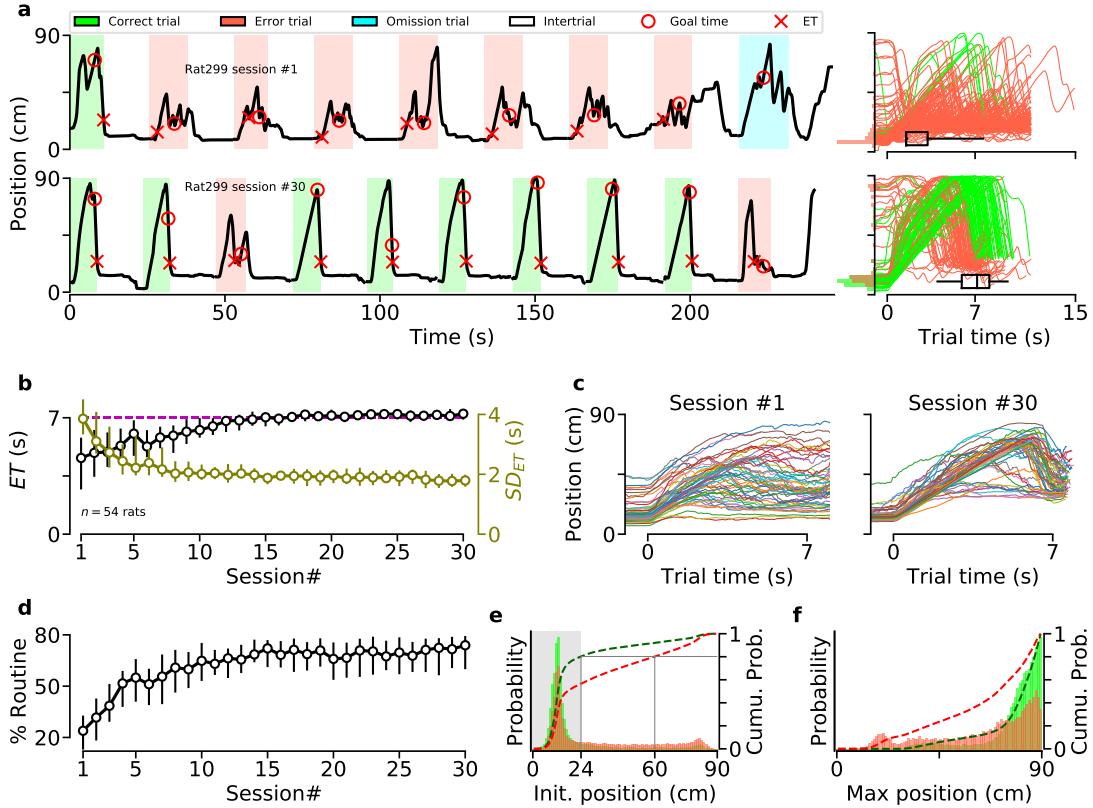


Figure 3.1: Animals developed a unique stereotyped motor sequence. **a)** *Left:* trajectory of a representative animal in 9 consecutive trials of the 1st (*top*) and 30th (*bottom*) sessions. On the y-axis, 0 and 90 indicate the treadmills front and rear wall, respectively. *Right:* trajectories for all trials of the corresponding sessions on the right. Distributions of initial positions for correct (green) and error (red) trials are shown on the y-axis. Black horizontal boxplots depict ET range (center line, median; box, 25th and 75th percentiles; whiskers, 5th and 95th percentiles). **b)** Median ET. Circles indicate group median and error bars, the median range (25th and 75th percentiles) across animals for ET and on the right y-axis, standard deviation of ET values. The magenta line shows the GT. **c)** Median trajectory for the 1st (*left*) and 30th (*right*) training sessions. Each line represents a single animal ($n = 54$). **d)** Percentage of trials in which animals performed the stereotyped routine. **e)** Probability distribution function (PDF) of the position of the animals at the beginning of each correct (green) and error (red) trial, from sessions #20 to #30. Dashed lines represent cumulative distribution functions (right y-axis). The gray area indicates that in trained animals, 80% of correct trials began with the animal located near the front of the treadmill. **f)** PDF of the maximum position along the treadmill. Only trials in which animals were initially located in the front of the treadmill (gray area in panel e) were included.

3.2 Variable Speed Condition

It could be argued that task parameters (length of the treadmill, its speed, position of the infrared beam,...) favored the development of this stereotyped strategy. Indeed,

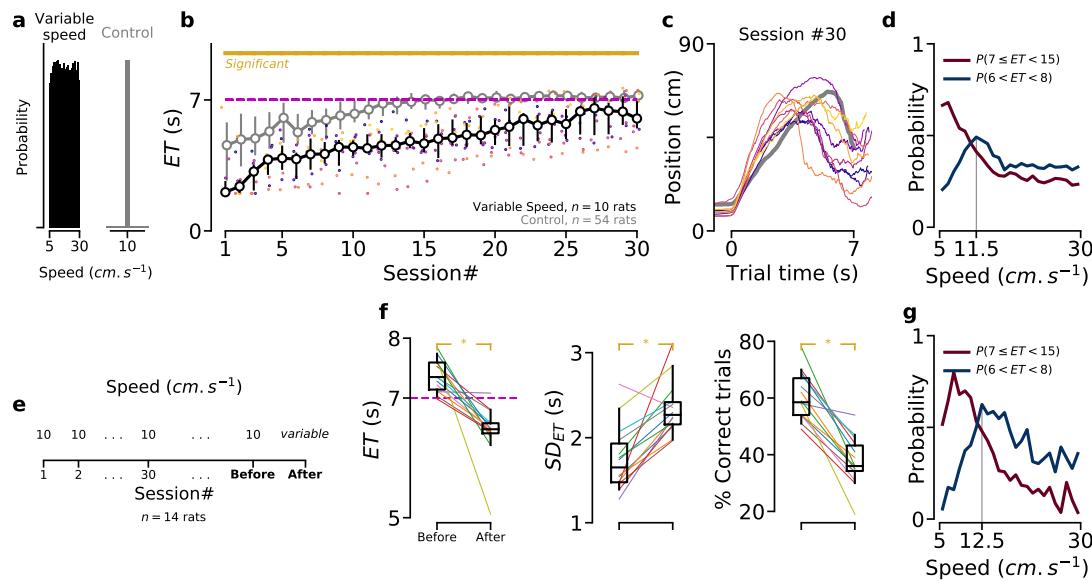


Figure 3.2: Decreased temporal accuracy when the treadmill speed randomly changed every trial. **a)** For each trial, treadmill speed was either fixed at 10 cm/s (control condition, same data as in Figure 3.1), or randomly selected from a uniform distribution between 5 and 30 cm/s (variable speed condition). **b)** Median ET for animals trained in the variable speed (black), and control (gray) conditions. Colored dots indicate individual “variable speed” animals. Golden line in this manuscript shows statistically significant differences between groups (permutation test). **c)** Median trajectory of variable speed animals in session #30 (same colors as in panel b). **d)** Probability of correct ($7 \leq ET < 15$ s) and precise ($6 < ET < 8$ s) trials, given the treadmill speed, for variable speed animals (session # ≥ 20). **e)** After extensive training in the control condition, some animals ($n = 14$) were tested in a probe session with variable speed. **f)** Median ET (left), SD of ET (middle), and percentage of correct trials (right) in the sessions before and after the change in the speed condition. Each line represents a single animal. Asterisks indicate significant differences (non-parametric paired comparison). **g)** Similar to panel d, for the data collected from the probe session.

depending on the initial position of the animal body at trial onset, it can take up to 7 or 8 seconds for the animals to passively reach the back of the treadmill (Figure 3.1a) after which they can start running toward the reward area without the need to estimate time at all! Thus, in the following experiments, we examined how accurately animals respected the GT, when distinct task parameters were modified in a way that hampered the use of this simple wait-and-run motor routine. First, we trained a new group of rats in a version of the task in which, for each trial, the speed of the treadmill was randomly selected from a uniform distribution between 5 and 30 cm/s (Figure 3.2a). We found that,

during the course of training, these animals consistently failed to wait as long as the animals trained in the control version of the task ('control' group, [Figure 3.2b](#)). Still, the average trajectories of animals extensively trained in this "variable speed" condition revealed that they followed a front-back-front trajectory ([Figure 3.2c](#)). Accordingly, the probability of performing a correct trial, given different speeds, fell rapidly from 5 to ~15 cm/s and was lowest for the fastest treadmill speeds ([Figure 3.2d](#)). Indeed, it shows that when the treadmill speed was fast, performing the wait-and-run strategy resulted in error trials, as animals reached the back region of the treadmill earlier, compared to when the treadmill speed was slow. Interestingly, we also found that the probability of precise approaches, i.e., entering the reward area at the GT ± 1 s sharply peaked for a treadmill speed (11.5 cm/s) that is suitable to perform the wait-and-run motor sequence ([Figure 3.2d](#), notice that this speed is very close to the speed in the control condition). Finally, when rats, extensively trained in the control version of the task, underwent a single probe session with variable speed ([Figure 3.2e](#)), all measures of performance dropped significantly ([Figure 3.2f](#)). Examining the probability of correct trials and precise approaches given the treadmill speed resembled those of animals well-trained in the variable condition and suggested that rats kept performing the wait-and-run routine they previously learned in the control condition (compare [Figure 3.2g](#) and [Figure 3.2d](#)).

3.3 No-Timeout Condition

In the control condition, ~80% of correct trials started while animals were in the reward area ([Figure 3.1e](#)). If rats relied on an internal clock-based algorithm to accurately time their entrance in the reward area, they should adapt relatively easily to a perturbation in their initial starting position. To test this prediction, we trained a group of rats in a modified version of the task that penalized starting the trials in the front region of

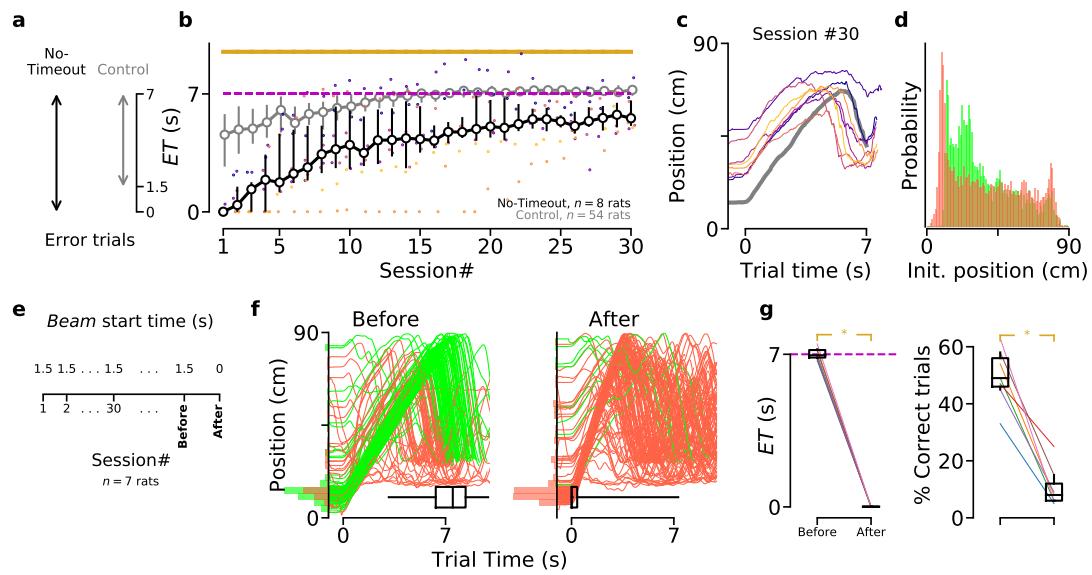


Figure 3.3: Decreased temporal accuracy when animals are punished for starting trials in the reward area. **a)** In the control condition, animals had a 1.5 s timeout period to leave the reward area after motor onset. In the “no-timeout” condition, crossing the infrared beam any time before 7 s registered as an error trial. **b)** Median ET for animals trained in the no-timeout (black), and control (gray) conditions. Colored dots indicate performance for individual no-timeout animals. **c)** Median trajectory of no-timeout animals (same colors as in panel b) in session #30. **d)** PDF of the no-timeout animals’ positions at the beginning of each trial, from sessions #20 to #30. **e)** After extensive training in the control condition, animals ($n = 7$) were tested in a no-timeout probe session, in which the beam started at the beginning of the trial, rather than 1.5 s later. **f)** Trajectories of a representative animal in the last control session (*left*), and the probe session (*right*). **g)** Median ET (*left*), and percentage of correct trials (*right*) in the sessions before and after the change in beam start time. Each line represents a single animal. Asterisks indicate significant differences (non-parametric paired comparison).

the treadmill. This was done by activating the infrared beam as soon as the motor was turned on, i.e., the trial start. Opposite to the control condition that the infrared beam was initially inactive for a **timeout** period that lasted 1.5 s after treadmill onset to allow the animals to be carried out of the reward area by the conveyor belt. In this “no-timeout” condition, error trials corresponded to ETs occurring between 0 and 7 s after motor onset (Figure 3.3a). Animals trained in this condition never reached the level of timing accuracy displayed by animals in the control condition (Figure 3.3b). Still, no-timeout animals followed a front-back-front trajectory (Figure 3.3c) and correct trials were associated with the animals starting the trials just behind the infrared beam (Figure 3.3d).

The stereotyped reliance on the wait-and-run strategy was also demonstrated by the fact that rats extensively trained in the control condition kept performing the exact same trajectory when tested in a single probe session under the no-timeout condition, leading to many error trials and punishments ([Figure 3.3e-g](#)).

3.4 Short Goal Time and Sharp Reward Conditions

We next examined how animals behaved when the GT was set to 3.5 seconds ([Figure 3.4](#)), a condition in which the performing the wait-and-run strategy would lead to late ETs (and smaller rewards, and more running time), because it can take up to ~8 s for animals to passively travel from the front to the rear portion of the treadmill. Animals successfully entered the reward area after 3.5 s and reduced their variability across training sessions ([Figure 3.4a](#)), but as a group, they demonstrated an elevated ET variability compared to animals trained in the control condition, with GT set to 7 s ([Figure 3.4e](#)). From the averaged trajectories of “short GT” animals measured once their performance plateaued, it appeared that 3 subjects out 7 followed a front-back-front trajectory by running toward the rear portion of the treadmill. The other 4 animals remained still when the treadmill started and accelerated forward before reaching the rear wall ([Figure 3.4b](#)). Interestingly, after training, in 67% of the error trials, the rats started running forward before reaching even the middle of the treadmill ([Figure 3.4c](#), compared to the red histogram in [Figure 3.1f](#)). Conversely, after initiating a trial in the reward area, the probability of visiting a deeper portion of the treadmill was much stronger in correct than error trials, reinforcing the idea that accurate timing was accomplished by exploiting the most salient physical features of the environment, i.e., touching the rear wall ([Figure 3.4c](#)). Accordingly, the 3 rats that followed the front-back-front trajectory by running toward the back were less variable than those that passively stayed still before running toward the reward area from the middle of the treadmill.

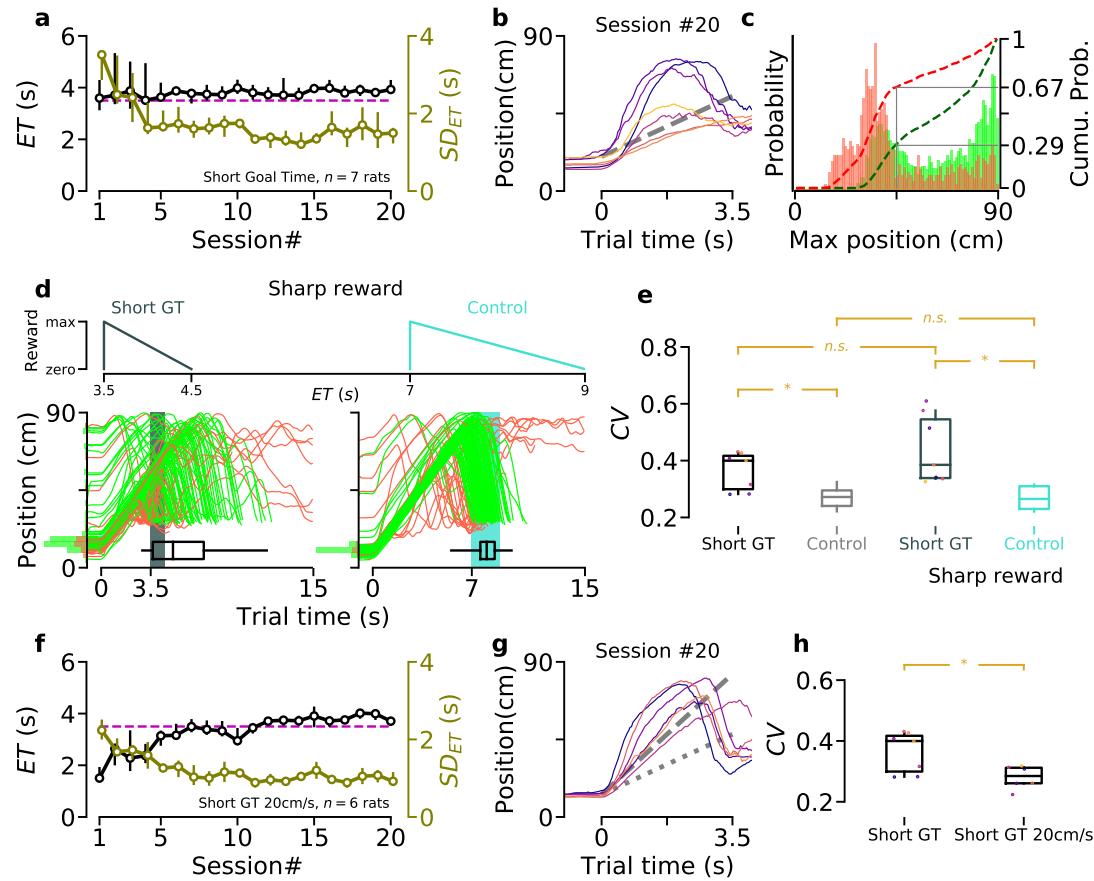


Figure 3.4: Decreased temporal accuracy when the goal time is short. **a)** Median ET during training (GT = 3.5 s). **b)** Median trajectory of “short GT” animals after training. Dashed line’s slope shows the treadmill speed (10 cm/s). **c)** PDF of the maximum position of the short GT animals for correct (green) and error (red) trials. Dashed lines represent cumulative distributions (right y-axis). Data collected from session # \geq 15. **d)** Sharp reward condition applied to short GT and control experiments. *Top:* reward profiles of the sharp reward condition in the short GT (dark) and the control experiments (light). *Bottom:* trajectories of 2 illustrative sessions after extensive training in sharp condition (*left*, short GT; *right*, control). Highlighted areas indicate the reward window. **e)** Coefficient of variation (CV) for short GT and control experiments with normal (the first two boxes), and sharp (the last two boxes) reward profiles. Data collected and averaged once performance plateaued. Short GT vs. Control: $p < 0.0001$; Sharp short GT vs. Sharp control: $p < 0.0001$. **f)** Similar to panel a, for another group of animals trained to wait 3.5 s while the treadmill speed was 20 cm/s. **g)** Similar to panel b, for animals of panel f. Dashed line’s slope shows the treadmill speed (20 cm/s). Dotted line’s slope shows 10 cm/s. **h)** CV for short GT and short GT at 20 cm/s conditions (same colors as in panels b, g). Data collected and averaged once performance plateaued.

(Figure 3.4e, same color code as in panel b). In addition, among animals trained in the short goal time condition, we found that the magnitude of the backward displacement

on the treadmill was negatively correlated with ET variability ($r = -0.49, p = 2.7 \times 10^{-3}$, Pearson's correlation).

In the short GT condition, animals became proficient more rapidly than in the control condition (compare [Figure 3.4a](#) with [Figure 3.1c](#)). However, their variability remained similar, which is why short GT animals have a higher coefficient of variation ([Figure 3.4e](#)). The increased ET variability when the GT is 3.5 s may be explained by the fact that the task is generally easier in this condition and that animals do not need to be very precise. To test this possibility, we increased the punishment for error trials and decreased the reward size for late ETs. In this “sharp reward” condition, the performance of the animals trained with the short GT was even more variable, while animals trained in the control experiment managed to adapt and perform with similar accuracy ([Figure 3.4d-e](#)). This result confirms that under short GT condition animals can not accurately time their entrance in the reward area, even when exposed to harsher punishments.

Finally, another group of animals was trained with GT set to 3.5 s and treadmill speed set to 20 cm/s (i.e., twice as fast as in the control condition). This experiment once again provided the animals with an *easy* wait-and-run motor strategy that would result in ETs close to the GT ([Figure 3.4f](#)). Expectedly, after treadmill start, these animals stayed immobile until reaching the end of the treadmill, utilizing the aforementioned strategy, similar to the animals trained in the control condition ([Figure 3.4g](#)). Higher treadmill speeds usually should be regarded as less comfortable, nonetheless these animals displayed reduced ET variability compared to the animals trained at 10 cm/s ([Figure 3.4h](#)).

3.5 Immobile Treadmill Condition

The above results suggest that, in a task requiring animals to produce a motor response according to a fixed temporal constraint, the possibility to perform a stereotypical motor sequence adapted to salient features of the environment (here, taking advantage of the full treadmill length and its physical boundaries) critically determines temporal accuracy. However, it could still be argued that by starting the treadmill motor and moving the animals in a certain direction, we are priming them to develop a stereotyped motor response. Although the short GT condition was designed to remedy that, it still had a moving belt. To further de-bias our approach, we trained a group of animals in a version of the task in which the treadmill never started (trial onset was signaled by switching the ambient light on). In this condition, animals displayed a strong impairment in respecting the GT, compared to animals trained in the control condition, to the degree that a few of the animals did not show signs of learning even after extensive training ([Figure 3.5a, b](#)). On average, animals entered the reward area later and later across sessions, but displayed a constant high variability in ET ([Figure 3.5c](#)), as opposed to learning in the control condition that is accompanied by both increasing ETs and falling variability ([Figure 3.1b](#)). Interestingly, we noticed that correct trials preferentially occurred when animals crossed the treadmill from the rear wall to the reward area, as evident in [Figure 3.5a, d, e](#). Moreover, after extensive training, a robust correlation was observed between the percentage of correct trials and displacement of the animal on the treadmill ([Figure 3.5f](#)). In other words, more locomotor activity was associated with better timing performance. In a related analysis, we showed that the probability of a correct trial given different displacement values is an ascending function ([Figure 3.5g](#)). For example, chances of doing a correct trial without much displacement (i.e., ≤ 10 cm) are ~ 0.1 , while the three rats that performed trials with over 100 cm displacement on the treadmill, succeeded almost 80% of the time.

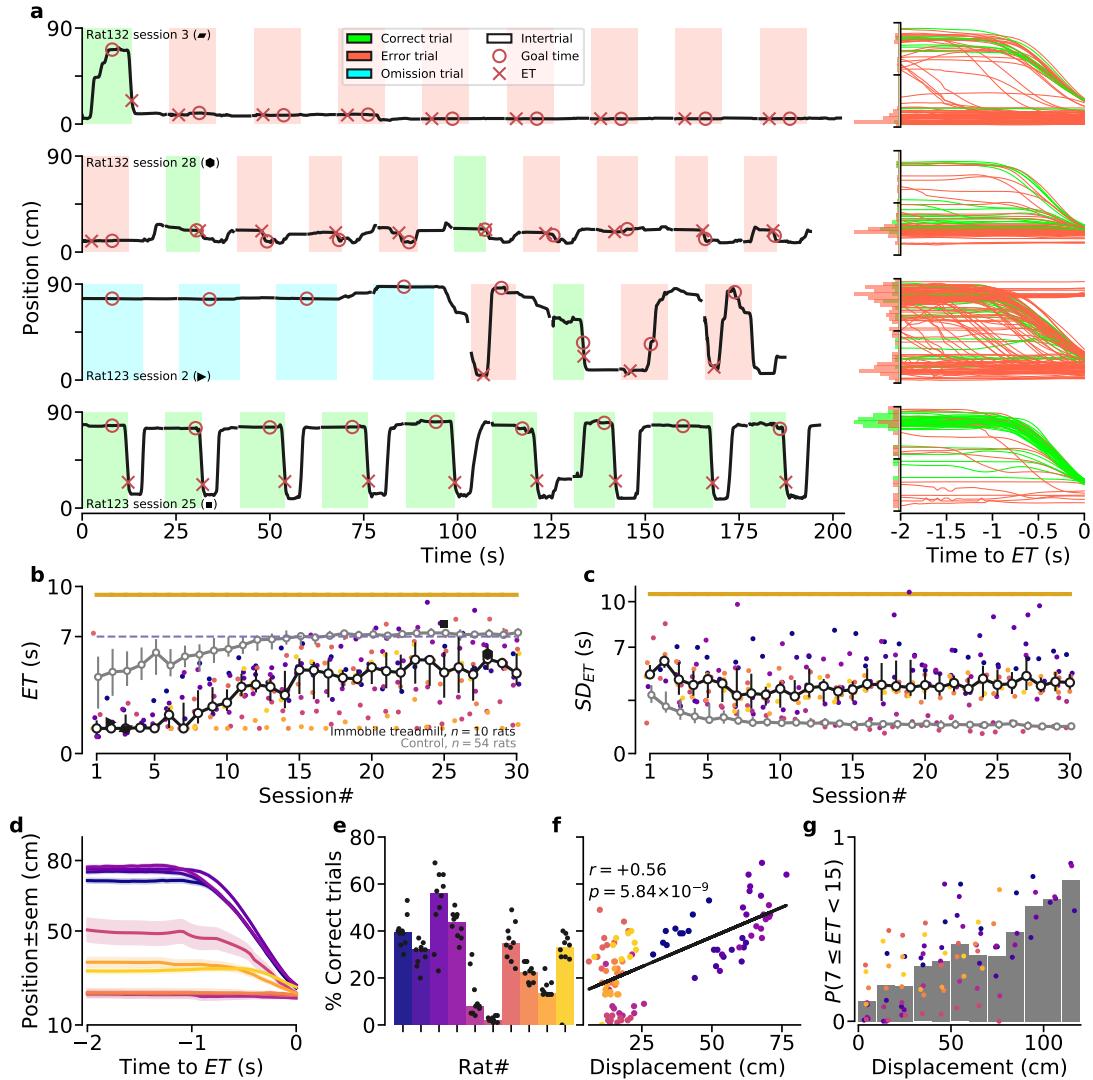


Figure 3.5: Performance of animals trained while the treadmill remained immobile. a) Left: trajectory illustrations of two animals on the immobile treadmill, early (1st row: Rat #132-session #3, 3rd row: Rat #123-session #2) and late (2nd row: Rat #132-session #28, 4th row: Rat #123-session #25) during training. Right: trajectories for all the trials of the corresponding sessions on the left, aligned to the ET. **b)** Median ET across sessions for “immobile treadmill” animals. Filled black markers correspond to the sessions illustrated in panel a. **c)** Similar to panel b, for the SD_{ET}. **d)** Median correct trial trajectory aligned to ET of each immobile treadmill animal (from sessions #20 to #30; shaded area denotes standard error). **e)** Median percentage of correct trials for each animal. Each dot represents one session. **f)** Repeated measures correlation between the percentage of correct trials and average displacement during a session. Each dot represents one session. Correlation statistics: $r = +0.56$, $p = 5.84 \times 10^{-9}$. **g)** PDF of a correct trial, given the displacement of an animal. Each bar represents the average probability for an individual animal, during a single session. (e-g) Analyses include the same sessions as in panel d. Individual animal color code is preserved in panels b-g.

Lastly, animals well-trained in the immobile treadmill condition during several weeks were then challenged in the control condition—by simply setting the treadmill speed at 10 cm/s. These animals improved their behavior at the same pace and with the same wait-and-run routine as naïve animals (Figure A.3a-c). Thus, animals that previously learned to wait in one version of the task did not learn faster than naïve animals when challenged in a second version of the task with distinct movement requirement but an identical temporal constraint. This, once again, demonstrated that task proficiency relied primarily on the acquisition of a motor sequence, rather than an abstract knowledge of time that would be transferable among different versions of the task.ⁱⁱ

ⁱⁱI naturally tried to test the opposite experiment as well. I passed a few animals, well-trained in the normal treadmill task, to the immobile task. However, it proved to be futile! Animals used to run on a moving treadmill found an immobile one boring and after a while fell asleep on it.

Chapter 4

Striatum and Effort

In the last chapter, I presented many experiments, all in support of the hypothesis that time estimation is embodied and that accurate timing requires stereotyped interaction with the environment. Stereotyped interactions appear as motor routines to the external observer, e.g., the superstitious behavior of pigeons ([section 1.3.1](#)) and the wait-and-run routine of rats ([chapter 3](#)). Thus, the question of how the brain measures the elapsed time is translated to how the brain generates or controls motor routines. In this study, we focused on the striatum, the main input nuclei of the basal ganglia (BG), since its motor-related functions are long-reported, well-known, and still debated.ⁱ We took advantage of the motor routine developed by the animals in the treadmill task, i.e., the wait-and-run motor routine ([Figure 3.1d](#)) to investigate the role of the striatum in performing and controlling the kinematics of motor routines.

To obtain a drop of sweetened water, rats had to wait for a fixed goal time (GT) of 7 s from trial onset before entering the reward area located at the front of the treadmill, while the belt was slowly moving backward ([Figure 4.1A](#)). Across training sessions, each composed of ~130 trials, animals learned to wait longer and longer to enter the reward area just after the GT and achieve higher percentage of correct trials ([Figure 4.1B](#), and

ⁱThe materials related to striatal function in this document were largely borrowed from [134].

[Figure A.4](#)). Task proficiency was clearly associated with the acquisition and reliable performance of the following routine ([Figure 4.1C](#)):

- I. during the intertrial, following the consumption of the reward, rats remained in the reward area;
- II. when the treadmill was turned on (trial onset), they did not move and let the belt carry them away from the reward area;
- III. when they reached the rear wall of the treadmill, they started outrunning the opposing treadmill to reenter the reward area, i.e., the entrance time (ET) just after 7 s (ET \geq GT).

After 2–3 weeks of daily practice, rats used this wait-and-run routine in about 75% of the trials ([Figure 4.1C](#), see [section 2.3](#) for the operational definition of this routine). Finally, learning this routine was paralleled by a robust invigoration of the running phase of the motor routine toward the reward area ([Figure 4.1D](#)).

4.1 Striatal Lesion

Once the performance was stable, after at least 30 training sessions, we performed fiber-sparing lesions of the striatum ($n = 57$ animals, for the lesion protocol, see [section 2.2.1](#)). The lesions targeted either the dorsolateral striatum (DLS) or the dorsomedial striatum (DMS), or both territories, the entire dorsal striatum (DS) ([Figure 4.1E-G](#), see also [Figure 2.2](#)). Behavioral testing resumed two weeks after the lesion surgery. Visually, the animals had normal behavior (locomotion, food/water intake) in their homecage at the end of the recovery period.

After the lesion, the behavior of the animals could be divided into an ‘acute’ phase in the first few sessions post-lesion, and a ‘stable’ phase that begins ~9 sessions after the lesion and persists. This dichotomy does not apply to every animal, apparently animals with bigger lesions have a stronger acute effect. This can be seen in example animals of

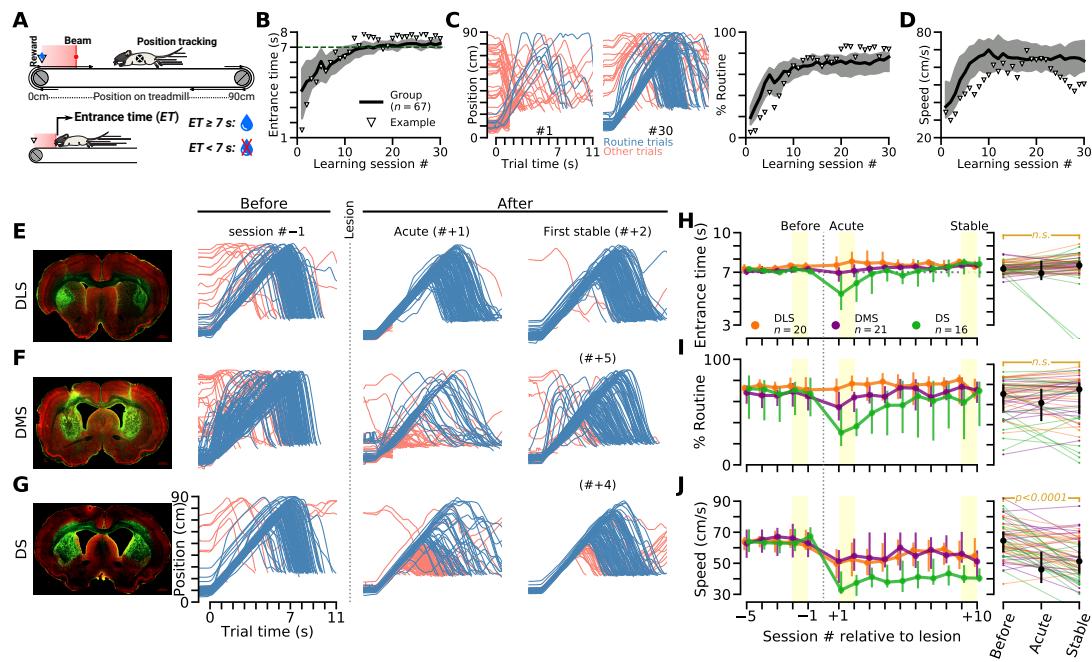


Figure 4.1: The dorsal striatum is necessary to invigorate the running component of a motor routine. A) Experimental apparatus and task rules, also refer to Figure 2.1. **B)** Median ET across training sessions for all the rats trained in this task. Shaded area represents the 25th and 75th percentiles. Triangular markers in panels B to D indicate the performance for the example animal whose trajectories are shown in panel C, left. **C)** Trajectories of an example animal on the treadmill, for all the trials performed in sessions #1 and #30 (*left*). Percentage of trials during which animals performed the wait-and-run routine, across training sessions (*right*). **D)** The running speed with which animals ran toward the reward area, across training sessions. **E-G)** Histology (*left*, GFAP in green shows gliosis, red is NeuN) and trajectories of single animals with bilateral lesions of the striatum (*right*) in sessions before and after the lesion. '#' indicates session number relative to the lesion operation. **H-J)** *Left:* time course of the lesion effect on behavioral measures. *Right:* statistical comparison of the group data before vs. (long) after the lesion (10000 resamples). Trajectory plots in panels C, and E-G are cut at the ET.

Figure 4.1F, G, and at the population level in Figure 4.1H, however, the case illustrated in Figure 4.1E is an example of a rat with smaller lesion and no acute condition. To better visualize the acute effect, I grouped the first two post-lesion sessions and presented their average statistics throughout this manuscript. Similarly, sessions +9 and +10 were also grouped to represent the stable effect of the lesion. Animals with this acute effect ran toward the reward area prematurely after trial onset and, consequently, a drop in the usage of the wait-and-run routine was observed during these first post-lesion

sessions ([Figure 4.1I](#)). Surprisingly, most of these animals recovered from this initial impairment and after a few additional sessions, task proficiency was similar to the pre-lesion level ([Figure 4.1H-I](#), right panels, compare the stable condition to the ‘before’ condition). Moreover, for most of the animals with a lesion restricted to the DLS and DMS, task proficiency was virtually unaltered when resuming behavioral testing. We then looked at animals’ speed (see [section 2.3](#) for the technical definition), the velocity with which they outran the opposing treadmill in the third step of the wait-and-run motor routine. Strikingly, the animals’ speed was irreversibly reduced following striatal lesion ([Figure 4.1I](#)). This was not the case when animals were given just a break of the same duration as the lesion recovery period ([Figure A.5](#)). In addition, the difference in speed after the lesion was strongly correlated with the size of the lesion ([Figure A.6A](#)). Moreover, the maintained task proficiency following striatal lesion suggested that the motivation of the animals to perform the task and to obtain rewards was preserved. In agreement with this statement, animals with a striatal lesion kept licking the reward after committing correct trials ([Figure 4.2A](#)). The number of times they licked after a reward delivery and also their peak lick frequency was not affected ([Figure 4.2C-D](#)). However, they systematically started to lick later ([Figure 4.2B](#)). Much like the speed, this effect was also irreversible, and might be a measure of slower speed in approaching the reward port after crossing the infrared beam (which is ~10 cm from the reward port), or slower postural adjustments to consume the delivered reward. Thus far, these results suggest that the striatum is selectively critical for the invigoration of the reward-oriented active component of the wait-and-run routine.

4.2 Spared Routine Execution

What was the reason for the acute effect right after the break? At this stage, we can not rule out that the transient impairment in performance induced by large striatal

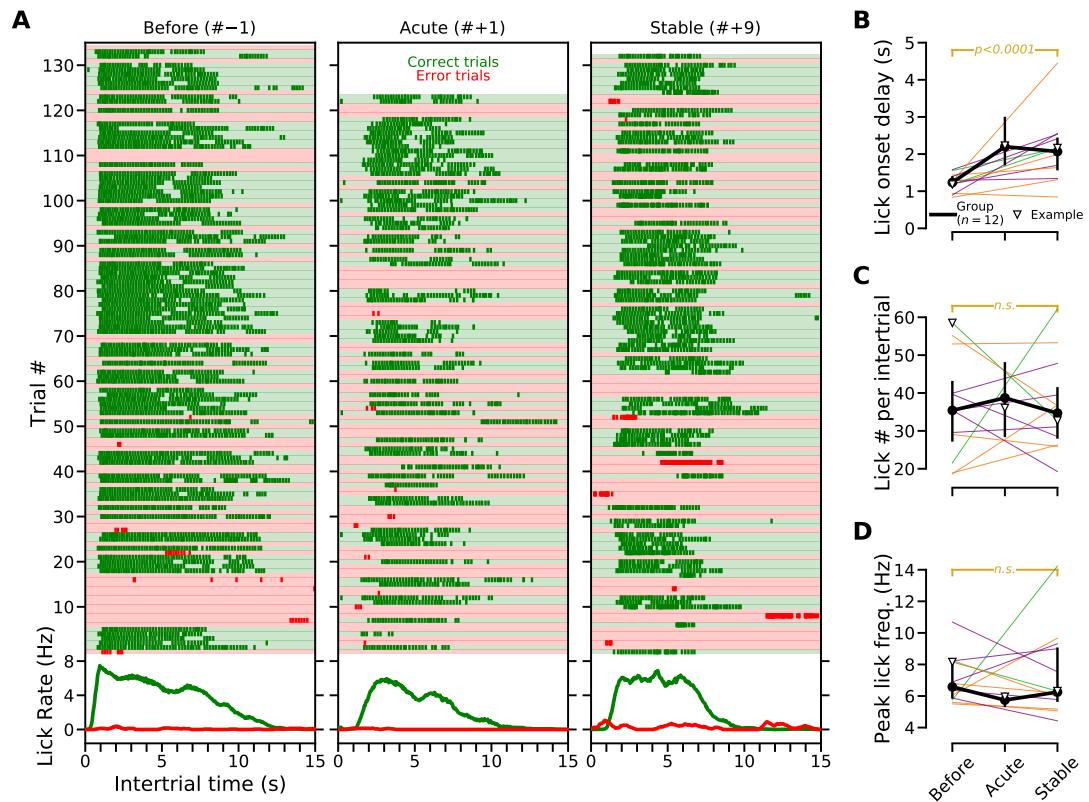


Figure 4.2: Licking behavior mostly unaffected by the striatal lesion. **A)** Trial-by-trial licking pattern (*top*) and averaged lick rate aligned to intertrial onset for a single animal in 3 sessions (1 just before and 2 after lesion). Each tick shows one lick in the reward delivery port. **B-D)** Effect of striatal lesion on lick onset delay (*B*), number of licks per intertrial (*C*) and peak licking frequency (*D*). Same color code for individual lesion type as in [Figure 4.1](#).

lesions reflects deterioration of the motor routine and reversal to the behavior expressed before routine acquisition, i.e., staying in the front, possibly to get the reward (see [Figure 3.1e](#) and [Figure A.1](#)). This impairment then could have been compensated in subsequent post-lesion sessions through a striatum-independent learning process. To test this hypothesis we modified the task such that the treadmill belt moved slowly toward the reward area, instead of away from it. This configuration, hereafter called the ‘reverse’ treadmill, allows the animals to locomote to the back of the treadmill during the intertrial while the treadmill is not moving, stay still upon trial onset and be passively transported to the reward port at the right time ($ET \geq GT$). Such a “run-and-

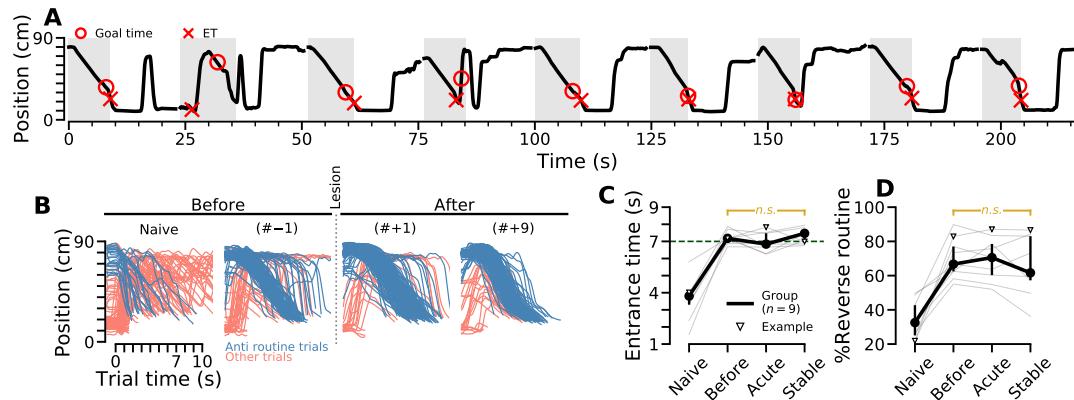


Figure 4.3: Striatal lesion spared the performance of a motor routine. **A)** Trajectory of a proficient animal trained in a version of the treadmill task in which the belt moved toward the reward area (rather than away from it, see section 2.1.6). 9 consecutive trials (shaded areas) and intertrials (white areas) are shown. **B)** Trajectories from a single representative animal in two sessions before and two sessions after lesion. **C-D)** Comparison of ET (C) and percentage of the “run-and-wait” (reverse) routine usage (D), before and after DLS lesion.

“wait” motor routine is qualitatively comparable to the original wait-and-run routine, and critically, initiates in the back of the treadmill, hence we can dissociate routine initiation from reversal to the behavior expressed before routine acquisition. Another group of animals were trained in this version of the task and learned to proficiently perform the task by adopting the run-and-wait routine described above (Figure 4.3A). That is, after extensive training, animals were in the back of the treadmill at trial onset in a bigger fraction of the trials. If the striatal lesion abolished the ability to perform this motor routine, we expect animals to start the trials close to the reward area, at least in the first post-lesion sessions. On the contrary, the performance of the run-and-wait routine was spared by striatal lesions (Figure 4.3C-D). It is noteworthy that lack of effect of the striatal lesion on the performance of the motor routine could be due to the fact that learning the reverse treadmill task was easier than the normal treadmill task, thus the relearning procedure might have happened during the very first session after the lesion. This is unlikely to be the case since initial learning of the reverse treadmill task took a similar curve compared to that of the normal treadmill task (Figure A.7).

Altogether, these results indicate that the striatum is not required to initiate or execute the sequential steps of the learned motor routine, but it is critical to invigorate its reward-oriented running phase.

4.3 Intact Motor Function

To better understand the origin of this vigor deficit, we examined whether striatal lesions affected elementary motor abilities of the animals. First, we tested basic locomotor activity in a novel environment without any rewards. We tracked their position during the first 10 min of exploration in a novel treadmill (without any food or water restriction prior to this test, see [section 2.1.7](#) for more details). Rats with DLS lesions had an identical amount of displacement on the treadmill compared to the control ones ([Figure 4.4A](#)). Thus, basic locomotion is spared by lesion of the striatum. Then, we aimed to examine whether lesioned animals have the ability to outrun the treadmill, i.e., run faster than ~10 cm/s. We progressively increased the treadmill speed across 30 s long trials, interleaved by 30 s long intertrials. Same groups of animals as in the last test ($n = 12$ rats in each group) performed similarly in this free running task ([Figure 4.4B](#)). Therefore, lesioned animals are able to run at speeds much faster than 10 cm/s if they are forced to. Of note, the average speed of animals with a striatal lesion during the trials was similar to normal rats, but only for slower treadmill speeds. In trials in which the treadmill moved faster than 20 cm/s, even though lesioned rats managed to keep running, their speed had the tendency to be marginally slower than control animals. This effect mimics the overall tendency of the animals to ‘choose’ a slower pace, be it in approaching the reward area or starting to lick the available reward. Next, we dived into the speed profile of the animals to investigate the essential ability of modulating the running speed. We compared their running speed in trials in which the running epoch was initiated from the rear portion of the treadmill, versus the middle of the

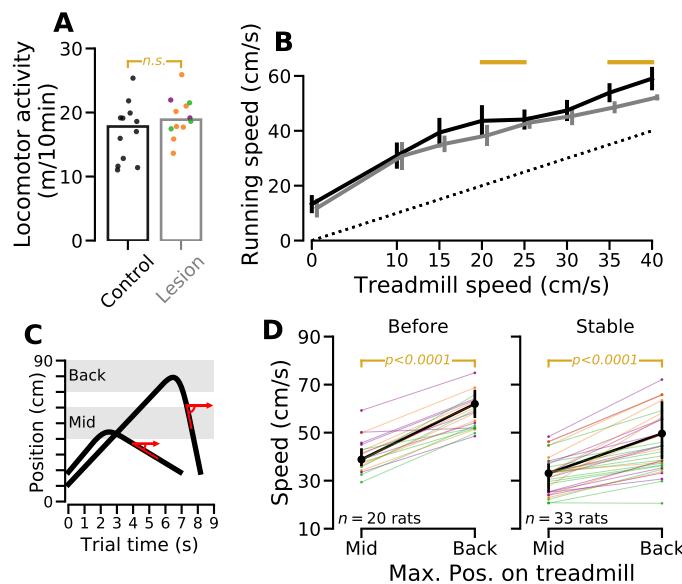


Figure 4.4: Preserved spontaneous locomotor activity and modulation of running speed following striatal lesion. **A)** Displacement while exploring a new (and immobile) treadmill for non-lesioned (control, $n = 12$) and lesioned rats ($n = 12$, same color code for individual lesion type as in Figure 4.1). **B)** Average running speed in a free running task (no reward) in which control and lesioned rats were submitted to trials with incremental treadmill speed (same color code as in panel A, see section 2.1.7). Golden lines indicate significant differences between groups (corrected for multiple comparisons). **C)** Trials were split into 2 categories depending on whether rats initiated their run from the middle or back portion of the treadmill. Speed was computed and averaged across trial type for sessions with stable performance. **D)** Speed of the runs initiated from either the middle or back portion of the treadmill, and calculated for each animal over the last 5 sessions before lesion (*left*) and the last 5 stable sessions after lesion (*right*).

treadmill (in Figure 4.4C: Back vs. Mid). Non-lesioned animals ran faster when they initiated their runs from the back of the treadmill (Figure 4.4D). Interestingly, this modulation, too, was maintained after striatal lesions, although running speeds were generally slower following the lesion.

4.4 (Mostly) Preserved Routine Learning

Our results indicate that the striatum is not required for the execution of motor routines (at least those similar to the wait-and-run), rather it is influencing kinematics of learned

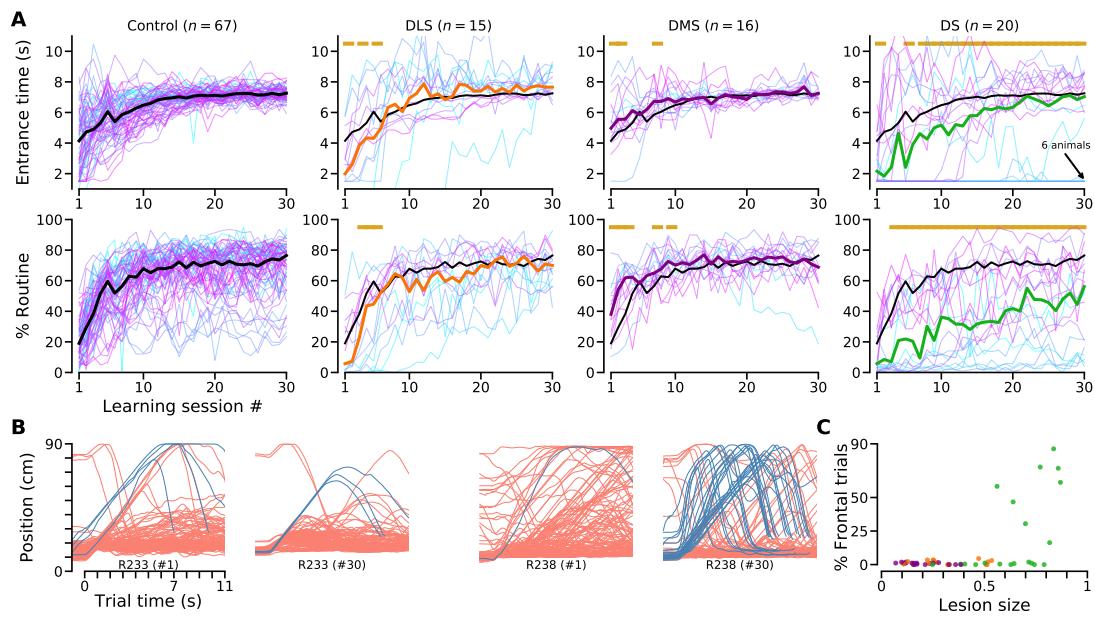


Figure 4.5: Learning the task is preserved in naïve animals with striatal lesions. **A)** Session-by-session improvement in performance for animals without lesion (control, *first column*) and for animals that received a lesion prior to training (*second to last columns*). Black lines indicate the control group median. Thin colored lines indicate single animals. Thick colored lines (same color code as in [Figure 4.1](#)) in 3 rightmost columns indicate group performance for comparison (8 lesion animals with fewer than 30 training sessions are not shown, which explains the difference in the number of animals in this figure and in [Figure 2.2](#)). Horizontal golden lines indicate significant differences between control and lesion groups (corrected for multiple comparisons). Notice that several animals with entire DS lesions fail to improve their performance. **B)** Trajectories before and after extensive training (sessions #1 and #30) for two animals with large DS lesions. Note that, after extensive practice, R238 was capable of performing the wait-and-run routine. Trajectory color code is the same as in [Figure 4.1](#). **C)** Percentage of trials in which animals remained in the front region of the treadmill (computed for sessions #25 to #30) versus their lesion size.

behaviors. Performing striatal lesion prior to learning the task, i.e., in naïve animals, further confirmed earlier results. We found that striatal lesions performed in naïve rats did not compromise their ability to learn the wait-and-run routine ([Figure 4.5A](#)). Both groups of animals, with lesion in either DLS or DMS, learned the task with similar profile to control (non-lesioned) rats. Those animals with lesion in the entire DS, however, showed a different trait. A few of them with relatively larger lesion, failed to display performance improvement ([Figure 4.5A](#)). All of these animals ran most of the time

in the front region of the treadmill ([Figure 4.5B, C](#)). The rest of this group, similar to the DLS and DMS groups, eventually improved their performance. In animals with striatal lesion performed before training, a robust reduction of running speed was also observed, an effect that was correlated with lesion size as well ([Figure A.6B](#)).

4.5 Effort, The Underlying Mechanism

Since the striatal lesion spared the rats' ability to learn the motor routine, execute it, and modulate their running speed, the most parsimonious account of our results is that lesioned animals 'preferred' slower speeds. We took advantage of the optimal control framework that relies on the assumption that animal behavior is optimal with respect to a cost function. A simple model was implemented to simulate the optimal trajectory taking into account costs related to energy expenditure (effort) and those imposed by the task rules (running in the front is costly as it leads to premature ET, which is punished). Four cost functions were used to model speed/force-based effort, and localized/diffuse penalty related to staying in the front of the treadmill (see [[134](#)] for more details). We found that higher effort sensitivity, regardless of exact cost function parameters, resulted in optimal trajectories with smaller "maximum position", i.e., earlier run-phase initiation ([Figure 4.6A](#)). Hence, combination of late initiation of the run-phase together with fast running speeds was not used. This result is not only in agreement with the reduced running speed observed following the lesion, but is also reminiscent of the behavior observed during the very first post-lesion sessions, when animals with larger DS lesions ran mainly close to the reward area ([Figure 4.1F, G](#), and also [Figure A.8](#)). We thus reanalyzed the effect of striatal lesion on the trajectory, focusing on animals with a significant reduction in running speed ([Figure 4.6B](#)). We also limited the analysis to trials during which animals perfectly executed the wait-and-run routine, since those are the trials for which defining the maximum position is relevant.

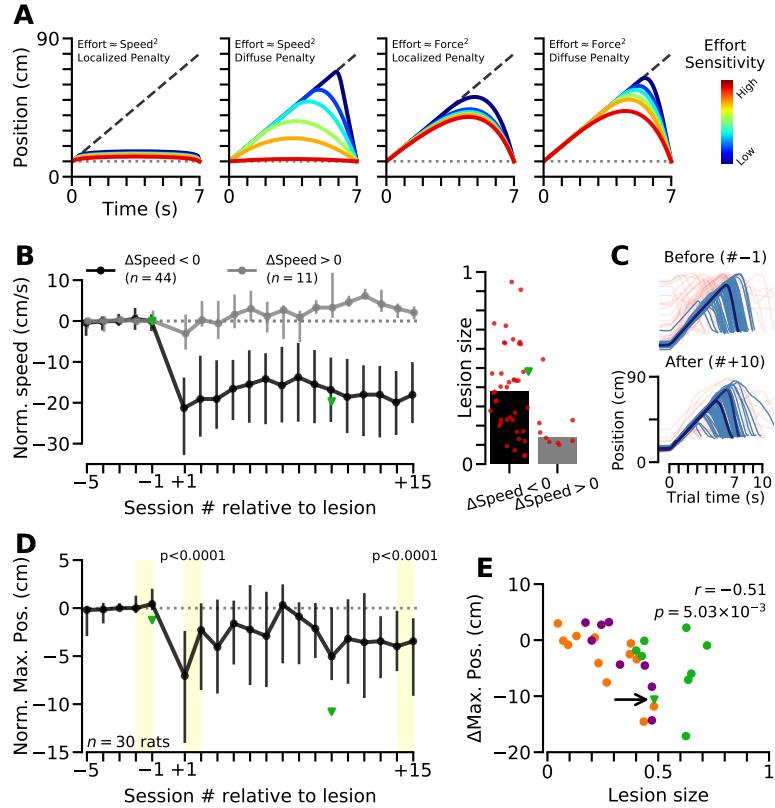


Figure 4.6: Optimal trajectory vs. effort sensitivity and experimental validation. **A)** Optimal trajectories predicted by models with different effort and spatial costs approximations. The cost of premature entrance in the reward area (spatial cost) was simulated using a Heaviside function that was either localized (~step function with non-zero value within the reward area) or diffuse (~a sigmoid function whose value gradually decreases toward zero away from the reward area). Effort was approximated as the square value of either the modeled muscular force produced by the animals or of its speed. **B)** *Left:* animals were divided into two groups based on the impact of the striatal lesion on their running speed. *Right:* lesion size for animals in those two groups. Green triangles in panels B, D, and E are data points from the example animal whose trajectories, before and after lesion, are shown in panel C. **C)** Effect of striatal lesion on the trajectories of a single animal. Only trials in which the routine was executed (thin blue lines) were taken into account to find the trajectory of median maximum position (thick blue line). The shadow of the trajectory of median maximum position before lesion is displayed in the bottom plot for comparison. **D)** Effect of striatal lesion on the median maximum position in routine trials. **E)** Effect of striatal lesion on the median maximum position vs. lesion size. Same color code for individual lesion type as in Figure 4.1.

Strikingly, following striatal lesions of various sizes and locations, rats started running forward earlier relative the length of the treadmill, i.e., a smaller maximum position (Figure 4.6D). This effect too, similar to speed, persisted after three weeks of daily

sessions post-lesion. Indeed, comparing stable sessions of all the lesioned animals (regardless of whether the lesion was performed before or after learning the task, whether there was an impact on their speed, and location of the lesion), with all the control animals, showed a smaller maximum position in lesioned rats ([Figure A.9](#)). Also, the reduction in maximum position was well-correlated with lesion size, the bigger the lesion, the bigger the reduction ([Figure 4.6E](#)). Overall, these results suggest a selective role for the striatum in setting the sensitivity to effort.

Chapter 5

Discussion

They said we'd sought and not found. He said I desire that which cannot be found!

Rumi, Divan

In this chapter, for each set of experiments, I first summarize the results and discuss their more general implications. Then, I present a short conclusion of the entire work, attempting to reconcile all the ideas. Next, I will describe some points that I think might have imposed limitations on the interpretation of this work. Finally, some ideas and directions for my future-self are presented that can complement and strengthen this manuscript.

5.1 Time Estimation

In this study, we used a treadmill-based behavioral assay in which rats, once the treadmill started moving, were required to wait for 7 s before approaching the reward location. Objectively, animals may accurately time their approaches using either one of the following two mechanisms:

- I. They may rely on a purely *internal* mechanism (e.g., self-sustained neuronal dynamics read by their motor system) to learn how long they should wait and

decide when to approach the reward port. In this case, performance accuracy should be largely independent of variations in *external* factors (e.g., the speed of the treadmill, the animal position on the treadmill at trial onset,...). Additionally, to save up energy, animals would probably stay close to the reward area for most of the duration of the trial.

- II. Animals may discover, by trial-and-error, a motor routine adapted to the apparatus and task parameters, whose complete execution would take them into the reward area at the right time, i.e., around the goal time (GT). In this case, timing accuracy would be related to the stereotyped performance of that routine and should heavily depend on task-specific features of the environment or the order of the elements composing the motor sequence.

The dominance of either of the algorithms can be directly inferred from behavioral experiments in which critical task parameters are manipulated. The results of our behavioral experiments clearly favor the latter embodied strategy. Also, using two distinct reinforcement learning-based agents that either incorporated or lacked time representation, we further showed that the behavior of our animals is incompatible with them accessing an internal explicit knowledge of elapsed time [133].

We report that to accurately wait 7 seconds before approaching the reward port, most rats developed the following “wait-and-run” motor routine. First, they waited for the beginning of each trial in the reward area. Then, upon trial onset, they stayed relatively still while the treadmill carried them to the rear wall of the treadmill. Finally, as soon as they reached the back of the treadmill, they ran straight to the reward port, without pause. In this experimental ‘control’ condition (see section 3.1), the accuracy of the animals reached its peak after 15 to 20 training sessions. However, even for proficient animals, the probability of performing a correct trial was almost null when they started a trial in the back region of the treadmill. In addition, when animals started a trial in the reward area, performing a correct trial was almost exclusively associated

with the animals reaching the back portion of the treadmill. Finally, following extensive training in the control condition, when we modified the task parameters to penalize the stereotyped performance of this front-back-front trajectory, the behavioral proficiency and accuracy of the animals dropped dramatically. These results support the hypothesis that, in our task, performing the motor routine is necessary for accurate performance.

It could be argued that the animals' tendency to develop this front-back-front trajectory resulted from the structure of the task that provided an easy solution that animals used instead of estimating time while continuously running just behind the infrared beam. In other words, had the task not favored the usage of an readily available motor routine, rats might have timed their reward approaches by relying on an internal representation of time that might have arisen from the ability of recurrent neural networks to generate self-sustained time-varying patterns of neural activity [135]. With several additional experiments we showed that rats have limited ability to use an internal representation of time when the task parameters are set such as to prevent the usage of a stereotyped motor sequence to solve the task.

First, we trained a group of animals while the treadmill speed randomly changed every trial (see [section 3.2](#)). Compared to animals trained in the control condition, those trained with variable speed were less accurate. Additionally, these animals attempted to use the same front-back-front trajectory, evident by an increased probability of correct trials when the treadmill speed allowed it. Second, we trained a different group of rats in a version of the task that penalized them when they started the trials in the reward area (see [section 3.3](#)). In this condition, solving the task is not possible using the usual routine and rats trained in this condition displayed strong accuracy impairment. Moreover, they kept trying to develop a modified front-back-front trajectory and started the trials as close as possible to the infrared beam (note that the infrared beam location was not marked). In all the above experiments, during trials, the treadmill pushed the animals away from the reward area which favors the usage of the wait-and-run routine.

To avoid this possible bias, in our last experiment, we trained a group of rats on an immobile treadmill (see [section 3.5](#)). Rats' performance was poor in this condition, with some animals failing to show any signs of learning, and others failing to reduce their variability. The increased variability is likely to result from the fact that, when the treadmill is immobile, a motor sequence to fit in 7 s is more difficult to be reproduced reliably across trials, rather than in the control condition in which most of the sequence is a passive wait on the treadmill until the animal reached the rear wall. Moreover, we noticed that the best rats in the immobile treadmill condition systematically ran to the back region of the treadmill where they performed a series of rearing and wall-touching movements, just before crossing the treadmill toward the reward area. With our video tracking system, we could not quantify these movements, however, by visual inspection, I speculate that those movement were also rather stereotypical, not unlike those reported by Kawai and others in [\[40\]](#). Altogether, we conclude from this set of experiments that rats, forced to wait for several seconds before approaching the reward, did not seem capable of using a purely internal and disembodied representation of time, but always attempted to develop a motor routine in the confined space of the treadmill, a routine whose execution duration amounted to the time they needed to wait. This conclusion was also supported by the experiment whereby animals were less accurate in timing their entrance in the reward area when the GT was set to 3.5 s, compared to the control GT of 7 s. Indeed, in this short GT condition, the wait-and-run strategy is not optimal, as animals would enter the reward area too late. Thus, the increased variability might be explained by the difficulty for the rats to "self-estimate" when to start running forward without the help of a salient sensory cue (such as touching the back wall). In support of this idea, in 67% of the error trials, the rats started running forward before reaching even the middle of the treadmill. In addition, a few animals trained in the short goal time condition developed a new stereotyped motor sequence, i.e., running from front to back and back to front. Interestingly, their entrance times

(ETs) were less variable than animals that remained immobile after trial onset and tried to estimate when to run forward in the middle portion of the treadmill.

A practical limitation of our work is whether its conclusion is relevant beyond the specifics of our experimental protocol, i.e., a suprasecond long motor timing task in which the rewarding action is a locomotor activity, not a distinct response (e.g., a lever press). Interestingly, in a study in which a group of rats had to perform two lever presses interleaved by 700 ms, each animal developed an idiosyncratic motor sequenceⁱ lasting precisely 700 ms [40]. The large inter-individual variability reported in this study may arise from the multiple possibilities of simple action sequences that can be squeezed in such a short time interval and easily reproduced across trials, taking advantage of the proximity of the front wall and lever. If the time interval was longer, all the animals might have developed the same motor sequence (e.g., running back and forth in the experimental cage between the two lever presses). Nevertheless, this study provides an additional example in which virtually all animals developed a motor strategy, even if compared to our task, the time interval was much shorter (<1 s) and the terminal operant response was distinct (a single lever press). It is well-known that temporal regularities in animal conditioning protocols favor the development of automatic motor sequences. In one of the rare studies that continuously recorded and quantified the full body dynamics of rats performing a sensory duration categorization choice task, authors reported that animals developed highly stereotyped motor sequences during presentation of the sensory cues and that perceptual report of the animals could be predicted from these motor sequences [39]. Thus, animals use embodied strategies in tasks requiring them to categorize (short or long) the duration of time intervals too, suggesting that our results are not just due to the particularities of the task. Moreover, these results are in line with an earlier study showing that the prediction of rats' temporal judgment (a 6 s long versus a 12 s long luminous signal) was always better if

ⁱConsider the following as an example: 1# press the lever with the left paw; 2# touch the wall above the lever twice with the right paw; 3# second press on the lever with the left paw.

based on the collateral behaviors performed by the animal at the end of the signal than if based on the actual time [38]. In such temporal discrimination tasks, a stereotyped sequences of movements (collateral behavior) might serve as an external clock and the choice of the animals might be primarily determined by what the animal is doing when a sensory cue disappears rather than by an internal estimation of the duration of that cue. That timing could be primarily embodied might seem counter-intuitive with our innerly-rooted feeling of time. Nonetheless, humans display poor temporal judgment accuracy when prevented to count covertly or overtly [43] and several studies have reported that movements improve the perception of intervals [33, 136, 137]. It has been recently proposed that the explicit perception of time in humans may be constructed implicitly through the association between the duration of an interval and its sensorimotor content [45]. Embodied timing, by replacing time per se with various processes depending on tasks and contexts, explains why such a diverse set of brain regions, including but not limited to the prefrontal cortex, motor cortex, basal ganglia (BG), cerebellum, supplementary motor area, entorhinal cortex, and hippocampus have been associated with time representation [18, 46, 93, 95, 96, 138–141].ⁱⁱ

It has been previously proposed that timing could be mediated through motor routines whose precise execution is internally controlled [21, 142, 143]. So, one could argue that accurate timing in our task was also ultimately driven by internal neuronal dynamics. I must stress that our conclusion that animals rely on an embodied strategy, rather than internal neuronal clocks (dedicated or emergent), does not mean that internal brain activity is irrelevant to well-timed behavior. We do not question that representations/correlations of elapsed time have been observed in individual and population neuronal activity in various brain regions during time-constrained tasks or that perturbation of neuronal activity impairs timing accuracy. For example, in a novel task where head-fixed mice learned to remain still for 6 s before accelerating toward the

ⁱⁱIn my opinion, the fact that this many brain structures have been implicated in timing should, in and of itself, raise more questions than it answers.

reward at the end of a virtual track, multiple *time cells* were identified in the entorhinal cortex that were sequentially active during the interval, and scaled proportional to the waiting time [141]. Mice during the immobility period did not have any locomotor activity (they had subthreshold locomotion), and there is no other behavioral report. I would confidently say, based on my limited experience with rodents, that no mouse remains frozen for 6 s. Temporal correlations, in turn, could be covariates of any other motor activity. Similarly, Wang and others found temporally scaling dynamics during a timing task in both the prefrontal cortex *and* the dorsomedial striatum (DMS) of monkeys [18]. This type of results can not be used as definitive evidence in favor of a neuronal clock, **read** by animals as we, humans, read a clock [65, 144, 145]. Our behavioral results are not easily compatible with the idea that neural representations of time are a signature of a **clock-like** algorithm for time estimation. Rather, they are compatible with the idea that timing emerges from the dynamics of neural circuits [5], as long as these dynamics are not assumed to be entirely internally generated and also reflect feedback from the environment. For instance, I speculate that the timing deficits induced by striatal inactivation in a similar version of the treadmill task [41] might be explained by considering the role of this brain region in accumulating sensory information before taking a decision, or in invigorating the ongoing behavior [129, 146]—more on the role of the striatum later on. In our experimental setting, one could assume that rats, by gathering sensory evidence, decide when to start running and how fast. Thus, it may be relevant to consider the process governing when the rats will run forward as an accumulation of sensorimotor evidence. The dorsal striatum (DS) is critical for processing sensorimotor information [85] and has been proposed to contribute to the process of evidence accumulation during decision making [146]. Interestingly, it has been recently proposed that a competition between the direct and indirect BG pathways, tuned by dopamine (DA) modulation, may determine the speed of evidence accumulation toward decision taking [129]. Such a model predicts an increase (*decrease*) in DA

activity will speed up (*slow down*) the accumulation of sensorimotor information and will lead to an early (*delayed*) response.

In conclusion, I point out that the embodied mechanism for motor timing is the most parsimonious, can explain a large body of experimental data, and by taking advantage of modern tracking technologies [147], can potentially be applied in other types of time-estimation tasks. By adopting the embodiment perspective, I raise the question that while animals naturally use motor strategies in time-constrained situations, why should there exist an independent internal clock?

5.2 Striatal Function

The striatum can powerfully influence the production of purposive movements. Indeed, it is well-known that striatal dysfunction is the primary cause of motor impairments (akinesia, bradykinesia, levodopa-induced dyskinesia) seen in Parkinson's disease (PD) [71, 89, 115]. DA depletion in PD differentially affects striatal D1 dopamine receptor (D1) and D2 dopamine receptor (D2) expressing neurons. Activation of striatal D1 (D2) medium spiny neurons (MSNs) forming the direct (*indirect*) BG pathway facilitates (*prevents*) movement production through disinhibition (*inhibition*) of brainstem and forebrain motor regions [86]. This fundamental feature of BG's functional anatomy, combined with recordings and perturbations of striatal activity in various behavioral tasks has led to two prevailing hypotheses regarding how the striatum contributes to the control of purposive movements:

- learning and performing action sequencesⁱⁱⁱ [87, 108, 110, 111];
- modulation of movement speed [41, 88, 107, 128, 148].

The validity of these hypotheses is debated [for instance, see 62] and, interestingly, they face common shortcomings. For example, they fall short of explaining why lesioning

ⁱⁱⁱAction sequences are sometimes referred to as “procedural memories” [110].

or inactivating striatum's anatomical targets (i.e., the BG output nuclei) in non-human primates only marginally alters the execution and speed profile of overlearned motor sequences [118] and it even alleviates motor deficits observed in PD patients [67]. Moreover, in behavioral tasks typically used to probe the striatal motor function through perturbation of neuronal activity, it is next to impossible to disentangle whether failure to perform is due to inability to implement a decision into movement, or due to an impairment in higher-level processes (e.g., sensory processing and decision making), despite functional motor systems.^{iv}

In this part of the study, to understand how the striatum contributes to the control of purposive actions, while limiting the performance confound as much as possible, we took advantage of the behavior displayed by animals in the treadmill task (Figure 3.1). This task was identical to the one used in the time experiments under the 'normal' condition (Figure 2.1a, and Figure 4.1A). We trained a group of animals, including the same animals presented in Figure 3.1. They mostly developed the wait-and-run routine on the treadmill (but also see Figure A.2). After their performance on the task plateaued, they were randomly assigned to striatal lesion groups in different areas: dorsolateral striatum (DLS), DMS, or the entire DS. Excitotoxic lesions, the kind we used here (section 2.2.1), compared to lesions induced by electrical currents, have the benefit of sparing the passing fibers. Moreover, due to their permanent nature, lesions are probably a more direct way to assess the function of the manipulated area [119]. Following the lesion, animals were allowed to recover for ~2 weeks. After this recovery period, visually, they had normal behavior in their homecage. Then, they resumed the training with identical task parameters to the sessions prior to the lesion. After the striatal lesion, most animals^v could still perform in the task, with comparable proficiency

^{iv}This is referred to as the **performance confound**. I only understood this concept after my supervisor came up with this rather bitter example: *Imagine you cut up someone's legs and then conclude that they cannot learn to run.*

to that of the pre-lesion sessions. In addition, motivation does not seem to be affected, since the animals still engaged in the task, and consumed the reward in correct (and thus rewarded) trials (Figure 4.2). The most striking effect was a marked reduction in the running speed toward the reward. This slowdown was irreversible (Figure 4.1J) and well-correlated with the size of the lesion (Figure A.6A). The delayed consumption of the reward (Figure 4.2B) is also another measure related to reduced speed, due to either slower locomotion toward the reward port, or slower postural adjustments to start licking. Interestingly, animals with reduced speed, also started to run earlier toward the reward, i.e., the maximum position of their trajectories was smaller. This trait was also well-correlated with the lesion size and was also irreversible (Figure 4.6), but not trivial to explain using the aforementioned models of the striatal function (more on this later).

Noticeably, in a number of animals, arguably the ones with relatively larger lesions, executing the routine was impaired for the first few sessions ($\sim <5$), and recovered afterward. They mostly stayed in front of the infrared beam and committed many error trials. It could be argued that the lesion prevented the performance of the motor routine, and especially animals with larger lesions stayed in the front since it is associated with the reward, evident by the strong place preference for the reward area in both naïve and trained rats (Figure A.1). This is also supported by a recent preprint from Dhawale and others proposing that the DLS, and not DMS, controls the detailed structure of learned behaviors on a moment-to-moment basis, and thus DLS lesions bring back pre-learning behaviors [149]. To further investigate this possibility, we designed a variant of the task to directly evaluate whether lesioned animals lost the ability to perform motor routines (or at least a comparable motor routine). In this ‘reverse’ treadmill task, the conveyor belt moved toward the reward area. Animals could just move to the back of the treadmill during the relatively-long intertrial (while the treadmill motor

^vExcept for two rats with the largest lesions ($> 80\%$). These animals are, for instance, the two lines in Figure 4.1H, right that drop out of the axes limits.

was turned off, this would be a simple locomotion which was not affected in lesioned animals, [Figure 4.4A](#)) and following the trial start, stay still while the treadmill carried them to the reward area at the right time ($ET \geq GT$). Importantly, impaired execution of this “run-and-wait” motor routine could be clearly observed, because the animals should similarly stay in the front. Thus, this task resolves the issue of the performance confound, since even a compromised motor system can execute this routine. However, the experimental data confirmed, animals kept performing the routine with no sign of deficiency ([Figure 4.3](#)). These results demonstrate the spared ability of animals to perform motor routines with lesioned striatum.

We also formally confirmed normal locomotor activity by measuring the total displacement during the first 10 min in an unfamiliar environment ([Figure 4.4A](#), see [section 2.1.7](#) for details). Furthermore, we investigated whether lesioned animals were able to run at faster speeds. Some of the control and lesioned animals were tested in a new paradigm, consisting in trials of 30 s followed by intertrials of 30 s. There was no reward available and the speed of the treadmill progressively increased across trials (see [section 2.1.7](#) for details). Interestingly, lesioned animals were capable of running at speeds much higher than the treadmill speed—up to 40 cm/s compared to the treadmill speed of 10 cm/s ([Figure 4.4B](#)). Similar results have been reported in PD patients using different behavioral paradigms [[116](#), [117](#)].

Another possible explanation of our data may be lack of more general motor control abilities, such as modulation of speed. For example, it has been previously shown that the speed of reward-oriented movements increases with movement length to minimize the cost of time (CoT) [[54](#)]. By further analysis of our data, I found that, for every single control animal, trials with higher maximum position were indeed faster ([Figure 4.4D](#)). Importantly, this effect was preserved after striatal lesion, although all the speeds were generally lower than control animals. These results show that animals’ elementary ability to modulate their locomotion speed was also maintained after striatal lesion.

Performing striatal lesions in naïve animals and then training them with the usual protocol yields similar behaviors as control animals ([Figure 4.5A](#)). Learning the wait-and-run routine should also be added to the list of abilities preserved after the DS lesion. These “early lesion” animals are also slower, and their treadmill crossing speed anti-correlates with their lesion size ([Figure A.6B](#)). Some animals with larger lesions, however, failed to learn the task ([Figure 4.5B](#)), they constantly stayed in the front of the treadmill. This is reminiscent of the behavior of some rats, also with the largest lesions in [Figure 4.1](#) and [Figure A.8](#). Staying in the front could be considered as the extreme (and persistent) version of the ‘acute’ effect observed after the lesion. While after striatal lesion, majority of animals kept arriving on time in the reward area, but they started to run earlier (i.e., from a more frontal portion of the treadmill) and at a slower velocity ([Figure 4.6](#), and [Figure A.9](#)).^{vi} Running at slower speeds could be explained by current models of striatal function, but the tendency to start running early is surprising. Alternatively, animals could have reached similar positions on the treadmill and still used a slower speed to approach the reward. The major disadvantage of such hypothetical strategy may be a longer running distance which incurs more energetic cost. Indeed, optimal control models predicted that higher sensitivity to energy expenditure (effort) leads to a similar strategy: starting to run earlier and slower [[134](#)]. Our results thus support the view that the striatal lesion increased animals’ sensitivity to effort which led them to modify the kinematics of the wait-and-run routine. In other words, our work suggests that DS contributes to the generation of an effort signal that influences the kinematic parameters of purposive actions. Therefore, the tendency to remain in the front of the treadmill after large DS lesions in any of our experiments could simply reflect a heightened conservative energy policy. Metaphorically speaking,

^{vi}Concerning the timing mechanisms discussed in [section 5.1](#), the temporal accuracy (standard deviation of ET) was also irreversibly increased following striatal lesions ([Figure A.10](#)). This is consistent with the embodied argument that considers an important role for a salient sensory cue, such as touching the back wall of the treadmill in time estimation. Following the striatal lesion, increased variability might be due to the shorter waiting bout and starting to run before arriving to the back wall, which similar to the short GT experiments ([Figure 3.4](#)) led to increased variability.

the same effect would have been expected had we forced control non-lesioned rats to perform the task with extra weight on their back.

Such a function is congruent with the hypothesis, derived from PD patients, that DA projections to the striatum provide a signal for implicit motor motivation (or global effort sensitivity), which in turn influences the vigor of goal-directed movements [116], and lack thereof causes bradykinesia (also suggested by others like [98, 150]). In addition, progressive degeneration of DAergic neurons in a mouse model of PD suggests a critical role of DA in the DS for the control of movement vigor [88]. On the other hand, whether the DS is critical for action selection/initiation/repression has been an important topic of debate [62, 67]. In this context, our study provides compelling evidence for a specific role of the DS in setting the sensitivity to effort. Our results indicate that striatal lesions change the kinematics of a well-learned motor routine as a result of increased sensitivity to effort, without altering the animals' capacity to run at different speeds. It is known that selective perturbation of the activity of striatal projection neurons bidirectionally modulates the speed of goal-directed movements [128] and spontaneous locomotion [86]. Our results complement these studies by suggesting that the DS is not the primary controller of movements, but provides a second layer of modulation that tunes their kinematics according to cost/benefit considerations [98, 150]. More generally, the role of the BG in contributing to the cost/benefit analysis of actions has a explanatory power beyond the kinematic modulation as it can reconcile different hypotheses regarding the BG function. Of course, I do not claim it can account for every single BG study, however following, I present an alternative reading of several examples:

- I. The seminal work of Kravitz and others [86] could be reinterpreted as cost oversensitivity caused by indirect pathway activation that manifests as freezing, and cost undersensitivity by direct pathway activation that promotes locomotion.

Therefore, this framework also predicts a prokinetic role for DA in the striatum [151], due to its dual effect on MSNs.

- II. The insightful paper of Yttri and Dudman [128] shows that activation of either direct and indirect pathway is sufficient to produce sustained increase and decrease in movement velocity. Similar results are predicted with the cost hypothesis, assuming the bidirectional control of cost sensitivity by direct and indirect pathways, the same as the item I. above: actions deemed less costly due to the stimulation of D1 MSNs are later preferred, and those co-occurring with D2 stimulation are less likely to be repeated.
- III. Many works in the instrumental learning field also reported altered engagement in the task (usually different lever press rate) as a sign of impaired learning and/or execution [125]. In a recent example [152], in two similar tasks, mice with genetic ablation of D2 expressing neurons showed increased lever-press rates compared to the control mice. This, once again, is in line with our hypothesis, i.e., lever pressing in the absence of the ‘skeptic’ D2 neurons is more likely.^{vii}

These examples represent the explanatory capacity of our proposed function of the striatum. However, striatal or BG manipulations sometimes lead to conflicting results. For instance, our proposed function of the dorsal BG to set the sensitivity to effort has implications for time estimation as well. Soares and others demonstrated that “activation or inhibition of dopamine neurons was sufficient to slow down or speed up time estimation, respectively” [100]. Assuming a prokinetic role for DA, our framework (embodied timing, plus the effort function of the BG), would suggest that mice might have executed a subtle motor routine during the to-be-estimated interval, the ending of which would have been used as a reference point to determine shorter or longer intervals. The execution of this routine presumably was sped up upon DA photo-stimulation,

^{vii}“The direct–indirect competition implements a decision by weighing the arguments of a Believer (e.g., direct pathway) against those of a Skeptic (e.g., indirect pathway). Because the default state of the BG is heavily motor suppressing..., the burden of proof falls on the Believer and thus actions are only executed when the accrued evidence sufficiently reduces the Skeptic’s uncertainty” [129].

and slowed down by DA inhibition, based on the aforementioned item I., causing overestimation and underestimation of the interval, respectively. This prediction, however in line with some previous reports [see 7, for a review], contradicts the actual results! One possible reason might be that it is non-trivial how manipulating the activity of DA neurons is reflected in actual DA release in the striatum [for instance, see 153]. Moreover, striatal perturbation sometimes does not cause a vigor deficit. Dhawale and others trained rats to wait 700 ms between two lever presses (similar to [40]). They showed that following DLS lesions, the lever pressing behavior was similar to naïve rats (thus seemingly no vigor deficit), however animals did not perform their idiosyncratic routine during the interval [149]. Lack of impact on lever pressing might be caused by **automaticity** after more than ten thousand trials. In that case, when the animal is in the experimental apparatus, pressing the lever might become motivation independent, and not reflect vigor at all [62].

It is generally believed that the DMS mediates goal-directed strategies, especially in early stages of learning by encoding the response-outcome associations, while the DLS is implicated in habitual behavior (after early acquisition of a behavior) by encoding the stimulus-response associations [84]. For example, Gremel and Costa showed that lesioning the DMS (*DLS*), deprived animals of the goal-directed (*habitual*) system, so they shifted toward habitual (*goal-directed*) strategies [154]. This framework predicts, if nothing else, a learning deficit in DMS-lesioned animals [125]. However, the DMS and DLS groups performed similarly in our task and there might be a few reasons why. First, the wait-and-run routine does not completely conform to either of the goal-directed or habitual behaviors, because not delivering any reward made the behavior more variable (evidence against habit), and devaluing the reward did not prevent the motor routine (evidence against goal-directedness). Notably, the argument against goal-directed behavior is weaker, since the routine is partly imposed to the animals due to the structure of the task, i.e., having to run on top of a treadmill. Second, the mentioned division

of labor between the DMS and DLS is not that clear after all. Indeed, Vandaele and others showed that although neuronal activity in DLS and DMS was different in early learning, it did not follow behavioral improvement over ensuing sessions and became similar after extended training [155]. Third, as discussed before (section 1.4.1), it was recently illustrated that the sensorimotor striatum (DLS) is much larger than previously imagined, so the DLS/DMS distinction solely based on the mediolateral coordinate may be unrealistic [74, 75]. Fourth, learning the treadmill task, which requires sensory integration and locomotion, might be largely independent of the associative striatum (DMS), and therefore early lesions of the DMS did not affect the learning ability.

Finally, expending effort to produce faster movements lowers the CoT as well [51]. In sensory guided decision-making tasks, the CoT can also be reduced by limiting the duration of deliberation [52]. Interestingly, recent evidence supports a specific role of the BG in signaling the urgency to commit to an action choice [52, 127]. Thus, our proposed function of the DS might provide a common framework to reconcile seemingly heterogeneous findings across motor control and decision-making fields.

5.3 Conclusion

In short, accurate timing requires stereotyped interaction with the environment and the striatum determines the effort invested in this interaction [133, 134].

That the perception of elapsed time is somehow related to the movement of things is not a surprise to anyone. In this work, however, we attempted to determine the necessity of movements. In other words, whether there is an internal mechanism which can provide a measure of time that drives behavior, or time is perceived through actions that fill the interval of interest. Multiple experiments designed to interfere with the usage of stereotyped motor routines, all led to drastic decline in temporal accuracy. These results suggest that the hypothetical internal timer does not suffice to produce a

timely motor response in the suprasecond timescale. We thus argue that time intervals in the brain may be represented with the movements that happen to take that long to execute. Thus, the problem of time perception is translated to a motor control problem, learning and performing adaptive motor routines.

The dorsal striatum has been implicated in initiation and selection of movements, as well as in controlling their speed. We took advantage of the wait-and-run motor routine, consistently developed by animals in the treadmill task, to delineate the role of the striatum. Using a number of original tasks, for a large group of animals, we illustrated that permanently lesioning different areas of the dorsal striatum does not affect neither the ability to learn the motor routine by trial and error, to perform the learned motor routine, to run fast, to modulate the running speed as needed, nor the motivation to acquire the reward. However, lesioned animals robustly performed a less effortful routine by waiting less and running slower, two traits that well-correlated with the size of the lesion. Hence, we propose that the main motor function of the striatum may be setting the sensitivity to effort in purposive actions. Such an elementary function has the potential to reconcile a large body of seemingly contrasting hypotheses.

5.4 Reservations

The idea that the future is unpredictable is undermined every day by the ease with which the past is explained.

Daniel Kahneman, Thinking, Fast and Slow

It is time to discuss weak points of this project, some possible flaws that might result in interpretive limitations. First issue relates to the structure of the task. The treadmill task does not require a clear and distinct operant response, rather the animal crosses the infrared beam, the location of which is unmarked and unknown to the animal. This is uncharacteristic for a time-estimation task. In retrospect, had we installed a simple lever or nose-poke above the reward port to register the entrance times, it

would have provided a more straightforward timing task. The task was originally designed to be used at faster speeds (30 cm/s) and such a mechanism was perhaps deemed impractical. Next point is also with regards to the task. In its nature, I think, the treadmill task favors a motor strategy, and this might have biased our results. Aside from the immobile condition, the treadmill always moves and so imposes a dynamic environment to the agent, an environment in which avoiding motor activity is not even possible, since eventually the animal would arrive to the back wall and *has to* move. The immobile condition was an attempt to remedy this problem. Indeed, we showed that better performance was correlated with more movement along the treadmill and visually, we observed that our best-performing animal developed a stereotyped ritual in interaction with the back wall of the treadmill. However, even in this condition, animals couldn't simply stay in the reward area, and presumably *estimate* the goal time duration, at least they had to move a few centimeters backward to prevent premature interruption of the beam. Ideally, to test the embodied view, the time-estimation task should not allow any motor activity, perhaps by penalizing movements or incentivizing immobility. However, a new problem arises: what would be the ecological relevance of such a task, especially in suprasecond timescale? And this is closely linked to my last remark. Even though learning about embodiment and its implications immensely influenced my thinking, I fear that in the context of timing, it might be unfalsifiable. For instance, even if human subjects are asked to not move at all during a time-estimation task, and they perfectly follow the protocol, one could argue (and I do argue) that they still mentally picture a motor activity or a moving object [also 45]. Overall, the best argument in favor of embodied time-estimation is its parsimony, and that adopting this perspective affords a great explanatory power.

The lesion experiments are also not perfect. One issue is that the quantity of reward progressively decreased for correct trials with larger entrance times (8 s vs. 9 s, [Figure 2.1](#)). Thus, had lesioned animals started running at a position similar to normal

rats using a slower speed, they would have received a slightly smaller drop of reward. The most skeptical reader might suggest that this is the reason why animals tend to wait less, to avoid smaller rewards. However, the reward magnitude drops at a low rate, therefore I do not think a ~7% smaller reward is noticeable. In any case, at least for the lesion experiments, a constant reward size after the goal time would have been preferred. Lastly, one issue that might have downgraded our effect sizes, especially with regards to the maximum position analysis, was the behavioral variability. Some animals developed different strategies to solve the task ([Figure A.2](#)). At the time, to respect the diversity of natural behavior, we indiscriminately carried on with the lesion experiments for all the animals. Later on, while processing the data, I realized most outlier data points belonged to animals with strange pre-lesion behavior, but at this stage we did not have any excuse to exclude those animals, and we did not. Instead, we explicitly set criteria for including animals in the maximum position analysis ([Figure 4.6](#)). These criteria might seem arbitrary to some, although they served the purpose of the analysis and were set blind to the performance of individual animals. I suppose performing the lesion only in animals that behaviorally conformed to the wait-and-run routine would have rid us of much of the *extra* variability and also would have been scientifically justified.

5.5 Future Work

Thus far, I presented, hopefully, convincing evidence in support of the necessity of motor routines for accurate timing and that the DS sets the sensitivity to the expended effort in motor routines. Then some limitations in the design of the task and the interpretation of our data were discussed and now I propose some directions for future research.

We showed that the timing performance deteriorates in the absence of an *easy* motor strategy, i.e., a motor routine that is adapted to the environment, like the wait-and-run routine in the control treadmill task. The worst performances were observed in the versions of the task wherein stereotyped execution of a 7 s long motor routine was arguably the hardest, like the immobile condition. I would suggest that this is due to the inherent difficulty of reliably executing a suprasecond motor routine in a static environment, while in the control condition, the environment provides a reliable and salient cue, i.e., touching the back wall. It remains speculative whether in the immobile condition (or any other condition) animals developed a different idiosyncratic routine, either postural or with their limbs, that we couldn't capture with our position-tracking system. Better behavioral quantification, possible with the advent of modern technologies such as *DeepLabCut* [147], in ecologically-valid timing tasks [156] could detect such previously-unnoticed routines. Furthermore, it also requires future investigations into theoretical reasons why inferring time from internal dynamics of neural networks seemingly results in higher variability than relying on physical interactions with the environment.

In the second part, we used permanent fiber-sparing lesions to study the role of the striatum in development, execution, and control of the wait-and-run motor routine. Lesion is a useful tool to establish a causal ‘instructive’ function for the striatum [119], however it does not provide any information as to how direct/indirect pathways are involved. Recent genetic tools allow pathway-specific perturbation of neural activity in rats [157], which is absolutely compatible with our task and setup and would complement our conclusions tremendously. I speculate that direct (*indirect*) pathway stimulation would cause under- (*over-*) sensitivity to cost, somewhat contrary (*similar*) to what we observed by lesions. Moreover, dopamine manipulation would also further this work’s proposition. It has been suggested that dopamine in the striatum carries a ‘motor motivation’ signal, and its disruption in Parkinson’s disease leads to

a more conservative energy-expending policy [116]. Therefore, I suppose that animal models of Parkinson's, dopamine-depleted either by 6-hydroxydopamine lesions or progressive degeneration of dopaminergic neurons [88], would show similar results to our striatal lesioned animals. Similarly, transient dopamine activity manipulation using optogenetics could be another future direction. However, the treadmill task does not allow for clear behavioral predictions, since both prokinetic behavior due to the up-regulated dopamine, and energy-efficient behavior due to dopamine paucity may seem identical: remaining near the reward port. Finally, I reiterate that the theories of *urgency* in decision-making and *effort* in motor control might indeed reflect a common underlying function of the basal ganglia to maximize the capture rate (section 1.3.2). Direct assessment of this postulate could be possible in a task wherein the agent reports a decision (e.g., by a nose poke) via a discernible motor output (e.g., by running toward the nose port). For instance, consider a T-maze task with a sensory cue at the base of the central stem determining the arm in which the reward will be delivered [i.e., a combination of 110, 158]. Such a setup would illustrate the urgency in decision making with the time the animal takes to commit [127], and the effort in motor control with the velocity with which it approaches the reward port. Manipulating the neural activity could then reveal how urgency and effort are related. Future studies are needed to delineate this possibility and the role of the dopamine in the effort framework.

Appendix A

Supplementary Figures

The supplementary figures are presented in the following pages.

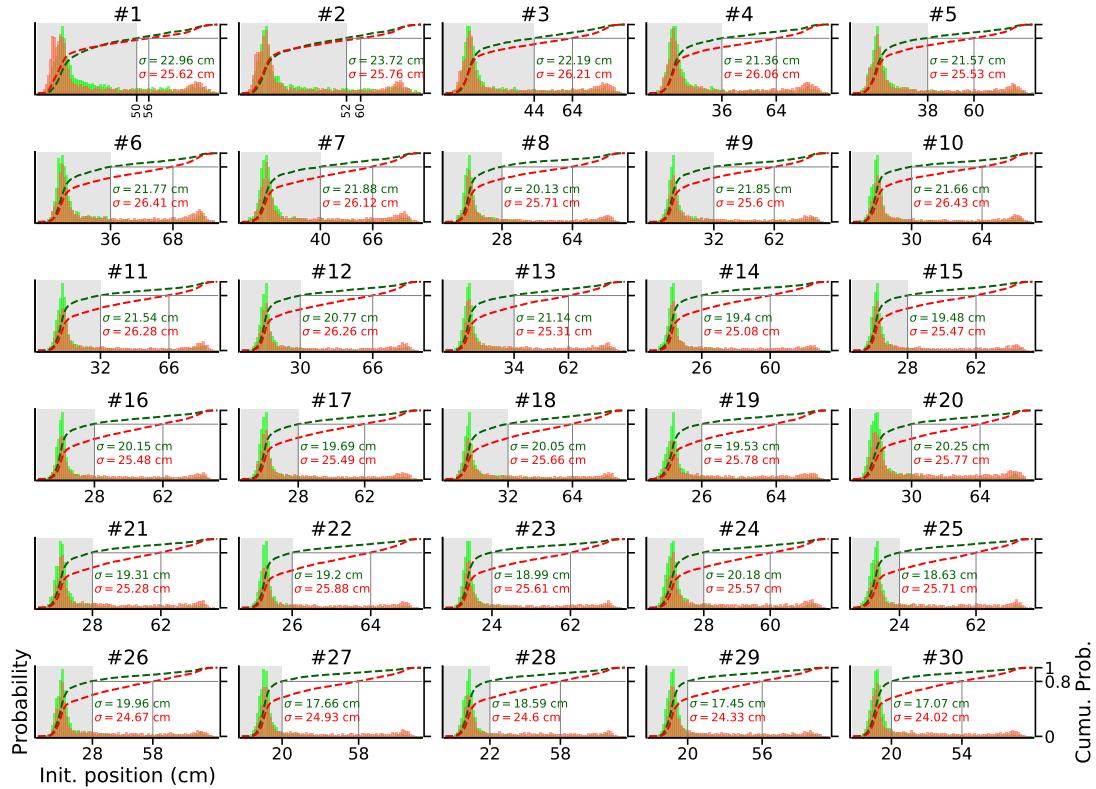


Figure A.1: Initial position distributions for correct and error trials diverged progressively during training. Similar to Figure 3.1e, each panel shows PDF of the initial position of the animals for correct (green) and error (red) trials, but plotted separately for each training session (#1 to #30). Dashed lines represent cumulative distribution functions (right y-axis). For each PDF, ‘ σ ’ values denote the standard deviation. Each PDF included pooled data from all the animals trained in the control condition ($n = 54$).

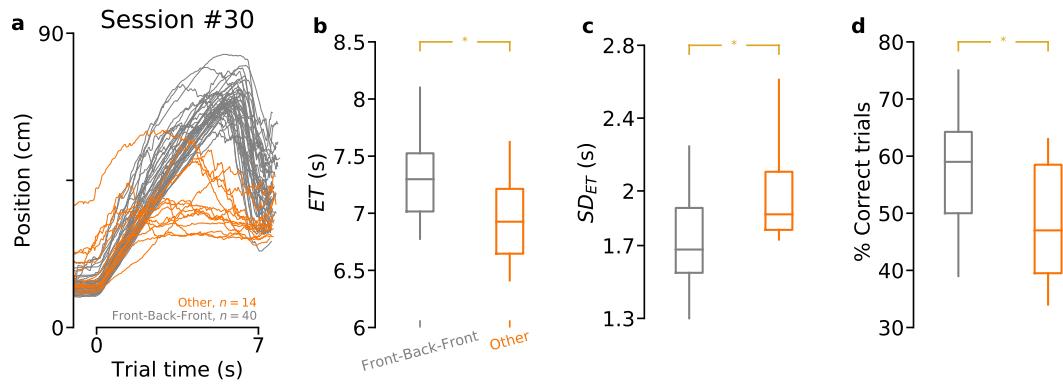


Figure A.2: Task proficiency according to the type of trajectory performed by animals.
a) Same as Figure 3.1, panel c, right, but the animals were divided in two groups according to whether they performed the front-back-front trajectory (gray) or not (other, orange). **b)** Entrance times. $p = 0.0066$ (permutation test). **c)** SD of ET. $p = 0.03$ (permutation test). **d)** Percentage of correct trials. $p = 0.01$ (permutation test). For panels b–d, same color code as in panel a. Data from sessions $\# \geq 20$ were averaged for each animal.

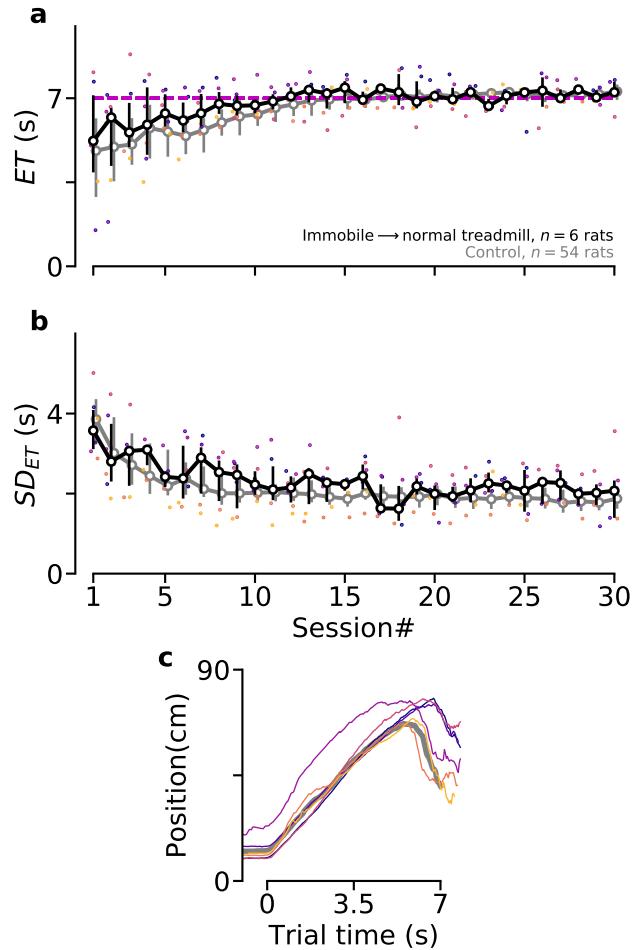


Figure A.3: Lack of temporal knowledge transfer across task protocols. After extensive training on the immobile treadmill, animals were trained under normal conditions (GT= 7 s, treadmill speed= 10 cm/s). **a)** Median ET across sessions under control condition. **b)** Similar to panel a, for the standard deviation of entrance times (SD_{ET}). **c)** Median trajectory of the individual animals after relearning the task under the control condition. **a-c)** Individual animal color code is preserved in all panels.

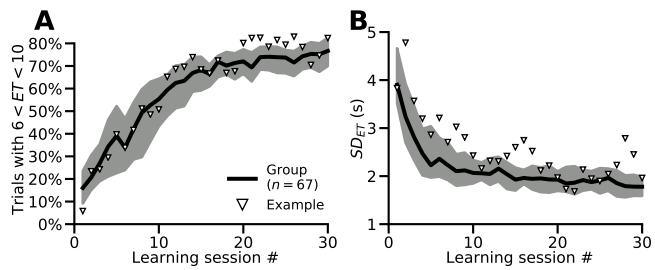


Figure A.4: Task performance improvement across sessions. **A)** Percentage of trials in which animals entered the reward area close to the GT ($6 \text{ s} < ET < 10 \text{ s}$), session-by-session. **B)** Session-by-session standard deviation of ET. Triangles show performance improvement for the example animal in Figure 4.1.

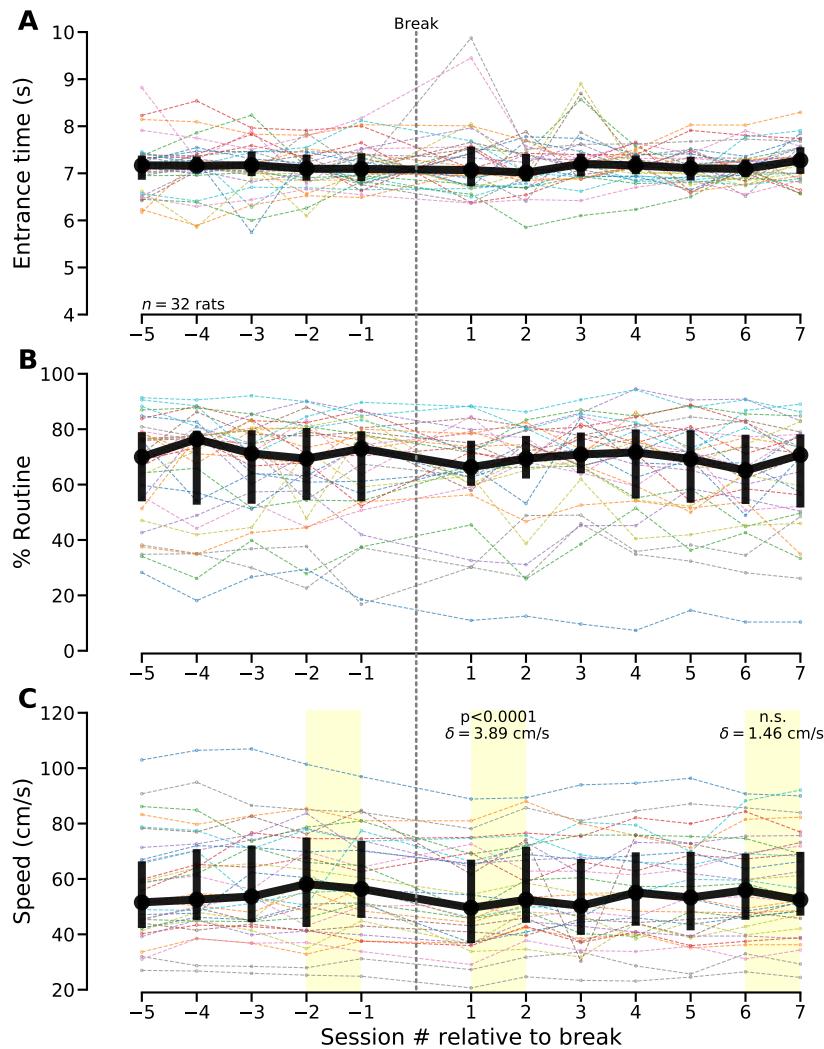


Figure A.5: Impact of two weeks of break on performance. Task performance before and after a two week-long break in practice. Non-lesioned animals had stable performance before the two week-long break (same duration than lesion recovery period) in practice (A: ET; B: percentage of trials during which animals used the wait-and-run routine; C: speed of the animals when they ran toward the reward area). A small but significant reduction in running speed was observed just after the break (δ denotes the effect size) that was restored after a few more training sessions.

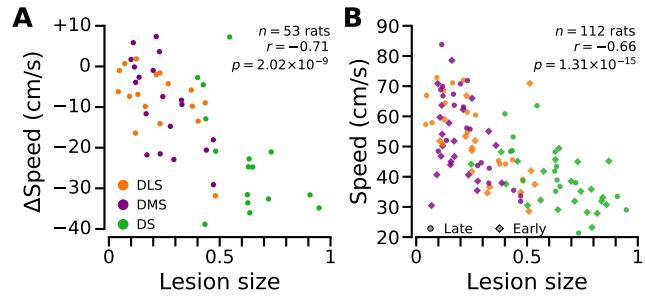


Figure A.6: The running speed negatively correlates with the size of the striatal lesion.

A) Average change in running speed (speed after lesion – speed before lesion) versus the lesion size, for all the rats that received a striatal lesion after training (late lesion). All speed values were averaged across 5 consecutive sessions before (last 5 sessions before lesion) and after (sessions #4 to #9, relative to lesion break) lesion. **B)** Average running speed versus lesion size for all the animals that underwent surgical lesion of the striatum. This dataset ($n = 112$ animals) includes animals that underwent striatal lesion after extensive training (Late group, $n = 53$, same animals as in panel A), and animals that underwent lesion before training (Early group, $n = 59$ animals). Speed was computed as in A, except that average was done over the last 5 sessions (for both Early and Late groups).

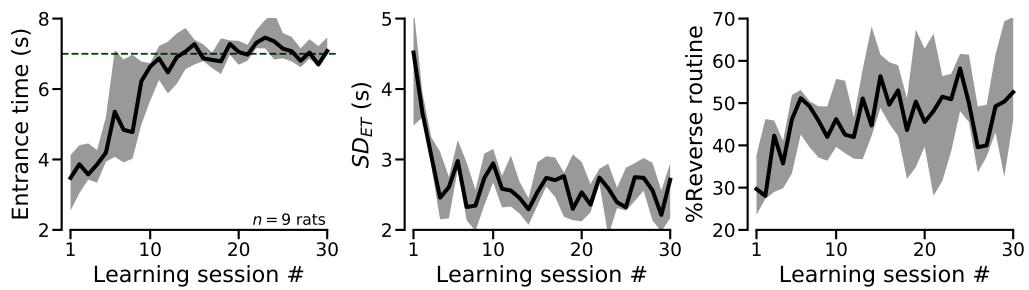


Figure A.7: Performance improvement in the reverse treadmill task. *Left:* Entrance time across learning sessions. *Middle:* Session-by-session standard deviation of ET. *Right:* Percentage of trials during which animals used the run-and-wait (reverse) routine. Time course of learning the reverse treadmill task is similar to that of the normal treadmill task.

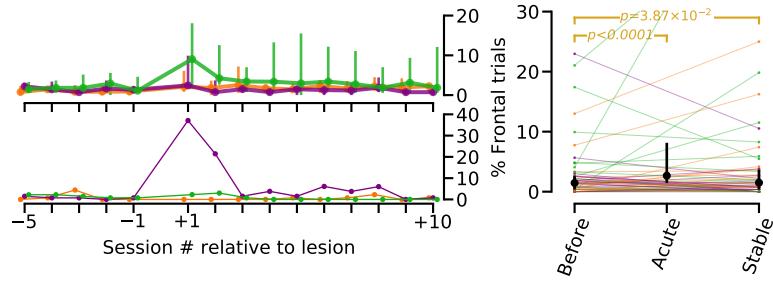


Figure A.8: Dorsal striatum lesions induced a transient increase in the percentage of trials during which animals remained close to the reward area. *Upper left:* Session-by-session percentage of trials in which animals remained close to the reward area (i.e., frontal trials). Group data for animals with DLS, DMS and DS lesion. Same color code for lesion types as in [Figure 4.1](#). *Lower left:* Same as above, but for the illustrative animals, shown in [Figure 4.1E-G](#). *Right:* Group statistical comparisons before and after striatal lesion. There is an acute increase that is mostly restored after a few sessions.

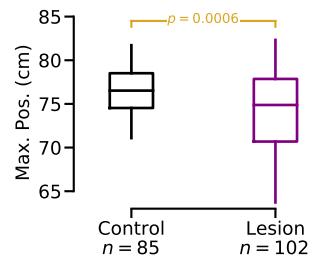


Figure A.9: Comparing the maximum position for the entire dataset. Each boxplot represents the range of the Max. Pos. (center line, median; box, 25th and 75th percentiles; whiskers, 5th and 95th percentiles) across a group of animals. For every animal, the median value of the last 5 sessions in the control condition (*Control*), or after the striatal lesion (*Lesion*) was considered. The lesion group includes every lesioned animal, regardless of lesion location (DLS, DMS, DS) and lesion type (early lesion, late lesion). Comparison using the permutation test (10000 permutations).

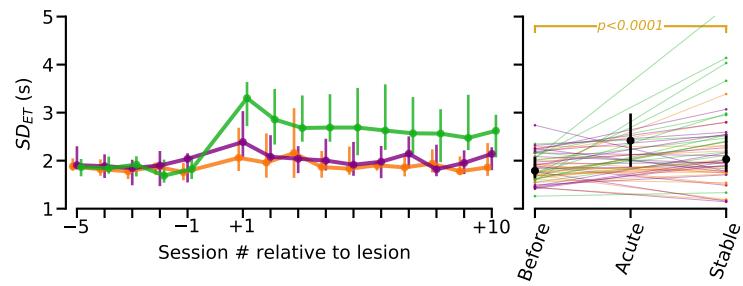


Figure A.10: Temporal variability increased after striatal lesions. *Left:* session-by-session standard deviation of entrance times relative to the lesion. colored traces show lesion groups (DLS, DMS, DS, same as in [Figure 4.1](#)). *Right:* statistical comparison of ET variability. Each line represents one animal.

Bibliography

- [1] Peter D Balsam and C Randy Gallistel. “Temporal maps and informativeness in associative learning”. In: **Trends in neurosciences** 32.2 (2009), pp. 73–78 (cited on page 1).
- [2] Anna C Nobre and Freek van Ede. “Anticipated moments: temporal structure in attention”. In: **Nature Reviews Neuroscience** 19.1 (2018), p. 34 (cited on page 1).
- [3] Alex Kacelnik and Dani Brunner. “Timing and foraging: Gibbon’s scalar expectancy theory and optimal patch exploitation”. In: **Learning and Motivation** 33.1 (2002), pp. 177–195 (cited on page 1).
- [4] Charles R Gallistel. **The organization of learning**. The MIT Press, 1990 (cited on page 1).
- [5] Joseph J Paton and Dean V Buonomano. “The neural basis of timing: distributed mechanisms for diverse functions”. In: **Neuron** 98.4 (2018), pp. 687–705 (cited on pages: 2, 4, 5, 15, 22, 24, 82).
- [6] Sundeep Teki, Manon Grube, Sukhbinder Kumar, and Timothy D Griffiths. “Distinct neural substrates of duration-based and beat-based auditory timing”. In: **Journal of Neuroscience** 31.10 (2011), pp. 3805–3812 (cited on page 2).
- [7] Catalin V Buhusi and Warren H Meck. “What makes us tick? Functional and neural mechanisms of interval timing”. In: **Nature reviews neuroscience** 6.10 (2005), p. 755 (cited on pages: 3–5, 90).
- [8] John Gibbon. “Scalar expectancy theory and Weber’s law in animal timing.” In: **Psychological review** 84.3 (1977), p. 279 (cited on pages: 3, 4).
- [9] Christopher Miall. “The storage of time intervals using oscillating neurons”. In: **Neural Computation** 1.3 (1989), pp. 359–371 (cited on pages: 3, 5).
- [10] Thiago S Gouvêa, Tiago Monteiro, Asma Motiwala, Sofia Soares, Christian Machens, and Joseph J Paton. “Striatal dynamics explain duration judgments”. In: **Elife** 4 (2015), e11386 (cited on pages: 3, 22, 23).
- [11] Marc Wittmann. “The inner sense of time: how the brain creates a representation of duration”. In: **Nature Reviews Neuroscience** 14.3 (2013), p. 217 (cited on pages: 3, 6, 15).

- [12] Patrick Simen, Fuat Balci, Laura deSouza, Jonathan D Cohen, and Philip Holmes. “A model of interval timing by neural integration”. In: **Journal of Neuroscience** 31.25 (2011), pp. 9238–9253 (cited on page 4).
- [13] Helga Lejeune and JH Wearden. “The comparative psychology of fixed-interval responding: Some quantitative analyses”. In: **Learning and Motivation** 22.1-2 (1991), pp. 84–111 (cited on page 4).
- [14] Brian C Rakitin, John Gibbon, Trevor B Penney, Chara Malapani, Sean C Hinton, and Warren H Meck. “Scalar expectancy theory and peak-interval timing in humans.” In: **Journal of Experimental Psychology: Animal Behavior Processes** 24.1 (1998), p. 15 (cited on pages: 4, 11, 12).
- [15] Simon Whitaker, CF Lowe, and JH Wearden. “Multiple-interval timing in rats: Performance on two-valued mixed fixed-interval schedules”. In: **Journal of Experimental Psychology: Animal Behavior Processes** 29.4 (2003), p. 277 (cited on page 4).
- [16] Wilbert Zarco, Hugo Merchant, Luis Prado, and Juan Carlos Mendez. “Subsecond timing in primates: comparison of interval production between human subjects and rhesus monkeys”. In: **Journal of neurophysiology** 102.6 (2009), pp. 3191–3202 (cited on page 4).
- [17] Sean C Hinton and Warren H Meck. “Frontal–striatal circuitry activated by human peak-interval timing in the supra-seconds range”. In: **Cognitive Brain Research** 21.2 (2004), pp. 171–182 (cited on page 4).
- [18] Jing Wang, Devika Narain, Eghbal A Hosseini, and Mehrdad Jazayeri. “Flexible timing by temporal scaling of cortical responses”. In: **Nature neuroscience** 21.1 (2018), p. 102 (cited on pages: 4, 81, 82).
- [19] CR Gallistel, Adam King, and Robert McDonald. “Sources of variability and systematic error in mouse timing behavior.” In: **Journal of Experimental Psychology: Animal Behavior Processes** 30.1 (2004), p. 3 (cited on page 4).
- [20] John Gibbon, Russell M Church, Warren H Meck, and others. “Scalar timing in memory”. In: **Annals of the New York Academy of sciences** 423.1 (1984), pp. 52–77 (cited on page 4).
- [21] Peter R Killeen and J Gregor Fetterman. “A behavioral theory of timing”. In: **Psychological review** 95.2 (1988), p. 274 (cited on pages: 4, 10, 81).
- [22] Matthew S Matell and Warren H Meck. “Cortico-striatal circuits and interval timing: coincidence detection of oscillatory processes”. In: **Cognitive brain research** 21.2 (2004), pp. 139–170 (cited on page 5).
- [23] Mehrdad Jazayeri and Michael N Shadlen. “A neural mechanism for sensing and reproducing a time interval”. In: **Current Biology** 25.20 (2015), pp. 2599–2609 (cited on page 5).

- [24] Jeffrey P Gavornik, Marshall G Hussain Shuler, Yonatan Loewenstein, Mark F Bear, and Harel Z Shouval. “Learning reward timing in cortex through reward dependent expression of synaptic plasticity”. In: **Proceedings of the National Academy of Sciences** 106.16 (2009), pp. 6826–6831 (cited on page 6).
- [25] Uma R Karmarkar and Dean V Buonomano. “Timing in the absence of clocks: encoding time in neural network states”. In: **Neuron** 53.3 (2007), pp. 427–438 (cited on page 6).
- [26] Oswaldo Pérez and Hugo Merchant. “The synaptic properties of cells define the hallmarks of interval timing in a recurrent neural network”. In: **Journal of Neuroscience** 38.17 (2018), pp. 4186–4199 (cited on page 6).
- [27] Rolf Pfeifer and Josh Bongard. **How the body shapes the way we think: a new view of intelligence**. MIT press, 2006 (cited on pages: 8, 9).
- [28] Rodney A Brooks. “Intelligence without representation”. In: **Artificial intelligence** 47.1-3 (1991), pp. 139–159 (cited on page 8).
- [29] Alex Gomez-Marin and Asif A Ghazanfar. “The life of behavior”. In: **Neuron** 104.1 (2019), pp. 25–36 (cited on page 8).
- [30] Rolf Pfeifer, Max Lungarella, and Fumiya Iida. “Self-organization, embodiment, and biologically inspired robotics”. In: **science** 318.5853 (2007), pp. 1088–1093 (cited on page 8).
- [31] George Lakoff and Rafael E Núñez. **Where mathematics comes from: How the embodied mind brings mathematics into being**. Basic Books, 2000 (cited on page 8).
- [32] Esther Thelen, Donna M Fisher, and Robyn Ridley-Johnson. “The relationship between physical growth and a newborn reflex”. In: **Infant Behavior and Development** 7.4 (1984), pp. 479–493 (cited on page 9).
- [33] Martin Wiener, Weiwei Zhou, Farah Bader, and Wilsaan M Joiner. “Movement Improves the Quality of Temporal Perception and Decision-Making”. In: **eNeuro** 6.4 (2019) (cited on pages: 9, 12, 81).
- [34] Bodo Winter, Tyler Marghetis, and Teenie Matlock. “Of magnitudes and metaphors: Explaining cognitive interactions between space, time, and number”. In: **Cortex** 64 (2015), pp. 209–224 (cited on page 9).
- [35] Burrhus Frederic Skinner. “Superstition in the pigeon”. In: **Journal of experimental psychology** 38.2 (1948), p. 168 (cited on page 9).
- [36] Maurice P Wilson and Fred S Keller. “On the selective reinforcement of spaced responses”. In: **Journal of Comparative and Physiological Psychology** 46.3 (1953), p. 190 (cited on pages: 9, 10).
- [37] John L Falk. “The nature and determinants of adjunctive behavior”. In: **Physiology & Behavior** 6.5 (1971), pp. 577–588 (cited on page 10).
- [38] J Gregor Fetterman, Peter R Killeen, and Scott Hall. “Watching the clock”. In: **Behavioural processes** 44.2 (1998), pp. 211–224 (cited on pages: 10, 81).

- [39] Thiago S Gouvêa, Tiago Monteiro, Sofia Soares, Bassam V Atallah, and Joseph J Paton. “Ongoing behavior predicts perceptual report of interval duration”. In: **Frontiers in neurorobotics** 8 (2014), p. 10 (cited on pages: 11, 80).
- [40] Risa Kawai, Timothy Markman, Rajesh Poddar, Raymond Ko, Antoniu L Fantana, Ashesh K Dhawale, Adam R Kampff, and Bence P Ölveczky. “Motor cortex is required for learning but not for executing a motor skill”. In: **Neuron** 86.3 (2015), pp. 800–812 (cited on pages: 11, 79, 80, 90).
- [41] Pavel E Rueda-Orozco and David Robbe. “The striatum multiplexes contextual and kinematic information to constrain motor habits execution”. In: **Nature neuroscience** 18.3 (2015), p. 453 (cited on pages: 11, 30, 31, 34, 82, 83).
- [42] Hugo Merchant and Kielan Yarrow. “How the motor system both encodes and influences our sense of time”. In: **Current Opinion in Behavioral Sciences** 8 (2016), pp. 22–27 (cited on page 11).
- [43] Anne-Claire Rattat and Sylvie Droit-Volet. “What is the best and easiest method of preventing counting in different temporal tasks?” In: **Behavior Research Methods** 44.1 (2012), pp. 67–80 (cited on pages: 11, 81).
- [44] Friedrich Wilkening, Iris Levin, and Sara Druyan. “Children’s counting strategies for time quantification and integration”. In: **Developmental Psychology** 23.6 (1987), p. 823 (cited on page 11).
- [45] Jennifer T Coull and Sylvie Droit-Volet. “Explicit understanding of duration develops implicitly through action”. In: **Trends in cognitive sciences** 22.10 (2018), pp. 923–937 (cited on pages: 11, 81, 93).
- [46] Benjamin Morillon and Sylvain Baillet. “Motor origin of temporal predictions in auditory attention”. In: **Proceedings of the National Academy of Sciences** 114.42 (2017), E8913–E8921 (cited on pages: 12, 81).
- [47] Daniel V Meegan, Richard N Aslin, and Robert A Jacobs. “Motor timing learned without motor training”. In: **Nature neuroscience** 3.9 (2000), p. 860 (cited on page 12).
- [48] Lilian Fautrelle, Denis Mareschal, Robert French, Caspar Addyman, and Elizabeth Thomas. “Motor activity improves temporal expectancy”. In: **PloS one** 10.3 (2015), e0119187 (cited on page 12).
- [49] Florie Monier, Sylvie Droit-Volet, and Jennifer T Coull. “The beneficial effect of synchronized action on motor and perceptual timing in children”. In: **Developmental science** (2019), e12821 (cited on page 12).
- [50] Tehrim Yoon, Robert B Geary, Alaa A Ahmed, and Reza Shadmehr. “Control of movement vigor and decision making during foraging”. In: **Proceedings of the National Academy of Sciences** 115.44 (2018), E10476–E10485 (cited on page 12).
- [51] Reza Shadmehr, Thomas R Reppert, Erik M Summerside, Tehrim Yoon, and Alaa A Ahmed. “Movement vigor as a reflection of subjective economic utility”. In: **Trends in neurosciences** (2019) (cited on pages: 12, 14, 91).

- [52] Matthew A Carland, David Thura, and Paul Cisek. “The Urge to Decide and Act: Implications for Brain Function and Dysfunction”. In: **The Neuroscientist** 25.5 (2019), pp. 491–511 (cited on pages: 12, 31, 91).
- [53] Jennie ES Choi, Pavan A Vaswani, and Reza Shadmehr. “Vigor of movements and the cost of time in decision making”. In: **Journal of neuroscience** 34.4 (2014), pp. 1212–1223 (cited on page 13).
- [54] Reza Shadmehr, Jean Jacques Orban De Xivry, Mennan Xu-Wilson, and Ting-Yu Shih. “Temporal discounting of reward and the cost of time in motor control”. In: **Journal of Neuroscience** 30.31 (2010), pp. 10507–10516 (cited on pages: 13, 14, 86).
- [55] Bastien Berret, Carole Castanier, Simon Bastide, and Thomas Deroche. “Vigour of self-paced reaching movement: cost of time and individual traits”. In: **Scientific reports** 8.1 (2018), p. 10655 (cited on pages: 13, 14).
- [56] Reza Shadmehr, Helen J Huang, and Alaa A Ahmed. “A representation of effort in decision-making and motor control”. In: **Current biology** 26.14 (2016), pp. 1929–1934 (cited on page 13).
- [57] Bastien Berret and Frédéric Jean. “Why don’t we move slower? the value of time in the neural control of action”. In: **Journal of neuroscience** 36.4 (2016), pp. 1056–1070 (cited on pages: 13, 14).
- [58] David Thura, Ignasi Cos, Jessica Trung, and Paul Cisek. “Context-dependent urgency influences speed–accuracy trade-offs in decision-making and movement execution”. In: **Journal of Neuroscience** 34.49 (2014), pp. 16442–16454 (cited on pages: 13, 31).
- [59] Leroy L Long III and Manoj Srinivasan. “Walking, running, and resting under time, distance, and average speed constraints: optimality of walk–run–rest mixtures”. In: **Journal of The Royal Society Interface** 10.81 (2013), p. 20120980 (cited on page 14).
- [60] Christopher M Harris and Daniel M Wolpert. “The main sequence of saccades optimizes speed–accuracy trade-off”. In: **Biological cybernetics** 95.1 (2006), pp. 21–29 (cited on page 14).
- [61] Eric Allen Yttri and Joshua Tate Dudman. “A Proposed Circuit Computation in Basal Ganglia: History-Dependent Gain”. In: **Movement Disorders** 33.5 (2018), pp. 704–716 (cited on pages: 14, 32).
- [62] Joshua T Dudman and John W Krakauer. “The basal ganglia: from motor commands to the control of vigor”. In: **Current opinion in neurobiology** 37 (2016), pp. 158–166 (cited on pages: 14, 83, 88, 90).
- [63] Thomas R Reppert, Karolina M Lempert, Paul W Glimcher, and Reza Shadmehr. “Modulation of saccade vigor during value-based decision making”. In: **Journal of Neuroscience** 35.46 (2015), pp. 15369–15378 (cited on page 14).

- [64] DJ Willshaw, P Dayan, and RGM Morris. “Memory, modelling and Marr: a commentary on Marr (1971) ‘Simple memory: a theory of archicortex’”. In: **Philosophical Transactions of the Royal Society B: Biological Sciences** 370.1666 (2015), p. 20140383 (cited on page 15).
- [65] John W Krakauer, Asif A Ghazanfar, Alex Gomez-Marin, Malcolm A MacIver, and David Poeppel. “Neuroscience needs behavior: correcting a reductionist bias”. In: **Neuron** 93.3 (2017), pp. 480–490 (cited on pages: 15, 82).
- [66] Eric Jonas and Konrad Paul Kording. “Could a neuroscientist understand a microprocessor?” In: **PLoS computational biology** 13.1 (2017), e1005268 (cited on page 15).
- [67] Robert S Turner and Michel Desmurget. “Basal ganglia contributions to motor control: a vigorous tutor”. In: **Current opinion in neurobiology** 20.6 (2010), pp. 704–716 (cited on pages: 15, 84, 88).
- [68] Sten Grillner and Brita Robertson. “The basal ganglia over 500 million years”. In: **Current Biology** 26.20 (2016), R1088–R1100 (cited on pages: 16–18).
- [69] Dorothy E Oorschot. “Total number of neurons in the neostriatal, pallidal, subthalamic, and substantia nigral nuclei of the rat basal ganglia: a stereological study using the cavalieri and optical disector methods”. In: **Journal of Comparative Neurology** 366.4 (1996), pp. 580–599 (cited on page 16).
- [70] Peter Redgrave, Manuel Rodriguez, Yoland Smith, Maria C Rodriguez-Oroz, Stephane Lehericy, Hagai Bergman, Yves Agid, Mahlon R DeLong, and Jose A Obeso. “Goal-directed and habitual control in the basal ganglia: implications for Parkinson’s disease”. In: **Nature Reviews Neuroscience** 11.11 (2010), p. 760 (cited on pages: 16, 28).
- [71] Jonathan W Mink. “The basal ganglia: focused selection and inhibition of competing motor programs”. In: **Progress in neurobiology** 50.4 (1996), pp. 381–425 (cited on pages: 16, 19, 26, 83).
- [72] Joshua T Dudman and Charles R Gerfen. “The basal ganglia”. In: **The rat nervous system**. Elsevier, 2015, pp. 391–440 (cited on pages: 16–18, 20, 21).
- [73] Julia Cox and Ilana B Witten. “Striatal circuits for reward learning and decision-making”. In: **Nature Reviews Neuroscience** 20.8 (2019), pp. 482–494 (cited on page 16).
- [74] Houri Hintiryan, Nicholas N Foster, Ian Bowman, Maxwell Bay, Monica Y Song, Lin Gou, Seita Yamashita, Michael S Bienkowski, Brian Zingg, Muye Zhu, and others. “The mouse cortico-striatal projectome”. In: **Nature neuroscience** 19.8 (2016), p. 1100 (cited on pages: 17, 19, 20, 91).
- [75] Barbara J Hunnicutt, Bart C Jongbloets, William T Birdsong, Katrina J Gertz, Haining Zhong, and Tianyi Mao. “A comprehensive excitatory input map of the striatum reveals novel functional organization”. In: **Elife** 5 (2016), e19103 (cited on pages: 17, 19, 91).

- [76] Robert S. Turner and Benjamin Pasquereau. “Basal ganglia function”. In: **Journal of anatomy**. Vol. 196 (Pt 4. Journal of anatomy, 2000, pp. 543–554 (cited on pages: 17, 20, 21).
- [77] Charles J Wilson. “GABAergic inhibition in the neostriatum”. In: **Progress in brain research** 160 (2007), pp. 91–110 (cited on pages: 17, 18).
- [78] Eric R Kandel, James H Schwartz, Thomas M Jessell, Department of Biochemistry, Molecular Biophysics Thomas Jessell, Steven Siegelbaum, and AJ Hudspeth. **Principles of neural science**. Vol. 4. McGraw-hill New York, 2000 (cited on pages: 17, 22).
- [79] Gregory J Gage, Colin R Stoetzner, Alexander B Wiltschko, and Joshua D Berke. “Selective activation of striatal fast-spiking interneurons during choice execution”. In: **Neuron** 67.3 (2010), pp. 466–479 (cited on page 18).
- [80] Garrett E Alexander, Mahlon R DeLong, and Peter L Strick. “Parallel organization of functionally segregated circuits linking basal ganglia and cortex”. In: **Annual review of neuroscience** 9.1 (1986), pp. 357–381 (cited on page 18).
- [81] Marjan Jahanshahi, Ignacio Obeso, John C Rothwell, and José A Obeso. “A fronto-striato-subthalamic-pallidal network for goal-directed and habitual inhibition”. In: **Nature Reviews Neuroscience** 16.12 (2015), pp. 719–732 (cited on page 19).
- [82] Thomas Boraud, Arthur Leblois, and Nicolas P Rougier. “A natural history of skills”. In: **Progress in neurobiology** 171 (2018), pp. 114–124 (cited on page 19).
- [83] Regina M Carelli and Mark O West. “Representation of the body by single neurons in the dorsolateral striatum of the awake, unrestrained rat”. In: **Journal of Comparative Neurology** 309.2 (1991), pp. 231–249 (cited on page 19).
- [84] Henry H Yin and Barbara J Knowlton. “The role of the basal ganglia in habit formation”. In: **Nature Reviews Neuroscience** 7.6 (2006), p. 464 (cited on pages: 19, 90).
- [85] David Robbe. “To move or to sense? Incorporating somatosensory representation into striatal functions”. In: **Current opinion in neurobiology** 52 (2018), pp. 123–130 (cited on pages: 20, 82).
- [86] Alexxai V Kravitz, Benjamin S Freeze, Philip RL Parker, Kenneth Kay, Myo T Thwin, Karl Deisseroth, and Anatol C Kreitzer. “Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry”. In: **Nature** 466.7306 (2010), p. 622 (cited on pages: 21, 26, 31, 83, 88).
- [87] Guohong Cui, Sang Beom Jun, Xin Jin, Michael D Pham, Steven S Vogel, David M Lovinger, and Rui M Costa. “Concurrent activation of striatal direct and indirect pathways during action initiation”. In: **Nature** 494.7436 (2013), p. 238 (cited on pages: 21, 26, 31, 83).

- [88] Babita Panigrahi, Kathleen A Martin, Yi Li, Austin R Graves, Alison Vollmer, Lars Olson, Brett D Mensh, Alla Y Karpova, and Joshua T Dudman. “Dopamine is required for the neural representation and control of movement vigor”. In: **Cell** 162.6 (2015), pp. 1418–1430 (cited on pages: [21](#), [28](#), [83](#), [88](#), [96](#)).
- [89] Matthew M McGregor and Alexandra B Nelson. “Circuit mechanisms of Parkinson’s disease”. In: **Neuron** 101.6 (2019), pp. 1042–1056 (cited on pages: [21](#), [28](#), [83](#)).
- [90] Elijah A Petter, Samuel J Gershman, and Warren H Meck. “Integrating models of interval timing and reinforcement learning”. In: **Trends in cognitive sciences** 22.10 (2018), pp. 911–922 (cited on page [22](#)).
- [91] Yi Li and Joshua Tate Dudman. “Mice infer probabilistic models for timing”. In: **Proceedings of the National Academy of Sciences** 110.42 (2013), pp. 17154–17159 (cited on page [22](#)).
- [92] Stephen M Rao, Andrew R Mayer, and Deborah L Harrington. “The evolution of brain activation during temporal processing”. In: **Nature neuroscience** 4.3 (2001), p. 317 (cited on page [22](#)).
- [93] Viviane Pouthas, Nathalie George, Jean-Baptiste Poline, Micha Pfeuty, Pierre-François VandeMoortele, Laurent Hugueville, Anne-Marie Fernandez, Stéphane Lehéricy, Denis LeBihan, and Bernard Renault. “Neural network involved in time perception: an fMRI study comparing long and short interval estimation”. In: **Human brain mapping** 25.4 (2005), pp. 433–441 (cited on pages: [22](#), [81](#)).
- [94] Matthew S Matell, Warren H Meck, and Miguel AL Nicolelis. “Interval timing and the encoding of signal duration by ensembles of cortical and striatal neurons”. In: **Behavioral neuroscience** 117.4 (2003), p. 760 (cited on page [23](#)).
- [95] Gustavo BM Mello, Sofia Soares, and Joseph J Paton. “A scalable population code for time in the striatum”. In: **Current Biology** 25.9 (2015), pp. 1113–1122 (cited on pages: [23](#), [24](#), [81](#)).
- [96] Konstantin I Bakurin, Vishwa Goudar, Justin L Shobe, Leslie D Claar, Dean V Buonomano, and Sotiris C Masmanidis. “Differential encoding of time by prefrontal and striatal network dynamics”. In: **Journal of Neuroscience** 37.4 (2017), pp. 854–870 (cited on pages: [23](#), [81](#)).
- [97] Benjamin J De Corte, Lucia M Wagner, Matthew S Matell, and Nandakumar S Narayanan. “Striatal dopamine and the temporal control of behavior”. In: **Behavioural brain research** 356 (2019), pp. 375–379 (cited on page [24](#)).
- [98] Joshua D Berke. “What does dopamine mean?” In: **Nature neuroscience** 21.6 (2018), p. 787 (cited on pages: [24](#), [88](#)).
- [99] Yuji K Takahashi, Angela J Langdon, Yael Niv, and Geoffrey Schoenbaum. “Temporal specificity of reward prediction errors signaled by putative dopamine neurons in rat VTA depends on ventral striatum”. In: **Neuron** 91.1 (2016), pp. 182–193 (cited on page [24](#)).

- [100] Sofia Soares, Bassam V Atallah, and Joseph J Paton. “Midbrain dopamine neurons control judgment of time”. In: **Science** 354.6317 (2016), pp. 1273–1277 (cited on pages: 24, 89).
- [101] Christopher D Howard, Hao Li, Claire E Geddes, and Xin Jin. “Dynamic nigrostriatal dopamine biases action selection”. In: **Neuron** 93.6 (2017), pp. 1436–1450 (cited on page 24).
- [102] Ariel W Snowden and Catalin V Buhusi. “Neural Correlates of Interval Timing Deficits in Schizophrenia”. In: **Frontiers in human neuroscience** 13 (2019) (cited on page 25).
- [103] Yarden Dankner, Lilach Shalev, Marisa Carrasco, and Shlomit Yuval-Greenberg. “Prestimulus inhibition of saccades in adults with and without attention-deficit/hyperactivity disorder as an index of temporal expectations”. In: **Psychological Science** 28.7 (2017), pp. 835–850 (cited on page 25).
- [104] Thomas E Cope, Manon Grube, Baldev Singh, David J Burn, and Timothy D Griffiths. “The basal ganglia in perceptual timing: timing performance in Multiple System Atrophy and Huntington’s disease”. In: **Neuropsychologia** 52 (2014), pp. 73–81 (cited on page 25).
- [105] Deborah L Harrington, Kathleen Y Haaland, and Neal Hermanowitz. “Temporal processing in the basal ganglia.” In: **Neuropsychology** 12.1 (1998), p. 3 (cited on page 25).
- [106] Simone Dalla Bella, Charles-Etienne Benoit, Nicolas Farrugia, Peter E Keller, Hellmuth Obrig, Stefan Mainka, and Sonja A Kotz. “Gait improvement via rhythmic stimulation in Parkinson’s disease is linked to rhythmic skills”. In: **Scientific reports** 7 (2017), p. 42005 (cited on page 25).
- [107] Giovanni Barbera, Bo Liang, Lifeng Zhang, Charles R Gerfen, Eugenio Culurciello, Rong Chen, Yun Li, and Da-Ting Lin. “Spatially compact neural clusters in the dorsal striatum encode locomotion relevant information”. In: **Neuron** 92.1 (2016), pp. 202–213 (cited on pages: 26, 31, 83).
- [108] Andreas Klaus, Gabriela J Martins, Vitor B Paixao, Pengcheng Zhou, Liam Paninski, and Rui M Costa. “The spatiotemporal organization of the striatum encodes action space”. In: **Neuron** 95.5 (2017), pp. 1171–1180 (cited on pages: 26, 83).
- [109] Xin Jin, Fatuel Tecuapetla, and Rui M Costa. “Basal ganglia subcircuits distinctively encode the parsing and concatenation of action sequences”. In: **Nature neuroscience** 17.3 (2014), pp. 423–430 (cited on page 27).
- [110] Terra D Barnes, Yasuo Kubota, Dan Hu, Dezhe Z Jin, and Ann M Graybiel. “Activity of striatal neurons reflects dynamic encoding and recoding of procedural memories”. In: **Nature** 437.7062 (2005), pp. 1158–1161 (cited on pages: 27, 83, 96).

- [111] Xin Jin and Rui M Costa. “Start/stop signals emerge in nigrostriatal circuits during sequence learning”. In: **Nature** 466.7305 (2010), pp. 457–462 (cited on pages: 27, 83).
- [112] Nuné Martiros, Alexandra A Burgess, and Ann M Graybiel. “Inversely active striatal projection neurons and interneurons selectively delimit useful behavioral sequences”. In: **Current Biology** 28.4 (2018), pp. 560–573 (cited on page 27).
- [113] Carola Sales-Carbonell, Wahiba Taouali, Loubna Khalki, Matthieu O Pasquet, Ludovic F Petit, Typhaine Moreau, Pavel E Rueda-Orozco, and David Robbe. “No discrete start/stop signals in the dorsal striatum of mice performing a learned action”. In: **Current Biology** 28.19 (2018), pp. 3044–3055 (cited on pages: 27, 28).
- [114] Jeffrey E Markowitz, Winthrop F Gillis, Celia C Beron, Shay Q Neufeld, Keira-marie Robertson, Neha D Bhagat, Ralph E Peterson, Emalee Peterson, Minsuk Hyun, Scott W Linderman, and others. “The striatum organizes 3D behavior via moment-to-moment action selection”. In: **Cell** 174.1 (2018), pp. 44–58 (cited on pages: 27, 31).
- [115] Oleh Hornykiewicz. “The discovery of dopamine deficiency in the parkinsonian brain”. In: **Parkinson’s Disease and Related Disorders**. Springer, 2006, pp. 9–15 (cited on pages: 28, 83).
- [116] Pietro Mazzoni, Anna Hristova, and John W Krakauer. “Why don’t we move faster? Parkinson’s disease, movement vigor, and implicit motivation”. In: **Journal of neuroscience** 27.27 (2007), pp. 7105–7116 (cited on pages: 28, 29, 86, 88, 96).
- [117] Liane Schmidt, Baudouin Forgeot d’Arc, Gilles Lafargue, Damien Galanaud, Virginie Czernecki, David Grabli, Michael Schüpbach, Andreas Hartmann, Richard Lévy, Bruno Dubois, and others. “Disconnecting force from money: effects of basal ganglia damage on incentive motivation”. In: **Brain** 131.5 (2008), pp. 1303–1310 (cited on pages: 29, 86).
- [118] Michel Desmurget and Robert S Turner. “Motor sequences and the basal ganglia: kinematics, not habits”. In: **Journal of Neuroscience** 30.22 (2010), pp. 7685–7690 (cited on pages: 29, 30, 84).
- [119] Timothy M Otchy, Steffen BE Wolff, Juliana Y Rhee, Cengiz Pehlevan, Risa Kawai, Alexandre Kempf, Sharon MH Gobes, and Bence P Ölveczky. “Acute off-target effects of neural circuit manipulations”. In: **Nature** 528.7582 (2015), p. 358 (cited on pages: 30, 84, 95).
- [120] Kathleen R Bailey and Robert G Mair. “The role of striatum in initiation and execution of learned action sequences in rats”. In: **Journal of Neuroscience** 26.3 (2006), pp. 1016–1025 (cited on page 30).
- [121] Anna Castañé, David EH Theobald, and Trevor W Robbins. “Selective lesions of the dorsomedial striatum impair serial spatial reversal learning in rats”. In: **Behavioural brain research** 210.1 (2010), pp. 74–83 (cited on page 30).

- [122] Hadley C Bergstrom, Anna M Lipkin, Abby G Lieberman, Courtney R Pinard, Ozge Gunduz-Cinar, Emma T Brockway, William W Taylor, Mio Nonaka, Olena Bukalo, Tiffany A Wills, and others. “Dorsolateral striatum engagement interferes with early discrimination learning”. In: **Cell reports** 23.8 (2018), pp. 2264–2272 (cited on page 30).
- [123] Stefan M Lemke, Dhakshin S Ramanathan, Ling Guo, Seok Joon Won, and Karunesh Ganguly. “Emergent modular neural control drives coordinated motor actions”. In: **Nature neuroscience** (2019), p. 1 (cited on page 30).
- [124] Claire E Geddes, Hao Li, and Xin Jin. “Optogenetic editing reveals the hierarchical organization of learned action sequences”. In: **Cell** 174.1 (2018), pp. 32–43 (cited on page 30).
- [125] Genevra Hart, Laura A Bradfield, Sandra Y Fok, Billy Chieng, and Bernard W Balleine. “The bilateral prefronto-striatal pathway is necessary for learning new goal-directed actions”. In: **Current Biology** 28.14 (2018), pp. 2218–2229 (cited on pages: 30, 89, 90).
- [126] Rafal Bogacz, Eric-Jan Wagenmakers, Birte U Forstmann, and Sander Nieuwenhuis. “The neural basis of the speed–accuracy tradeoff”. In: **Trends in neurosciences** 33.1 (2010), pp. 10–16 (cited on page 30).
- [127] David Thura and Paul Cisek. “The basal ganglia do not select reach targets but control the urgency of commitment”. In: **Neuron** 95.5 (2017), pp. 1160–1170 (cited on pages: 30, 31, 91, 96).
- [128] Eric A Yttri and Joshua T Dudman. “Opponent and bidirectional control of movement velocity in the basal ganglia”. In: **Nature** 533.7603 (2016), p. 402 (cited on pages: 31, 32, 83, 88, 89).
- [129] Kyle Dunovan and Timothy Verstynen. “Believer-Skeptic meets Actor-Critic: Rethinking the role of basal ganglia pathways during decision-making and reinforcement learning”. In: **Frontiers in neuroscience** 10 (2016), p. 106 (cited on pages: 32, 33, 82, 89).
- [130] Shigeyoshi Fujisawa, Asohan Amarasingham, Matthew T Harrison, and György Buzsáki. “Behavior-dependent short-term assembly dynamics in the medial prefrontal cortex”. In: **Nature neuroscience** 11.7 (2008), p. 823 (cited on page 46).
- [131] Bradley Efron and Robert J Tibshirani. **An introduction to the bootstrap**. CRC press, 1994 (cited on page 47).
- [132] Raphael Vallat. “Pingouin: statistics in Python”. In: **Journal of Open Source Software** 3.31 (2018), p. 1026 (cited on page 47).
- [133] Mostafa Safaie, Maria-Teresa Jurado-Parras, Stefania Sarno, Jordane Louis, Corane Karoutchi, Ludovic F. Petit, Matthieu O. Pasquet, Christophe Eloy, and David Robbe. “The Embodied Nature of Well-Timed Behavior”. In: **bioRxiv** (2019), p. 716274 (cited on pages: 47, 51, 77, 91).

- [134] Maria-Teresa Jurado-Parras, Mostafa Safaie, Stefania Sarno, Jordane Louis, Corane Karoutchi, Bastien Berret, and David Robbe. “The dorsal striatum energizes rather than select purposive actions”. In: **bioRxiv** (2020), ? (Cited on pages: 47, 64, 73, 87, 91).
- [135] Dean V Buonomano and Rodrigo Laje. “Population clocks: motor timing with neural dynamics”. In: **Space, Time and Number in the Brain**. Elsevier, 2011, pp. 71–85 (cited on page 78).
- [136] Yi-Huang Su and Ernst Pöppel. “Body movement enhances the extraction of temporal structures in auditory sequences”. In: **Psychological research** 76.3 (2012), pp. 373–382 (cited on page 81).
- [137] Fiona Manning and Michael Schutz. ““Moving to the beat” improves timing perception”. In: **Psychonomic Bulletin & Review** 20.6 (2013), pp. 1133–1139 (cited on page 81).
- [138] Benjamin J Kraus, Robert J Robinson II, John A White, Howard Eichenbaum, and Michael E Hasselmo. “Hippocampal “time cells”: time versus path integration”. In: **Neuron** 78.6 (2013), pp. 1090–1101 (cited on page 81).
- [139] Bon-Mi Gu, Keshav Kukreja, and Warren H Meck. “Oscillation patterns of local field potentials in the dorsal striatum and sensorimotor cortex during the encoding, maintenance, and decision stages for the ordinal comparison of sub- and supra-second signal durations”. In: **Neurobiology of learning and memory** 153 (2018), pp. 79–91 (cited on page 81).
- [140] Ricarda I Schubotz, Angela D Friederici, and D Yves Von Cramon. “Time perception and motor timing: a common cortical and subcortical basis revealed by fMRI”. In: **Neuroimage** 11.1 (2000), pp. 1–12 (cited on page 81).
- [141] James G Heys and Daniel A Dombeck. “Evidence for a subcircuit in medial entorhinal cortex representing elapsed time during immobility”. In: **Nature neuroscience** 21.11 (2018), pp. 1574–1582 (cited on pages: 81, 82).
- [142] Valentin Dragoi, JER Staddon, Richard G Palmer, and Catalin V Buhusi. “Interval timing as an emergent learning property.” In: **Psychological review** 110.1 (2003), p. 126 (cited on page 81).
- [143] JER Staddon and JJ Higa. “Time and memory: Towards a pacemaker-free theory of interval timing”. In: **Journal of the experimental analysis of behavior** 71.2 (1999), pp. 215–251 (cited on page 81).
- [144] György Buzsáki and Rodolfo Llinás. “Space and time in the brain”. In: **Science** 358.6362 (2017), pp. 482–485 (cited on page 82).
- [145] György Buzsáki and David Tingley. “Space and time: The hippocampus as a sequence generator”. In: **Trends in cognitive sciences** 22.10 (2018), pp. 853–869 (cited on page 82).
- [146] Michael M Yartsev, Timothy D Hanks, Alice Misun Yoon, and Carlos D Brody. “Causal contribution and dynamical encoding in the striatum during evidence accumulation”. In: **Elife** 7 (2018), e34929 (cited on page 82).

- [147] Alexander Mathis, Pranav Mamidanna, Kevin M Cury, Taiga Abe, Venkatesh N Murthy, Mackenzie Weygandt Mathis, and Matthias Bethge. “DeepLabCut: markerless pose estimation of user-defined body parts with deep learning”. In: **Nature neuroscience** 21.9 (2018), p. 1281 (cited on pages: [83](#), [95](#)).
- [148] Namsoo Kim, Joseph W Barter, Tatyana Sukharnikova, and Henry H Yin. “Striatal firing rate reflects head movement velocity”. In: **European Journal of Neuroscience** 40.10 (2014), pp. 3481–3490 (cited on page [83](#)).
- [149] Ashesh K Dhawale, Steffen BE Wolff, Raymond Ko, and Bence P Ölveczky. “The basal ganglia can control learned motor sequences independently of motor cortex”. In: **BioRxiv** (2019), p. 827261 (cited on pages: [85](#), [90](#)).
- [150] Jeff A Beeler, Cristianne RM Frazier, and Xiaoxi Zhuang. “Putting desire on a budget: dopamine and energy expenditure, reconciling reward and resources”. In: **Frontiers in integrative neuroscience** 6 (2012), p. 49 (cited on page [88](#)).
- [151] Mark W Howe and Daniel A Dombeck. “Rapid signalling in distinct dopaminergic axons during locomotion and reward”. In: **Nature** 535.7613 (2016), pp. 505–510 (cited on page [89](#)).
- [152] Miriam Matamales, Alice E McGovern, Jia Dai Mi, Stuart B Mazzone, Bernard W Balleine, and Jesus Bertran-Gonzalez. “Local D2-to D1-neuron transmodulation updates goal-directed learning in the striatum”. In: **Science** 367.6477 (2020), pp. 549–555 (cited on page [89](#)).
- [153] Ali Mohebi, Jeffrey R Pettibone, Arif A Hamid, Jenny-Marie T Wong, Leah T Vinson, Tommaso Patriarchi, Lin Tian, Robert T Kennedy, and Joshua D Berke. “Dissociable dopamine dynamics for learning and motivation”. In: **Nature** 570.7759 (2019), pp. 65–70 (cited on page [90](#)).
- [154] Christina M Gremel and Rui M Costa. “Orbitofrontal and striatal circuits dynamically encode the shift between goal-directed and habitual actions”. In: **Nature communications** 4.1 (2013), pp. 1–12 (cited on page [90](#)).
- [155] Youna Vandaele, Nagaraj R Mahajan, David J Ottenheimer, Jocelyn M Richard, Shreesh P Mysore, and Patricia H Janak. “Distinct recruitment of dorsomedial and dorsolateral striatum erodes with extended training”. In: **eLife** 8 (2019) (cited on page [91](#)).
- [156] Hedderik van Rijn. “Towards ecologically valid interval timing”. In: **Trends in cognitive sciences** 22.10 (2018), pp. 850–852 (cited on page [95](#)).
- [157] Jeffrey R Pettibone, Y Yu Jai, Rifka C Derman, Thomas W Faust, Elizabeth D Hughes, Wanda E Filipiak, Thomas L Saunders, Carrie R Ferrario, and Joshua D Berke. “Knock-in rat lines with Cre recombinase at the dopamine D1 and adenosine 2a receptor loci”. In: **eNeuro** (2019) (cited on page [95](#)).
- [158] Yanfang Zuo and Mathew E Diamond. “Rats generate vibrissal sensory evidence until boundary crossing triggers a decision”. In: **Current Biology** 29.9 (2019), pp. 1415–1424 (cited on page [96](#)).

Acronyms

BG basal ganglia. 15–19, 21–24, 26, 28–34, 64, 81–84, 88, 89, 91

CoT cost of time. 13, 14, 86, 91

D1 D1 dopamine receptor. 20, 21, 24, 26, 27, 31–33, 83, 89

D2 D2 dopamine receptor. 20, 21, 24, 26, 27, 31–33, 83, 89

DA dopamine. 16, 17, 21, 24, 25, 28, 32, 82, 83, 88–90

DLS dorsolateral striatum. 18–20, 27, 31, 34, 45, 65, 67, 69, 70, 72, 73, 84, 85, 90, 91

DMS dorsomedial striatum. 19, 20, 32, 34, 45, 65, 67, 72, 73, 82, 84, 85, 90, 91

DS dorsal striatum. 16, 18–20, 23, 24, 43–45, 65, 72, 73, 82, 84, 87, 88, 91, 94

ET entrance time. 37–41, 46, 51, 52, 54, 55, 57–61, 65, 66, 68, 69, 73, 79, 86, 87

FSI fast spiking interneuron. 18

GPe globus pallidus externus. 16, 20, 21, 30

GPi globus pallidus internus. 16, 20, 21, 29–31

GT goal time. 38–40, 51, 52, 54–56, 58, 60, 61, 64, 65, 68, 77, 79, 86

HDG history-dependant gain. 32

MSN medium spiny neuron. 17, 18, 20, 21, 26, 27, 32, 83, 89

PD Parkinson's disease. 21, 22, 25, 28, 29, 83, 84, 86, 88

SNc substantia nigra pars compacta. 16, 21, 29

SNr substantia nigra pars reticulata. 16, 20, 21

STN subthalamic nucleus. 16, 20, 21