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Embodied Time Estimation and the Contribution of the Dorsal Striatum

Defended on 28/04/2020 before the jury composed of:

Philippe Faure	Sorbonne University	Reviewer
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Joseph J. Paton	Champalimaud Centre for the Unknown	Examiner
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Mostafa SAFAIE

Estimation du Temps D'incarnation et Contribution du Striatum Dorsal

Soutenue le 28/04/2020 devant le jury composé de :

Philippe FAURE	Sorbonne Université	Rapporteur
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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 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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Chapter 1

Introduction

For humans and other animals, in any given context, an adaptive behavior is defined as the capacity to execute the action that will maximize immediate or future rewards, while minimizing energetic 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 appearance of the cue, this action must be initiated [1, 2]. For instance, athletes performing sprint races learn by experience that the *go* command, signalling them to start running, will be given in two seconds after the *set* command. False starts, i.e., beginning to run too early, demonstrates athletes' accurate estimation of 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 to use in this manuscript. Then I discuss two possible mechanisms that could give rise to the perception of elapsed time. Later, I will present 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 explicit 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 solve and hence, 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. There is evidence of differential neural mechanisms at play for simple timing tasks (such as reproducing a duration) as opposed to tasks where the global temporal structure of the stimuli is determinant (such as recognizing the tempo of a song) [6].

[i] This 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 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: $S = klogI$, 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 [5]. 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.,

[iii] Mathematically, 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, activity of each neuron, if isolated, would decay after stimulus presentation. However, by introducing recurrent connections, lateral propagation of activity in the network decreases each neuron's activity decay rate 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 processes 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 different. 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. Paton and Buonomano reviewed many of these models in a recent paper [5].

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 delicacies 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].

Since then, 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 [29]. 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 [29].

In the animal kingdom, embodiment enables both cognition–even the most abstract processes, like mathematical reasoning [30]– 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 [31]. 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 [31]. 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 developing nervous system, Thelen and others showed that loss of stepping behavior

[iv] According to the Oxford dictionary, embodiment is defined as: "A tangible or visible form of an idea, quality, or feeling".

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, one pigeon was conditioned to turn counter-clockwise in the cage two or three times between each reward delivery which was every 5 s, irrespective of the animal's behavior. 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 too engaged in a recognizable chain of behaviors that the authors called 'collateral'. These behaviors were also unique to each animal. Interestingly, with increasing the interval between reward deliveries, more links were added to the chain of collateral behaviors [36]. Both studies mentioned

[v] It 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].

above explain these behaviors as being accidentally reinforced by 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 judgement than the passage of time [38]. In one of the rare studies 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

[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.

[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!

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

1.3.2 Costs 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].

Optimizing 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, maximizing the capture rate translates to performing a motor strategy with the following properties: 1) It is of appropriate duration and reproducible to generate reliable well-timed responses; 2) 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 translates 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 parameters defining the capture rate become interdependent is passage of time itself.

[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].

Cost of Time

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 impulsively, 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 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 reflects 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].

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 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

[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].

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, basal ganglia (BG) is of unique interest. For decades, 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 timing behavior through sensorimotor mechanisms.

1.4.1 The Basal Ganglia

The basal ganglia 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

[x] So 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]

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 [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.

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].

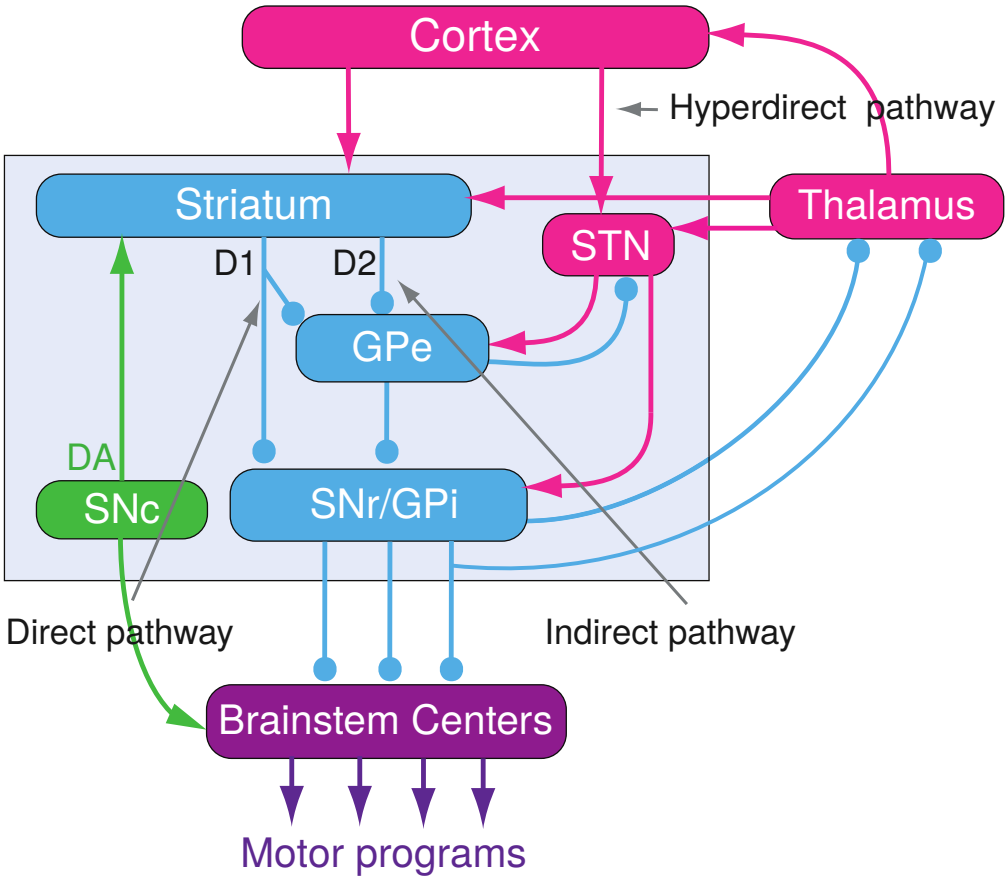

Figure 1.1 – Anatomy of the basal ganglia. STN: subthalamic nucleus; GPe: globus pallidus externus; SNc: substantia nigra pars compacta; SNr: substantia nigra pars reticulata; GPi: globus pallidus internus; DA: Dopamine. Figure slightly modified from [68].

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 It has been long known that corticostriatal projections are topographical, roughly following the rostro-caudal and latero-medial organization in the cerebral cortex. For instance, frontal cortices project to rostral areas, sensorimotor cortex provides input to dorsal striatum, 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 dorsolateral striatum (DLS), ventrolateral thalamus, and sensorimotor cortices. Similarly, the limbic (emotional) loop includes the ventral striatum, dorsomedial thalamus, and limbic areas (amygdala, limbic cortices, and hippocampus). Finally, the cognitive (associative) loop comprise 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 dorsal striatum, 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., forelimb, neck, snout,…) were generally located in close proximity, generating a somatotopic map [83]. Such an anatomical mapping from sensorimotor cortices to DLS has recently been quantitatively scrutinized in mice [74, 75]. These studies, using multiple injections of anterograde tracers, constructed a comprehensive excitatory input map of the dorsal striatum. 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,

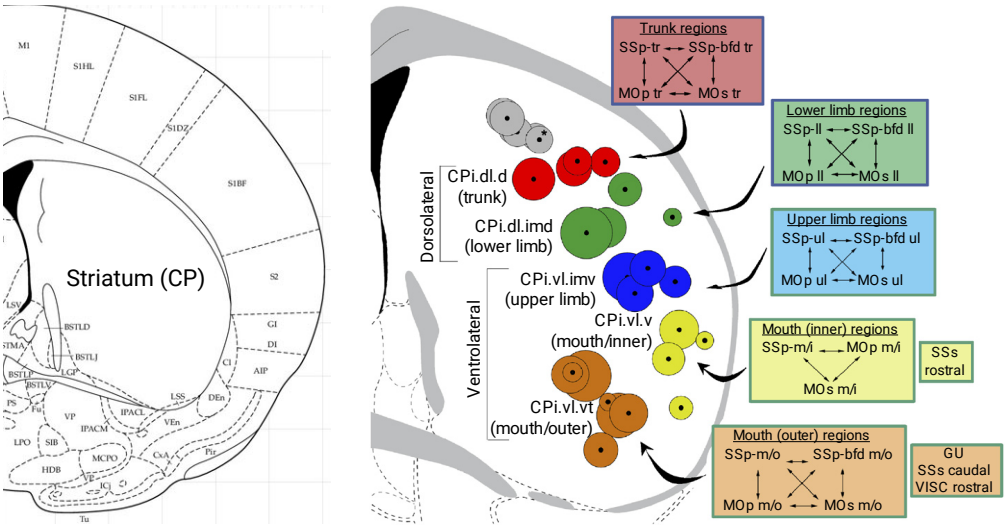

Figure 1.2 – Somatotopic map of cortical inputs to DLS. *Left*: striatum in the rat brain atlas. *Right*: input from somatosensory cortices form a topographic map in the DLS. Abbreviations are defined in the original reference and are not important for the purposes of this work. Figure adopted from [74].

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 motor

[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.

cortex, somatosensory cortex, but also frontal association cortex, amygdala, and prelimbic cortex, and expands medially much larger than what has been traditionally regarded as DLS. It has since been suggested that the sensorimotor information in the dorsal striatum 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 pathway* (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, thus releasing the target areas of the BG from inhibition. On the contrary, indirect pathway activity, through GPe and STN, disinhibits the output nuclei and in turn causes further inhibition of BG targets.

DA significantly modulates neuronal activity in the striatum. 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 86, 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 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.

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 [87]. 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 [88]. 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 [89].

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" [90]. Moreover, Pouthas and others

[xii] This paradigm is commonly referred to as "interval categorization task".

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" [91]. Similar evidence exists in other species as well. Gouvêa and others trained rats in a sensory categorization task to judge whether an interval 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 dorsal striatum (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 is similar. The authors then suggest that a population of duration-coding cells, each tune to different values, could accurately represent the elapsed time [92]. Mello and others also used a similar task for intervals ranging between 12 s to 60 s [93]. They found striatal cells that rescaled their activity when intervals changed. As rats adjusted to the new interval, time estimations decoded form 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 behavioral readout of temporal perception [94]. 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

[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.

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 [94].

Another 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" [95]. Dopamine neurons encode reward prediction errors which requires accurate reward predictions [see 96]. 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-dependant component of reward prediction of DA neurons might rely on the ventral striatum [97]. In an interesting study, Soares and others measured and manipulated the activity of DA neurons in a 1.5 s interval categorization task [98]. 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 [93], DA concentration

[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.

in the DS is also scalable to time intervals in several second time range [99]. 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 [99].

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 (SMA) [see 100]. Furthermore, it has been reported that individuals with attention deficit/hyperactivity disorder do not benefit from temporal predictabilities in an oculomotor task that displayed a target after a random delay [101]. Additionally, timing deficiency has also been reported in Huntington's disease (HD). 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 the HD [102]. 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 [103]. Interestingly, it has been proposed that frequent exposure to temporally-structured tones might alleviate motor symptoms of the PD, especially gait and stride length [104].

1.4.3 Basal Ganglia as a Cost Machine

> 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, importance of volitional movement is trivial. Control of movements has been associated with BG for a long time. This link dates back to the first descriptions of the behavioral deficits of PD 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, 86, 105].

Although symptoms differ from patient to patient, three behavioral deficits are typical for PD: 1) resting tremor, which is the most apparent; 2) rigidity and stiffness of muscles; 3) bradykinesia—reduced movement vigor. Reduced vigor in PD has been investigated to distinguish between 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 [106]. 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 (denoted 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 is not caused by a different speed-accuracy trade-off, rather 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 [106]. 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 [107].

Available methods in animal research provide an opportunity to further dissect the BG circuits. 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.[xv]Desmurget and Turner took advantage of this technique to acutely inactivate the sensorimotor territory of the GPi in monkeys [108]. Monkeys were trained to move a cursor using a joystick to a peripheral target and then 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 execution but not its production nor storage of learned sequences [108]. In general, reduced vigor is the most common phenomenon in conditions of perturbed BG activity [41, 110–115]. 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.

Many decisions are based on partial information that is gathered over time. For instance, deciding whether the approaching animal is a predator or a prey, or choosing the *best* restaurant for dinner [116]. 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 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 [117]. 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 jump 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, i.e., the faster they jump, the more hasty decisions are justified. They performed electrophysiological recordings in behaving animals from the motor and premotor areas as well as the GPi and GPe.

[xv] 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 [109].

They showed that during deliberation, information about selection of a target exists in the motor areas, but it is much weaker in the BG output. They observed ramping activity in GPi that "invigorate[s] the decision-making process by providing an urgency signal". This urgency signal grows over time and and is adjusted to different speed-accuracy trade-off policies, but does not reflect the amount of evidence or the target chosen by the animal [117]. 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 translated 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 is correlated with locomotion speed in mice [118]. Moreover, simultaneous recording of calcium activity and mouse 3-D exploratory behavior shows that direct (indirect) pathway activity correlates (anti-correlates) with movement velocity. Nonetheless, ongoing kinematics is best decoded from the activity of both pathways, suggesting that they contain non-redundant information [119].

Contrary to the classic model of the BG, in which direct pathway activity is pro-kinetic and indirect pathway activity inhibits movement [120], and to the action selection model of the BG that proposes that direct pathway promotes the selected action while indirect pathway concurrently suppresses the competing actions [121], 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 forelimb movements to obtain a delayed water reward [122]. 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 photostimulation 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 activation of MSNs was sufficient to produce bidirectional control of movement velocity. The authors then argue that reinforcement learning models of the BG cannot readily act on a continuous kinematic parameter of movement and they propose 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, 122]. 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 DA, which in turn represents a recent history of reward. Thus, the bidirectional control of vigor by either pathway in [122] is due to altered relative synaptic weights of D1/D2 neurons upon stimulation. HDG 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 [122].

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 [123]. 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 [123]. 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 seem unrelated, but in this chapter I tried to present them on a conceptual continuum. 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. Such a 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 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 this hypothesis, I used a novel behavioral paradigm developed by Rueda-Orozco and Robbe 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 of 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.

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 earlier work in the lab suggest that the overall behavior of the animals following transient inactivation of the DLS remains intact, although more variable [41]. Thus, 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 overall view of my Ph.D. project and discuss its meaning and implications, as well as some of the shortcomings and directions for future works in chapter 5.

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 often, overlooked. Therefore, interpretations might have been biased toward disregarding the actual behavioral algorithms, in favor of the neuronal correlations. Here, using a novel behavioral paradigm allowed studying the motor activity of the animals –and the function of the dorsal striatum (DS)– as well as their timing performance. In this chapter, I will discuss the behavioral task in detail, along with all the experimental and analytical methods used in this project.

2.1 Experimental Tools

In this section, all the conditions used in the time-estimation experiments and other experimental methods 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 for 30 min after every experimental session, while their body weights were 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 (solenoid valve) was installed on the front (relative to the turning direction of the belt) wall of the treadmill and released a ~80 μL 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.

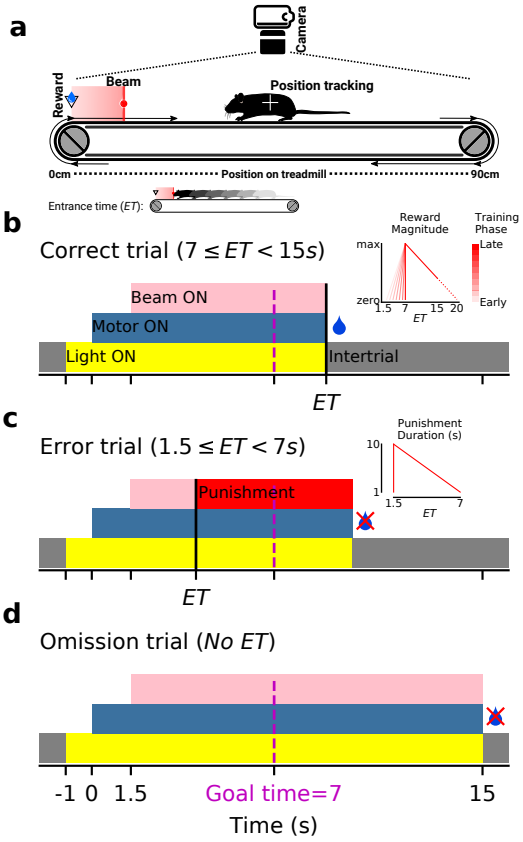

Figure 2.1 – Treadmill task and trial types. a) Rats were enclosed on a powered treadmill. The infrared beam marked the reward area (red shaded area). During each trial, the belt pushed the animals away from the reward area and the first infrared beam interruption defined the ET. During trials and intertrials, the animal's position was tracked via a ceiling-mounted 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. However, the smallest ET value that triggered reward delivery was progressively raised during learning. **c)** Schematic description of an error trial. Early ETs triggered an extra-running penalty and an audio noise. *Inset*: the duration of the penalty period 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.

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.

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, 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 the 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 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 ET 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 the reward was delivered 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.

2.2 Technical Tools

2.2.1 Statistics

All statistical comparisons were performed using a permutation test previously described in [124]. This non-parametric method alleviates many concerns in 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.

To simplify the description, let's assume, we have $\mathbf{X} = [X_1, X_2, ..., X_n]$, where X_i is the set of ETs of session i. Similarly, we have $\mathbf{Y}$ that contains ETs of all the sessions from another 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 $\sigma = 0.05$) $\mathbf{X}$ and $\mathbf{Y}$ for each session i: $D_0(i)$. At this point, we generated one set of surrogate data by assigning each ET of session i to either X_i or Y_i, randomly. For each set of surrogate data, the test statistic was calculated, i.e., $D_m(i)$. This process was repeated 10,000 times for all the statistical comparisons in this study, 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 [see 124]. 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, 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 $\mathbf{Y}$.

In cases of comparing only two sets of data points, 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).

Chapter 3

Time Experiments

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: Trials in which animals entered the reward area after the GT were classified as correct ($7 \leq ET < 15$, Figure 2.1b);

[i] The materials related to time experiments in this document were largely borrowed from [125].

Trials in which animals entered the reward area before the GT were classified as error ($1.5 \leq ET < 7$, Figure 2.1c); Finally, if in 15 s an 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 consists of the following steps: First, animals began each trial in the reward area, i.e., they stayed in the reward area during the intertrials; Then, when the trial started, they remained

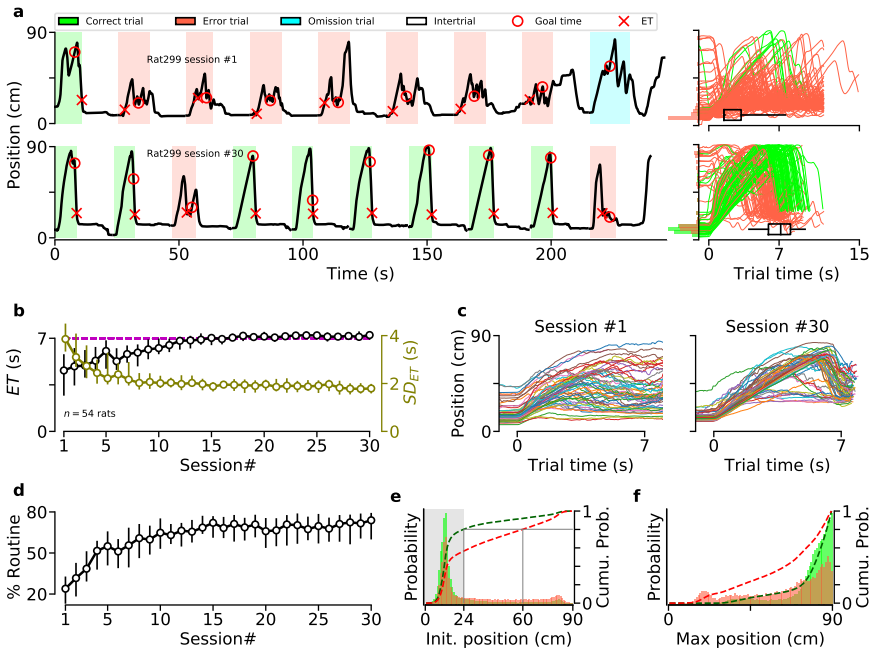

Figure 3.1 – Most animals developed a unique stereotyped motor sequence. a) *Left*: illustration of an animal's trajectory on the treadmill during 9 consecutive trials of the 1st (*top*) and 30th (*bottom*) training sessions. On the y-axis, 0 and 90 indicate the treadmill's front (reward port) and rear wall, respectively. *Right*: trajectories for all trials during the 1st (*top*) and 30th (*bottom*) sessions (same animal as in left panels). Distributions of initial positions for correct (green) and error (red) trials are shown on the y-axis. Black horizontal boxplots depict entrance time range (center line, median; box, 25th and 75th percentiles; whiskers, 5th and 95th percentiles). **b)** Median entrance time (ET) in the reward area for the first 30 daily training sessions. Circles indicate group median and error bars, the median range (25th and 75th percentiles) across animals for ET and on the right y-axis,SD of ET (SD_{ET}) values. The dashed magenta line shows the goal time (7 s). **c)** Median trajectory of all the trials for the 1st (*left*) and 30th (*right*) training sessions. Each line represents a single animal (n = 54). **d)** Session-by-session percentage of trials during which animals performed the stereotyped front-back-front routine (see Methods). Circles indicate group median and error bars, the median range across animals (25th and 75th percentiles). **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 reached by animals before crossing the beam (= ET). Only trials in which animals were initially located in the front of the treadmill (gray area in panel e) were included.

largely still while being pushed away from the reward area until they reached the rear wall; Finally, 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, 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.

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, 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

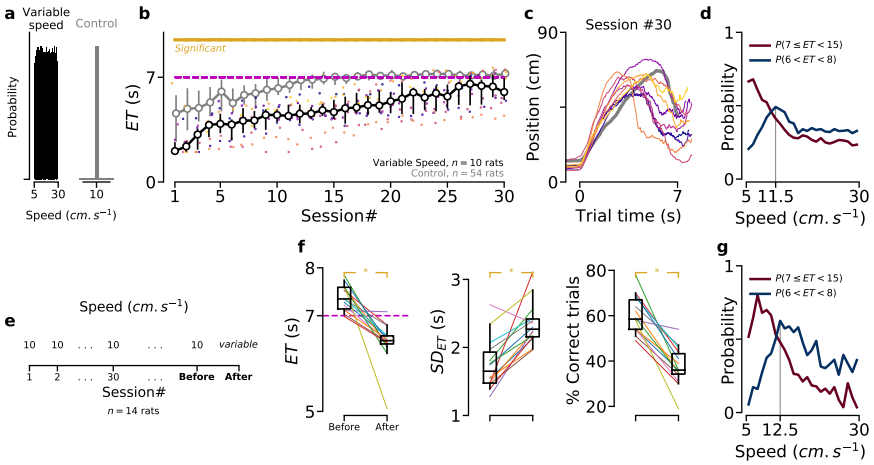

Figure 3.2 – Decreased temporal accuracy when the treadmill speed changes across trials. a) For each trial, treadmill speed was either fixed at 10 cm/s (control condition, same data as in Figure 3.1), or randomly selected from a uniform distribution between 5 and 30 cm/s (variable speed condition). **b)** Median ET for animals trained in the variable speed (black), and control (gray) conditions. Colored dots indicate individual performance for "variable speed" animals. Yellow line shows statistically significant differences between groups (permutation test, see section 2.2). **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 control condition, animals ($n = 14$) were tested in a probe session with variable speed. **f)** Median ETs (*left*), SD of ETs (*middle*) and percentage of correct trials (*right*) in the sessions immediately before and after the change in speed condition. Each line represents a single animal. Asterisks indicate significant differences (non-parametric paired comparison, see section 2.2). **g)** Similar to panel d, for the data collected from the probe session.

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 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

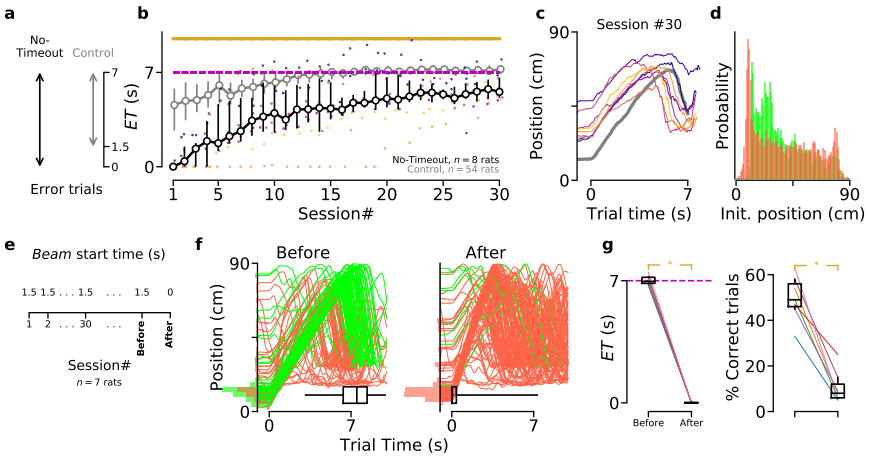

Figure 3.3 – Decreased temporal accuracy when animals are penalized for starting trials in the reward area. a) In the control condition, animals had a 1.5 s timeout period to leave the reward area after motor onset. In "no-timeout" condition, crossing the infrared beam any time before 7 s registers as 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 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*s (*left*), and percentage of correct trials (*right*) in the sessions immediately before and after the change in beam start time. Each line represents a single animal. Asterisks indicate significant differences (non-parametric paired comparison, see section 2.2).

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 performance of 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 the 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 3.4e, 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

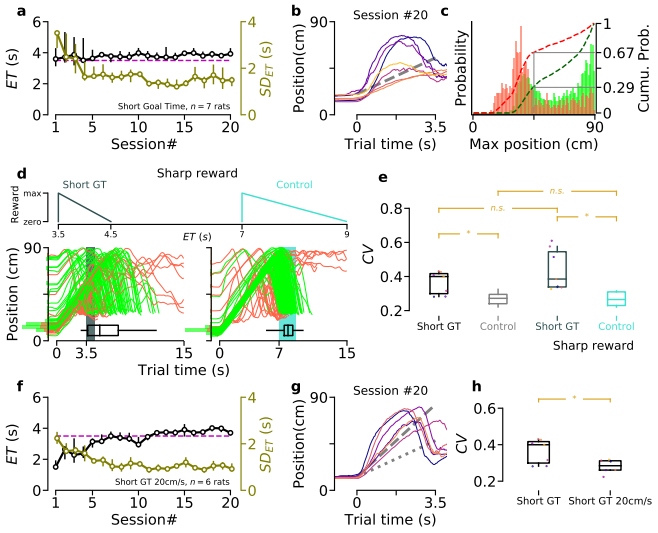

Figure 3.4 – Decreased temporal accuracy when the goal time is shortened. a) Median entrance time (ET) during training. The dashed magenta line shows the goal time (GT = 3.5 s). The right y-axis shows standard deviation (SD) of ET. **b)** Median trajectory of "short GT" animals after training. Colored lines indicate performance of individual animals. Dashed line's slope shows the treadmill speed (i.e., 10 cm/s). **c)** PDF of the maximum position reached by the short GT animals before approaching the reward area for correct (green) and incorrect (red) trials. Dashed lines represent cumulative distribution functions (right y-axis). Data collected from session # ≥ 15. **d)** Sharp reward condition applied to short GT and control experiments. *Top*: reward profiles in the sharp reward condition applied to the short GT experiments (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 (after session #15 for short GT, sessions #20 to #30 for control, and the last 5 sessions for the sharp condition experiments). short GT vs. Control: $p < 0.0001$ (permutation test, see section 2.2); Sharp short GT vs. Sharp control: $p < 0.0001$ (permutation test); short GT vs. Sharp short GT: Non significant (non-parametric paired comparison); Control vs. Sharp control: $p = 0.79$ (permutation test). **f)** Similar to panel a, for another group of animals that were trained to wait for 3.5 s while the speed of the treadmill was 20 cm/s. **g)** Similar to panel b, for animals trained in short goal time at 20 cm/s condition (panel f). Dashed line's slope shows the treadmill speed (i.e., 20 cm/s). Dotted line's slope indicates control treadmill speed (i.e., 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 (after session #15). short GT vs. short GT 20 cm/s: Asterisk indicates significant difference (10,000 resamples with replacement, see Methods).

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., $\leq$ 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.

Lastly, animals well-trained in the immobile treadmill condition during several weeks were then challenged in the control condition (i.e., 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 time constraint, once again demonstrating that task proficiency relied primarily on the acquisition of a motor sequence rather than an abstract knowledge of time.

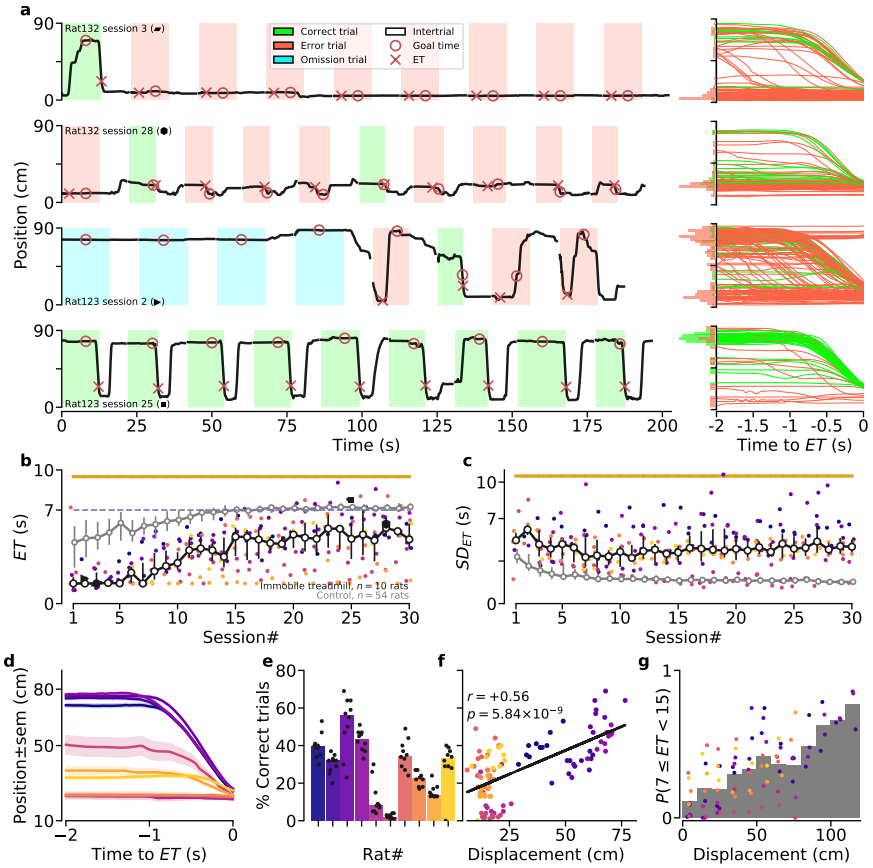

Figure 3.5 – Performance of animals trained while the treadmill remained immobile. **a)** *Left*: illustrations of the positions of two animals on the immobile treadmill for 9 consecutive trials, early (*1st row:* Rat #132-session #3, *3rd row:* Rat #123-session #2) and late (*2nd row:* Rat #132-session #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. Distributions of positions 2 s before ET, for correct (green) and error (red) trials are shown on the y-axis. **b)** Median ET across sessions for "immobile treadmill" animals. Filled black markers correspond to the sessions illustrated in panel a. Horizontal line indicates significant group difference (permutation test). **c)** Similar to panel b, for the standard deviation of entrance times (SD_{ET}). **d)** Median trajectory aligned to ET of each immobile treadmill animal (only correct trials from sessions #20 to #30 are considered; shaded area denotes standard error). **e)** Median percentage of correct trials for each immobile treadmill 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. **g)** PDF of a correct trial, given the displacement of an animal. Each dot 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.

Chapter 4

Lesion Experiments

Data here!

Chapter 5

Discussion

In this chapter, for each set of experiments, I will first summarize the results, and then discuss their more general implications. Then I present a short conclusion of the entire work, trying to reconcile all the ideas. Next, I will describe some of the weak points from which I think this work might be suffering. 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. First, 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 that 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,…). In addition, to save up energy, animals would probably stay close to the reward area for most of the duration of the trial. Alternatively, by trial-and-error, animals may discover 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., the goal time (GT). In that 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. Using two distinct reinforcement learning-based agents that either incorporated or lacked time representation, we showed that the behavior of our animals is incongruent with them accessing an internal explicit knowledge of elapsed time [125].

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 [126]. 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 sequence (e.g., 1# first press on the lever with the left paw; 2# touching the wall above the lever with the right paw; 3# second press on the lever with the left paw), 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, suggesting that our results are not just due to the particularities of the task. More generally, these results are reminiscent of an earlier study showing that the prediction of rats' temporal judgement (a 6 s long versus a 12 s long luminous signal) was always better if 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, 127, 128] 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]. The fact that motor timing may be fundamentally related to movement in space for both animals and humans could explain why brain regions involved in movement control and spatial representation, such as the motor cortex, basal ganglia, cerebellum, supplementary motor area (SMA), and hippocampus have been consistently associated with time representation [46, 91, 93, 94, 129–131].

It has been previously proposed that timing could be mediated through motor routines whose precise execution is internally controlled [21, 132, 133]. 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. I do not question that representations 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 or discrimination. However, this type of result can not be used as definitive evidence in favor of a neuronal representation of time, *read* by the animals as we, humans, read a clock [65, 134, 135]. 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. Indeed, here we report that timing accuracy was reduced when the task parameters prevented the animals from taking advantage of the physical structure of the treadmill to learn the motor routine.

Thus, in our task, something more than an internal process (be it a dedicated clock or the self-sustained population dynamics emerging from recurrently connected circuits) was required for accurate timing: the reciprocal and repetitive interactions between the nervous system and the body (sensors and actuators) on the one hand, and the surrounding environment on the other hand.

Our results, however, are compatible with the idea that timing emerges from the dynamics of neural circuits [5], as long as these dynamics are not entirely internally generated and also reflect feedback from the environment. For instance, I speculate that the timing deficits induced by striatal inactivation [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 [123, 136, 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 is critical for processing sensorimotor information [85] and has been proposed to contribute to the process of evidence accumulation during decision making [136]. Interestingly, it has been recently proposed that a competition between the direct and indirect basal ganglia (BG) pathways, tuned by dopamine (DA) modulation, may determine the speed of evidence accumulation toward decision taking [123]. 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. A recent study validates this model in mice performing an auditory duration categorization task, showing that increased DAergic activity in the substantia nigra pars compacta (SNc) was associated with the animals perceiving long tones as short ones [98]. Finally, I point out that the embodied mechanism for motor timing is parsimonious, can explain a large body of experimental data, and can potentially be applied other types of time-estimation tasks.

5.2 Striatal Function

Our results support the view that the striatal lesion increased the animals' sensitivity to effort which led them to modify the kinematics of the wait-and-run routine. Theoretically, remaining very close to the reward area minimizes energy expenditure (effort) by avoiding the usage of fast speeds. This extreme strategy was observed during the first post-lesion session of a few rats with large lesions (Fig. 1F and G). But it exposed these animals to premature entrances in the reward area (Fig. 1H) and consequently, to an abrupt reduction in rewards obtained during this session. Across post-lesion sessions, the same rats progressively waited longer before running toward the reward area, which allowed them to recover task proficiency (Fig. 1, C to F). This suggested that the animals' ability to progressively wait longer before running toward the reward area was spared by the dS lesion. Accordingly, we found that dS lesions performed before training did not compromise the rats' ability to learn the wait-and-run routine (fig. S7) but did reduce their speed, an effect that was also correlated with lesion size (fig. S4).

Overall, our results indicate that rats with dS lesions did not display fundamental impairment in motor control or action selection but behaved in a way that is most parsimoniously explained by a higher sensitivity to effort with preserved motivation. Indeed, after dS lesion, animals kept arriving on time in the reward area, but they started to run earlier (i.e., on a more intermediate portion of the treadmill) and at a slower speed. Metaphorically speaking, the same effect would have been expected had we forced non-lesioned rats to perform the task with extra weight on their back. Thus, our work suggests that the dS contributes to the generation of an effort signal that influences the kinematic parameters of purposive actions. Such a function is in line with the hypothesis that the dopamine projection to the dS provides a signal for implicit motor motivation (or global effort sensitivity), which in turn influences the vigor of most of the goal-directed movements performed human or animal subjects

[**Mazzoni2007JN**, **Treadway2012JN**, **Reppert2018JNPhys**]. But, what would be the specific contribution of dS neurons to such function? A possible answer is that dS neurons integrate motivational- and feedback-related dopaminergic signals with context- and action-specific information derived from their massive cortical and thalamic inputs [**Hunnicutt2016Elife**, **Hooks2018NatCom**]. If one considers that dS projection neurons can bidirectionally regulate the output activity of the basal ganglia [**Kravitz2010**], our proposed function of the dS as computing action-specific effort signals can account for seemingly heterogeneous findings, such as modulations of the relative preference for a particular velocity [**Yttri2016**], action [**Tai2012NN**, **Kravitz2012NN**] or behavioral state [**Kravitz2010**] by selective optogenetic stimulation of dS neurons. Biologically, expending effort to produce faster movements allows limiting the temporal discounting of reward (i.e., cost of time, [51]). In sensory guided decision-making tasks, the cost of time can also be reduced by limiting the duration of deliberation [**Carland2019**]. Interestingly, recent evidence supports a specific role of the basal ganglia in signaling the urgency to commit to a choice [**Thura2017Neuron**, **Carland2019**]. Future studies should investigate whether signaling effort and urgency are the two sides of a unique function implemented in the basal ganglia to maximize the reward rate while minimizing costs.

5.3 Conclusion

5.4 On the Other Hand

text about the shortcomings of the project

5.5 Future Work

Still, why animals and humans seem to favor embodied and interactive timing strategies over purely internal mechanisms is not clear. Insights regarding this question might be obtained by considering adaptive behavior in an evolutionary perspective[**Cisek2019**] and time in the context of ecologically valid timing tasks[**vanRijn2018**].

Future work should further investigate how to mathematically capture the algorithms underlying temporally-constrained actions and decisions and the possible contribution of the striatum to processing multimodal (sensorimotor, cognitive, emotional) contextual information together with dopamine-mediated feedback and motivational signals.

Appendix A

Supplementary Figures

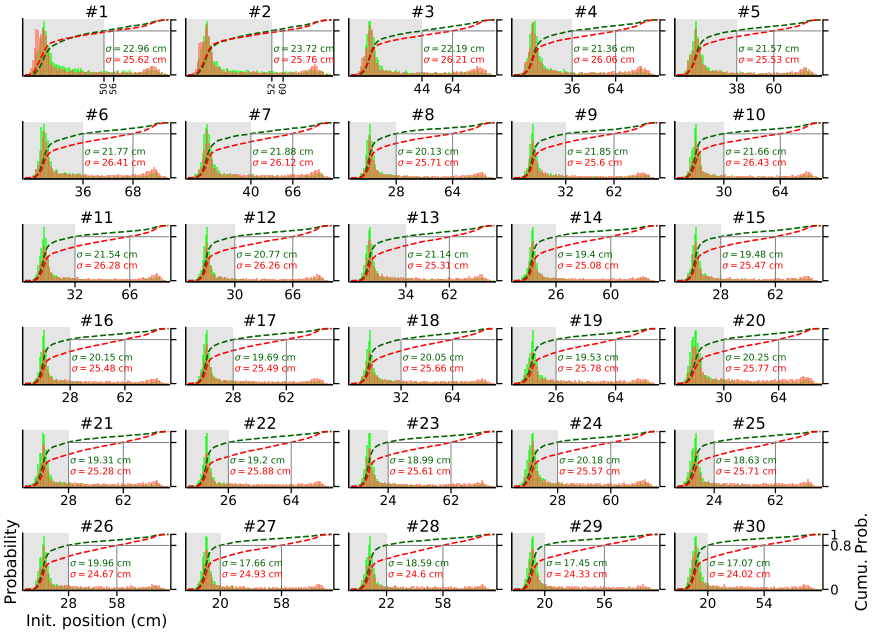

Figure A.1 – Initial position distributions for correct and error trials diverged progressively during training. Similar to Figure 3.1e, each panel shows PDF of the initial position of the animals for correct (green) and error (red) trials, but plotted separately for each training session (#1 to #30). 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).

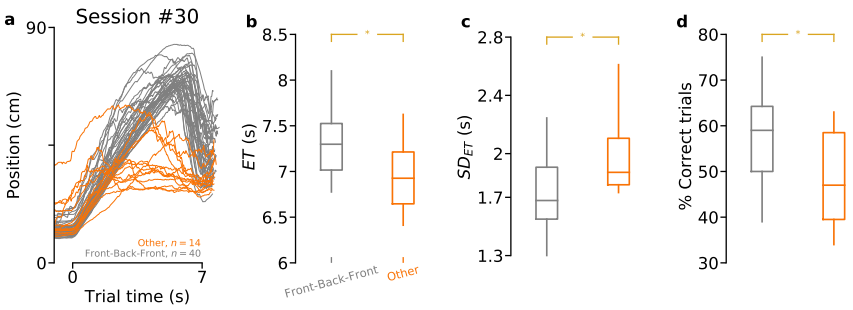

Figure A.2 – Task proficiency according to the type of trajectory performed by animals. **a)** Same as Figure 3.1, panel c, right, but the animals were divided in two groups according to whether they performed the front-back-front trajectory (gray) or not (other, orange). **b)** Entrance times(ETs).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

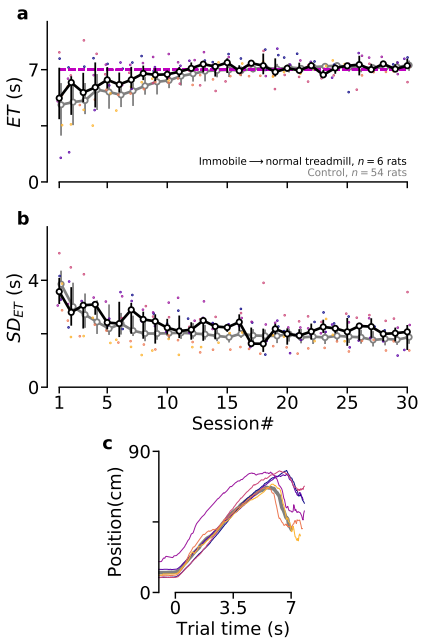

Figure A.3 – Lack of temporal knowledge transfer across task protocols. After extensive training on the immobile treadmill, animals were trained under normal conditions (GT= 7 s, treadmill speed= 10 cm/s). **a)** Median ET across sessions under control condition. **b)** Similar to panel a, for the standard 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.

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Acronyms

BG basal ganglia. 15, 16, 18, 20–23, 25–31, 59

CoT cost of time. 13, 14

D1 D1 dopamine receptor. 20, 21, 23, 28–30

D2 D2 dopamine receptor. 20, 21, 23, 28–30

DA dopamine. 16, 20, 21, 23–25, 29, 59

DLS dorsolateral striatum. 18–20, 28, 31

DMS dorsomedial striatum. 18, 19, 29, 31

DS dorsal striatum. 22–24, 33

ET entrance time. 34–41, 45, 47–50, 56

FSI fast spiking interneuron. 17, 18

GPe globus pallidus externus. 16, 20, 27

GPi globus pallidus internus. 15, 16, 20, 26–28

GT goal time. 35–38, 40, 41, 44, 45, 47–50, 54, 56

HD Huntington's disease. 24

HDG history-dependant gain. 29

MSN medium spiny neuron. 16, 17, 20, 21, 29

PD Parkinson's disease. 20, 21, 24–26

SMA supplementary motor area. 24, 58

SNc substantia nigra pars compacta. 16, 20, 26, 59

SNr substantia nigra pars reticulata. 15, 16, 20

STN subthalamic nucleus. 15, 16, 20