A robust role for motor cortex

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Abstract

The role of motor cortex in the direct control of movement remains unclear, particularly in non-primate mammals. More than a century of research using stimulation, anatomical and electrophysiological studies has implicated neural activity in this region with all kinds of movement. However, following the removal of motor cortex, or even the entire cortex, rats retain the ability to execute a surprisingly large range of adaptive behaviours, including previously learned

skilled movements. In this work we revisit these two conflicting views of motor cortical control by asking what the primordial role of motor cortex is in non-primate mammals, and how it can be effectively assayed. In order to motivate the discussion we present a new assay of behaviour in the rat, challenging animals to produce robust responses to unexpected and unpredictable situations while navigating a dynamic obstacle course. Surprisingly, we found that rats with motor cortical lesions show clear impairments in dealing with an unexpected collapse of the obstacles, while showing virtually no impairment with repeated trials in many other motor and cognitive metrics of performance. We propose a new role for motor cortex: extending the robustness of sub-cortical movement systems, specifically to unexpected situations demanding rapid motor responses adapted to environmental context. The implications of this idea for current and future research are discussed.

1 Introduction

Since its discovery 150 years ago, the role of motor cortex has been a topic of controversy and confusion [1, 2, 3, 4]. Here we report our efforts to establish a teleology for cortical motor control. Motor cortex may play roles in "understanding" the movements of others [5], imagining one's own movements [6], or in learning new movements [7], but here we will focus on its role in directly controlling movement.

Stimulating motor cortex causes movement; motor cortex is active during movement

Motor cortex is broadly defined as the region of the cerebral hemispheres from which movements can be evoked by low-current stimulation, following Fritsch and Hitzig's original experiments in 1870 [8]. Stimulating different parts of the motor cortex elicits movement in different parts of the body, and systematic stimulation surveys have revealed a topographical representation of the entire skeletal musculature across the cortical surface [9, 10, 11]. Electrophysiological recordings in motor cortex have routinely found correlations between neural activity and many different movement parameters, such as muscle force [12], movement direction [13], speed [14], or even anisotropic limb mechanics [15] at the level of both single neurons [12, 16] and populations [13, 17]. Determining what exactly this activity in motor cortex controls [18] has been further complicated by studies using long stimulation

durations in which continuous stimulation at a single location in motor cortex evokes complex, multi-muscle movements [19, 20]. However, as a whole, these observations all support the long standing view that activity in motor cortex is involved in the direct control of movement.

Motor cortex lesions produce different deficits in different species

What types of movement require motor cortex? In humans, a motor cortical lesion is devastating, resulting in the loss of muscle control or even paralysis; movement is permanently and obviously impaired [21]. In non-human primates, similar gross movement deficits are observed after lesions, albeit transiently [9]. The longest lasting effect of a motor cortical lesion is the decreased motility of distal forelimbs, especially in the control of individual finger movements required for precision skills [9, 22]. But equally impressive is the extent to which other movements fully recover, including the ability to sit, stand, walk, climb and even reach to grasp, as long as precise finger movements are not required [9, 22, 23]. In non-primate mammals, the absence of lasting deficits following motor cortical lesion is even more striking. Careful studies of skilled reaching in rats have revealed an impairment in paw grasping behaviours [24, 25], comparable to the long lasting deficits seen in primates, but this is a limited impairment when compared to the range of movements that *are* preserved [24, 7]. In fact, even after complete decortication, rats, cats and dogs retain a shocking amount of their movement repertoire [26, 27, 28]. If we are to accept the simple hypothesis that motor

cortex is the structure responsible for "voluntary movement production", then why is there such a blatant difference in the severity of deficits caused by motor cortical lesions in humans versus other mammals? With over a century of stimulation and electrophysiology studies clearly suggesting that motor cortex is involved in many types of movement, in all mammalian species, how can these divergent results be reconciled?

There are anatomical differences in corticospinal projections between primates and other mammals

In primates, the conspicuous effects of motor cortical lesion can also be produced by sectioning the pyramidal tract, the direct monosynaptic projection that connects motor cortex, and other cortical regions, to the spinal cord [29, 30]. The corticospinal tract is thought to support the low-current movement responses evoked by electrical stimulation in the cortex, as evidenced by the increased difficulty in obtaining a stimulation response following section at the level of the medulla [31]. In monkeys, and similarly in humans, this fibre system has been found to directly terminate on spinal motor neurons responsible for the control of distal muscles [9, 32]. However, in all other mammals, including cats and rats, the termination pattern of the pyramidal tract in the spinal cord largely avoids these ventral motor neuron pools and concentrates instead on intermediate zone interneurons and dorsal sensory neurons [33, 34]. Furthermore, in humans, the rubrospinal tract—a descending pathway originating in the brainstem and terminating in the intermediate zone—is

degenerated compared to other primates and mammals [35], and is thought to play a role in compensating for the loss of the pyramidal tract in non-human species [36, 23]. These differences in anatomy might explain the lack of conspicuous, lasting movement deficits in non-primates, but leaves behind a significant question: what is the motor cortex actually controlling in all these other mammals?

What is the role of motor cortex in non-primate mammals?

In the rat, a large portion of cortex is considered "motor" based on anatomical [37], stimulation [37, 11] and electrophysiological evidence [38]. However, the most consistently observed long-term deficit following motor cortical lesion has been an impairment in supination of the wrist and individuation of digits during grasping, which in turn impairs reaching for food pellets through a narrow vertical slit [24, 25]. Despite the fact that activity in rodent motor cortex has been correlated with movements in every part of the body (not just distal limbs) [39, 40], it would appear we are led to conclude that this large high-level motor structure, with dense efferent projections to motor areas in the spinal cord [33], basal ganglia [41, 42], thalamus [43], cerebellum [44] and brainstem [45], as well as to most primary sensory areas [46, 47], evolved simply to facilitate more precise wrist rotations and grasping gestures. Maybe we are missing something. Might there be other problems in movement control that motor cortex is solving, but that we may be overlooking with our current assays?

A role in modulating the movements generated by lower motor centres

A different perspective on motor cortex emerged from studying the neural control of locomotion, suggesting that the corticospinal tract plays a role in the *adjustment* of ongoing movements that are generated by lower motor systems. In this view, rather than motor cortex assuming direct control over muscle movement, it instead modulates the activity and sensory feedback in spinal circuits in order to adapt a lower movement controller to challenging conditions. This idea that the descending cortical pathways superimpose speed and precision on an existing baseline of behaviour was also suggested by lesion work in primates [36], but has been investigated most thoroughly in the context of cat locomotion.

It has been known for more than a century that completely decerebrate cats are capable of sustaining the locomotor rhythms necessary for walking on a flat treadmill utilizing only spinal circuits [48]. Brainstem and midbrain circuits are sufficient to initiate the activity of these spinal central pattern generators [49], so what exactly is the contribution of motor cortex to the control of locomotion? Single-unit recordings of pyramidal tract neurons (PTNs) from cats walking on a treadmill have shown that a large proportion of these neurons are locked to the step cycle [50]. However, we know from the decerebrate studies that this activity is not necessary for the basic locomotor pattern. What then is its role?

Lesions of the lateral descending pathways (containing corticospinal and

rubrospinal projections) produce a long term impairment in the ability of cats to step over obstacles [51]. Recordings of PTN neurons during locomotion show increased activity during these visually guided modifications to the basic step cycle [52]. These observations suggest that motor cortex neurons are necessary for precise stepping and adjustment of ongoing locomotion to changing conditions. However, long-term effects seem to require complete lesion of *both* the corticospinal and rubrospinal tracts [51]. Even in these animals, the voluntary act of stepping over an obstacle does not disappear entirely, and moreover, they can adapt to changes in the height of the obstacles [51]. Specifically, even though these animals never regain the ability to gracefully clear an obstacle, when faced with a higher obstacle, they are able to adjust their stepping height in such a way that would have allowed them to comfortably clear the lower obstacle [51]. Furthermore, deficits caused by lesions restricted to the pyramidal tract seem to disappear over time [53], and are most clearly visible only the first time an animal encounters a new obstacle [53].

The view that motor cortex in non-primate mammals is principally responsible for adjusting ongoing movement patterns generated by lower brain structures is appealing. What is this modulation good for? What does it allow an animal to achieve? How can we assay its necessity?

Towards a new teleology; new experiments required

It should now be clear that the involvement of motor cortex in the direct control of all "voluntary movement" is human-specific. There is a role for motor cortex across mammals in the control of precise movements of the extremities, especially those requiring individual movements of the fingers, but these effects are subtle in non-primate mammals. Furthermore, what would be a devastating impairment for humans may not be so severe for mammals that do not depend on precision finger movements for survival. Therefore, generalizing this specific role of motor cortex from humans to all other mammals would be misleading. We could be missing another, more primordial role for this structure that predominates in other mammals, and by doing so, we may also be missing an important role in humans.

The proposal that motor cortex induces modifications of ongoing movement synergies, prompted by the electrophysiological studies of cat locomotion, definitely points to a role consistent with the results of various lesion studies. However, in assays used, the ability to modify ongoing movement generally recovers after a motor cortical lesion. What are the environmental siutations in which motor cortical modulation is most useful?

Cortex has long been proposed to be the structure responsible for integrating a representation of the world and improving the predictive power of this representation with experience [54, 55]. If motor cortex is the means by which these representations can gain influence over the body, however subtle and "modulatory", can we find situations (i.e. tasks) in which this cortical

control is required?

The necessity of cortex for various behavioural tasks has been actively investigated in experimental psychology for over a century, including the foundational work of Karl Lashley and his students [56, 57]. In the rat, large cortical lesions were found to produce little to no impairment in movement control, and even deficits in learning and decision making abilities were difficult to demonstrate consistently over repeated trials. However, Lashley did notice some evidence that cortical control may be involved in postural adaptations to unexpected perturbations [56]. These studies once again seem to recapitulate the two most consistent observations found across the entire motor cortical lesion literature in non-primate mammals since Hitzig [8], Goltz [26], Sherrington [58] and others [59, 28]. One, direct voluntary control over movement is most definitely not abolished through lesion; and two, certain aspects of some movements are definitely impaired, but only under certain challenging situations. The latter are often reported only anecdotally. It was this collection of intriguing observations in animals with motor cortical lesions that prompted us to expand the scope of standard laboratory tasks to include a broader range of motor control challenges that brains encounter in their natural environments.

In the following, we report an experiment that was designed to provide controlled exposure of animals to more naturally challenging environments. The results of this experiment have led us to formulate a new teleology for cortical motor control that we will present in the discussion.

2 Experiment Introduction

In the natural world, an animal must be able to adapt locomotion to any surface, not only in anticipation of upcoming terrain, but also in response to the unexpected perturbations that often occur during movement. This allows animals to move robustly through the world, even when navigating a changing environment. Testing the ability of the motor system to generate a robust response to an unexpected change can be difficult as it requires introducing a perturbation without cueing the animal about the altered state of the world. Marple-Horvat and colleagues built a circular ladder assay for cats that was specifically designed to record from motor cortex during such conditions [60]. One of the modifications they introduced was to make one of the rungs of the ladder fall unexpectedly under the weight of the animal. When they recorded from motor cortical neurons during the rung drop, they noticed a marked increase in activity, well above the recorded baseline from normal stepping, as the animal recovered from the fall and resumed walking. However, whether this increased activity of motor cortex was necessary for the recovery response has never been assayed.

3 Results

To investigate whether the intact motor cortex is required for the robust control of movement in response to unexpected perturbations, we designed a reconfigurable dynamic obstacle course where individual steps can be made stable or unstable on a trial-by-trial basis (Figure 1, also see Methods). In this assay, rats shuttle back and forth across the obstacles, in the dark, in order to collect water rewards. We specifically designed the assay such that modifications to the physics of the obstacles could be made covertly. In this way, the animal has no explicit information about the state of the steps until it actually contacts them. Water deprived animals were trained daily for 4 weeks, throughout which they encountered increasingly challenging states of the obstacle course. Our goal was to characterize precisely the conditions under which motor cortex becomes necessary for the control of movement, and this motivated us to introduce an environment with graded levels of uncertainty.

We compared the performance of 22 animals: 11 with bilateral ibotenic acid lesions to the primary and secondary forelimb motor cortex, and 11 age and gender matched controls (5 sham surgery, 6 wild-types). Animals were given ample time to recover, 4 weeks post-surgery, in order to specifically isolate behaviours that are chronically impaired in animals lacking the functions enabled by motor cortical structures. Histological examination of serial coronal sections revealed significant variability in the extent of dam-

aged areas (Figure 2), which was likely caused by mechanical blockage of the injection pipette during lesion induction at some sites. Nevertheless, volume reconstruction of the serial sections allowed us to accurately quantify the size of each lesion, identify each animal (from Lesion A to Lesion K; largest to smallest), and use these values to compare observed behavioural effects as a function of lesion size.

During the first sessions in the "stable" environment, all animals, both lesions and controls, quickly learned to shuttle across the obstacles, achieving stable, skilled performance after a few days of training (Figure 3). Even though the distance between steps was fixed for all animals, the time taken to adapt the crossing strategy was similar irrespective of body size. When first encountering the obstacles, animals adopted a cautious gait, investigating the location of the subsequent obstacle with their whiskers, stepping with the leading forepaw followed by a step to the same position with the trailing paw (Video 1: "First Leftwards Crossing"). However, over the course of only a few trials, all animals exhibited a new strategy of "stepping over" the planted forepaw to the next obstacle, suggesting an increased confidence in their movement strategy in this novel environment (Video 1: "Second Leftwards Crossing"). This more confident gait developed into a coordinated locomotion sequence after a few additional training sessions (Video 1: "Later Crossing"). The development of the ability to move confidently and quickly over the obstacle course was observed in both lesion and control animals (Video 2).

In addition to the excitotoxic lesions, in three animals we performed larger

frontal cortex aspiration lesions in order to determine whether the remaining trunk and hindlimb representations were necessary to navigate the elevated obstacle course. Also, in order to exclude the involvement of other corticospinal projecting regions in the parietal and rostral visual areas [61], we included three additional animals which underwent even more extensive cortical lesion procedures (Figure 4A,B, see Methods). These *extended* lesion animals were identified following chronological order (from Extended Lesion A to Extended Lesion F; where the first three animals correspond to frontal cortex aspiration lesions and the remaining animals to the more extensive frontoparietal lesions). In these extended cortical lesions, recovery was found to be overall slower than in lesions limited to the motor cortex, and animals required isolation and more extensive care during the recovery period.

Nevertheless, when tested in the shuttling assay, the basic performance of these extended lesion animals was similar to that of controls and animals with excitotoxic motor cortical lesions (Figure 4C). Animals with large frontoparietal lesions did exhibit a very noticeable deficit in paw placement throughout the early sessions (Figure 4D). Interestingly, detailed analysis of paw placement behaviour revealed that this deficit was almost entirely explained by impaired control of the hindlimbs. Paw slips were much more frequent when stepping with a hindlimb than with a forelimb (Figure 4E,F). In addition, when a slip did occur, these animals failed to adjust the affected paw to compensate for the fall (e.g. keeping their digits closed), which significantly impacted their overall posture recovery. These deficits in paw placement are

consistent with results from sectioning the entire pyramidal tract in cats [53], and reports in ladder walking following motor cortical lesion in rodents [62], but surprisingly we did not observe deficits in paw placement in animals with ibotenic acid lesions limited to forelimb motor cortex (Figure 4D). Furthermore, despite this initial impairment, animals with extended lesions were still able to improve their motor control strategy up to the point where they were moving across the obstacles as efficiently as controls and other lesioned animals (Figure 4C, Video 2). Indeed, in the largest frontoparietal lesion, which extended all the way to rostral visual cortex, recovery of a stable locomotion pattern was evident over the course of just ten repeated trials (Video 3). The ability of this animal to improve its motor control strategy in such a short period of time seems to indicate the presence of motor learning, not simply an increase in confidence with the new environment.

In subsequent training sessions we progressively increased the difficulty of the obstacle course, by making more steps unstable. The goal was to compare the performance of the two groups as a function of difficulty. Surprisingly, both lesion and control animals were able to improve their performance by the end of each training stage even for the most extreme condition where all steps were unstable (Figure 3, Video 4). This seems to indicate that the ability of these animals to fine-tune their motor performance in a challenging environment remained intact.

One noticeable exception was the animal with the largest ibotenic acid lesion. This animal, following exposure to the first unstable protocol, was

unable to bring itself to cross the obstacle course (Video 5). Some other control and lesioned animals also experienced a similar form of distress following exposure to the unstable obstacles, but eventually all these animals managed to start crossing over the course of a single session. In order to test whether this was due to some kind of motor disability, we lowered the difficulty of the protocol for this one animal until it was able to cross again. Following a random permutation protocol, where any two single steps were released randomly, this animal was then able to cross a single released obstacle placed in any location of the assay. After this success, it eventually learned to cross the highest difficulty level in the assay in about the same time as all the other animals, suggesting that there was indeed no lasting motor execution or learning deficit, and that the disability must have been due to some other unknown, yet intriguing, (cognitive) factor.

Having established that the overall motor performance of these animals was similar across all conditions, we next asked whether there was any difference in the strategy used by the two groups of animals to cross the unstable obstacles. We noticed that during the first week of training, the posture of the animals when stepping on the obstacles changed significantly over time (Figure 5B,C). Specifically, the centre of gravity of the body was shifted further forward and higher during later sessions, in a manner proportional to performance. However, after the obstacles changed to the unstable state, we observed an immediate and persistent adjustment of this crossing posture, with animals assuming a lower centre of gravity and reducing their speed

as they approached the unstable obstacles (Figure 5C,D). Interestingly, we also noticed that a group of animals adopted a different strategy. Instead of lowering their centre of gravity, they either kept it unchanged or shifted it even more forward and performed a jump over the unstable obstacles (Figure 6A,B). These two strategies were remarkably consistent across the two groups, but there was no correlation between the strategy used and the degree of motor cortical lesion (Figure 5E,F, 6C). In fact, we found that the use of a jumping strategy was best predicted by the body weight of the animal (Figure 6C).

During the two days where the stable state of the environment was reinstated, the posture of the animals was gradually restored to pre-manipulation levels (Figure 5B,C), although in many cases this adjustment happened at a slower rate than the transition from stable to unstable. Again, this postural adaptation was independent of the presence or absence of forepaw motor cortex.

We next looked in detail at the days where the state of the obstacle course was randomized on a trial-by-trial basis. This stage of the protocol is particularly interesting as it reflects a situation where the environment has a persistent degree of uncertainty. For this analysis, we were forced to exclude the animals that employed a jumping strategy, as their experience with the manipulated obstacles was the same irrespective of the state of the world. First, we repeated the same posture analysis comparing all the stable and unstable trials in the random protocol in order to control for whether

there was any subtle cue in our motorized setup that the animals might be using to gain information about the current state of the world. There was no significant difference between randomly presented stable and unstable trials on the approach posture of the animal (Figure 7A). However, classifying the trials on the basis of past trial history revealed a significant effect on posture (Figure 7B). This suggested that the animals were adjusting their body posture when stepping on the affected obstacles on the basis of their current expectation about the state of the world, which is updated by the previously experienced state. Surprisingly, this effect again did not depend on the presence or absence of frontal motor cortical structures (Figure 7C,D).

Finally, we decided to test whether general motor performance was affected by the randomized state of the obstacles. If the animals do not know what state the world will be in, then there will be an increased challenge to their stability when they cross over the unstable obstacles, possibly demanding a quick change in strategy when they learn whether the world is stable or unstable. In order to evaluate the dynamics of crossing, we compared the speed profile of each animal across these different conditions (Figure 8, see Methods). Interestingly, two of the animals with the largest lesions appeared to be significantly slowed down on unstable trials, while controls and the animals with the smallest lesions instead tended to accelerate after encountering an unstable obstacle. However, the overall effect for lesions versus controls was not statistically significant (Figure 8C).

Nevertheless, we were intrigued by this observation and decided to in-

vestigate, in detail, the first moment in the assay when a perturbation is encountered. In the random protocol, even though the state of the world is unpredictable, the animals know that the obstacles might become unstable. However, the very first time the environment becomes unstable, the collapse of the obstacles is completely unexpected and demands an entirely novel motor response.

A detailed analysis of the responses to the first collapse of the steps revealed a striking difference in the strategies deployed by the lesion and control animals. Upon the first encounter with the manipulated steps, we observed three types of behavioural responses from the animals (Video 6): investigation, in which the animals immediately stop their progression and orient towards, whisk, and physically manipulate the altered obstacle; compensation, in which the animals rapidly adjust their behaviour to negotiate the unexpected instability; and halting, in which the ongoing motor program ceases and the animals' behaviour simply comes to a stop for several seconds. Remarkably, these responses depended on the presence or absence of motor cortex (Figure 9). Animals with the largest motor cortical lesions, upon their first encounter with the novel environmental obstacle, halted for several seconds, whereas animals with an intact motor cortex, and those with the smallest lesions, were able to rapidly react with either an investigatory or compensatory response (Video 7,8).

The response of animals with extended lesions was even more striking. In two of these animals, there was a failure to recognize that a change had

occurred at all (Video 9). Instead, they kept walking across the now unstable steps for several trials, never stopping to assess the new situation. One of them gradually noticed the manipulation and stopped his progression, while the other one only fully realized the change after inadvertently hitting the steps with its snout (Video 9: Extended Lesion A). This was the first time we ever observed this behaviour, as all animals with or without cortical lesions always displayed a clear switch in behavioural state following the first encounter with the manipulation. In the remaining animals with extended lesions, two of them clearly halted their progression following the collapse of the obstacles, in a way similar to the large motor cortex ibotenic lesions (Video 10). The third animal (Extended Lesion B) actually collapsed upon contact with the manipulated step, falling over its paw and digits awkwardly and hitting the obstacles with its snout. Shortly after this there was a switch to an exploratory behaviour state, in a way similar to Extended Lesion A.

4 Experiment Discussion

In this experiment, we assessed the role of motor cortical structures by making targeted lesions to areas responsible for forelimb control [7, 63]. Consistent with previous studies, we did not observe any conspicuous deficits in movement execution for rats with bilateral motor cortex lesions when negotiating a stable environment. Even when exposed to a sequence of unstable obstacles, animals were able to learn an efficient strategy for crossing these more challenging environments, with or without motor cortex. These movement strategies also include a preparatory component that might reflect the state of the world an animal expected to encounter. Surprisingly, these preparatory responses also did not require the presence of motor cortex.

It was only when the environment did not conform to expectation, and demanded a rapid adjustment, that a difference between the lesion and control groups was obvious. Animals with extensive damage to the motor cortex did not deploy a change in strategy. Rather, they halted their progression for several seconds, unable to robustly respond to the new motor challenge. In an ecological setting, such hesitation could easily prove fatal.

5 Extended Discussion

Is "robust control" a problem worthy of high level cortical input? Recovering from a perturbation, to maintain balance or minimize the impact of a fall, is a role normally assigned to our lower level postural control systems. The

corrective responses embedded in our spinal cord [64, 65], brainstem [66] and midbrain [49] are clearly important components of this stabilizing network, but are they sufficient to maintain robust movement in the dynamic environments that we encounter on a daily basis? Some insight into the requirements for a robust control system can be gained from engineering attempts to build robots that navigate in natural environments.

In the field of robotics, feats of precision and fine movement control (the most commonly prescribed role for motor cortex), are not a major source of difficulty. Industrial robots have long since exceeded human performance in both accuracy and execution speed [67]. More recently, using reinforcement learning methods, they are now able to automatically learn efficient movement strategies, given a human-defined goal and many repeated trials for fine-tuning [68]. What then are the hard problems in robotic motor control? Why are most robots still confined to factories, i.e. controlled, predictable environments? The reason is that as soon as a robot encounters natural terrain, a vast number of previously unknown situations arise. The resulting "perturbations" are dealt with poorly by the statistical machine learning models that are currently used to train robots in controlled settings.

Let's consider a familiar example: You are up early on a Sunday morning and head outside to collect the newspaper. It is cold out, so you put on a robe and some slippers, open the front door, and descend the steps leading down to the street in front of your house. Unbeknownst to you, a thin layer of ice has formed overnight and your foot is now quickly sliding out from underneath

you. You are about to fall. What do you do? Well, this depends. Is there a railing you can grab to catch yourself? Were you carrying a cup of coffee? Did you notice the frost on the lawn and step cautiously, anticipating a slippery surface? Avoiding a dangerous fall, or recovering gracefully, requires a rich knowledge of the world, knowledge that is not immediately available to spinal or even brainstem circuits. This rich context relevant for robust movement is readily available in cortex, and cortex alone.

Imagine now that you are tasked with building a robot to collect your morning newspaper. This robot, in order to avoid a catastrophic and costly failure, would need to have all of this contextual knowledge as well. It would need to know about the structure of the local environment (e.g. hand railings that can support its weight), hot liquids and their viscosities, and even the correlation of frozen dew with icy surfaces. To be a truly robust movement machine, a robot must *understand* the physical structure of the world.

Reaching to stop a fall while holding a cup of coffee is not exactly the kind of feat for which we praise our athletes and sports champions, and this might explain why the difficulty of such "feats of robustness" are often overlooked. However, it would not be the first time that we find ourselves humbled by the daunting complexity of a problem that we naively assumed was "trivial". Vision, for example, has remained an impressively hard task for a machine to solve at human-level performance, yet it was originally proposed as an undergraduate summer project [69]. Perhaps a similar misestimate has clouded our designation of the hard motor control problems worthy of cortical

input.

Inspired by the challenges confronting roboticists, as well as our rodent behavioural results, we are now in a position to posit a new role for motor cortex.

A primordial role for motor cortex

We are seeking a role for motor cortex in non-primate mammals, animals that do not require this structure for overt movement production. The struggles of roboticists highlight the difficulty of building movement systems that robustly adapt to unexpected perturbations, and the results we report in this study suggest that this is, indeed, the most conspicuous deficit for rats lacking motor cortex. So let us propose that, in rodents, motor cortex is primarily responsible for extending the robustness of the subcortical movement systems. It is not required for control in stable, predictable, non-perturbing environments, but instead specifically exerts its influence when unexpected challenges arise. This, we propose, was the original selective pressure for evolving a motor cortex, and thus, its primordial role. This role persists in all mammals, mediated via a modulation of the subcortical motor system (as is emphasized in studies of cat locomotion), and has evolved in primates to include direct control of the skeletal musculature. Our proposal of a "robust" teleology for motor cortex has a number of interesting implications.

Implications for non-primate mammals

One of the most impressive traits of mammals is the vast range of environmental niches that they occupy. While most other animals adapt to change over evolutionary time scales, mammals excel in their flexibility, quickly evaluating and responding to unexpected situations, and taking risks even when faced with challenges that have never been previously encountered [70]. This success requires more than precision, it requires resourcefulness: the ability to quickly come up with a motor solution for any situation and under any condition [71]. The Russian neurophysiologist Bernstein referred to this ability with an unconventional definition of "dexterity", which he considered to be distinct from a simple harmony and precision of movements. In his words, dexterity is required only when there is "a conglomerate of unexpected, unique complications in the external situations, [such as] in a quick succession of motor tasks that are all unlike each other" [71].

If Bernstein's "robust dexterity" is the primary role for motor cortex, then it becomes clear why the effects of lesions have thus far been so hard to characterize: assays of motor behaviour typically evaluate situations that are repeated over many trials in a stable environment. Such repeated tasks were useful, as they offer improved statistical power for quantification and comparison. However, we propose that these conditions specifically exclude the scenarios for which motor cortex originally evolved. It is not easy to repeatedly produce conditions that animals have not previously encountered, and the challenges in analysing these unique situations are considerable.

The assay reported here represents our first attempt at such an experiment, and it has already revealed that such conditions may indeed be necessary to isolate the role of motor cortex in rodents. We thus propose that neuroscience should pursue similar assays, emphasizing unexpected perturbations and novel challenges, and we have developed new hardware and software tools to make their design and implementation much easier [72].

Implications for primate studies

In contrast to other mammals, primates require motor cortex for the direct control of movement. However, do they also retain its role in generating robust responses? The general paresis, or even paralysis, that results from motor cortical lesions in these species obscures the involvement of cortex in directing rapid responses to perturbations. Yet there is evidence that a role in robust control is still present in primates, including humans. For example, stroke patients with partial lesions to the distributed motor cortical system will often recover the ability to move the affected musculature. However, even after recovering movement, stroke patients are still prone to severe impairments in robust control: unsupported falls are one of the leading causes of injury and death in patients surviving motor cortical stroke [73]. We thus suggest that stroke therapy, currently focused on regaining direct movement control, should also consider strategies for improving robust responses.

Even if we acknowledge that a primordial role of motor cortex is still apparent in primate movement control, it remains to be explained why the

motor cortex of these species acquired direct control of basic movements in the first place. This is an open question.

Some speculation on the role of direct cortical control

What happens when cortex acquires direct control of movement? First, it must learn how to use this influence, bypassing or modifying lower movement controllers. While functional corticospinal tract connections may be established prenatally [74], the refinement of corticospinal dependent movements, which must override the lower motor system, takes much longer and coincides with the lengthy maturation period of corticospinal termination patterns [75]. Humans require years of practice to produce and refine basic locomotion and grasping [76, 77], motor behaviours that are available to other mammals almost immediately after birth. This may be the cost of giving cortex direct control of movement—it takes more time to figure out how to move the body—but what is the benefit?

Giving motor cortex direct control over the detailed dynamics of movement might simply have extended the range and flexibility of robust responses. This increased robustness may have been required for primates to negotiate more difficult unpredictable environments, such as the forest canopy. Direct cortical control of the musculature may have evolved because it allowed primates to avoid their less "dexterous" predators simply by ascending, and robustly negotiating, the precarious branches of tree tops. However, the consequences of this cortical "take-over" might be even more

profound.

With motor cortex in more direct control of overt movements, the behaviour of a primate is a more direct reflection of cortical state: when you watch a primate move you are directly observing cortical commands. For species that live in social groups, this would allow a uniquely efficient means of communicating the state of cortex between conspecifics, a rather significant advantage for group coordination and a likely prerequisite for human language. This novel role for motor cortex—communication—might have exerted the evolutionary pressure to give cortex more and more control over basic movements, ultimately obscuring its primordial, and fundamental, role in robust control.

Some preliminary conclusions

Clearly our results are insufficient to draw any final conclusion, but that is not our main goal. We present these experiments to support and motivate our attempt to distil a long history of research, and ultimately suggest a new approach to investigating the role of motor cortex. This approach most directly applies to studies of non-primate mammals. There is now a host of techniques to monitor and manipulate cortical activity during behaviour in these species, but we propose that we should be monitoring and manipulating activity during behaviours that actually require motor cortex.

This synthesis also has implications for engineers and clinicians. We suggest that acknowledging a primary role for motor cortex in robust control,

a problem still daunting to robotics engineers, can guide the development of new approaches for building intelligent machines, as well as new strategies to assess and treat patients with motor cortical damage. We concede that our results are still naïve, but propose that the implications are worthy of further consideration.

6 Methods

All experiments were approved by the Champalimaud Foundation Bioethics Committee and the Portuguese National Authority for Animal Health, Direcção-Geral de Alimentação e Veterinária (DGAV).

Lesions: Ibotenic acid was injected bilaterally in 11 Long-Evans rats (ages from 83 to 141 days; 9 females, 2 males), at 3 injection sites with 2 depths per site (-1.5 mm and -0.75 mm from the surface of the brain). At each depth we injected a total amount of 82.8 nL using a microinjector (Drummond Nanoject II, 9.2 nL per injection, 9 injections per depth). The coordinates for each site, in mm with respect to Bregma, were: +1.0 AP / 2.0 ML; +1.0 AP / 4.0 ML; +3.0 AP / 2.0 ML, following the protocol reported by Kawai et al. for targeting forelimb motor cortex [7]. Five other animals were used as sham controls (age-matched controls; 3 females, 2 males), subject to the same intervention, but where ibotenic acid was replaced with physiological saline. Six additional animals were used as wildtype, no-surgery, controls (age-matched controls; 6 females).

For the frontal cortex aspiration lesions, the margins of the craniotomy were extended to cover from -2.0 to +5.0 mm AP relative to Bregma and laterally from 0.5 mm up to the temporal ridge of the skull. After removal of the skull, the exposed dura was cut and removed, and the underlying tissue aspirated to a depth of 2 to 3 mm with a fine pipette [78]. For the frontoparietal cortical lesions, the craniotomy extended from -6.0 to +4.0

mm AP relative to Bregma and laterally from 0.5 mm up to the temporal ridge. Two of these animals underwent aspiration lesions as described above. In the remaining animal, the lesion was induced by pial stripping in order to further restrict the damage to cortical areas. After removal of the dura, the underlying pia, arachnoid and vasculature were wiped with a sterile cotton swab until no vasculature was visible [79].

Recovery period: After the surgeries, animals were given a minimum of one week (up to two weeks) recovery period in isolation. After this period, animals were handled every day for a week, after which they were paired again with their age-matched control to allow for social interaction during the remainder of the recovery period. In total, all animals were allowed at least one full month of recovery before they were first exposed to the behaviour assay.

The three largest frontoparietal lesioned animals were originally prepared for a study of behaviour in a dynamic visual foraging task, which they were exposed to for one month in addition to the recovery period described above. This task did not, however, require any challenging motor behaviours besides locomotion over a completely flat surface. This period was also used to monitor the overall health condition of the animals and to facilitate sensorimotor recovery as much as possible. The animal with the largest lesion (Extended Lesion F) was prevented from completing the behaviour protocol due to deteriorating health conditions following the first two days of testing.

Histology: All animals were perfused intracardially with 4% paraformal-

dehyde in phosphate buffer saline (PBS) and brains were post-fixed for at least 24 h in the same fixative. Serial coronal sections (100 µm) were Nissl-stained and imaged for identification of lesion boundaries. In two of the largest frontoparietal lesions (Extended Lesions D and E), serial sections were taken sagittally.

In order to reconstruct lesion volumes, the images of coronal sections were aligned and the outlines of both brain and lesions were manually traced in Fiji [80] and stored as two-dimensional regions of interest. Lesion volumes were calculated by summing the area of each region of interest multiplied by the thickness of each slice. The stored regions were also used to reconstruct a 3D polygon mesh for visualization of lesion boundaries.

Behaviour assay: During each session the animal was placed inside a behaviour box for 30 min, where it could collect water rewards by shuttling back and forth between two nose pokes (Island Motion Corporation, USA). To do this, animals had to cross a 48 cm obstacle course composed of eight 2 cm aluminium steps spaced by 4 cm (Figure 1A). The structure of the assay and each step in the obstacle course was built out of aluminium structural framing (Bosch Rexroth, DE, 20 mm series). The walls of the arena were fabricated with a laser-cutter from 5 mm thick opaque black acrylic and fixed to the structural framing. A transparent acrylic window partition was positioned in front of the obstacle course in order to provide a clear view of the animal. All experiments were run in the dark by having the behavioural apparatus enclosed in a light tight box.

A motorized brake allowed us to lock or release each step in the obstacle course (Figure 1B). The shaft of each of the obstacles was coupled to an acrylic piece used to control the rotational stability of each step. In order to lock a step in a fixed position, two servo motors are actuated to press against the acrylic piece and hold it in place. Two other acrylic pieces were used as stops to ensure a maximum rotation angle of approximately +/- 100°. Two small nuts were attached to the bottom of each step to work as a counterweight that gives the obstacles a tendency to return to their original flat configuration. In order to ensure that noise from servo motor actuation could not be used as a cue to tell the animal about the state of each step, the motors were always set to press against an acrylic piece, either the piece that keeps the step stabilized, or the acrylic stops. At the beginning of each trial, the motors were run through a randomized sequence of positions in order to mask information about state transitions and also to ensure the steps were reset to their original configuration. Control of the motors was done using a Motoruino board (Artica, PT) along with a custom workflow written in the Bonsai visual programming language [72].

Data acquisition: The behaviour of the animals was recorded with a high-speed and high-resolution videography system (1280x680 @ 120 Hz) using an infrared camera (Flea3, PointGrey, CA), super-bright infrared LED front lights (SMD5050, 850 nm) and a vari-focal lens (Fujinon, JP) positioned in front of the transparent window partition. A top view of the assay was simultaneously recorded with the same system at a lower frame-rate (30 Hz)

for monitoring purposes. All video data was encoded with MPEG-4 compression for subsequent offline analysis. Behaviour data acquisition for the nose poke beam breaks was done using an Arduino board (Uno, Arduino, USA) and streamed to the computer via USB. All video and sensor data acquisition was recorded in parallel using the same Bonsai workflow used to control the behaviour assay.

Behaviour protocol: The animals were kept in a state of water deprivation for 20 h prior to each daily session. For every trial, rats were delivered a 20 µL drop of water. At the end of each day, they were given free access to water for 10 min before initiating the next deprivation period. Sessions lasted for six days of the week from Monday to Saturday, with a day of free access to water on Sunday. Before the start of the water deprivation protocol, animals were run on a single habituation session where they were placed in the box for a period of 15 min.

The following sequence of conditions were presented to the animals over the course of a month (see also Figure 1A): day 0, habituation to the box; day 1-4, all the steps were fixed in a stable configuration; day 5, 20 trials of the stable configuration, after which the two center steps were made unstable (i.e. free to rotate); day 6-10, the center two steps remained unstable; day 11, 20 trials of the unstable configuration, after which the two center steps were again fixed in a stable state; day 12, all the steps were fixed in a stable configuration; day 13-16, the state of the center two steps was randomized on a trial-by-trial basis to be either stable or unstable. Following the end

of the random protocol, animals continued to be tested in the assay for a variable number of days (up to one week) in different conditions. At the end of the testing period, all animals were exposed to a final session where all steps were made free to rotate in order to assay locomotion performance under challenging conditions.

Data analysis: All scripts and custom code used for data analysis are available online[1]. The raw video data was first pre-processed using a custom Bonsai workflow in order to extract features of interest. Tracking of the nose was achieved by background subtraction and connected component labelling of segmented image elements. First we compute the ellipse best-fit to the largest object in the image. We then mark the tip of the nose as the furthermost point, in the segmented shape of the animal, along the major axis of the ellipse. In order to analyse stepping performance, regions of interest were defined around the surface of each step and in the gaps between the steps. Background subtracted activity over these regions was recorded for every frame for subsequent detection and classification of steps and slips.

Analysis routines were run using the NumPy scientific computing package [81] and the Pandas data analysis library [82] for the Python programming language. Crossings were automatically extracted from the nose trajectory data by first detecting consecutive time points where the nose was positively identified in the video. In order for these periods to be successfully marked as crossings, the starting position of the nose must be located on the opposite

[1]https://bitbucket.org/kampff-lab/shuttling-analysis

side of the ending position. Inside each crossing, the moment of stepping with the forelimb on the centre steps was extracted by looking at the first peak above a threshold in the first derivative of the activation signal in the corresponding region of interest. False positive classifications due to hindlimb or tail activations were eliminated by enforcing the constraint that the position of the head must be located before the next step. Visual confirmation of the classified timepoints showed that spurious activations were all but eliminated by this procedure as stepping with the hindlimb or tail requires the head to be further ahead in space unless the animal turned around (in which case the trajectory would not be marked as a crossing anyway). The position of the nose at the moment of each step was extracted and found to be normally distributed, so statistical analysis of the step posture in the random condition used an unpaired t-test to check for independence of different measurement groups.

In order to evaluate the dynamics of crossing in the random condition, we first measured for every trial the speed at which the animals were moving on each spatial segment of the assay. To minimize overall trial-by-trial variation in individual animal performance, we used the average speed at which the animal approached the manipulated step as a baseline and subtracted it from the speed at each individual segment. To summarize differences in performance between stable and unstable trials, we then computed the average speed profile for each condition, and then subtracted the average speed profile for unstable trials from the average speed profile for stable trials. Fi-

nally, we computed the sum of all these speed differences at every segment in order to obtain the speedup index for each animal, i.e. an index of whether the animal tends to accelerate or decelerate across the assay on stable versus unstable trials.

Video classification: Classification of paw placement faults (i.e. slips) was performed in semi-automated fashion. First, possible slip timepoints were detected automatically using the peak detection method outlined above. All constraints on head position were relaxed for this analysis in order to exclude the possibility of false negatives. A human classifier then proceeded to manually go through each of the slip candidates and inspect the video around that timepoint in order to assess whether the activation peak was a genuine paw placement fault. Examples of false positives include tail and head activations as well as paw activations that occur while the animal is actively engaged in exploration, rearing, or other activities that are unrelated to crossing the obstacles.

Classification of behaviour responses following first exposure to the unstable condition was done on a frame-by-frame analysis of the high-speed video aligned on first contact with the manipulated step. The frame of first contact was defined as the first frame in which there is noticeable movement of the step caused by animal contact. Three main categories of behaviour were observed to follow the first contact: compensation, investigation and halting. Behaviour sequences were first classified as belonging to one of these categories and their onsets and offsets determined by the following criteria.

Compensation behaviour is defined by a rapid and adaptive postural correction to the locomotion pattern in response to the perturbation. Onset of this behaviour is defined by the first frame in which there is visible rapid contraction of the body musculature following first contact. Investigation behaviour consists of periods of targeted interaction with the steps, often involving manipulation of the freely moving obstacle with the forepaws. The onset of this behaviour is defined by the animal orienting its head down to one of the manipulated steps, followed by subsequent interaction. Halting behaviour is characterized by a period in which the animal stops its ongoing motor program, and maintains the same body posture for several seconds, without switching to a new behaviour or orienting specifically to the manipulated steps. This behaviour is distinct from a freezing response, as occasional movements of the head are seen. Onset of this behaviour is defined by the moment where locomotion and other motor activities besides movement of the head come to a stop. A human classifier blind to the lesion condition was given descriptions of each of these three main categories of behaviour and asked to note onsets and offsets of each behaviour throughout the videos. These classifications provide a visual summary of the first response videos; the complete dataset used for this classification is included as supplementary movies.

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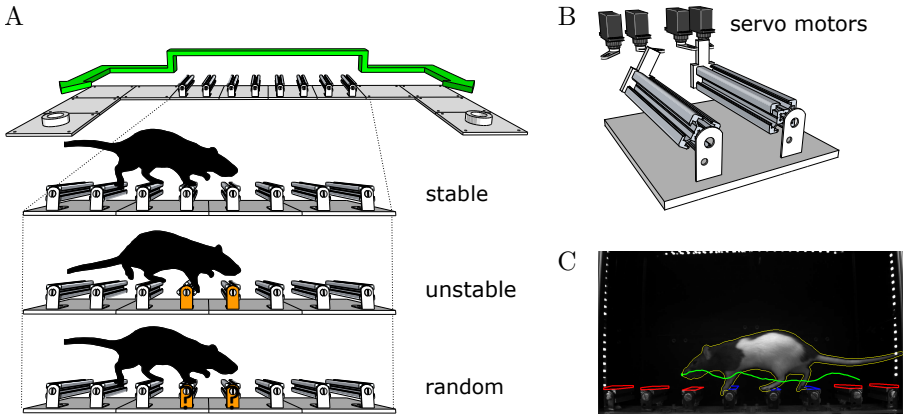

Figure 1: An obstacle course for rodents. (**A**) Schematic of the apparatus and summary of the different conditions in the behaviour protocol. Animals shuttle back and forth between two reward ports at either end of the enclosure. (**B**) Schematic of the locking mechanism that allows each individual step to be made stable or unstable on a trial-by-trial basis. (**C**) Example video frame from the behaviour tracking system. Coloured overlays represent regions of interest and feature traces extracted automatically from the video.

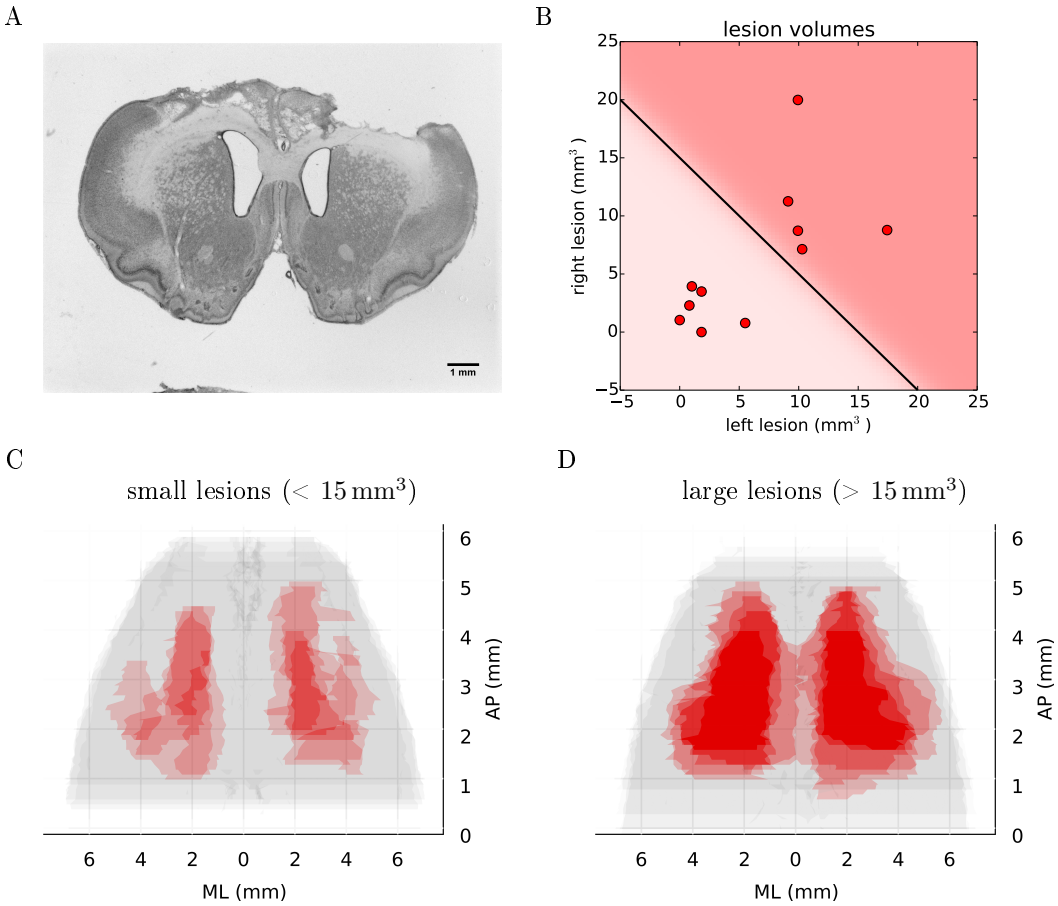

Figure 2: Histological analysis of lesion size. (**A**) Representative example of Nissl-stained coronal section showing bilateral ibotenic acid lesion of primary and secondary forelimb motor cortex. (**B**) Distribution of lesion volumes in the left and right hemispheres for individual animals. A lesion was considered "large" if the total lesion volume was above $15\,\mathrm{mm}^3$. (**C**) Super-imposed reconstruction stacks for all the small lesions ($n = 6$). (**D**) Super-imposed reconstruction stacks for all the large lesions ($n = 5$).

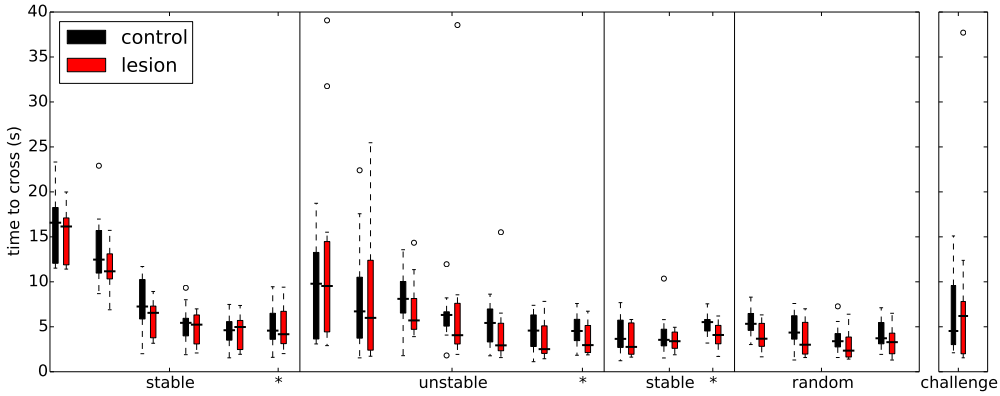

Figure 3: Overall performance on the obstacle course is similar for both lesion ($n = 11$) and control animals ($n = 11$) across the different protocol stages. Each set of coloured bars represents the distribution of average time to cross the obstacles on a single session. Asterisks indicate sessions where there was a change in assay conditions during the session (see text). In these transition sessions, the average performance on the 20 trials immediately preceding the change is shown to the left of the solid vertical line whereas the performance on the remainder of that session (after the change) is shown to the right.

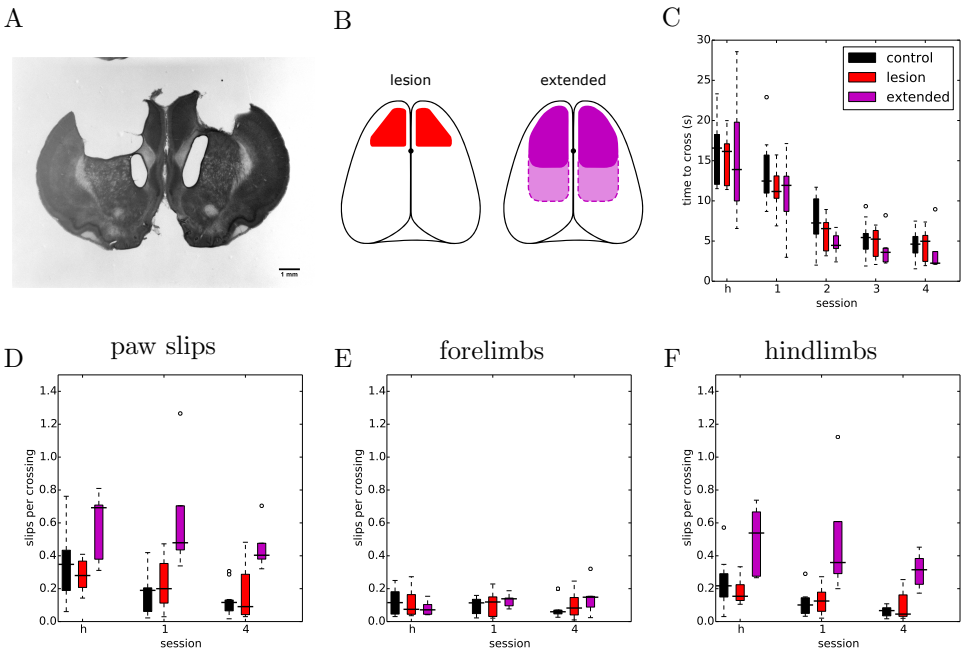

Figure 4: Extended frontoparietal cortex lesions perform as well as control animals despite impaired hindlimb control. (**A**) Representative example of Nissl-stained coronal section showing bilateral aspiration lesion of forelimb sensorimotor cortex. (**B**) Schematic depicting targeted lesion areas in the different animal groups. Left: outline of bilateral ibotenic acid lesions to the motor cortex. Right: outline of extended bilateral frontoparietal cortex lesions. Solid outline represents frontal cortex targeted lesions and dotted outline the more extensive frontoparietal lesions. (**C**) Average time required to cross the obstacles in the stable condition for extended lesions ($n = 5$). Performance of the other groups is shown for comparison. (**D**) Average number of slips per crossing in early versus late sessions of the stable condition. (**E**) Same data showing only forelimb slips. (**F**) Same data showing only hindlimb slips.

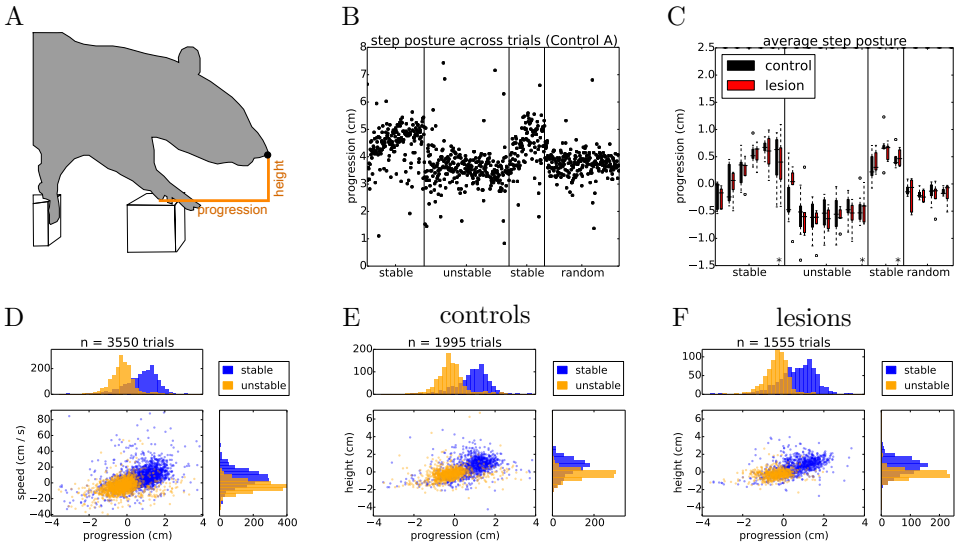

Figure 5: Rats adapt their postural approach to the obstacles after a change in physics. (**A**) Schematic of postural analysis image processing. The position of the animal's nose is extracted whenever the paw activates the ROI of the first manipulated step (see methods). (**B**) The horizontal position, i.e. progression, of the nose in single trials for one of the control animals stepping across the different conditions of the shuttling protocol. (**C**) Average horizontal position of the nose across the different protocol stages for both lesion and control animals. Asterisks indicate the average nose position on the 20 trials immediately preceding a change in protocol conditions (see text). (**D**) Distribution of horizontal position against speed for the last two days of the stable (blue) and unstable (orange) protocol stages. (**E-F**) Distribution of nose positions for control and lesion animals over the same sessions.

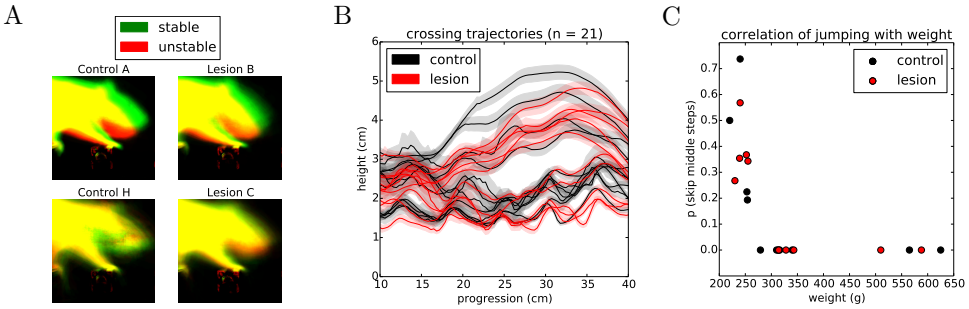

Figure 6: Animals use different strategies for dealing with the unstable obstacles. (**A**) Example average projection of all posture images for stable (green) and unstable (red) sessions for two non-jumper (top) and two jumper (bottom) animals. (**B**) Average nose trajectories for individual animals crossing the unstable condition. The shaded area around each line represents the 95% confidence interval. (**C**) Correlation of the probability of skipping the center two steps with the weight of the animal.

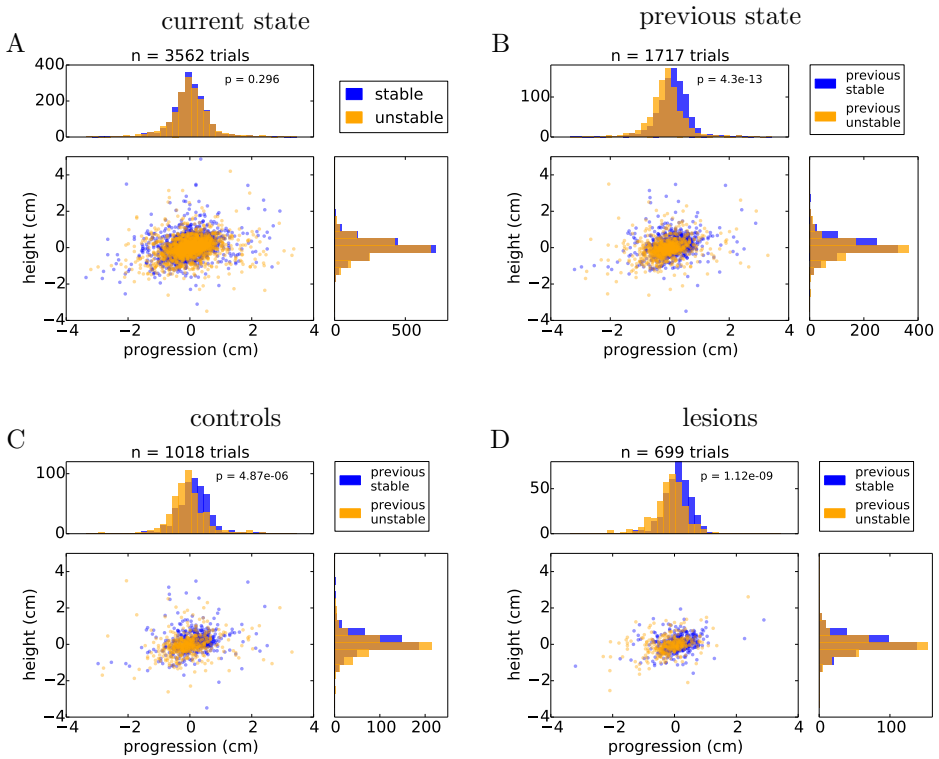

Figure 7: Animals adjust their posture on a trial-by-trial basis to the expected state of the world. (**A**) Distribution of nose positions on the randomized protocol when stepping on the first manipulated obstacle, for trials in which the current state was stable (blue) or unstable (orange). (**B**) Distribution of nose positions for trials in which the previous two trials were stable (blue) or unstable (orange). (**C-D**) Same data as in (**B**) split by the control and lesion groups. p values from Student's unpaired t-test are indicated.

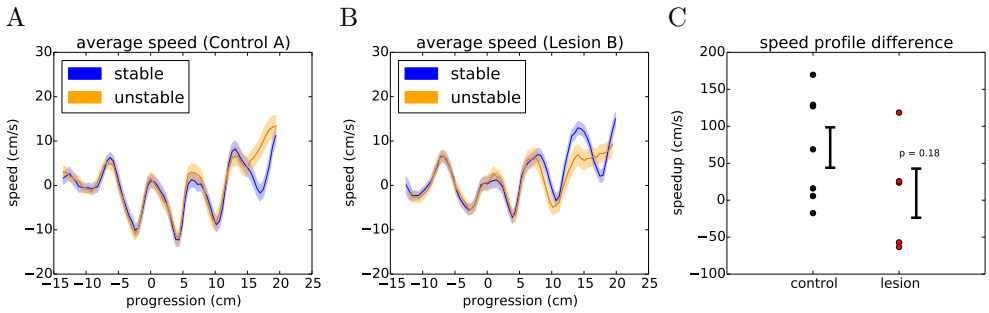

Figure 8: Encountering different states of the randomized obstacles causes the animals to quickly adjust their movement trajectory. (**A**) Example average speed profile across the obstacles for stable (blue) and unstable (orange) trials in the randomized sessions of a control animal (see text). The shaded area around each line represents the 95% confidence interval. (**B**) Respectively for one of the largest lesions. (**C**) Summary of the average difference between the speed profiles for stable and unstable trials across the two groups of animals. Error bars show standard error of the mean. p value from Student's unpaired t-test is indicated.

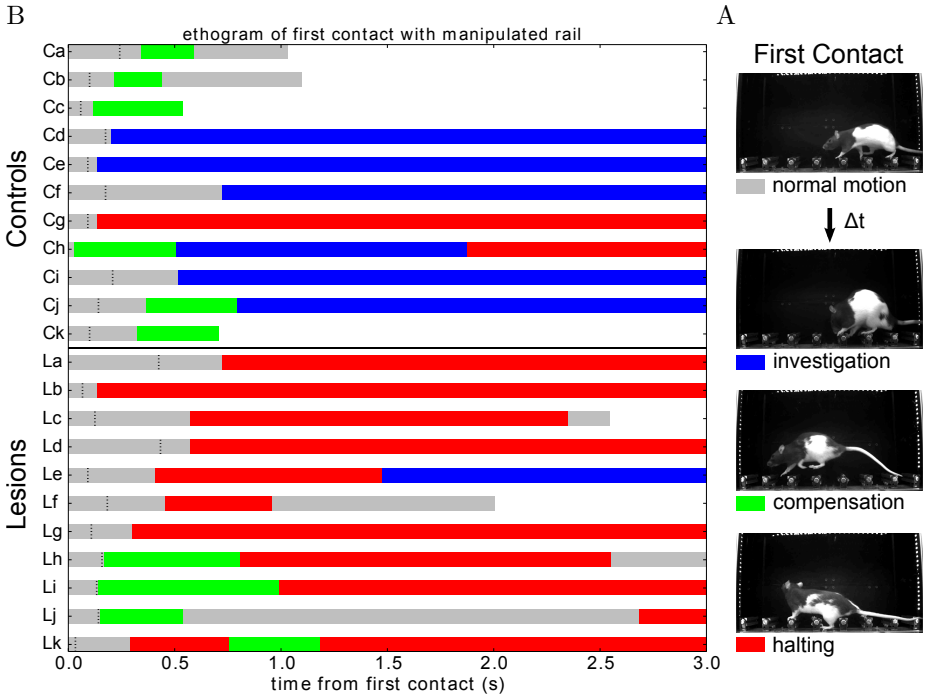

Figure 9: Responses to an unexpected change in the environment. (**A**) Response types observed across individuals upon first encountering an unpredicted instability in the state of the centre obstacles. (**B**) Ethogram of behavioural responses classified according to the three criteria described in (**A**) and aligned (0.0) on first contact with the newly manipulated obstacle. Black dashes indicate when the animal exhibits a pronounced ear flick. White indicates that the animal has crossed the obstacle course.

References

[1] K. L. Tyler and R. Malessa. "The Goltz-Ferrier debates and the triumph of cerebral localizationalist theory." In: *Neurology* 55 (2000), pp. 1015–1024. DOI: 10.1212/WNL.56.10.1424.

[2] C. G. Gross. "The discovery of motor cortex and its background." In: *Journal of the history of the neurosciences* 16.3 (2007), pp. 320–31. DOI: 10.1080/09647040600630160.

[3] K. S. Lashley. "Studies of cerebral function in learning: V. The retention of motor habits after destruction of the so-called motor areas in primates". In: *Archives of Neurology and Psychiatry* 12.3 (1924), pp. 249–276. DOI: 10.1001/archneurpsyc.1924.02200030002001.

[4] J. G. D. de Barenne. ""Corticalization" of function and functional localization in the cerebral cortex". In: *Archives of Neurology And Psychiatry* 30.4 (1933), pp. 884–901. DOI: 10.1001/archneurpsyc.1933.02240160196012.

[5] G. Rizzolatti and L. Craighero. "The Mirror-Neuron System". In: *Annual Review of Neuroscience* 27.1 (2004), pp. 169–192. DOI: 10.1146/annurev.neuro.27.070203.144230.

[6] C. A. Porro et al. "Primary motor and sensory cortex activation during motor performance and motor imagery: a functional magnetic resonance imaging study." In: *The Journal of neuroscience : the official journal of the Society for Neuroscience* 16.23 (1996), pp. 7688–7698.

[7] R. Kawai et al. "Motor Cortex Is Required for Learning but Not for Executing a Motor Skill". In: *Neuron* (2015), pp. 1–13. DOI: 10.1016/j.neuron.2015.03.024.

[8] G. Fritsch and E. Hitzig. "Über die elektrische Erregbarkeit des Grosshirns". In: *Archiv fur Anatomie, Physiologie und Wissenschaftliche* 37 (1870), pp. 300–332.

[9] A. S. F. Leyton and C. S. Sherrington. "Observations on the excitable cortex of the chimpanzee, orang-utan, and gorilla". In: *Experimental Physiology* 11.2 (1917), pp. 135–222. DOI: 10.1113/expphysiol.1917.sp000240.

[10] W. Penfield and E. Boldrey. "Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation." In: *Brain* 60.4 (1937), pp. 389–443.

[11] E. Neafsey et al. "The organization of the rat motor cortex: a microstimulation mapping study". In: *Brain Research Reviews* 11.1 (1986), pp. 77–96.

[12] E. V. Evarts. "Relation of pyramidal tract activity to force exerted during voluntary movement." In: *Journal of neurophysiology* 31.1 (1968), pp. 14–27.

[13] A. Georgopoulos, A. Schwartz, and R. Kettner. "Neuronal population coding of movement direction". In: *Science* 233.4771 (1986), pp. 1416–1419. DOI: 10.1126/science.3749885.

[14] A. B. Schwartz. "Motor cortical activity during drawing movements: population representation during sinusoid tracing." In: *Journal of neurophysiology* 70.1 (1993), pp. 28–36.

[15] S. H. Scott et al. "Dissociation between hand motion and population vectors from neural activity in motor cortex". In: *Nature* 413.6852 (2001), pp. 161–165.

[16] M. M. Churchland and K. V. Shenoy. "Temporal complexity and heterogeneity of single-neuron activity in premotor and motor cortex". In: *J Neurophysiol* 97.6 (2007), pp. 4235–4257. DOI: 10.1152/jn.00095.2007.

[17] M. M. Churchland et al. "Neural population dynamics during reaching." In: *Nature* 487.7405 (2012), pp. 51–6. DOI: 10.1038/nature11129.

[18] E. Todorov. "Direct cortical control of muscle activation in voluntary arm movements: a model." In: *Nature neuroscience* 3.4 (2000), pp. 391–8. DOI: 10.1038/73964.

[19] M. S. A. Graziano, C. S. R. Taylor, and T. Moore. "Complex Movements Evoked by Microstimulation of Precentral Cortex". In: *Neuron* 34 (2002), pp. 841–851.

[20] T. N. Aflalo and M. S. A. Graziano. "Possible origins of the complex topographic organization of motor cortex: reduction of a multidimensional space onto a two-dimensional array." In: *The Journal of neu-*

roscience : the official journal of the Society for Neuroscience 26.23 (2006), pp. 6288–97. DOI: 10.1523/JNEUROSCI.0768-06.2006.

[21] D. Laplane et al. "Motor consequences of motor area ablations in man". In: *Journal of the Neurological Sciences* 31.1 (1977), pp. 29–49. DOI: 10.1016/0022-510X(77)90004-1.

[22] W. G. Darling, M. A. Pizzimenti, and R. J. Morecraft. "Functional recovery following motor cortex lesions in non-human primates: experimental implications for human stroke patients". In: *Journal of Integrative Neuroscience* 10.3 (2011), pp. 353–384. DOI: 10.1142/S0219635211002737.

[23] B. Zaaimi et al. "Changes in descending motor pathway connectivity after corticospinal tract lesion in macaque monkey". In: *Brain* 135.7 (2012), pp. 2277–2289. DOI: 10.1093/brain/aws115.

[24] I. Q. Whishaw et al. "The impairments in reaching and the movements of compensation in rats with motor cortex lesions: an endpoint, videorecording, and movement notation analysis". In: *Behavioural brain research* 42 (1991), pp. 77–91.

[25] M. Alaverdashvili and I. Q. Whishaw. "Motor cortex stroke impairs individual digit movement in skilled reaching by the rat." In: *The European journal of neuroscience* 28.2 (2008), pp. 311–22. DOI: 10.1111/j.1460-9568.2008.06315.x.

[26] F. Goltz. "Über die Verrichtungen des Grosshirns". In: *Pflügers Archiv gesamte Physiologie des Menschen und der Tiere* 42 (1888), pp. 419–467.

[27] L. M. Bjursten, K. Norrsell, and U. Norrsell. "Behavioural repertory of cats without cerebral cortex from infancy". In: *Experimental brain research* 130.2857 (1976), pp. 115–130.

[28] P. Terry, B. A. Herbert, and D. A. Oakley. "Anomalous patterns of response learning and transfer in decorticate rats." In: *Behavioural brain research* 33.1 (1989), pp. 105–9.

[29] S. Tower. "Pyramidal lesion in the monkey". In: *Brain* 63.1 (1940), pp. 36–90.

[30] D. G. Lawrence and H. G.J. M. Kuypers. "The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions". In: *Brain* 91.1 (1968), pp. 1–14.

[31] C. N. Woolsey et al. "Complete unilateral section of the pyramidal tract at the medullar level in Macaca mulatta". In: *Brain Research* 40.1 (1972), pp. 119–123.

[32] C. G. Bernhard and E. Bohm. "Cortical representation and functional significance of the corticomotoneuronal system". In: *Archives of Neurology And Psychiatry* 72.4 (1954), pp. 473–502. DOI: `10.1001/archneurpsyc.1954.02330040075006`.

[33] H. G.J. M. Kuypers. "Anatomy of the descending pathways". In: *Comprehensive Physiology* (1981), pp. 597–666.

[34] H.-W. Yang and R. N. Lemon. "An electron microscopic examination of the corticospinal projection to the cervical spinal cord in the rat: lack of evidence for cortico-motoneuronal synapses." In: *Experimental brain research* 149.4 (2003), pp. 458–69. DOI: 10.1007/s00221-003-1393-9.

[35] P. W. Nathan and M. C. Smith. "The rubrospinal and central tegmental tracts in man". In: *Brain* 105.2 (1982), pp. 223–269. DOI: 10.1093/brain/105.2.223.

[36] D. G. Lawrence and H. G.J. M. Kuypers. "The functional organization of the motor system in the monkey. II. The effects of lesions of the descending brain-stem pathways". In: *Brain* 91.1 (1968), pp. 15–36.

[37] J. Donoghue and S. P. Wise. "The motor cortex of the rat: cytoarchitecture and microstimulation mapping." In: *The Journal of comparative neurology* 212.1 (1982), pp. 76–88. DOI: 10.1002/cne.902120106.

[38] B. Hyland. "Neural activity related to reaching and grasping in rostral and caudal regions of rat motor cortex". In: *Behavioural Brain Research* 94.2 (1998), pp. 255–269. DOI: 10.1016/S0166-4328(97)00157-5.

[39] D. N. Hill et al. "Primary motor cortex reports efferent control of vibrissa motion on multiple timescales". In: *Neuron* 72.2 (2011), pp. 344–356. DOI: 10.1016/j.neuron.2011.09.020.

[40] J. C. Erlich, M. Bialek, and C. D. Brody. "A cortical substrate for memory-guided orienting in the rat." In: *Neuron* 72.2 (2011), pp. 330–43. DOI: 10.1016/j.neuron.2011.07.010.

[41] R. S. Turner and M. R. DeLong. "Corticostriatal activity in primary motor cortex of the macaque." In: *The Journal of neuroscience : the official journal of the Society for Neuroscience* 20.18 (2000), pp. 7096–7108.

[42] J. H. Wu, J. V. Corwin, and R. L. Reep. "Organization of the corticostriatal projection from rat medial agranular cortex to far dorsolateral striatum". In: *Brain Research* 1280 (2009), pp. 69–76. DOI: 10.1016/j.brainres.2009.05.044.

[43] S. Lee, G. E. Carvell, and D. J. Simons. "Motor modulation of afferent somatosensory circuits." In: *Nature neuroscience* 11.12 (2008), pp. 1430–8. DOI: 10.1038/nn.2227.

[44] M. R. Baker, M. Javid, and S. A. Edgley. "Activation of cerebellar climbing fibres to rat cerebellar posterior lobe from motor cortical output pathways". In: *Journal of Physiology* 536.3 (2001), pp. 825–839. DOI: 10.1111/j.1469-7793.2001.00825.x.

[45] H. Jarratt and B. Hyland. "Neuronal activity in rat red nucleus during forelimb reach-to-grasp movements". In: *Neuroscience* 88.2 (1999), pp. 629–642. DOI: 10.1016/S0306-4522(98)00227-9.

[46] L. Petreanu et al. “Activity in motor–sensory projections reveals distributed coding in somatosensation”. In: *Nature* 489.7415 (2012), pp. 299–303. DOI: 10.1038/nature11321.

[47] D. M. Schneider, A. Nelson, and R. Mooney. “A synaptic and circuit basis for corollary discharge in the auditory cortex”. In: *Nature* 513.7517 (2014), pp. 189–194. DOI: 10.1038/nature13724.

[48] T. Graham Brown. “The Intrinsic Factors in the Act of Progression in the Mammal”. In: *Proceedings of the Royal Society B: Biological Sciences* 84.572 (1911), pp. 308–319. DOI: 10.1098/rspb.1911.0077.

[49] S. Grillner and M. L. Shik. “On the descending control of the lumbosacral spinal cord from the "mesencephalic locomotor region"”. In: *Acta Physiol Scand.* 87.0001-6772 (1973), pp. 320–333.

[50] D. M. Armstrong and T. Drew. “Discharges of pyramidal tract and other motor cortical neurones during locomotion in the cat.” In: *The Journal of Physiology* 346 (1984), pp. 471–495.

[51] T. Drew, W. Jiang, and W. Widajewicz. “Contributions of the motor cortex to the control of the hindlimbs during locomotion in the cat.” In: *Brain research. Brain research reviews* 40.1-3 (2002), pp. 178–91.

[52] T. Drew et al. “Role of the motor cortex in the control of visually triggered gait modifications.” In: *Canadian journal of physiology and pharmacology* 74.4 (1996), pp. 426–42.

[53] E. Liddell and C. Phillips. "Pyramidal section in the cat". In: *Brain* 67.1 (1944), pp. 1–9.

[54] H. Barlow. "Cerebral cortex as model builder". In: *Models of the visual cortex* 1985 (1985), pp. 37–46.

[55] K. Doya. "What are the computations of the cerebellum, the basal ganglia and the cerebral cortex?" In: *Neural networks : the official journal of the International Neural Network Society* 12.7-8 (1999), pp. 961–974.

[56] K. S. Lashley. "Studies of cerebral function in learning. III. The motor areas". In: *Brain* 44 (1921), pp. 255–285. DOI: 10.1037/h0070668.

[57] K. S. Lashley. "In search of the engram". In: *Symposia of the Society for Experimental Biology* (1950).

[58] C. S. Sherrington. "On Secondary and Tertiary Degenerations in the Spinal Cord of the Dog". In: *Journal of Physiology* 6.4 (1885), pp. 177–191. DOI: 10.1113/jphysiol.1885.sp000195.

[59] D. A. Oakley. "Cerebral cortex and adaptive behaviour". In: *Brain, Behaviour and Evolution.* 1979, pp. 154–188.

[60] D. Marple-Horvat et al. "Changes in the discharge patterns of cat motor cortex neurones during unexpected perturbations of on-going locomotion." In: *Journal of Physiology* 462 (1993), pp. 87–113.

[61] M. W. Miller. "The origin of corticospinal projection neurons in rat". In: *Exp Brain Res* 67.2 (1987), pp. 339–351. DOI: 10.1007/BF00248554.

[62] G. A. Metz and I. Q. Whishaw. "Cortical and subcortical lesions impair skilled walking in the ladder rung walking test: a new task to evaluate fore- and hindlimb stepping, placing, and co-ordination." In: *Journal of neuroscience methods* 115.2 (2002), pp. 169–79.

[63] T. M. Otchy et al. "Acute off-target effects of neural circuit manipulations". In: *Nature* (2015). DOI: 10.1038/nature16442.

[64] C. S. Sherrington. "Note on the Knee-jerk and the Correlation of Action of Antagonistic Muscles". In: *Proceedings of the Royal Society of London* 52.315-320 (1893), pp. 556–564.

[65] C. S. Sherrington. "Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing". In: *The Journal of physiology* 40.1-2 (1910), pp. 28–121. DOI: 10.1113/jphysiol.1910.sp001362.

[66] M. S. Arshian et al. "Vestibular nucleus neurons respond to hindlimb movement in the decerebrate cat". In: *J Neurophysiol* 111.March 2014 (2014), pp. 2423–2432. DOI: 10.1152/jn.00855.2013.

[67] T. Senoo et al. "Skillful manipulation based on high-speed sensory-motor fusion". In: *2009 IEEE International Conference on Robotics and Automation* (2009), pp. 1611–1612. DOI: 10.1109/ROBOT.2009.5152852.

[68] A. Coates, P. Abbeel, and A. Y. Ng. "Learning for control from multiple demonstrations". In: *Proceedings of the 25th international conference*

on Machine learning - ICML '08 (2008), pp. 144–151. DOI: 10.1145/1390156.1390175.

[69] S. Papert. *The summer vision project*. 1966.

[70] M. Spinka, R. C. Newberry, and M. Bekoff. "Mammalian Play: Training for the Unexpected". In: *Source: The Quarterly Review of Biology* 76.2 (2001), pp. 141–168. DOI: 10.1086/393866.

[71] N. A. Bernstein. *Dexterity and its Development*. Ed. by M. L. Latash and M. Turvey. L. Erlbaum Associates, 1996.

[72] G. Lopes et al. "Bonsai: An event-based framework for processing and controlling data streams". In: *Frontiers in Neuroinformatics* 9.7 (2015). DOI: 10.3389/fninf.2015.00007.

[73] J. V. Jacobs. "Why we need to better understand the cortical neurophysiology of impaired postural responses with age, disease, or injury." In: *Frontiers in integrative neuroscience* 8.August (2014), p. 69. DOI: 10.3389/fnint.2014.00069.

[74] J. A. Eyre et al. "Functional corticospinal projections are established prenatally in the human foetus permitting involvement in the development of spinal motor centres." In: *Brain : a journal of neurology* 123 (Pt 1 (2000), pp. 51–64. DOI: 10.1093/brain/123.1.51.

[75] D. G. Lawrence and D. A. Hopkins. "The development of motor control in the rhesus monkey: evidence concerning the role of corticomo-

toneuronal connections." In: *Brain : a journal of neurology* 99.2 (1976), pp. 235–54. DOI: 10.1093/brain/99.2.235.

[76] E. Thelen. "Developmental origins of motor coordination: leg movements in human infants." In: *Developmental psychobiology* 18.1 (1985), pp. 1–22. DOI: 10.1002/dev.420180102.

[77] C. von Hofsten. "Mastering Reaching and Grasping: The Development of Manual Skills in Infancy". In: *Advances in Psychology* 61.C (1989), pp. 223–258. DOI: 10.1016/S0166-4115(08)60023-0.

[78] I. Q. Whishaw. "Loss of the innate cortical engram for action patterns used in skilled reaching and the development of behavioral compensation following motor cortex lesions in the rat". In: *Neuropharmacology* 39.5 (2000), pp. 788–805. DOI: 10.1016/S0028-3908(99)00259-2.

[79] T. D. Farr and I. Q. Whishaw. "Quantitative and qualitative impairments in skilled reaching in the mouse (Mus musculus) after a focal motor cortex stroke". In: *Stroke* 33.7 (2002), pp. 1869–1875. DOI: 10.1161/01.STR.0000020714.48349.4E.

[80] J. Schindelin et al. "Fiji: an open-source platform for biological-image analysis." In: *Nature methods* 9.7 (2012), pp. 676–82. DOI: 10.1038/nmeth.2019.

[81] S. van der Walt, S. C. Colbert, and G. Varoquaux. "The NumPy Array: A Structure for Efficient Numerical Computation". In: *Computing in*

Science & Engineering 13.2 (2011), pp. 22–30. DOI: 10.1109/MCSE.2011.37.

[82] W. McKinney. "Data Structures for Statistical Computing in Python". In: *Proceedings of the 9th Python in Science Conference* (2010), pp. 51–56.