Movement without dopamine: striatal dopamine is required to maintain but not to perform learned actions

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Abstract

The different populations of dopaminergic neurons located in the ventral mesencephalon have long been associated with distinct functional roles. The nigrostriatal projection is considered necessary for efficient motor performance, while the mesolimbocortical projection is usually associated with reward signalling. However, a number of recent studies in our laboratory suggest that the divergence between these two functions of dopamine is not as delineated as it may once have seemed. In these experiments, we have been developing improved behavioural methods for assessing the nature of the deficit in rats with unilateral dopamine lesions, as well as the efficacy of various experimental cell and gene therapies for Parkinson’s disease. The behavioural task we selected is a lateralized nose-poking task in which rats are trained to respond to stimulus lights on either side of their heads. This task not only allows us to accurately measure aspects of motor performance, but, because it requires extensive training, it also allows us to assess aspects of motor learning. The concurrence of motor performance parameters (which are considered to be dependent on striatal dopamine) and motor learning parameters (which are thought to be dependent on mesolimbocortical reward signalling) within the same task has revealed some surprising consequences of dopamine lesions and neuroprotective/neuroreparative approaches to repair in rat models of Parkinson’s disease. The data generated using this task suggest that the motor deficits that occur as a consequence of dopamine lesions may be downstream of a deficit in reward signalling. If so, this could redefine our perception of the role of dopamine in controlling motor function.

Parkinson’s disease: the promise of experimental therapies

Parkinson’s disease is a progressive neurodegenerative motor disorder that is characterized by slowness of movement, rigidity and tremor [1]. The motor impairments that characterize Parkinson’s disease are caused by degeneration of nigrostriatal dopaminergic neurons in the substantia nigra pars compacta and the consequent loss of the neurotransmitter dopamine from the neostriatum [2]. The principal therapeutic option currently in widespread use for Parkinson’s disease is to restore striatal dopamine transmission pharmacologically with the precursor L-dopa or agonists such as bromocriptine [3]. However, none of these approaches actually offer a ‘cure’ for the disease, and neither do they slow the unrelenting degeneration of the nigrostriatal neurons. Some alternative experimental approaches promise to improve on the current pharmacological approaches. For example, deep brain stimulation seeks to bypass the dopamine loss and restore excitatory and inhibitory balance in downstream projections of the striatum [4]; growth factor therapy offers the possibility of slowing or halting the disease progression in earlier-stage patients [5], whereas cell transplantation could replace the dopaminergic neurons once they have degenerated [6]. Although each of these experimental approaches has already reached the clinic, it is imperative that they are subjected to rigorous scrutiny in valid animal models of Parkinson’s disease both to refine the alternative technologies and to understand the different mechanisms of neuroprotection and/or neuroreparation that apply in each case.

Modelling the Parkinsonian deficit in rats

In one of the most common experimental models of Parkinson’s disease, the nigrostriatal neurons on one side of the brain are lesioned by injection of the selective catecholamine neurotoxin 6-hydroxydopamine [7,8]. In rats, this leads to a well-characterized behavioural syndrome that is manifest by spontaneous and drug-induced rotation, contralateral sensorimotor neglect, contralateral akinesia and impaired contralateral forelimb use. At present, the efficacy of most experimental therapies for Parkinson’s disease is routinely validated in this model using simple screens for motor asymmetry such as drug-induced rotation. However, the Parkinsonian deficit is significantly more complex than this, and alternative tests that permit a more detailed analysis of the functional mechanisms of impairment and

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The lateralized reaction time task

The task is conducted in the nine-hole box apparatus (A). When fully trained on the task (B), rats are required to make a sustained nose-poke in the centre hole following presentation of a centre stimulus light. After a variable delay (50, 100, 150 and 200 ms), a brief stimulus of light (200 ms) is presented on one side of the rat’s head at random, and the rat is rewarded for nose-poking on the side of stimulus presentation. During each daily session (30 min), rats are presented with equal numbers of left and right stimuli in random order. Thus the selection, initiation and execution of movements ipsilateral and contralateral to the side of the lesion can be analysed separately.

Movement without dopamine

At its core, the lateralized reaction time task is a motor learning task in which rats are trained to make a conditioned response (a lateral nose-poke) following presentation of a conditioned stimulus (the lateral stimulus light). Following an extensive period of training, the lateral responses to the stimulus lights become governed by automatic stimulus–response associations, that is, they become habitual. Moreover, the task includes two separate stimulus–response associations, one on the side ipsilateral to the lesion, and one on the contralateral side. When rats that have been trained on the lateralized reaction time task are returned to the nine-hole box after a unilateral 6-hydroxydopamine lesion of the medial forebrain bundle, they are impaired on numerous parameters of the task (Figure 2A and see [9–13]). Not surprisingly, they are slower to react to the stimulus light on the contralateral side, and are also slower to complete their contralateral nose-pokes. But, strikingly, these motor deficits are not apparent when the rats are first reintroduced into the boxes; rather, they become manifest over several days of testing. Thus, when they are first returned to the nine-hole boxes, lesioned rats can initiate and execute contralateral nose-pokes as efficiently as their non-lesioned counterparts. This is despite the fact that the lesion destroys almost all of the nigrostriatal neurons, and yields near-complete dopaminergic deafferentation of the striatum (~2% of nigrostriatal neurons survive the medial forebrain bundle lesion). Such efficient movement initiation and execution in the absence of striatal dopamine contradicts the long-standing dogma that striatal dopamine is required for effective motor performance. In the lateralized reaction time task, this ‘movement without dopamine’ almost certainly occurs because the lateralized nose-pokes are governed by stimulus–response associations. That is, when they are first reintroduced to the boxes, the rats respond to the lateral stimuli lights ‘out of habit’. This stimulus–response association is clearly powerful enough to negate, at least temporarily, the effect of the dopamine lesion on motor performance.

A motor deficit or a reward deficit?

Although the rats are not impaired on the lateralized reaction time task when they are first reintroduced to the boxes, they do develop deficits over a few days of testing. Thus a simple motor-output hypothesis, i.e. an inability to initiate a response to contralateral space, cannot account for the impairments seen. Rather, the pattern of deficits observed appears to imply a deficit in motor learning, involving extinction and spontaneous re-emergence of the contralateral conditioned response. This is particularly evident for the contralateral selection deficit (see contralateral accuracy data, Figure 2A). It is now well established that conditioned stimuli (such as the lateral stimulus lights) are associated with activation of ‘rewarding’ dopamine neurons in the substantia nigra and ventral tegmental area [14,15]. This reinforcing signal is required to maintain the conditioned response. In the lesion model used in these studies, 6-hydroxydopamine is injected into the ascending dopaminergic neurons as they traverse the medial forebrain bundle. This results in the degeneration of dopaminergic neurons from both the substantia nigra and the ventral tegmental area. As a consequence, the dopamine reward signal is absent from the lesioned side of the brain in these rats. Thus, although the rats correctly respond to the contralateral stimulus light when first returned to the boxes, the contralateral conditioned nose-poke gradually extinguishes because the reward signal has been eliminated.
Figure 2 | Performance of the lateralized reaction time task

Rats were tested on the task before, and 2 and 12 weeks after induction of the unilateral 6-hydroxydopamine medial forebrain bundle lesion (A). When the rats are returned to the nine-hole boxes 2 weeks after lesion surgery, they are initially as efficient as their unlesioned counterparts at reacting to contralateral stimuli and executing contralateral nose-pokes, although they do have a slightly reduced accuracy for contralateral stimuli. However, within a few days they develop a profound deficit in contralateral responding that is manifest by an increased reaction time, an increased movement time and a reduced accuracy for contralateral stimuli. Strikingly, when they are returned to the nine-hole boxes after a delay of 10 weeks, these deficits are no longer apparent initially, but they do re-emerge over a few days of testing. These data appear to reflect an underlying deficit in motor learning manifest by extinction and spontaneous re-emergence of the contralateral response. The progressive decline in contralateral accuracy seen after the unilateral medial forebrain bundle lesion is directly comparable with that observed when unlesioned rats are rewarded for correct nose-pokes on one side only (B). These data support the hypothesis that the contralateral accuracy deficit seen in lesioned rats is due to the absence of the dopamine reward signal on the lesioned side of the brain (see the text for a more detailed discussion).

B

6-hydroxydopamine lesion

Differential reinforcement

Accuracy (%) 1 2 3 4 5 6 7 8 9 10

Days of testing

ipsilateral side

contralateral side

rewarded side

unrewarded side

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In support of this hypothesis, the profile of extinction observed following a unilateral dopamine lesion is directly comparable with that observed in unlesioned rats when the actual food reward is omitted following all responses on one side (Figure 2B) (E. Dowd and S.B. Dunnett, unpublished work). Also in support of this hypothesis is the finding that rats with selective unilateral lesions of the nigrostriatal pathway, with sparing of the mesolimbocortical pathway, do not develop these motor deficits [11,12]. These results suggest that the impairments in movement initiation and execution seen in this task may be downstream of the loss of the dopamine reward signal. Intriguingly, this suggests that rats performing conditioned movements do not need dopamine for efficient motor performance itself, but rather for ‘stamping-in’ (i.e. both initial learning and subsequent maintenance) of the conditioned response. When this response fails to be reinforced, then the motor consequences of the lack of striatal dopamine become evident. If this is truly the case, then this could redefine our perceptions of the role of dopamine in controlling/facilitating motor function.

Repairing versus protecting the hemi-Parkinsonian rat brain

Ultimately, the aim of this series of studies is to obtain a more detailed analysis of both the nature of the deficit in the hemi-Parkinsonian rat as well as the functional capacity of various experimental neuroreparative and neuroprotective approaches. We have so far focused on two experimental approaches: primary foetal dopaminergic cell transplantation into the striatum [10], and lentiviral vector-mediated overexpression of glial cell line-derived neurotrophic factor in the striatum and above the substantia nigra [13]. On the lesioned side of the brain, these two approaches lead to quite different outcomes in terms of anatomical connectivity between the substantia nigra and its dopaminergic projection site, the striatum. In the 6-hydroxydopamine medial forebrain bundle lesion model, there is complete dopaminergic disconnection between the substantia nigra and the striatum unilaterally. Transplanting dopaminergic neurons into an ectopic location in the striatum replaces a local dopamine input into the striatum but does not reconnect the nigrostriatal circuitry. In contrast, striatal injection of neuroprotective viral vectors partially protects the host nigrostriatal pathway from 6-hydroxydopamine-induced degeneration, and therefore retains at least partial connectivity between the substantia nigra and the striatum. These differences have interesting implications in terms of the predicted functional capacity of neuroprotective and neuroreparative approaches to Parkinson’s disease: the ectopic dopamine cell transplant in the striatum should only be capable of restoring functions dependent on tonic or locally regulated dopamine release, whereas the neuroprotective virus should be capable of protecting functions dependent on dopamine release evoked by patterned signals originating from the substantia nigra.

Interestingly, one function that is known to be dependent on evoked dopamine release is reward signalling. Numerous electrophysiological studies have revealed that dopaminergic neurons in the substantia nigra and ventral tegmental area are activated by rewarding events (or reward-predicting stimuli) in the environment [14,15]. In terms of performance on the lateralized reaction time task, this means that the contralateral accuracy deficit (if it is a reflection of impaired reward...
signalling) should be prevented by neuroprotection of the ascending dopaminergic neurons, but not restored by graft-derived striatal dopamine replacement. Indeed, when the functional efficacy of these two approaches is compared on the operant task, some intriguing differences emerge. The progressive decline in contralateral accuracy, which reflects behavioural extinction of the contralateral conditioned response, is not seen in neuroprotected rats that received a lentiviral vector overexpressing glial cell line-derived neurotrophic factor (Figure 3). In contrast, in neurorepaired rats that received a dopamine cell transplant into the striatum, this progressive decline is still evident (although they do not decline to the same level as lesioned rats that did not receive a transplant). The effect of repairing versus protecting the brain on motor performance is less clear. Protecting the brain from the 6-hydroxydopamine lesion does spare both reaction and movement time performance, whereas in this experiment at least, reaction time performance is not restored by the transplant. More recent experiments, however, suggest that larger grafts do have the capacity to restore reaction time performance (E. Dowd and S.B. Dunnett, unpublished work).

The dual role of dopamine

The data generated by the lateralized reaction time task are indeed intriguing. They show that rats with near-complete dopamine lesions of the nigrostriatal and mesolimbocortical pathways can still initiate and execute pre-learned actions as efficiently as unlesioned rats. This appears to be possible because the rats are responding to the stimulus lights out of habit (i.e. they are making conditioned responses to conditioned stimuli). However, when the pre-learned action is extinguished, the motor consequences of the dopamine lesion become apparent: the rats become slower to react to the stimulus lights and to execute nose-pokes. In these rats, extinction of the pre-learned action appears to occur because the lesion destroys the neuronal substrate for reward signalling.

This hypothesis is strengthened by data from unlesioned rats showing that a similar pattern of extinction occurs when the actual food reward is omitted for correct responses on one side.

The dopamine neurons of the ventral mesencephalon have long been associated with two divergent functional roles – controlling/facilitating motor function and signalling rewarding environmental events. However, the data generated by the reaction time task suggest that these functions may not be as divergent as once thought: the motor deficits in reaction and movement time that occur as a consequence of dopamine-depleting lesions in this task appear to be downstream of a deficit in reward signalling. Ultimately, the finding that rats can efficiently initiate and execute pre-learned actions in the absence of striatal dopamine could force us to redefine our perceptions of dopamine's role in controlling and/or facilitating motor function.

References


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