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Commentary

The education of a brain transplant

*John F. Marshall**

Department of Neurobiology and Behavior, 2205 Bio Sci II, University of California, Irvine, CA 92697-4550

Neurodegenerative diseases represent disorders of the nervous system characterized by the gradual loss of neurons. Although two of the most common neurodegenerative diseases, Alzheimer's and Parkinson's, affect primarily the elderly, Huntington's disease (HD) brings devastating consequences to younger brains. Although quite variable, the average age at symptom onset of afflicted individuals is about 40 years. Symptoms include involuntary choreic (i.e., dance-like) movements, declining cognitive capacities, and emotional disturbances. Patients survive, on average, about 15 years after their symptoms begin. The neuron loss in HD has been thoroughly described (1), and the most vulnerable neuron populations are those of the striatum (caudate nucleus, putamen) and frontal cortex. HD shows an autosomal dominant pattern of inheritance. The mutation consists of expanded CAG repeats in the *huntingtin* gene, leading to an excess number of glutamine residues in huntingtin, a protein product of unknown function (2). The cellular mechanisms by which huntingtin contributes to the neuron pathology are topics of ongoing investigation (3, 4), but it is presently unclear how this mutation gives rise to the selective neurodegeneration of particular forebrain cell populations (5).

Physicians have few good options available to treat the symptoms of HD and none to halt its progression. Some drug treatments (e.g., dopaminergic antagonists) can diminish the choreic movements and provide some symptomatic relief, but these often carry their own risks—drug-induced parkinsonism or, with prolonged administration, tardive dyskinesias (6). Partly in response to the lack of effective treatments for this disease, neuroscientists have long been intrigued by the possibility that transplanting donor striatal tissue into the degenerating striatum of HD patients could provide functional benefit. The article by Brasted *et al.* (7) in this issue of the *Proceedings* helps define the conditions under which striatal cell transplants should be expected to alleviate the movement disorders of HD patients. Using an animal model, these authors showed that the ability of the grafted tissue to survive and reconstitute the anatomical circuitry of the host brain is not sufficient to restore all lost motor skills. Rather, the animal must also relearn certain lost habits, thereby exposing the "naïve" transplant to the specific information it needs to participate in the behavior.

The animal model most frequently used to approximate the pathology of HD is the rat given intrastriatal infusions of an excitotoxin, which induces a rapid depletion of neurons within the infused striatum. To study effects of transplantation, tissue from embryonic striatal primordia is introduced into the injured striatum several days after the excitotoxin infusion, when the induced cell loss is nearly complete. Under the proper conditions, transplanted cells survive and become integrated into the circuitry of the host basal ganglia. Like normal striatal cells, grafted neurons receive topographically organized inputs from cerebral cortex (8, 9) and establish efferent projections to other nuclei of basal ganglia (globus pallidus, substantia nigra; ref. 10). Several studies have demonstrated that these restored circuits are physiologically active (11–14).

Of what significance are these observations to the possible amelioration of movement disorders in HD patients receiving transplants? Excitotoxic lesions of the rat striatum lead to abnormalities in a variety of motor functions, including locomotion, alternation learning, skilled paw reaching, and drug-induced movements, and the transplantation of striatal tissue can blunt these effects of the lesion (reviewed in refs. 15 and 16). On the basis of these observations, Björklund *et al.* (15) concluded that striatal transplants effect functional recovery in this animal model by restoring information relay within the reconstructed cortico-basal ganglia circuits. This conclusion offers hope for clinical trials; further, it suggests that the replacement of broken circuits is sufficient for recovery.

However, Mayer *et al.* (17) suggested that the replacement of broken circuits is not sufficient for the recovery of all lost motor functions. Rats were trained for food reward on a visually cued reaction time task ("nose poke"), which required the rats to move their snouts to the left or right of a central fixation point. The rats were then given excitotoxic striatal lesions in one hemisphere (each striatum controls responding to the opposite body side), and some of these lesioned rats subsequently received embryonic striatal cell transplants in the injured striatum. Importantly, the investigators waited 6 mo after surgery before retesting performance, a time at which the integration of the graft into the host forebrain should have been maximal. When retested, the rats with the excitotoxic lesion exhibited an enormous ipsilateral bias in responding on this task, such that few nose-poke responses were directed contralaterally to the lesion. The animals given the lesion + graft showed a very similar ipsilateral response bias when first retested. But, during 15 days of retesting, these grafted rats showed a significant improvement in contralateral nose pokes. The authors concluded that the retraining had produced a functional recovery of responding to contralateral space in grafted rats; however, it was unclear whether the retraining led to a general improvement of motor skills or to a relearning of a specific stimulus-response association.

Using a task similar to that used by Mayer *et al.* (17), Brasted *et al.* (7) have both clarified what the grafted animals learn during postoperative retraining and distinguished movement parameters that require explicit retraining from those that do not. Key to the design of this experiment is that grafted (or lesioned nongrafted) rats were retrained at 4 mo after surgery to make nose pokes both ipsilaterally and contralaterally to the injured hemisphere. Some rats received the ipsilateral and others the contralateral retraining first. If the retraining of grafted animals improves their performance by inducing a general improvement in their motor skills, then postsurgical retraining to turn ipsilaterally should confer benefit ("savings") to the animals when they are later retrained to turn contralaterally to the grafted striatum. However, the authors found that contralateral retraining resulted in the same ame-

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*To whom reprint requests should be addressed. E-mail: jfmarsha@uci.edu.

lioration of response bias whether or not ipsilateral retraining preceded it. Thus, what is learned during the contralateral retraining is specific to the lateralized stimulus-response requirements of that task.

Where and how does retraining improve the impaired motor functions of the grafted animals? The most likely locus for the retraining effects is the grafted striatal tissue, but it cannot be ruled out that, under the influence of the graft, the surviving host striatal tissue mediates the relearning. Whether the graft, the host, or their combination underlies this retraining effect, considerable evidence indicates that the dorsal striatum of adult mammals participates in the acquisition and retention of certain types of information, described as "habit," "motor," "procedural," or "stimulus-response" learning (18–22). This evidence comes from several experimental sources. Animals that experience dorsal striatal damage before they are trained on these types of tasks learn them more slowly and/or less completely. Posttraining intrastriatal infusions of agents that block striatal transmission interfere with later retention of these tasks, whereas posttraining intrastriatal infusions of stimulant drugs improve retention of these tasks. Impaired habit learning has also been reported in patients with Parkinson's disease (19), in whom striatal dopamine transmission is greatly reduced. Some characteristics of these striatally dependent forms of learning are that they involve simple associations between stimuli (or stimuli and responses), that these associations are often acquired only gradually, and that—in humans, at least—the learning can occur without the subject's awareness. The nose-poke task used by Brasted *et al.* (7) represents one example of stimulus-response learning.

How the graft—assuming that the graft is the relevant site—is retrained is a fascinating question about which we can presently only speculate. Most accounts of how stimulus-response learning occurs in the undamaged dorsal striatum begin with the observation that this structure receives extensive collateralized excitatory (glutamatergic) inputs from all sensory, motor, and premotor representations within the cerebral cortex. These corticostriatal projections constitute an informational pipeline through which striatal neurons are informed about the environment, motor commands, intentions to act, and the consequences of movements. Because a single striatal projection neuron may receive synaptic input from thousands of cortical cells (23), the opportunities for convergence of information from disparate cortical areas are extensive. Moreover, the firing of individual striatal projection neurons seems to require synchronous activity in only a small subset of their cortically derived synapses (23). Two forms of activity-dependent plasticity believed to be relevant to the formation of new associations within the striatum are long-term depression (LTD) and long-term potentiation (LTP). Each of these has been described after corticostriatal activation (24, 25). *In vivo*, LTP predominates, as high-frequency electrical stimulation of rat cortex produces a lasting potentiation of cortically-driven responses in recipient striatal neurons (25). Under conditions of habit learning, where new associations must be established between previously unassociated stimuli, the simultaneous depolarization of a striatal neuron by a set of cortical neurons (which encode the stimulus/response features to be associated) is thought to promote a long-lasting potentiation of that striatal neuron's response to those inputs (see ref. 26). Further, the strength of this potentiation is thought to accumulate with repetitions of synchronous activity within this cortical set, thereby contributing to the gradual acquisition of stimulus-response learning.

The striatal innervation by axons of dopaminergic neurons residing in the ventral midbrain constitutes another source of synaptic inputs believed essential for the associative plasticity of striatal neurons. The previously cited results (19) concerning impaired habit learning in patients with Parkinson's disease provide human experimental evidence for dopamine's importance to these tasks. Additionally, electrophysiological studies have shown that degeneration of nigrostriatal dopaminergic synapses in animals blocks both striatal LTD and LTD *in vitro* (24) and learning-dependent plasticity of striatal neuron responses in the awake monkey (27). The dependence of both habit learning and striatal plasticity on the integrity of the striatal dopamine innervation has at least two possible explanations. First, the dopaminergic innervation may simply provide a tonic background of dopamine receptor stimulation for the involved striatal neuron populations, permitting the glutamate-mediated synaptic events to sculpt new neuronal response patterns in ways demanded by the requirements of the new habit learning. A second, more dynamic, view of the role of dopamine suggests the training of striatal neuron responses depends on the phasic release of dopamine onto the involved striatal cell population in a fixed temporal relationship to the arrival of the relevant cortical signals. The elegant work of Schultz *et al.* supports this latter possibility (28). These investigators found that when monkeys learn a motor task, their dopamine cells fire specifically on presentation of rewards (or, later in training, on presentation conditioned stimuli paired with those rewards). The temporal specificity of the dopamine neuron's response during learning has excited interest in whether the striatal synaptic dopamine release during learning of these tasks contributes to the strengthening of particular corticostriatal synapses (28, 29).

Extrapolating these concepts to the striatal transplantation paradigm, it is feasible that the cortical and dopaminergic afferent fibers innervating the transplant carry the signals used for remapping of graft striatal neuron responses during retraining. Under conditions in which the grafted animal is retrained to make the nose-poke response when the cue light comes on, cortically-derived information concerning the motor responses and visual cues should become associated within grafted striatal neurons through mechanisms similar to those described in intact animals. Furthermore, the food reward should provide a phasic release of dopamine that could further reinforce these associations.

Finally, this perspective on graft-induced recovery of lost motor functions raises the following intriguing question: Why is it that certain movements, or movement parameters, of lesioned rats are improved by the graft independently of retraining, whereas others require retraining? As reviewed by Björklund *et al.* (15), numerous types of movement disorders (e.g., locomotor hyperactivity) induced by the striatal lesion spontaneously recover when the transplant is integrated into the host tissue. Also, in the report of Brasted *et al.* (7), the striatal transplant ameliorated the lesion-induced prolongation of movement time (a measure of the time taken to move the snout to the correct location), and this improvement was evident before retraining began. One possible explanation for this distinction is that some movements, or movement parameters, are simply less difficult for the animal, and that the animal needs to be retrained only for those tasks, e.g., direction of nose-poke response, that are the most demanding. Alternatively, a remapping of striatal graft neurons by task-specific patterned activity within the relevant circuits may be a feature common to all movements improved by the graft. Once the graft has been integrated into the host, this remapping could occur, for example, as the animal moves about its home cage, picks up food pellets, or orients toward unexpected sounds in its environment. This view implies that, even without explicit retraining, the grafted animal is continuously learning new stimulus-response associations, during which the striatal graft is retrained, and that this retraining underlies the restoration of previously impaired motor functions. When particular stimulus-response combinations are not encountered in the animal's home environment, however, explicit retraining will be needed to reinstate motor skills that depend on them. This

perspective carries substantial implications for the design of physical therapies in the treatment of neurological diseases.

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