The Neuropsychology of Movement and Movement Disorders: Neuroanatomical and Cognitive Considerations

Kathleen Y. Haaland,1 Richard P. Dum,2 Pratik K. Mutha,3 Peter L. Strick,2 AND Alexander I. Tröster4

1Departments of Psychiatry & Behavioral Sciences and Neurology, University of New Mexico, Albuquerque, New Mexico
2University of Pittsburgh Brain Institute, Systems Neuroscience Institute, Center for the Neural Basis of Cognition, and Department of Neurobiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
3Department of Biological Engineering and Center for Cognitive Science, Indian Institute of Technology Gandhinagar, Palaj, Gandhinagar, Gujarat, India
4Department of Clinical Neuropsychology and Center for Neuromodulation, Barrow Neurological Institute, Phoenix, Arizona


Abstract

This paper highlights major developments over the past two to three decades in the neuropsychology of movement and its disorders. We focus on studies in healthy individuals and patients, which have identified cognitive contributions to movement control and animal work that has delineated the neural circuitry that makes these interactions possible. We cover advances in three major areas: (1) the neuroanatomical aspects of the “motor” system with an emphasis on multiple parallel circuits that include cortical, corticostriate, and corticocerebellar connections; (2) behavioral paradigms that have enabled an appreciation of the cognitive influences on the preparation and execution of movement; and (3) hemispheric differences (exemplified by limb praxis, motor sequencing, and motor learning). Finally, we discuss the clinical implications of this work, and make suggestions for future research in this area. (JINS, 2017, 23, 768–777)

Keywords: Motor cortex, Premotor cortex, Parietal lobe, Basal ganglia, Cerebellum, Ideomotor limb apraxia, Learning, Parkinson’s disease, Huntington’s disease

INTRODUCTION

Motor deficits have not been a focus in the clinical neuropsychological evaluation. When movement is evaluated, psychomotor tasks such as finger tapping are used to determine if the pattern of cognitive and motor deficits is congruent. Neurologists evaluate motor deficits somewhat more specifically based on strength in various muscle groups, tremor, rigidity, and ataxia. Yet, even in these cases, the emphasis is on identifying the source of the deficits in terms of damage or dysfunction in the primary motor system, basal ganglia, or cerebellum. A neuropsychologist and neurologist may occasionally examine motor sequencing by requiring patients to make sequential finger movements or hand postures (e.g., knock, chop, slap), but the focus, at least in the latter, is on executive dysfunction (Luria, 1973). Complex motor skills, such as movement planning or even limb praxis, are more rarely examined clinically even though such deficits are strongly influenced by cognition and are known to significantly affect daily functioning (Buxbaum et al., 2008; Buxbaum & Kalenine, 2010).

This review emphasizes that movement and cognition are closely inter-related and are perhaps best viewed and studied as a single unit. We emphasize here the role of a variety of cortical regions, but also discuss the influence of striatal and cerebellar connections given the widespread appreciation that complex movements are dependent on broadly distributed cortical and subcortical circuits.

NEUROANATOMICAL CONSIDERATIONS

Understanding the biological basis of movement and movement disorders is complex and encompasses many disciplines including cell biology, neuroanatomy, behavior, neuropharmacology, functional imaging, and therapeutic interventions [deep brain stimulation (DBS)]. In this section, we highlight the evolution over the past 30 years of the contributions of neuroanatomy to understanding the neural substrate of movement and its disorders, and the circuits that enable cognitive influences on motor control. It is now well established that motor-related regions in the primate frontal...
lere include at least six premotor areas in addition to the primary motor cortex (M1; Dum & Strick, 1991, 2005). Each of the premotor areas projects directly to the primary motor cortex and to the spinal cord. In fact, the number of corticospinal neurons in the premotor areas constitutes approximately 50 percent of the total number of corticospinal neurons in the frontal lobe. Thus, each premotor area is a potential source of descending commands to the spinal cord meaning that M1 may not be the sole “upper motoneuron” for the control of movement.

Instead, it is possible that movements are generated by parallel descending commands from M1 and premotor areas. The premotor areas may provide alternative routes for generating movement when the motor cortex or its pathways are damaged. Functional imaging has substantiated the human homologs of these premotor areas (Amiez & Petrides, 2014; Genon et al., 2017; Picard & Strick, 2001). Thus, the premotor areas could play a critical role in the recovery of motor function that follows cortical strokes and spinal cord injuries given their role in imagining movements likely related to the presence of internal motor representations (Lefebvre et al., 2015).

Recent experiments using transsynaptic tracing with neurotropic viruses have demonstrated that direct (i.e., monosynaptic) cortical projections to spinal motoneurons in non-human primates are confined to the caudal portion of the primary motor cortex (“New” M1) (Rathelot & Strick, 2006, 2009), which is present solely in some higher primates and humans. The direct access of New M1 to motoneurons enables it to bypass some spinal cord circuits and sculpt novel patterns of motor output, essential for highly skilled movements (Griffin, Hoffman, & Strick, 2015; Lemon, 2008). This result suggests that certain types of motor performance rely heavily on M1.

How do cognitive, somatosensory, and affective systems influence the generation of movement? Cortical inputs to the primary motor cortex (New and Old M1) arise exclusively from frontal premotor areas and parietal somatosensory areas (Dum & Strick, 2005). The premotor areas provide multiple access points for prefrontal (cognitive influences), posterior parietal (visuo-spatial integration), and limbic (affective influences) cortices to access the motor system. The ventral premotor area and the more rostral cingu late motor areas (CMAr, CMAv), in particular, receive diverse cortical inputs from prefrontal, posterior parietal, and limbic cortices (Dum & Strick, 2005).

One example of these higher order influences is evident in the “mirror” neuron system (Rizzolatti & Fogassi, 2014). Portions of the ventral premotor cortex and the inferior parietal lobule form the core of a network that contains a population of visuomotor neurons termed “mirror” neurons (Caspers, Ziles, Laird, & Eickhoff, 2009; Rizzolatti & Fogassi, 2014). The key feature of mirror neurons is that they respond to the observation of motor acts performed by another individual as well as execution of similar motor acts by the subject. A series of clever experiments showed that mirror neuron responses were aligned to the goal of the motor action rather than the specific manner in which it was performed (e.g., left hand, right hand, or with a tool that had a normal or a reversed action) (reviewed in Rizzolatti & Fogassi, 2014).

The fact that the specific population of neurons responds to both observation and execution of the same motor goal suggests that these neurons may intrinsically define the intention of the motor act. Notably, some elements of reward value, context and intention are present in subsets of mirror neurons in the ventral premotor and parietal areas. Although some have proposed that the mirror mechanism may underlie higher order processes like learning through imitation (Buccino et al., 2004), speech production or understanding the intention of other’s actions, monkeys do not imitate or speak nor can we assess a monkey’s understanding of the reasons another individual performs an action. Thus, these more speculative interpretations are difficult to validate when comparing the results of monkey experiments with similar human fMRI studies (Hickok, 2009), but see recent human corticography study (Perry et al., 2017), which supports the monkey work’s general conclusions regarding the mirror neuron system.

Nevertheless, it is remarkable that some aspects of higher order processes such as reward value, context and motor goals are present in a premotor area, which has direct projections to the spinal cord and the primary motor cortex. These observations suggest that a number of elements of cognitive processes are integrated into the motor system at levels that are involved in the actual generation and execution of motor acts.

The basal ganglia and cerebellum have traditionally been recognized as being involved in the control of movement and in the genesis of movement disorders. These circuits were originally viewed as a means of funneling information from widespread regions of the cerebral cortex to the primary motor cortex. Anatomical experiments have provided the basis, in part, for a re-evaluation of this organization (Middleton & Strick, 2000; Strick, Dum, & Fiez, 2009). Their architecture is characterized by multiple, parallel circuits or “loops” that begin in the cerebral cortex, traverse through each subcortical system and return to the point of origination in the cerebral cortex. Outputs of the basal ganglia and cerebellum target motor, premotor, prefrontal, and posterior parietal areas of the cerebral cortex. Within each subcortical system, the output channels are segregated into separate motor and non-motor domains.

The physiological properties of neurons within the individual loops support the view that each one serves a different behavioral process. Lesions within the motor related subcortical loops result in movement disorders, whereas damage of subcortical loops with non-motor cortical areas result in impairments of cognitive functions including executive functions. Therefore, the motor and non-motor loops are segregated, which implies that higher order influences on motor control are likely to be limited within the basal ganglia and cerebellum. This parallel circuit architecture is also evident for loops originating in the face, arm, and leg.
representations of each motor area (M1 and the six premotor areas).

For instance, each loop originating in an arm representation of a motor area is located adjacent to all other arm loops in the output nuclei of the basal ganglia (pallidum) or cerebellum (deep nuclei) (Middleton & Strick, 2000; Strick et al., 2009). This clustering of loops serving a single body part implies that a focal lesion within either subcortical output nucleus may include several arm related loops arising from different cortical motor areas. As such, lesions in these subcortical structures may disrupt more aspects of movement control than a focal lesion confined to a single cortical motor area.

The nigral dopamine system within the basal ganglia has been proposed as a novel mechanism for providing access to the motor system from limbic and prefrontal cortices (Haber, 2014). Nigral dopamine neurons receiving striatal input from limbic and prefrontal territories are thought to form a feedback spiral by projecting to the motor regions of the striatum. In this manner, limbic and prefrontal regions of the striatum may utilize reward-related mechanisms to influence the motor system in goal directed behavior, motor learning, and habit formation. This dopamine circuit has an “open-loop” architecture as opposed to the closed loop architecture of the basal ganglia and cerebellum motor loops.

A similar open-loop structure has been reported to interact with the M1 motor loop (Kelly & Strick, 2004). This source originates in the limbic territory of the ventral striatum and may provide M1 with access to non-motor information. This circuit may have clinical correlates. Parkinson’s disease (PD) often results in impaired response initiation. However, during situations involving “fight or flight” responses, movement initiation time may appear normal possibly related to the pathway from the ventral striatum to the primary motor cortex, thereby enabling limbic circuits to activate motor action. Overall, these open loop circuits may provide alternative routes for cognitive and motivational influences on motor actions.

Assessment of movement disorders typically focuses on the frank physical disabilities that result from damage affecting the motor system. Recently, Dum, Leventhal, and Strick (2016) reported that damage to the motor system simultaneously disrupts autonomic function, and motor as well as cognitive and affective systems in the cerebral cortex communicate with the sympathetic nervous system. Surprisingly, the most direct projections to the adrenal medulla were co-localized within every motor area in the frontal lobe (primary motor cortex and six premotor areas). Heavy projections arose within cingulate motor areas involved in cognitive aspects of motor control (e.g., error detection, response selection) and planning, pain responses, and negative affect (Dum et al., 2016; Shackman et al., 2011). These results indicate that specific multi-synaptic circuits exist to link movement, cognition, and affect to the sympathetic output. Thus, lesions or disorders that disrupt motor performance are also likely to disrupt physiological responses to stress. However, this marriage of motor and autonomic systems may further complicate recovery from movement disorders.

COGNITION IMPACTS MOVEMENT

While neuroanatomical studies have begun to uncover the specific pathways and circuitry by which cognitive and affective systems influence movement, we have also witnessed tremendous progress in the past 30 years towards developing a behavioral framework of movement control that encompasses cognitive mechanisms. This has stemmed largely from studies of motor behavior that emphasize movement as a “cognitive-motor” function (Haaland, 2006; Hauert, 1986; Rowe & Siebner, 2012). It is now clear that even a simple key press choice reaction time task entails a cognitive component related to action selection, and is dependent on left frontal areas typically associated with cognitive and motor processing (Schluter, Rushworth, Passingham, & Mills, 1998).

In this section, we discuss a variety of paradigms that have validated this cognitive-motor view. We emphasize studies in patients with cortical damage, but also discuss studies in other populations that highlight the importance of corticostriate and corticocerebellar circuits for cognitive-motor control (see Rowe & Siebner, 2012 and Doyon & Benali, 2005, for reviews).

Motor Sequencing

Motor sequencing depends on action planning both before and during sequence execution, both of which are influenced by sequence complexity (e.g., sequence length, organizational structure). Functional neuroimaging of healthy individuals has shown that greater sequence complexity is associated with activity in a larger number of brain regions, including parietal (inferior and superior) and frontal (lateral and medial premotor, dorsolateral prefrontal) lobes. This has been interpreted as reflecting a greater contribution of cognitive functions such as planning and working memory, as well as organization, selection, and retrieval of responses commonly ascribed to these regions (Boecker, Jankowski, Ditter, & Scheef, 2008; Elsinger, Harrington, & Rao, 2006; Harrington et al., 2000; Haslinger et al., 2002; Kincses et al., 2008; Pannm et al., 2012; Serrien, Ivy, & Swinnen, 2006).

Of interest, different aspects of sequence complexity appear to map on to different neural substrates (Harrington et al., 2000). Specifically, superior parietal and cerebellar activation has been shown to vary with response selection requirements (number of fingers), which likely reflects the sensorimotor functions of the superior parietal region and cerebellum. In contrast, sequence organization, reflected as the number of finger changes in a sequence, was associated with bilateral inferior parietal and dorsal premotor activation suggesting a role for these areas in response organization and selection/retrieval. Two other fMRI studies arrived at similar conclusions by demonstrating that greater sequence
complexity was associated with either greater fronto-parietal activation (Pammi et al., 2012) or greater premotor-cerebellar-parietal activation (Haslinger et al., 2002).

Of interest, none of these studies noted significant activation in corticostriate circuits during motor sequencing. Striatal activation has indeed been less uniformly demonstrated, although patients with PD do show motor sequencing deficits (Harrington & Haaland, 1991b). Activation of the striatum appears to be more consistently observed in self-initiation paradigms. Two event-related fMRI studies in healthy adults support this view. Elsinger et al. (2006) found that striatum (putamen) activation was associated with sequence complexity (repetitive vs. heterogenous sequences) during planning but not execution of an internally generated sequence.

These findings were congruent with another report that showed that striatal activation was greater before movement for internally versus externally generated motor sequences (Boecker et al., 2008). Both studies support the importance of corticostriate interactions because the striatal activations were coupled with frontal (lateral or mesial premotor, dorsolateral prefrontal cortex) or frontoparietal activation. These findings suggest that the striatum plays a central role in planning complex sequences, possibly related to its importance in timing “when” a response should occur (see Merchant, Harrington, & Meck, 2013, for timing review). This may relate to impaired self-initiation or akinesia, which is common in PD patients. Furthermore, effective connectivity analysis shows that self-initiated movements in PD patients off-medication are associated with decreased connectivity in the striatum-cortical and striatum-cerebellar circuits, along with increased cortical and corticocerebellar connectivity; the latter is thought to be compensatory (Wu et al., 2011). In addition, numerous studies have supported the broad conclusion that PD is associated with hypoactivation of mesial premotor circuits and hyperactivation of lateral premotor circuits (See Rowe & Seibner, 2012 for review).

Finally, with regard to cortical contributions to motor sequencing, there is some evidence from functional imaging in healthy adults that the recruitment of brain areas is hemispherically lateralized. Sequences with greater planning requirements appear to be associated with greater activation only in left parietal and premotor (but not primary motor) areas when performance across both hands is pooled (Haaland, 2006; Haaland, Elsinger, Mayer, Durgerian, & Rao, 2004). Correlations between neural dynamics using electroencephalography (EEG) and sequencing behavior corroborate this view (Serrien & Sovijarvi-Spae, 2016).

Additionally, patients with left hemisphere damage demonstrate greater difficulty performing motor sequences (Harrington & Haaland, 1991a; Kimura & Archibald, 1974; Kolb & Milner, 1981). More specifically, left hemisphere damage is associated with deficits timing each response and chunking responses in the sequence, and this deficit is greater in patients with ideomotor limb apraxia (associated with left frontoparietal damage) (Harrington & Haaland, 1992). These fronto-parietal contributions are likely related to cognitive factors such as action selection, motor attention, and/or spatiotemporal motor representations.

Arm Reaching and Grasping

Like sequencing, gesture imitation (Fridman et al., 2006) and point-to-point reaching and grasping also involve a clear planning component. Planning in the context of reaching may be construed as a higher-level (more “cognitive”) sensorimotor transformation process where information about the environment, the target, and the body is transformed into a motor plan, which is then converted to motor commands specifying joint torques or muscle activation patterns via lower-level mechanisms. Sensorimotor transformations undoubtedly depend on internal representations (of the body, the environment and their interaction), are developed through experience, and are thought to be critically dependent on the parietal lobe (Buneo & Andersen 2006; Buxbaum, Johnson-Frey, & Bartlett-Williams, 2005; Goldenberg, 2009). Parietal damage disrupts the ability to maintain internal representations (Wolpert, Goodbody, & Husain, 1998) and also produces deficits in motor imagery, which requires retrieval of a stored representation (Sirigu et al., 1996). These functions of the parietal lobe have recently been used to allow a patient with spinal cord injury to move a prosthetic arm by imagining the movement (Aflalo et al., 2015).

The execution and online control of reach and grasp actions appears to be mediated by circuits that are distinct from those involved in planning such actions. For instance, functional neuroimaging in healthy adults during reach and grasp movements (Glover, Wall, & Smith, 2012) has revealed a distinct planning (lateral and mesial premotor cortex, basal ganglia, anterior cingulate, posterior medial parietal area, superior parietal occipital cortex, and middle intraparietal sulcus) and motor control (sensorimotor cortex, cerebellum, supramarginal gyrus, superior parietal lobe) network for such actions. Unfortunately, this study did not compare activation during the planning and execution phase of these tasks in order to further examine these two circuits and their potential interactions.

Other studies have led to similar conclusions, and have in fact suggested that planning and online control circuits may be lateralized to different brain hemispheres. Specifically, left, but not right hemisphere damage produces deficits in planning reflected as impaired control of movement direction during the early phases of movement, while right, but not left hemisphere damage causes problems achieving and stabilizing the arm at a desired goal location, a process more dependent on online use of sensory feedback and modulation of impedance mechanisms (Mutha, Stapp, Sainburg, & Haaland, 2014).

Motor and Other Forms of Learning

Studies on motor learning have also emphasized the contributions of cognitive mechanisms and the importance of
frontal and parietal cortices, and striatal and cerebellar regions for learning (see Doyon & Benali, 2005, for review). Basal ganglia dysfunction is associated with motor learning deficits particularly when the task involves implicit learning of a sequence of actions. The serial reaction time (SRT) paradigm has been extensively employed to demonstrate contributions of striatal circuits to motor learning. In this task, sequence-specific learning is shown via a reduction in reaction times for repetitive, but not random sequences. Explicit awareness of the sequence is also examined, typically by asking participants to generate or recognize the repeated action times for repetitive, but not random sequences. Implicit performance deficits but intact explicit knowledge and conscious awareness have been reported in non-demented PD and Huntington’s disease (HD) patients (Muslimovic, Post, Speelman, & Schmand, 2007; Nissen & Bullem, 1987; Willingham & Koroshetz, 1993; Doyon, 2008, for review, but also see Smith, Siegert, McDowall, & Abernethy, 2001).

A meta-analysis of studies in PD patients has supported this conclusion (Siegert, Taylor, Weatherall, & Abernethy, 2006). These deficits in PD are associated with disease severity and medication status (impaired off medication) rather than global cognitive status or even performance on individual cognitive domains (e.g., executive functions, visuospatial skills, working memory) (Muslimovic et al., 2007). However, the mechanism(s) for these implicit SRT deficits is (are) still uncertain, especially because fMRI activation is seen in similar corticostriate regions during implicit or explicit SRT tasks (Schendan, Searl, Melrose, & Stern, 2003; Willingham, Salidis, & Gabrielli, 2002).

The contributions of the basal ganglia to implicit learning have been made evident through non-motor learning tasks as well. Although many tasks have been used, a probabilistic learning task, such as the weather prediction task (WPT) is a useful illustrative exemplar. In WPT the prediction of two outcomes (rain, sun) is learned via trial-and-error feedback using four cues (shapes), none of which perfectly predicts an outcome. On any trial, 1, 2, or 3 cues can be present and based on feedback, probabilistic associations between cue(s) and outcome are established. Patients with PD and HD are impaired in the incremental learning of this task, despite intact explicit memory (Holl, Wilkinson, Tabrizi, Painold, & Jahanshahi, 2012; Knowlton, Mangels, & Squire, 1996).

Because this finding is the opposite of that observed in amnesia, it suggests that the basal ganglia support incremental stimulus-response learning. A theory of category learning assigning a role to the basal ganglia (COVIS) (Ashby, Alfonso-Reese, Turken, & Waldron, 1998) proposes that two functional systems are of particular importance. The explicit system relies on working memory and executive attentional control, and is critical to optimize rule-based category learning (and includes hippocampus and caudate as components). The procedural system is important in information integration. The basal ganglia, and especially caudate head, are thought important in maintaining candidate rules in working memory.

Similar to the implicit SRT motor paradigm (Schendan et al., 2003), neuroimaging findings are also consistent with the idea that hippocampus and basal ganglia are differentially involved in the WPT. Poldrack et al. (2001) have shown that medial temporal lobe is activated during initial learning of the WPT, but as learning progresses (presumably becoming more implicit) this activation subsides and is accompanied by increasing basal ganglia activation. This finding, along with the WPT data, questions the traditional view that implicit tasks are independent of the medial temporal lobe.

Because other forms of implicit learning (e.g., artificial grammar learning, dot pattern categorization) appear to be spared in PD, subsequent studies have examined more specific roles for the basal ganglia in learning, such as its importance in feedback-based learning. PD and HD patients are impaired on the WPT when learning depends upon feedback, but not when the task involves paired-associate learning (Holl, Wilkinson, Tabrizi, Painold, & Jahanshahi, 2012; Shohamy, Myers, Onlaor, & Gluck, 2004). Similarly, performance on tasks previously thought spared in PD (e.g., artificial grammar) are impaired when learning involves trial-by-trial feedback (Smith & McDowall, 2006; Wilkinson, Khan, & Jahanshahi, 2009).

Learning also depends on the immediacy of the feedback; learning is intact with immediate, but not delayed, feedback (Foerde & Shohamy, 2011). Feedback valence is also important. The direct and indirect cortico-basal ganglionic pathways (or go-no go paths predominantly populated by D1 and D2 receptors) facilitate response initiation and inhibition, respectively (Frank, Seeberger, & O’Reilly, 2004). Persons with PD who are dopamine-deficient have an overactive indirect pathway braking the thalamus and cortex (i.e., No Go), which results in intact learning “not-to-go” from negative feedback, but impaired learning from positive feedback (Go). The reverse pattern occurs when patients are medicated because dopamine shifts the balance toward the direct, go circuit. Learning from positive and negative feedback may be sensitive markers of the integrity of direct and indirect pathways in PD and HD (Mathar et al., 2017). Additional conceptualizations include proposals that ventral striatum facilitates general stimulus-stimulus associations regardless of feedback while dorsal striatum supports action selection especially under uncertainty (MacDonald et al., 2011), and ventral striatum mediates memory encoding while dorsal striatum mediates retrieval (MacDonald et al., 2013).

There is also additional evidence from motor learning paradigms of a key role for cerebellar and cortical regions. For instance, it is widely accepted that cerebellar damage results in a deficit in adapting movements to novel visuo-motor or dynamic perturbations (Martin, Keating, Goodkin, Bastian, & Thach, 1996; Smith & Shadmehr 2005; Tseng, Diedrichsen, Krakauer, Shadmehr, & Bastian, 2007). Similar conclusions have been drawn from studies that have modulated cerebellar function using transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) (Celnik, 2015). Other work has shown that damage or disruption of left, but not right, parietal cortex also disrupts
motor adaptation (Della-Maggiore, Malfait, Ostry, & Paus, 2004; Mutha, Sainburg, & Haaland, 2011). This suggests that parietal cortex is critical not just for motor planning, but also for updating and maintaining new internal representations that are important for motor planning.

Consistent with this view, a patient with bilateral parietal damage failed to maintain updated estimates of grip force when grasping an object (Wolpert et al., 1998). While motor adaptation has conventionally been viewed as an implicit learning process, recent work has argued that such learning may be driven by additional mechanisms including explicit and cognitive-strategy-based processes to use-dependent and reinforcement mechanisms (Huang et al., 2011; Taylor, Krakauer, & Ivry, 2014; Verstynen & Sabes, 2011). The relative contribution of each is influenced by the time available for movement preparation: greater preparation time is associated with greater reliance on the cognitive process, whereas less preparation time is associated with implicit processes (Haith, Huberdeau, & Krakauer, 2015).

Differential reliance on each process also determines how the learned information is then stored and recalled. While implicit updating of the internal representation depends on the cerebellum and parietal cortex, the additional mechanisms may be dependent on other neural substrates. In particular, use-dependent and reinforcement processes may rely on striatum-M1 circuits (Hosp, Pekanovic, Rioult-Pedotti, & Luft, 2011; Orban de Xivry, Criscimagna-Hemminger, & Shadmehr, 2011; Verstynen & Sabes 2011).

Limb Praxis

Studies employing different experimental tasks in patients with ideomotor limb apraxia have also been instrumental in identifying key aspects of cognitive contributions of movement. As far back as 1920, Liepmann (See Goldenberg, 2009) conceived of “movement formulas,” a precursor to internal representations of action, stored in the left hemisphere of the brain and contributing to limb praxis. Explicit support for such representations or “visuokinesthetic engrams” and their parietal lobe location was provided by demonstrating impaired gestural recognition (Heilman, Valenstein, & Roth, 1982) and impaired ability to imagine reaching movements after parietal damage (Sirigu et al., 1996). However, others have argued against the importance of such engrams for praxis, and have suggested that accurate tool use and pantomime is reconstructed each time based upon analysis of the spatial relationships between body parts and between body parts and tools, which are guided by the context (e.g., using a screwdriver to insert a screw vs. to poke someone’s eye in self-defense) (Goldenberg, 2009; Osuriak, Jarry, & LeGall, 2011). This notion has less widespread support, but the authors contend that it better explains the apraxic’s impaired use of novel tools and impaired imitation of meaningless movements.

Limb praxis is most commonly associated with frontoparietal regions of the left hemisphere, and especially the left parietal lobe (Vingerhoets, 2014), although studies have shown that left inferior frontal damage (Haaland, Harrington, & Knight, 2000) or corticostriate damage may also play a role. However, in the case of corticostriate damage, limb apraxia may be confounded by the associated motor disorder, for example, bradykinesia or tremor for PD and chorea in the case of HD. In general, limb apraxia in such disorders has been attributed to damage to the associated cortical areas or decreased connectivity between cortex and striatum (Hamilton, Haaland, Adair, & Brandt, 2003; Leiguarda, 2001).

Patients with ideomotor limb apraxia demonstrate planning deficits as evidenced by impaired directional and torque specification during the early phases of reaching movement (Mutha, Sainburg, & Haaland, 2010) and impaired ability to update motor plans through learning (Mutha, Stapp, Sainburg, & Haaland, 2017). This is in addition to the widely reported deficits performing transitive, intransitive and meaningless gestures elicited via verbal instruction, imitation or object use. Their Cardinal spatiotemporal deficits (e.g., jerky, vertical movements rather than smooth, horizontal movements when imitating a sawing gesture) are thought to arise primarily from damaged internal representations for action in the parietal lobe.

Newer studies have argued, however, that the organization of these representations might be modular; Kalenine, Buxbaum, and Coslett (2010) examined recognition of actions involving tool use in a large cohort of patients and showed that deficits could be associated with an impaired representation of spatial hand postures after left inferior parietal damage or an impaired representation of tool function after left temporal lobe damage. These findings suggest that the internal representation for actions might be composed of distinct representations for “how” to make an action and “what” the action might mean functionally, which are each mapped to different neural substrates.

Similarly, functional imaging in healthy individuals showed that decisions about object manipulation versus function were associated with left parietal and temporal lobe activation, respectively (Canessa et al., 2008). These new findings are thus beginning to uncover the specific nature of cognitive processes that contribute to motor control and suggest that cognitive contributions, especially for tool use actions, may go beyond action selection.

CONCLUSIONS AND FUTURE DIRECTIONS

It is clear that the neural control of movement relies extensively on cognitive mechanisms, and multiple intracortical as well as cortico-subcortical loops support such an interaction. In humans, this understanding has come from a variety of studies that employ sophisticated experimental tools made possible by technological advances. For instance, neuroimaging (structural and functional MRI, EEG, magnetoencephalography, corticography) can now be combined with concurrent brain stimulation protocols (TMS, tDCS,
DBS) to better specify the neural circuits that contribute to movement control (Rowe & Siebner, 2012).

While such sophistication is essential, the need for clever and rigorous behavioral paradigms must not be overlooked (Krakauer, Ghazanfar, Gomez-Marin, Maciver, & Poepppe, 2017). A recent study exemplifies how neural connectivity and white matter integrity data obtained from modern MRI protocols can be combined with meticulous behavioral analysis to provide fresh insight into the neural circuitry underlying motor control: Bi et al. (2015) demonstrated that tool use (“how”) and function (“what”) information may not be entirely segregated (as the data in the limb praxis section had suggested) but rather, parietal and temporal nodes may interact within the left parietofrontal circuits. This study is an excellent example of how conceptual behavioral frameworks derived from cognitive neuroscience can inform clinical findings, and vice versa (Rowe & Siebner, 2012).

Wider delineation of neural circuits that influence movement is another pressing need. Animal models are ideal in this regard. Currently, a revolution is occurring using normal mice and mouse models of neurological disorders. It is possible to genetically identify specific neuronal populations, insert genes into neurons with viral vectors, physiologically manipulate neurons with channel-rhodopsin or neurotransmitters, and assess behavior during stimulation/inhibition of these cell populations. This has enabled tremendous and rapid progress in terms of understanding neural circuitry. For instance, separate populations of dopamine neurons in the mouse substantia nigra have been identified based on their striatal targets (Lerner et al., 2015). These different populations have unique responses to aversive stimuli but similar responses to appetitive stimuli, which may provide insight into the potential for cognitive-motor integration in the feed-forward circuit originating in the substantia nigra (see above, Haber, 2014).

The challenge going forward of course will be whether these genetically based techniques can be adapted and applied to non-human primates and ultimately humans, which may spur progress in their understanding and in treatment. A deeper understanding of neural circuits is also essential since it has the potential to drive development of innovative therapeutic approaches and refinement of existing ones. DBS for PD is a good example of this. DBS is based on leveraging our understanding of the multiple parallel cortico-thalamo-striatal circuits (Strick et al., 2009). This has led to its clinical use to inhibit “downstream network activity in the thalamus, cortex, and brainstem” (Delong & Wichmann, 2015). Other approaches are in early stages of development. For example, we are now beginning to understand that dopaminergic and adrenergic medications have differential effects on PD behaviors and neural circuits (Borchert et al., 2016; Michely et al., 2015).

Finally, clinical rehabilitation practices must be informed by, and must exploit our advances in understanding of neural circuits underlying movement. For instance, it has been shown that stimulation of critical cortical nodes combined with motor practice in hemiparetic stroke patients enhances functional connectivity in the damaged hemisphere (Lefebvre et al., 2017). If these results can be replicated in other studies, rehabilitation practices could explore the use of brain stimulation to enhance recovery. Similarly, it appears that motor imagery, which engages planning processes similar to actual movement could potentially be appropriate for patients who might be unable to execute an action during rehabilitation (See DiRienzo et al., 2016 for review). Meta-analyses show that similar to movement execution, imagery involves extensive frontoparietal, striatal, and cerebellar activation (Hetu et al., 2013), with the parietal lobe being a critical node (Kraeutnner, Keebler, & Boe, 2015; McInnes, Friesen, & Boe, 2015; Sirigu et al., 1996).

Studies that have employed imagery have shown that it results in the same or similar benefit as actual execution in the healthy, and can be successfully used with athletes as well as clinical patients, especially after stroke. Alternative approaches, including coupling of execution and imagery or observation of the same movement could be considered as well. The benefits of sleep on motor consolidation (See DiRienzo et al., 2016, for review) could be leveraged to enhance retention of the learned actions post rehabilitation. Finally, new brain machine interfaces guided by deeper understanding of the role of different brain areas could be developed. For instance, Andersen and colleagues have recently demonstrated that signals from parietal association cortex (given its role in motor planning) rather than motor cortex can be used to control the movement of a neuroprosthetic arm in a patient with spinal cord injury (Aflalo et al., 2015). Such integration of animal and human work, and advances in technology will ensure that the next 30 years of understanding the neuropsychology or movement and its disorders are as exciting and productive as the past thirty.

ACKNOWLEDGMENTS

This work was supported in part by funds from NIH grants R01 NS24328 (PLS), P40 OD010996 (PLS), and P30 NS076405 (PLS), by the Ramanujan Fellowship (PKM), and grants from the Health Sciences Committee and the Cognitive Science Research Initiative of the Department of Science and Technology (Government of India) (PKM), and by the Barrow Neurological Foundation (AFT). None of the authors have any conflicts of interest.

REFERENCES


