Julie A Blendy[1]

[1]Department of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
E-mail: blendy@mail.med.upenn.edu

DISCLOSURE

The author declares no conflicts of interest.

Chen YZ, Jing D, Bath K, Ieraci A, Khan T, Siao C *et al* (2006). Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science* **314**: 140–143.

Lee EC, Yu D, Martinez de Velasco J, Tessarollo L, Swing DA, Court DL *et al* (2001). A highly efficient *Escherichia coli*-based chromosome engineering system adapted for recombinogenic targeting and subcloning of BAC DNA. *Genomics* **73**: 56–65.

Mague SD, Isiegas C, Huang P, Liu-Chen LY, Lerman C, Blendy JA (2009). Mouse model of *OPRM1* (A118G) polymorphism has sex-specific effects on drug-mediated behavior. *Proc Natl Acad Sci* **106**: 10847–10852.

Papaleo F, Crawley JN, Song J, Lipska BK, Pickel J, Weinberger DR *et al* (2008). Genetic dissection of the role of catechol-*O*-methyltransferase in cognition and stress reactivity in mice. *J Neurosci* **28**: 8709–8723.

Ramchandani VA, Umhau J, Pavon FJ, Ruiz-Velasco V, Margas W, Sun H *et al* (2010). A genetic determinant of the striatal dopamine response to alcohol in men. *Mol Psychiatry*; e-pub ahead of print 18 May 2010; doi:10.1038/mp.2010.56.

Yu D, Ellis HM, Lee EC, Jenkins NA, Copeland NG, Court DL (2000). An efficient recombination system for chromosome engineering in *Escherichia coli*. *Proc Natl Acad Sci USA* **97**: 5978–5983.

Neuropsychopharmacology Reviews (2011) **36,** 364–365; doi:10.1038/npp.2010.143

Cortical Circuits for Motor Control

Voluntary control of movement relies on activity in a subclass of layer 5B pyramidal neurons projecting to the spinal cord—corticospinal neurons (also called Betz cells or upper motor neurons) (Figure 1). In motor cortex, corticospinal neurons are one of the many classes of pyramidal neurons distributed over multiple layers and sublayers with diverse local and long-range projections. Studies in primates, the motor systems of which so closely resemble our own, have provided a wealth of information about the spiking activities of motor cortex neurons during action planning and execution. However, *in vivo* recording methods usually preclude identification of the precise laminar locations of neurons and their synaptic connectivity, and *in vitro* analysis is impractical in primates. Consequently, much remains to be learned about how local circuits are organized according to projection target and sublayer (Brown and Hestrin, 2009; Anderson *et al*, 2010), and how this organization influences spiking activity in different subclasses of projection neurons in motor cortex.

Recently, several groups have established the feasibility of motor behavior experiments with rodents, using not only electrophysiology, but with calcium imaging, also large-scale optical recordings (Dombeck *et al*, 2009). It is remarkable that this has now been combined with sophisticated within-session learning paradigms (Komiyama *et al*, 2010). There are, of course, limitations. One of the limitations is depth: only neurons in the upper layers of the cortex are easily imaged. However, this is hardly uninteresting, as microcircuit mapping studies have shown that layer 2/3 is the main source of synaptic output within motor cortex circuits, and is the major source of input to corticospinal neurons (Anderson *et al*, 2010).

Another intriguing issue is whether circuits in the remaining frontal agranular cortex—presumably involved in more 'cognitive' aspects of motor control—are organized in the form of primary motor cortex. If "thinking is the evolutionary internalization of

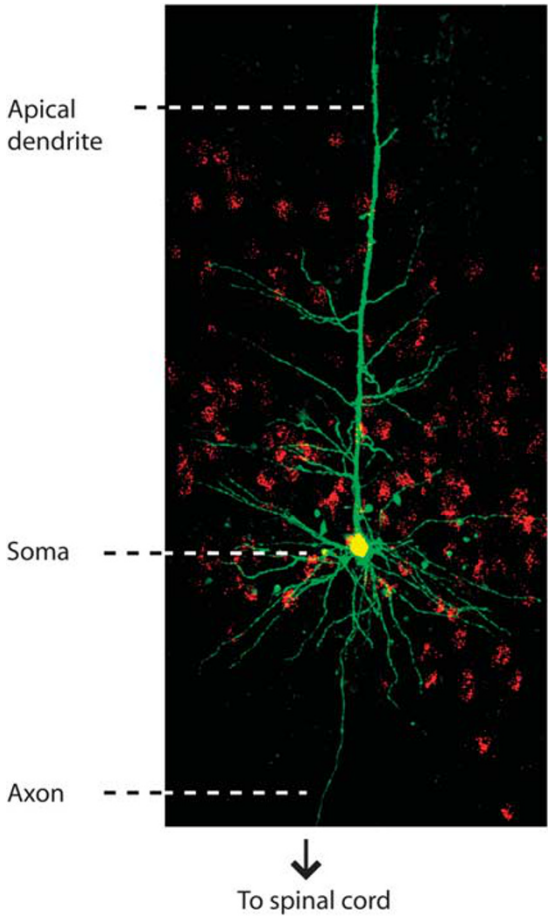

Figure 1. Corticospinal neurons in layer 5B of mouse motor cortex. Neurons were retrogradely labeled *in vivo* by injecting red fluorescent microspheres into the cervical spinal cord. Brain slices containing motor cortex were prepared, and a single corticospinal neuron was targeted for whole-cell patch recording with biocytin in the pipette solution. The slice was fixed and processed with streptavidin-conjugated green fluorescent dye for visualizing dendritic morphology. Red and green fluorescence images were acquired by 2-photon microscopy, and merged for display. Image provided by L Trapp and B Suter.

movement'' (Llinás, 2002), then one might expect so. In this view the cortical extent of the motor system extends beyond primary motor areas. Behavior, after all, is essentially synonymous with the activity of the motor system. Indeed, a compelling case can be made for the viewpoint that 'layer 5 is motor everywhere' (Diamond, 1979); in other words, layer 5B is 'motor cortex'. Should we regard layer 2/3 as 'premotor cortex'?

We expect that as research on motor/frontal cortex goes forward, a general framework for understanding behavioral 'control' mechanisms at the level of cortical circuits will emerge, which will link multiple levels of neural organization and have useful roles both in assimilating the rapidly accruing new information and in inspiring testable hypotheses. New opportunities for the neuropsychopharmacology of movement disorders are also likely to arise. For example, many cognitive disorders have a motor component, and vice versa; apraxias are classic examples. Also, the expression patterns of ion channel and intracellular signaling molecules is highly diverse in layer 5B (Allen Brain Atlas). This diversity presents a fertile substrate for exploring pharmacological strategies to selectively target pathological mechanisms in specific subclasses of cortical projection neurons involved in different aspects of voluntary movement.

ACKNOWLEDGEMENTS

Supported by grants from the NIH (NS061963, NS066675) and Whitehall Foundation.

Patrick L Sheets[1] and Gordon MG Shepherd[1]

[1]Department of Physiology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
E-mail: p-sheets@northwestern.edu or g-shepherd@northwestern.edu

DISCLOSURE

The authors declare no conflict of interest.

Anderson CT, Sheets PL, Kiritani T, Shepherd GM (2010). Sublayer-specific microcircuits of corticospinal and corticostriatal neurons in motor cortex. *Nat Neurosci* **13**: 739–744.

Brown SP, Hestrin S (2009). Intracortical circuits of pyramidal neurons reflect their long-range axonal targets. *Nature* **457**: 1133–1136.

Diamond IT (1979). The subdivision of neocortex: a proposal to revise the traditional view of sensory, motor and association areas. In: Sprague JM, Epstein AN, (eds). *Progress in Psychobiology and Physiological Psychology*. Academic Press: New York. pp 1–43.

Dombeck DA, Graziano MS, Tank DW (2009). Functional clustering of neurons in motor cortex determined by cellular resolution imaging in awake behaving mice. *J Neurosci* **29**: 13751–13760.

Komiyama T, Sato TR, O'Connor DH, Zhang YX, Huber D, Hooks BM *et al* (2010). Learning-related fine-scale specificity imaged in motor cortex circuits of behaving mice. *Nature* **464**: 1182–1186.

Llinás R (2002). *i of the vortex*. MIT Press: Cambridge, Massachusetts.

Neuropsychopharmacology Reviews (2011) **36,** 365–366; doi:10.1038/npp.2010.146

Oral Methylphenidate Normalizes Cingulate Activity and Decreases Impulsivity in Cocaine Addiction During an Emotionally Salient Cognitive Task

Deficits in dopaminergically modulated striato-thalamo-prefrontal circuits contribute to compromises in self-control and motivation in cocaine addiction (Goldstein and Volkow, 2002). Methylphenidate (MPH), a dopaminergic agonist, has been successfully used to enhance inhibitory control and salience attribution in attention-deficit hyperactivity disorder and other prefrontal psychopathologies (eg, frontotemporal dementia); indeed MPH has been suggested to improve signal-to-noise ratio (SNR) and optimize activity (eg, processing efficiency) in brain regions that modulate executive functions (Mehta *et al*, 2000; Volkow *et al*, 2008). However, in clinical trials on cocaine addiction, MPH did not reduce cocaine consumption (Volkow *et al*, 2004). We hypothesized that oral MPH would improve executive function in individuals with cocaine use disorders (CUDs), an effect that, when coupled with cognitive or behavioral interventions, may improve the clinical outcome.

In the current functional magnetic resonance imaging (fMRI) study, 13 CUDs (12 male subjects, mean age = 46.2 years, mean duration of cocaine use, predominantly smoked = 17.9 years, all meeting the current cocaine dependence criteria) matched on education and intellectual functioning with 14 healthy controls (all male, mean age = 38.8, group differences statistically controlled) received 20 mg oral MPH or placebo in a randomized and counterbalanced order over two consecutive MRI sessions (separated by a mean of 14 days, MRI performed on a 4-T whole-body Varian/Siemens scanner). During peak MPH effects (60–90 min post administration), subjects performed an emotional variant of the color-word Stroop task: subjects were monetary remunerated for correct pressing for color of drug-related and matched neutral words. This task engages the prefrontal cortex in CUD (Goldstein *et al*, 2007). Importantly, despite lack of group differences in task engagement or performance, compared with healthy controls, CUD showed robust anterior cingulate cortex (ACC) hypoactivations, encompassing the rostroventral ACC (rvACC) (extending to the medial orbitofrontal cortex (mOFC)) and the caudal–dorsal ACC (cdACC) (Goldstein *et al*, 2009).

Results showed that MPH did not increase task-related cocaine craving in CUD. Importantly, the current results demonstrated that compared with placebo, MPH during a salient cognitive task (1) enhanced the cdACC (Brodmann area (BA) 24, 32) and rvACC/mOFC (BA 10, 32) task response in the CUD; (2) the larger the signal increases in rvACC/mOFC (BA 10, 32), the greater the improvement in task accuracy; and (3) MPH decreased response impulsivity (errors of commission) in all subjects (see Figure 1).

These fMRI results are the first to show that oral MPH improved the response of the ACC and associated