Article

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Three Types of Cortical Layer 5 Neurons That Differ in Brain-wide Connectivity and Function

Highlights

- Genetic targeting reveals three types of L5 pyramidal neurons in mouse visual cortex
- Morphology, physiology, connectivity, and visual responses of L5 neurons are described
- CC and CS neurons receive different inputs from higher visual and association cortex
- CS neurons are more direction-selective and prefer faster stimuli than CC neurons

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In Brief

Kim et al. define and characterize three L5 neuron types in mouse primary visual cortex. These neurons display distinct morphology, physiology, brain-wide connectivity, and visual responses. Their results suggest different L5 neurons comprise distinct output channels for sensory information processing.

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Three Types of Cortical Layer 5 Neurons That Differ in Brain-wide Connectivity and Function

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SUMMARY

Cortical layer 5 (L5) pyramidal neurons integrate inputs from many sources and distribute outputs to cortical and subcortical structures. Previous studies demonstrate two L5 pyramid types: cortico-cortical (CC) and cortico-subcortical (CS). We characterize connectivity and function of these cell types in mouse primary visual cortex and reveal a new subtype. Unlike previously described L5 CC and CS neurons, this new subtype does not project to striatum [cortico-cortical, non-striatal (CC-NS)] and has distinct morphology, physiology, and visual responses. Monosynaptic rabies tracing reveals that CC neurons preferentially receive input from higher visual areas, while CS neurons receive more input from structures implicated in top-down modulation of brain states. CS neurons are also more direction-selective and prefer faster stimuli than CC neurons. These differences suggest distinct roles as specialized output channels, with CS neurons integrating information and generating responses more relevant to movement control and CC neurons being more important in visual perception.

INTRODUCTION

The cerebral cortex is populated by numerous types of excitatory and inhibitory neurons. Excitatory pyramidal neurons (PNs) are the source of nearly all cortical outputs and thus play an essential role in mediating interactions between brain areas. In contrast, cortical inhibitory neurons make primarily local connections and modulate cortical outputs. Many studies have capitalized on cell type specific mouse lines to explore the diversity of inhibitory neuron types and their unique roles in cortical computations (Adesnik et al., 2012; Fu et al., 2014; Lee et al., 2012, 2013; Nienborg et al., 2013; Taniguchi et al., 2011; Wilson et al., 2012). In contrast, mouse lines for exploring the diverse contributions of different types of cortical PNs have only recently become available (Gerfen et al., 2013; Gong et al., 2007; Li et al., 2015; Olsen et al., 2012). These lines have been used to investigate the functional properties and connections of layer 6 PN types (Kim et al., 2014; Olsen et al., 2012; Vélez-Fort et al., 2014), but most previous studies of layer 5 (L5) PN types have relied on more conventional cell targeting approaches (but see Li et al., 2015). Here, we identify and use mouse lines expressing Cre recombinase selectively in subtypes of L5 PNs to facilitate experiments using modern molecular, genetic, and viral tools to link distinct cell types to brain-wide connectivity and function in the visual cortex.

Previous studies of L5 PNs have revealed key details about the long-distance projections, morphology, intrinsic physiological properties, and local inputs of two major cell classes: cortico-cortical (CC) and cortico-subcortical (CS). Importantly, CC PNs (often referred to as L5A or intratelencephalic) project to other cortical areas, whereas CS neurons (L5B or pyramidal tract) project to subcortical structures including superior colliculus, thalamus, and brainstem (Bourassa and Deschênes, 1995; Groh et al., 2010; Hallman et al., 1988; Hattox and Nelson, 2007; Hübener and Bolz, 1988; Hübener et al., 1990; Kasper et al., 1994; Tsiola et al., 2003; Zarrinpar and Callaway, 2014). Both CC and CS L5 neurons project to the striatum (Cowan and Wilson, 1994; Levesque et al., 1996). L5 CC PNs have a relatively simple apical dendritic tuft, thin apical dendrite, and fire action potentials in regular trains (regular spiking, RS) following somatic current injections (Groh et al., 2010; Larsen et al., 2007). In contrast, L5 CS PNs have a complex apical dendritic tuft, thick apical dendrite, and are burst spiking (BS) (Groh et al., 2010). These differences suggest that CC and CS neurons likely function as distinct information channels for mediating different perceptual and behavioral demands.

In this study, we take advantage of bacterial artificial chromosome (BAC) Cre-expressing transgenic mouse lines, in vitro whole cell recording and dye-filling, viral tracers, and two-photon calcium imaging of visual responses to define and characterize distinct types of L5 output neurons in mouse primary visual cortex (V1). In addition to CC and CS L5 PNs, we identify and characterize a third type of L5 PN, which makes some CC connections, but does not project to striatum (CC-NS). We show that each cell class has unique in vitro electrophysiological and morphological properties. Furthermore, using monosynaptic rabies virus-based tracing methods, we show that CC neurons receive more of their