# Circuit Mechanisms Governing Local vs. Global Motion Processing in Mouse Visual Cortex

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A withstanding question in neuroscience is how neural circuits encode representations and perceptions of the external world. A particularly well-defined visual computation is the representation of global object motion by pattern direction-selective (PDS) cells from convergence of motion of local components represented by component direction-selective (CDS) cells. However, how PDS and CDS cells develop their distinct response properties is still unresolved. The visual cortex of the mouse is an attractive model for experimentally solving this issue due to the large molecular and genetic toolbox available. Although mouse visual cortex lacks the highly ordered orientation columns of primates, it is organized in functional sub-networks and contains striate- and extrastriate areas like its primate counterparts. In this Perspective article, we provide an overview of the experimental and theoretical literature on global motion processing based on works in primates and mice. Lastly, we propose what types of experiments could illuminate what circuit mechanisms are governing cortical global visual motion processing. We propose that PDS cells in mouse visual cortex appear as the perfect arena for delineating and solving how individual sensory features extracted by neural circuits in peripheral brain areas are integrated to build our rich cohesive sensory experiences.

Keywords: visual cortex, direction selectivity, local motion, global motion, pattern cell, component cell

## INTRODUCTION

A withstanding cardinal question in neurophysiology is how neural circuits in the cerebral cortex compute and construct our perceptions of the world based on dynamically changing activity patterns of sensory neurons. One fundamental task faced by the visual system is the computation of global motion of an object from the collection of local motion of the objects constituents (Movshon et al., 1985; Newsome et al., 1990). Such a task is not trivial; when seen through an aperture, as imposed by the small receptive field of a retinal ganglion cell or a primary visual cortex (V1) neuron, only the motion component orthogonal to a contour can be inferred, while the parallel motion component remains ambiguous (Adelson and Movshon, 1982; Movshon et al., 1985; Carandini et al., 2005). Due to this "*aperture problem*", one-dimensional local motion information from multiple contours needs to converge to unambiguously encode global two-dimensional object motion. To solve this challenging computational problem, it is generally assumed that visual circuits from retina to V1 first dissects direction of motion for components of the object, such as oriented contours (Yonehara et al., 2011, 2013; Cruz-Martín et al., 2014; Hillier et al., 2017) and neurons in extrastriate areas combine those component motions to form the global object motion representation (Adelson and Bergen, 1985; DeAngelis et al., 1993b; Albright and Stoner, 1995; Simoncelli and Heeger, 1998; Rust et al., 2006).
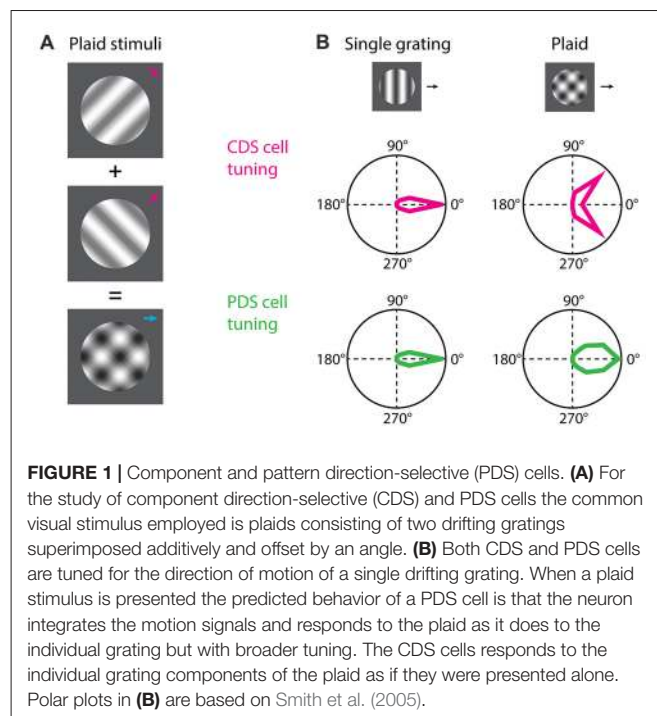
Global motion computations have been studied in a variety of animal species from flies (Saleem et al., 2012) to humans (Adelson and Movshon, 1982). In particular, non-human primates have been extensively used as a model (Movshon et al., 1985; Newsome and Paré, 1988; Britten et al., 1992; Tinsley et al., 2003; Smith et al., 2005; Majaj et al., 2007; Hedges et al., 2011; Solomon et al., 2011; Kumbhani et al., 2015; Chaplin et al., 2017), yielding seminal insights. Only now, are mice being investigated (Juavinett and Callaway, 2015; Muir et al., 2015; Palagina et al., 2017). The mouse offers several experimental advantages to primates and serves as an attractive model for elucidating the circuitry and single neuron computations underlying global motion processing, by granting access to the large genetic-, viral- and imaging toolboxes now available (Wickersham et al., 2007; Luo et al., 2008; Chen et al., 2013; Niell, 2015; Hawrylycz et al., 2016).

Here, we aim to provide a brief overview of the current experimental and theoretical literature on global motion processing based on works in primates and mice. Finally, we propose what experiments could propel the field forward and shed light on what circuit mechanisms are employed for this well-defined neural computation, by exploiting the mouse visual cortex as a model system.

## LOCAL AND GLOBAL MOTION IS ENCODED BY TWO GROUPS OF CORTICAL NEURONS

For studying neural encoding of global motion, the stimulus commonly employed is the additive plaid pattern (Adelson and Movshon, 1982; Movshon et al., 1985; Tinsley et al., 2003; Smith et al., 2005; Rust et al., 2006; Solomon et al., 2011; Juavinett and Callaway, 2015; **Figure 1A**). This stimulus is composed of two oriented drifting gratings, offset by an angle, whose directions of motion are symmetric relative to the coherent pattern motion (Adelson and Movshon, 1982; Muir et al., 2015; **Figure 1A**). By harnessing the local and global constituents of the plaid, foundational experiments have demonstrated the existence of two groups of cortical neurons, based on their response properties to plaids (Movshon et al., 1985; Smith et al., 2005; Solomon et al., 2011).
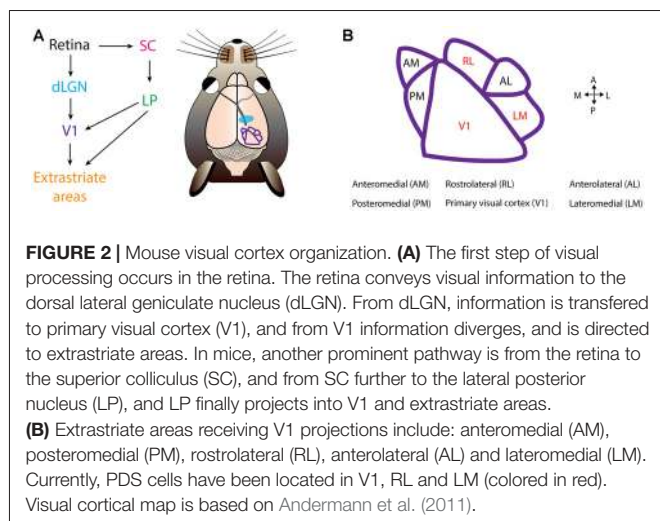
Neurons encoding local motion are called component direction-selective (CDS) cells (Movshon et al., 1985; DeAngelis et al., 1993a; Smith et al., 2005; Solomon et al., 2011). These are sensitive to the direction of motion for the individual gratings of the plaid, and respond when any one of the gratings is moving in its preferred direction (**Figure 1B**). These cells are observed both in V1 and extrastriate areas. On the other hand, neurons encoding global motion are called pattern direction-selective (PDS) cells (Movshon et al., 1985; Smith et al., 2005; Solomon et al., 2011). These cells are observed in the extrastriate middle temporal (MT) area (but see also Tinsley et al., 2003) and show sensitivity to the direction of motion of the plaid, and respond when the coherent motion of the plaid is moving in the preferred direction (**Figure 1B**).



**FIGURE 1 |** Component and pattern direction-selective (PDS) cells. **(A)** For the study of component direction-selective (CDS) and PDS cells the common visual stimulus employed is plaids consisting of two drifting gratings superimposed additively and offset by an angle. **(B)** Both CDS and PDS cells are tuned for the direction of motion of a single drifting grating. When a plaid stimulus is presented the predicted behavior of a PDS cell is that the neuron integrates the motion signals and responds to the plaid as it does to the individual grating but with broader tuning. The CDS cells responds to the individual grating components of the plaid as if they were presented alone. Polar plots in **(B)** are based on Smith et al. (2005).

Based on electrophysiology experiments and computational approaches, the current theory in primates for object motion representation is described with a two-stage model (Simoncelli and Heeger, 1998; Rust et al., 2006). The first stage involves a summation field, in which presynaptic neurons of a PDS cell encode local motion of oriented elements. These presynaptic neurons are hypothesized as CDS cells in V1, supported by evidence that V1 neurons projecting into MT are CDS (Movshon and Newsome, 1996) and PDS cells do not reach their fully selective state until 75 ms after the responses of CDS cells have stabilized (Smith et al., 2005). The PDS cells should receive excitatory inputs from CDS cells with a wide range of preferred directions to account for a wide tuning profile of PDS cells. The second stage involves a normalization stage, which helps to encode direction of global motion in PDS cells independently of local visual features (Zeki, 1974; Movshon et al., 1985; Movshon and Newsome, 1996; Carandini and Heeger, 2011). Normalization could explain various observed suppressions, such as cross-orientation suppression, within and across the receptive field of PDS cells (Britten and Heuer, 1999). It remains to be determined whether normalization operates exclusively on V1 neurons or also on MT neurons. Whilst substantial evidence supports this model, causal and mechanistic data on the computation performed by PDS cells still remains lacking.

## STUDYING LOCAL AND GLOBAL MOTION IN MOUSE VISUAL CORTEX

At this time, three groups have probed the existence of CDS and PDS cells in mouse visual cortex (Juavinett and Callaway, 2015;

**FIGURE 2 |** Mouse visual cortex organization. **(A)** The first step of visual processing occurs in the retina. The retina conveys visual information to the dorsal lateral geniculate nucleus (dLGN). From dLGN, information is transfered to primary visual cortex (V1), and from V1 information diverges, and is directed to extrastriate areas. In mice, another prominent pathway is from the retina to the superior colliculus (SC), and from SC further to the lateral posterior nucleus (LP), and LP finally projects into V1 and extrastriate areas. **(B)** Extrastriate areas receiving V1 projections include: anteromedial (AM), posteromedial (PM), rostrolateral (RL), anterolateral (AL) and lateromedial (LM). Currently, PDS cells have been located in V1, RL and LM (colored in red). Visual cortical map is based on Andermann et al. (2011).

Muir et al., 2015; Palagina et al., 2017). In the work by Juavinett and Callaway (2015), the proportion of PDS and CDS cells in layer 2/3 differed depending on the visual area. Mouse V1 is surrounded by extrastriate areas that receive V1 input (Wang and Burkhalter, 2007; Andermann et al., 2011; Marshel et al., 2011; Wang et al., 2012; Glickfeld et al., 2013a; Zhuang et al., 2017; **Figure 2**). The only areas that contained PDS cells were lateromedial (LM) and rostrolateral (RL; **Figure 2**). The fraction of PDS cells contained in LM and RL are 6% and 8%, respectively (Juavinett and Callaway, 2015). Both LM and RL are significantly interconnected with other visual areas (Wang et al., 2012), allowing them to combine inputs from many sources. It remains to be determined which mouse visual area is a homologous structure of MT, and it is possible this area lies outside the more commonly studied mouse extrastriate areas (Rosa, 1999). The other areas, including V1, contained no PDS cells, but only CDS cells (Juavinett and Callaway, 2015). However, others have suggested the existence of PDS cells in V1 (Muir et al., 2015; Palagina et al., 2017; **Figure 2**). The source of this discrepancy is unclear, but may partly originate from differences in plaid stimuli parameters. The work by Juavinett and Callaway (2015) presented additive plaids made from sinusoidal gratings, whereas the other works employed square-wave gratings for constructing the plaid (Muir et al., 2015; Palagina et al., 2017), yielding differences in spatial frequency content of the plaids. This could have potentially introduced differences in neuronal response properties. In congruence with this, human experiments have shown that the probability of a plaid percept is higher for square-wave gratings than for sinusoidal gratings (Burke et al., 1999). Another parameter is the temporal frequency of the plaid. PDS cells prefer drift rates of 2–16 Hz in non-human primates (Wang and Movshon, 2016). Juavinett and Callaway (2015) employed varying drift rates of 1, 1.5 or 2 Hz whereas Palagina et al. (2017) only used 2 Hz. The usage of low drift rates could have resulted in the underestimation of PDS responses in the work by Juavinett and Callaway (2015). In all instances, more experiments investigating the

existence of PDS cells in V1 are needed by exploring the plaid parameter space. This current discrepancy also casts an important question to settle, as the existence of PDS cells at the stage of V1 may suggest that the two-stage model proposed in primates operates within V1 in mice, rather than exclusively across visual areas. Alternatively, PDS activity in V1 may be brought by recurrent projection of PDS cells in LM or RL, given significant interconnections between extrastriate areas and V1 (Wang et al., 2012; D'Souza et al., 2016). More detailed characterization of inter-areal functional connectivity would be crucial for answering this question, and could be achieved by recently developed wide-field two photon imaging methods (Stirman et al., 2016a) combined with high-speed recording of neuronal spikes with voltage sensors for understanding connection hierarchies (Gong et al., 2015).

Overall, evidence exist that mouse visual cortex represents and computes local and global motion, and therefore, is a valid model system for studying biophysical and circuit mechanisms of global motion computations in great detail. However, it may be plausible, and not all that surprising, if details in the strategy employed by mouse visual cortex for computing global motion deviates from that employed by humans and non-human primates. We speculate that primates and mice may have fundamental differences in the computational strategy and behavioral requirements of pattern motion computations. First of all, mice lack fovea in their retina unlike primates. Primate MT has a marked emphasis on the fovea; the central 15° of the visual field occupies over half of MT's surface area (Van Essen et al., 1981), and signals from MT is important for the initiation of smooth pursuit, which is an eye movement for fixing a moving object on the fovea (Lisberger et al., 1987). Hence, pattern motion computation in mice would be less relevant for the smooth pursuit. Second, one of the most intriguing functional aspects of MT in primates is sensitivity to binocular disparity and depth perception. Since binocular areas are much smaller in mice compared to primates, pattern motion computations of mice may be specialized more for analyzing monocular motion, such as optic flow while running forward.

The functional organization of mouse and primate visual cortex differs on several levels (Huberman and Niell, 2011; Laramée and Boire, 2014). In rodent visual cortex, unlike primates, functionally selective cells are organized in a "salt-and-pepper" manner (Ohki et al., 2005; Bonin et al., 2011) and neurons with similar tuning are connected with each other (Ko et al., 2011; Li et al., 2012; Lee et al., 2016) in a layer-specific manner (Wertz et al., 2015) to form recurrent sub-networks. Differences upstream to visual cortex also exist. Given the high prevalence of direction-selective retinal ganglion cells (Vaney et al., 2012; Yonehara et al., 2013, 2016) and the finding of direction-selective dorsal lateral geniculate nucleus (dLGN) neurons and their feed-forward input to V1 (Cruz-Martín et al., 2014; Hillier et al., 2017), one might entertain the hypothesis that in mouse visual cortex, complex visual representations such as pattern motion develops at the stage of V1.

# FUTURE DIRECTIONS FOR STUDYING LOCAL AND GLOBAL MOTION PROCESSING IN THE MOUSE

We propose five key questions to be addressed where mouse visual cortex would serve as an excellent model. Note however, recent advances have introduced the marmoset monkey as an attractive primate model due to its rapidly evolving molecular and genetic toolbox available (Sadakane et al., 2015a,b; Ding et al., 2017) and the organizational similarities to the visual system in humans. Furthermore, it might be advantageous to complement these experiments with studies in a rodent species in which homologs to MT have already been identified, such as the squirrel (Paolini and Sereno, 1998).

First question is: what is the tuning of individual excitatory synaptic inputs onto PDS cells when single gratings or plaids are shown? Models derived from non-human primate research (Simoncelli and Heeger, 1998; Rust et al., 2006) predict that PDS cells receive direct feed-forward excitatory barrages from CDS cells, and robust responses to plaids likely arises from convergence of CDS inputs tuned for different directions (Rust et al., 2006; **Figure 1B**). This question can be addressed by advanced methodologies such as dendritic spine calcium imaging (Jia et al., 2010; Chen et al., 2013; Wilson et al., 2016; Iacaruso et al., 2017). Dendritic spine calcium signals can serve as a proxy for the activity of individual excitatory synaptic inputs, and hence allows tuning characterization of incoming barrages.

Second question is: at which synaptic stages does normalization operate? Normalization is a fundamental neuronal computation that operates throughout the visual system and in many other sensory modalities (Carandini and Heeger, 2011). Normalization is an essential aspect of PDS cell behavior (Simoncelli and Heeger, 1998). This question could be addressed again by dendritic spine calcium imaging; one could test whether cross-orientation stimuli suppresses the activity of individual synaptic inputs to PDS cells or PDS somatic activity without suppressing synaptic inputs. In relation to these questions, it remains to be determined which brain areas provide synaptic inputs to PDS cells. In primates, MT receives inputs mainly from V1 and inferior pulvinar nucleus (Lyon et al., 2010), as well as short latency retinal inputs via the LGN (Warner et al., 2010). For this question, single-cell-initiated, activity sensor-functionalized monosynaptic tracing combined with network calcium imaging (Yonehara et al., 2013; Wertz et al., 2015) would be a powerful approach.

Third question is: what kind of dendritic mechanisms in PDS cells are involved in the integration of synaptic inputs? The response properties of PDS cells seem to be predicted from supra-linear summation of excitatory inputs (Muir et al., 2015). Recording of neuronal membrane potentials as well as excitatory and inhibitory synaptic currents by *in vivo* whole-cell patch-clamp recordings (Haider et al., 2016; Adesnik, 2017; Petersen, 2017) may provide hints for the answer.

Fourth question is: what is the role of brain state on PDS cell tuning? Recordings from CDS and PDS cells are often performed in anesthetized animals (Movshon et al., 1985; Tinsley et al., 2003;

Smith et al., 2005; Solomon et al., 2011; Juavinett and Callaway, 2015; Palagina et al., 2017). However, it is now established that sensory experiences are shaped by the level of arousal, alertness and context (Albright and Stoner, 2002; Harris and Thiele, 2011; Keller et al., 2012; Lee and Dan, 2012; Lee et al., 2014; McGinley et al., 2015; Vinck et al., 2015). Motivating this question is recordings from MT (Pack et al., 2001), where the fraction of PDS cells were reduced in anesthetized animals compared to awake animals. These findings may suggest existence of top-down modulation of PDS cell tuning (Dent et al., 2010; Zhang et al., 2014). However, it should be noted that these findings have later been questioned in the field (Movshon et al., 2003). Here it was proposed that use of non-additive plaids could have affected the findings by Pack et al. (2001), leading to the discrepancy with previous work (Rodman and Albright, 1989; Stoner and Albright, 1992). Currently, there is no evidence that wakefulness changes the proportion of PDS cells in RL in mice (Juavinett and Callaway, 2015). Future experiments could address this question by performing population two photon calcium imaging in awake mice, for example, in a closed loop virtual reality, in which plaids motion coupled to locomotion are presented (Harvey et al., 2009; Keller et al., 2012; Roth et al., 2015).

Last question is: what is the role of PDS cells in perception and behavior? Previous work has implicated MT in psychophysical performance on object motion discrimination tasks (Newsome et al., 1990) and eye movement control (Newsome et al., 1985). However, whether PDS cells are the underlying biophysical substrate for the ability to discriminate object motion is unsettled (Tailby et al., 2010). Mice are capable of learning to discriminate between orientations or random-dot motion (Glickfeld et al., 2013b; Stirman et al., 2016b), allowing the possibility to track neural discriminability and tuning selectivity during learning of a visual task. We propose experiments where mice are trained to learn to discriminate plaid motion directions or global dot motion in more-or-less noisy conditions (Newsome and Paré, 1988), while two photon calcium imaging from PDS cells is simultaneously obtained, to directly compare neurometric and psychometric functions. Such experiments would provide correlational insights to the involvement of PDS cells in successful object motion discrimination and development of pattern motion selectivity over the learning period. Causality could be tested by single cell manipulation techniques such as two photon holographic optogenetics while performing the task (Packer et al., 2015; Carrillo-Reid et al., 2016; Dal Maschio et al., 2017).

Chemical lesion of MT caused deficits in smooth pursuit eye movements, important for following moving objects (Newsome et al., 1985). In concert with this, MT is known to project to several eye movement-related areas such as medial superior temporal cortex and pretectal nucleus of the optic tract (Mustari et al., 2009). In humans, perception of motion direction is well matched with the direction of fixation eye movements (Laubrock et al., 2008; Baker and Graf, 2010). Head or eye movements of mice could be used as a proxy for the output of cortical motion processing. Lastly, in a natural environment,

global motion would be encountered frequently as an optic flow when a mouse is coursing through the environment. It may be important to bear the ethological point of view in mind when investigating particular aspects of visual function in the particular animal model employed (Huberman and Niell, 2011; Hillier et al., 2017).

## CONCLUSION

How PDS cells develop their distinct response properties to single gratings and patterned plaids is still an open question. Due to the rapidly evolving ability to interrogate neural circuits and single neuron computations using genetic and molecular techniques, PDS cells in mouse visual cortex are the perfect arena for delineating and solving how individual sensory features extracted by neuronal circuits in earlier brain regions are integrated to build our rich cohesive sensory experiences.

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