Role of emergent neural activity in visual map development

Abstract

The structural and functional development of visual circuits in reptiles, birds, and mammals happens largely independent of sensory experience. Innate genetic programs code for gradients of molecules which provide gross positional information for developing nerve cells, yet much of the cytoarchitectural complexity and synaptogenesis of neurons depends on calcium influx, neurotransmitter release, and neural activity before the start of vision. In fact, specific spatiotemporal patterns of neural activity called retinal waves emerge among the earliest connections made between excitable cells in the developing eye. These patterns of spontaneous activity, which have been recorded from all amniote retinae examined to date, may be an evolved adaptation for species with long gestational periods before the start of vision, imparting an informational robustness and redundancy for the development of visual maps across the nervous system. Recent experiments indicate that retinal waves play a crucial role in the development of interconnections between different parts of the visual system, suggesting that these spontaneous patterns serve as a template-matching mechanism to prepare higher-order visually-associative circuits for the onset of visuomotor learning and behavior. Key questions in future studies will include determining the exact sources and nature of spontaneous activity during development, characterizing the interactions between neural activity and transcriptional regulation, and understanding the extent of circuit connectivity governed by retinal waves within and between sensory-motor systems.

Introduction

The visual system is organized such that information relayed through the optic nerve is processed in a set of hierarchal neural maps distributed throughout the thalamus, midbrain, and cortex. As with all biological tissues, construction of the circuits underlying these visual maps depends on innate genetic programs. However, the nervous system is unique with the extent to which it can be shaped by changes in the external world detected and relayed as nerve impulses by the sensory organs. This extraordinary plasticity of the nervous system was underscored in the visual deprivation experiments by Hubel and Wiesel on ocular dominance column development in visual cortex [#Hubel:1977a] and was experienced by each of us as we first learned our native language.

Given the many pieces of information that must be parsed from the photic signals in the eye to deconstruct and reconstruct the visual scene, one might think that visual experience is absolutely required to establish these visual representations. The debate between Herring and von Helmholz in the 19th century over whether the binocular coordination of eye movements [#King:2000] required for stereoscopic vision was innate or learned highlighted the always relevant problem regarding the roles for nature and nurture in developmental neuroscience. Though complex brain and behavioral development in the absence of learned experience is not surprising in animals – e.g. infant suckling in newborns – it is still remarkable that a considerable amount of intricate visual circuit structure and function forms before any patterned visual experience. As noted by Hubel and Wiesel [#Hubel:1977a] based on their recordings from primary visual cortex in newborn monkey:

> *That area 17 is in so many respects wired up and ready to go when the animal is born is perhaps not so surprising if one remembers that the machinery of area 17 represents building blocks of vision…*

Indeed both their studies and subsequent work by others has demonstrated that a number of visual maps are formed by the time of birth or eyelid opening including cortical maps for retinotopy, orientation selectivity, direction selectivity, and ocular dominance. Thus, with so many circuits established before birth it might seem that by knowing the genetic code and its patterns of expression we would understand all the instructions underlying visual map formation.

However, the genetic code does not work in isolation– the information required for organism development stems from the myriad interactions that occur within and outside of the cellular environment throughout the course of gestation. A factor that may be particularly relevant to the development and function of the nervous system is that spontaneous electrical activity and neurotransmitter release emerges among excitable cells in the developing nervous system, even in isolated cultures of immature neurons. Intriguingly, a number of studies have provided experimental evidence that specific *patterns* of neural activity are required for proper visual map formation in rodent, ferret, and cat indicating that spontaneous activity occurs in the immature nervous system and has a clear function in circuit development. These spontaneous patterns of activity increase the informational complexity that the genome can carry by serving to sculpt neural architecture and synaptic connections so that the nervous system can begin performing computations relevant for visual behavior, learning, and memory at the start of vision. Indeed, as any mother who has felt their baby kick inside the womb can attest, the developing brain is not quiet. And pediatric neurologists would direct our attention to the fetal brain malformations which occur when chemicals that interfere with neurotransmission are taken during pregnancy.

In this review we discuss recent work that highlights the function of spontaneous activity in visual system development. We will focus on studies that have examined the nature spontaneous activity in the developing brain as well as studies that have provided direct experimental evidence for the function of retinal waves in visual map development. We refer the reader to recent reviews on the crucial roles of molecular signaling gradients, such as eph/ephrins for visual circuit development [#Huberman:xxxx] as well as on the mechanisms by which patterned spontaneous activity is generated within developing neural circuits [#Feller:xxxx].

Spontaneous activity in the visual system: When, What, and Where?

Spontaneous oscillations play a prominent yet unclear role in brain function. Though it is unknown precisely how spontaneous oscillations of electrical activity arise within immature networks, there are numerous examples demonstrating that they do– such as the spontaneous activity found in cultures of isolated neurons [#Mazzoni:2007], as well as immmature in spinal cord [#Marder:2005], retina [#Maffei:1990,Meister:1991], and cortical circuits [#Leinekugel:2002,Khazipov:2006]. The function of spontaneous correlated activity may be to strengthen the synaptic weights between coactive cells through voltage-dependent calcium influx that mediates downstream changes in transcriptional regulation. Adjustments in gene expression could result in synaptic modifications through changes in ion channel or neurotransmitter receptor function, changes in receptor clustering at existing synapses, or formation of entirely new synapses with nearby cells.

So when do these spontaneous activities occur that can mediate these developmental changes? Spontaneous oscillations occur after eye opening and maturation of the visual system is complete such as standing waves and fast travelling waves [#Benucci:2007] (Y. Dan paper) that may serve a purpose in experiential pattern replay during sleep, such as occurs in the hippocampus with replay activations of place cells (M. Wilson). Yet spontaneous activity also occurs in the visual system before the onset of visual experience in all amniote species that have been examined [#Wong:1999]. Thus travelling ‘retinal waves’ of bursting activity sweeps across the retina before hatching or birth in some species including chicken, turtle, rabbit, monkey, and cat. In species more immature at birth, retinal waves occur after birth but before eye lid opening such as rodent, rabbit, and ferret. Thus amniote vertebrates have a long gestational timecourse which gives the change for these patterns to develop. But in non-amniote vertebrates, there is a short gestational timecourse before the beginning of locomotor and visuomotor behavior, so that the roles subserved by spontaneous activity can be be mediated by primarily sensory dependent activation in these species.

What kind of activity is occurring elsewhere in the visual system from isolated model systems?. Slice physiology in subplate, calcium imaging in slice around eye opening. But what about in vivo? Translating in vitro to in vivo can been a problem in studies of all sensorimotor systems…

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        * Subplate --
                * Subplate neurons are likely key to relaying oscillatory activity to developing cortic
al neurons Kanold and Luhmann review [#Kanold:2010] *Nice Ann Rev Neuosci review with summary table of
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references for species, cortical area, neurotransmitter, etc)*
                    * SPn removal in visual cortex prevents thalamocortical synapse maturation, maturat
ion of inhibition in L4, develeopment of orientation selectivity, and formation of ODCs [#Kanold:2010]
                    * physiology evidence for activity relay in vitro and in vivo in somatosensory cort
ex
                    * physiology evidence for activity relay in vitro cat visual cortex (old disynaptic
 response Friauf&Shatz 1991 paper, possibly Hanganu 2001, 2002, and Hirsch &Luhmann2008)
                * Ghosh/Kanold/Shatz subplate kainic acid excitotoxicity or immunotoxin work in cats su
ggests that subplate cells play a key role in ocular dominance column formation, but not known if this
role is activity-dependent [#Ghosh:1990][#Ghosh:1992][#Kanold:2003]
                    * ~~P. Kanold~~ *No one knows if subplate cells in occipital cortex exhibit
spontaneous activity during development*
                    * Only subplate cells in somatosensory cortex have been checked for spontaneous act
ivity (Luhmann, Hanganu, also Kanold JNS 2012 work) [#Hanganu:2001][#Hanganu:2002][#Dupont:2006][#Kanol
d:2006][#Tolner:2012]
            * Calcium waves
                * have been observed in several areas of rodent lateral and medial entorhinal cortex, t
emporal cortex, and fronto-parietal cortex, but none of the following groups (Konnerth, Peinado, Moody,
 Yuste/Ikegaya) has checked occiptial cortex before eye opening:
                    * ~~[#Garaschuk:2000], [#Peinado:2000], [#Corlew:2004], [#Namiki:2013]~~ *No
ne of these groups has done occipital cortex in vitro*
        * after eye opening
            * UP-DOWN states in mouse visual cortex [#Cossart:2003]
                * P14-P21 C57/BL6 brain slices
                * multicellular two-photon calcium imaging with Fura2 and patch clamp recordings
                * all cortical layers 2-5 imaged
                * average interval of synchronous population events was 55 ± 4 s (peak synchrony in his
tograms, considerably slower than slow oscillations of 0.1 - 0.5 Hz)
    * in vivo
        * early development - before eye opening
            * Rat
                * Correlated bursting among RGCs [#Maffei:1990]
                * 'Spindle bursts'
                    * spindle shaped field potential oscillations in visual cortex [#Hanganu:2006]
                * 'Slow activity transients'
                    * infra-slow LFP wave with nested fast oscillations
                        * field oscillations and bursting multiunit activity in visual cortex [#Colonne
se:2010]
                            * 87% of L4 MUA occured during slow activity transients
                            * extracellular recordings with glass electrode or multisite silicon probe
                                * age P5-P7
                                    * peak frequency (8 - 31 Hz, mostly 18-30 Hz) and duration form sin
gle distribution (400 ms - 5 s), likely all continuous 'spindle burst' oscillations within the slow wav
e
                                * age P9-P13
                                    * short duration events (<400 ms) first prominent around P9-P10 and
 increased frequency of these events until becoming the most common type by P13
                                    * very long duration (>5 s) encountered after P8 ('splitting of eve

nts with maturation')
                                    * two populations of events encountered:
                                        * long duration, beta band frequency (>5 s, 18-30 Hz)
                                        * short duration, alpha band frequency (<3 s, 10 Hz)
                                    * after P12 SATs less common and no longer dominant pattern-- continuous cortical activity and slow wave sleep (delta)

            * Mouse
                * retinal waves
                    * Primary source of patterned activity throughout neonatal visual system [#Ackman:2012]
                    * Retinal input modulates synchronous calcium signals in cortical neurons [#Siegel:2012]
                        * they possibly recorded some retinal waves?
                        * but most activity was independent of retinal input, and more likely 'spindle bursts'
                            * unknown if recordings were strictly from V1 or V2 (no method for identification)
                            * calcium recordings were not summed population signals
                        * *which might be same as the independent spontaneous V2 activity we saw* [#Ackman:2012]
            * Human
                * 'Slow activity transients'
                    * infra-slow LFP wave with nested fast oscillations
                        * EEG field oscillations and bursting multiunit activity in visual cortex [#Vanhatalo:2005][#Colonnese:2010a]
        * around eye opening
            * Ferret
                * Correlated bursting activity among LGN and visual cortical neurons [#Weliky:1999][#Chiu:2002]
            * Rat
                * 'Spindle bursts'
                    * field oscillations and bursting multiunit activity in visual cortex [#Colonnese:2010][#Colonnese:2010a]
                * 'Slow activity transients'
                    * infra-slow LFP wave with nested fast oscillations
                        * field oscillations and bursting multiunit activity in visual cortex [#Colonnese:2010][#Colonnese:2010a]

Regulation of cellular anatomy and physiology by spontaneous activity

Though sensory experience has a clear role in directing the refinement of synaptic connectivity, much of the coarse topography of neural circuits is established by molecular signalling early in development. For example, signalling gradients via Eph receptor tyrosine kinases and their ephrin ligands mediate much of the rostro-caudal and medio-lateral targeting of retinal ganglion cell afferents within the superior colliculus/optic tectum [#Lemke:2005]. The initial connectivity between axons and their target cells produces functional neuronal networks that are appropriate enough to make some aspects of visual processing available before the onset of sensory experience, such as retinotopy, ocular dominance, and orientation selectivity in the optic tectum and visual cortex [#Rakic:1976,Holt:1983,Crair:1998,Crowley:2000].

Functional synapse maturation at retinogeniculate (Hooks and Chen, 2006) and retinocollicular (Shah and Crair, 2008) synapses is dependent on spontaneous activity. At the retinogeniculate synapse, blockade of spontaneous activity by TTX application to the eye around and before the time of eye opening, prevents the normal developmental increase in synapse strength and arrested synaptic pruning (Hooks and Chen, 2006). Visual deprivation (by delaying eye opening) has no effect. Functional maturation at the retinocollicular synapse is also impaired in β2-nAChR KO (β2-/-) mice during the first week after birth (Shah and Crair, 2008), again suggesting that spontaneous retinal activity promotes the maturation of retinogufal synapses before normal vision is possible.

Regulation of visual map structure and function by spontaneous activity

The development of maps for visual stimulus features, such as retinotopy, ocular dominance and orientation, are also sensitive to the presence of ongoing spontaneous activity before eye opening. Disrupting retinal waves pharmacologically or genetically interferes with the development of both retinotopy and eye specific segregation in the dLGN and SC of mice [#McLaughlin:2003][#Chandrasekaran:2005][#Stellwagen:2002]. In the SC, of retinocollicular target zones and individual axon arbors are enlarged in β2-/- mice, and preferentially elongated along the nasal-temporal axis of the retina, corresponding the visual field azimuth [#Chandrasekaran:2005]; Dhande et a., 2011). Functional response properties of SC neurons are correspondingly impacted, with receptive fields dramatically enlarged, particularly along the visual field azimuth [#Chandrasekaran:2005][#Mrsic-Flogel:2005]. In the dLGN, retinal ganglion cell axon arbors are similarly enlarged β2-/- mice , but rather than enlarged receptive fields in individual dLGN neurons, the retinotopic map is disrupted because the receptive field location is scattered, particularly along the visual field azimuth [#Grubb:2003]. Remarkably, in both the dLGN [#Grubb:2003] and SC [#Chandrasekaran:2005] of β2-/- mice, the organization of response properties associated with on- or off-selectivity, which are not normally observed in mice, emerge. In the dLGN, on- and off-center cells are spatially segregated [#Grubb:2003], while in the SC, neurons become selective to either the onset or the offset of light stimulus, when they normally respond equally well to both. Thus, it appears that organization around new response features emerge in the dLGN and SC of β2-/- mice, possibly because of the delayed functional development of retinofugal synapses [#Hooks:2006][#Shah:2008] and the precocious presence of Stage III (glutamate receptor mediated) waves in β2-/- mice [#Bansal:2000].

Mechanisms of activity-dependent visual circuit development before vision

Conclusion

References