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Determinants of Synaptic and Circuit Plasticity in the Cerebral Cortex

Implications for Neurodevelopmental Disorders

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"Cortical plasticity" encompasses a broad set of mechanisms through which cortical circuits adapt their responsiveness to their history of input. In several brain systems, the field has now distilled robust regimes for examining and demonstrating plasticity at the circuit level. In recent years there has also been a rough consensus on cellular and signaling changes which can account for circuit plasticity. In contrast, the control signals that command adjustments in the circuit's "plasticity status" remain largely unknown, as do the specific cues that they monitor—candidate frameworks for these are emerging and are detailed below. A clear articulation of the phenomena, rules, and mechanisms that govern cortical plasticity during development is critical for understanding their

misregulation in specific neurodevelopmental disorders. This far-reaching vision, that mechanisms of developmental plasticity can be used to reveal mechanisms of brain disorders and even treat them, owes much to the work and scientific insights of Lamberto Maffei, whom this volume honors.

The Visual Cortex as a Model System for Experience-Dependent Plasticity

Many critical observations on plasticity in the nervous system have been made in the visual cortex. Wiesel and Hubel (1963) had the original insight that the two eyes represent distinct input sources which can be driven differentially with light to evaluate how a circuit responds over time. In a sense, it remains the most straightforward junction for probing the complex circuitry of the cerebral cortex with well-characterized sensory stimuli. More recently, progress in detailing the phenomena and mechanisms of cortical plasticity has been augmented through transgenic mice, which has allowed for the elucidation of a growing network of proteins and pathways, isolated to specific regions and distinct cell types.

Another useful property of the visual cortex for studies of plasticity is the enormous dynamic range of plasticity that it expresses during the course of development and with experience (Katz and Callaway, 1992). Over the life span of cortical circuits, synaptic refinement leads to an increase in organization and

correlated activity, while the malleability of the circuit is decreased concomitantly. Through cell-specific rules of plasticity (Desai et al., 2002), a large number of weak synapses with motile spines (the sites of excitatory synapses on cortical neurons) are sculpted into a refined number of strong synapses with stable spines (Majewska and Sur, 2003; Oray et al., 2004). As excitatory transmission is consolidated, it contributes to the release of feedback signals such as brain-derived neurotrophic factor (BDNF; Bonhoeffer, 1996), which eventually attains a critical level for the activation of inhibitory signaling (Buonomano and Merzenich, 1998). This onset of inhibition initiates a brief time frame of exceptional plasticity known as the "critical period" in which the pattern of cortical input is particularly important for organizing and strengthening a functional architecture for future processing (Hensch, 2004). As the synaptic architecture underlying this organization stabilizes, it comes to resist further change (Abraham and Bear, 1996; Bi and Poo, 1998), the specific balance of excitation and inhibition becomes important for delimiting plasticity (Artola and Singer, 1987; Maya Vetencourt et al., 2008), and a network of extracellular matrix proteins begins to entangle the entire circuit to provide an additional measure of circuit stability (Berardi et al., 2004).

Parameterizing Cortical Plasticity

Across development, circuit plasticity itself is modulated by the level of input drive, which stimulates key molecular pathways to reconfigure circuit properties. Received activity is coupled to downstream and intercellular molecular events, and this allows activity at input locations to impact circuit function and plasticity at multiple loci. Here we will review several "feedforward" mechanisms that can initiate circuit change, together with a host of emerging "feedback" network processes that respond to those changes.

Feedforward Synaptic Plasticity

Feedforward changes are initiatory events where input activity to a circuit triggers direct synaptic changes across its synapses, with subsequent reverberatory consequences elsewhere in the circuit. A cardinal example of a feedforward change is long-term potentiation (LTP), in which a pattern of robust input activity triggers the long-term strengthening of that same input to further stabilize its postsynaptic influence over the circuit (Bliss et al., 2003). LTP also provides a link between synaptic changes and the formation and maintenance of cortical maps (Buonomano and Merzenich, 1998). Its sister process is long-term depression (LTD), in which weak activity across a synapse leads to the long-term

weakening of that synapse, and loss of influence over the circuit. LTD has also been advanced as a basis for cortical phenomena such as ocular dominance plasticity (Smith et al., 2009). LTP and LTD are further complemented by mechanisms such as spike-timing dependent plasticity, which trigger synaptic plasticity based on how well matched the timing of an input is to firing of the postsynaptic cell (and circuit) on which it impinges (Song and Abbott, 2001; Dan and Poo, 2006). Together these canonical mechanisms lay a foundation for focal circuit changes upon and between cells that depend only on the magnitude and timing of the input itself, independent of the other inputs in the circuit. However, as we will see below, inputs across the cortical circuit are intimately connected via multiple pathways and time courses which add richness to a simple "push–pull" dissection of cortical plasticity phenomena.

Molecular Pathways of Feedforward Plasticity

Modifications to the strengths of excitatory synapses are likely to be enacted via postsynaptic changes in AMPA receptor number and conductance (Malenka and Bear, 2004), and.or presynaptic changes in probability of release (Bolshakov and Siegelbaum, 1995) and vesicular glutamate content (Edwards, 2007). Input strength can also be adjusted via synaptogenesis and synaptic elimination. However, the degree to which such plasticity occurs is gated by a host of

molecular pathways that determine the "plasticity status" of the synapse, cell, and circuit.

The NR2B.NR2A Switch

Plasticity is prominently gated by the activation of *N*-methyl-D-aspartate (NMDA) receptors, which respond to excitatory synaptic transmission by enabling calcium flux into the target synapse and its neuron, with more calcium triggering more plasticity and rearrangement. However, the receptor's capacity to drive plasticity depends on its subunit composition. Some receptors are built from "NR2B" subunits, which enable a high calcium permeability and thus enhanced plasticity, and some are built from "NR2A" subunits, which have a reduced calcium flux (Flint et al., 1997). The ratio of 2B.2A receptors in the synapse and the neuron thus has a pivotal effect on the overall calcium flux upon synaptic activation and determines the capacity for plasticity in response to arriving input.

Here again, a crucial determinant of plasticity is itself regulated by the activity level of the circuit. As animals are exposed to visual experience, the NR2B.NR2A ratio declines (Quinlan et al., 1999), thus reducing the capacity for further plasticity, whereas placing animals in the dark for extended periods recovers the NR2B.NR2A ratio (Chen and Bear, 2007), thereby restoring the capacity for plasticity. Thus, the molecular composition of NMDA receptors is a

critical determinant of calcium-mediated cellular plasticity that is directly responsive to activity levels.

Calcium-Calmodulin Kinase II Signaling

Calcium entry at synaptic sites upon activation leads to eventual synaptic change, prominently via calcium-calmodulin kinase II (CaMKII), which is extraordinarily abundant and accounts for 1% to 2% of the total protein found in neurons (Fink and Meyer, 2002). CaMKII is spatially positioned in the synaptic spine to directly sense NMDA-mediated calcium fluxes (Bayer et al., 2001) and respond by mobilizing additional AMPA receptors to synapses (Hayashi et al., 2000). Moreover, its binding and activation is directly specified by the NR2B.NR2A subunit composition described above (Barria and Malinow, 2005). α-CaMKII has been shown to be critical for cortical LTP, as well as for the consolidation of cortical memory traces (Frankland et al., 2001). It also has the interesting property of autophosphorylation, which allows it to undergo long-term modification, and has led to the proposal that it could provide a sort of "molecular memory" of synaptic activity (Lisman, 1994): persistently active CaMKII can indeed bring about LTP effects (Pettit et al., 1994). Interestingly, CaMKII seems be critical for synaptic plasticity yet without impacting large-scale cortical architecture, as its mutations prevent the consolidation of sensory plasticity without disrupting the topography of sensory cortex (Glazewski et al., 1996; Gordon et al., 1996).

The ERK.MAPK Pathway

Stimulation at the synaptic and cellular level drives the Raf.MEK.ERK pathway, which also serves to promote synapse stabilization (Sweatt, 2001). A direct link has been established between its downstream effector, extracellular signal-regulated kinase 1,2 (ERK, also called p42.44 mitogen-activated protein kinase) and insertion of AMPA receptors into activated synapses (Zhu et al., 2002). The degree of ERK activation also determines the magnitude of LTP in visual cortex and is required for ocular dominance plasticity (Di Cristo et al., 2001). As with several of the plasticity cues described above, the ERK pathway is responsive to activity levels (Fiore et al., 1993), as well as NMDA receptor-mediated calcium levels (Hardingham et al., 2001), and plasticity cues such as BDNF (Patterson et al., 2001). Its downstream targets include critical plasticity triggers such as cyclic AMP response element binding protein (CREB; Impey et al., 1998) and Arc (Ying et al., 2002), and transcription factors that regulate the expression of activity-dependent immediate early genes (Xia et al., 1996). Activity within the ERK pathway therefore offers a number of channels through which NMDA activation can stimulate cell-wide changes in synaptic function, thus promoting coherent integration of inputs between cells and networks (Thomas and Huganir, 2004).

The PI3K.Akt.mTOR Pathway

Along with the now-canonical plasticity pathways listed above, increasing attention has been paid to another protein kinase called mammalian target of rapamycin (mTOR). It is driven by both synaptic stimulation (Cammalleri et al., 2003) and PI3K.Akt activation (Jaworski and Sheng, 2006), which is known to strengthen synapses by delivering PSD-95 (a critical post-synaptic density protein) into dendrites (Yoshii and Constantine-Paton, 2007). Functionally, increased mTOR activity has been linked to larger and fewer spines with larger AMPA currents (Tavazoie et al., 2005) and seems to serve to facilitate and accentuate LTP (Ehninger et al., 2008b; Hoeffer et al., 2008). Consequently, mTOR signaling seems well placed for stimulating growth, elevating excitatory drive, and forging stronger and more stable synaptic circuits.

Feedback.Homeostatic Plasticity

When a change is exerted at one or more synaptic pathways via the mechanisms described above, a concurrent group of normative processes may arise to rebalance the net function of the circuit. These mechanisms are considered "homeostatic" or "feedback" events because they appear aimed at restoring the net excitability of the circuit back toward its original state prior to plasticity induction (Turrigiano and Nelson, 2000; Davis and Bezprozvanny, 2001).

Sites of Feedback Regulation

Feedback processes that rebalance the strength of excitatory synapses have been identified which operate postsynaptically, via AMPA receptor number and conductance (Turrigiano, 2008), and presynaptically, via probability of release (Murthy et al., 2001) and vesicular glutamate content (Wilson et al., 2005), among others. An input may also be renormalized by scaling its number of connections. Feedback processes that might rebalance at a network level beyond the excitatory synapse include modifications to inhibitory synapses (Maffei et al., 2006), homeostatic modifications to a cell's intrinsic excitability (Pratt and Aizenman, 2007), and changes to the excitatory drive onto inhibitory neurons (Wilson et al., 2007). Feedback regulation within cortical circuits has even been demonstrated to extend from one sensory modality to another (Goel et al., 2006).

Positive Feedback Regulation via TNF-Alpha

What are the signals that control feedback regulation? One molecule that has been shown to be both necessary and sufficient for the activity-dependent scaling up of AMPA receptor function is the tumor necrosis factor TNF-alpha (Stellwagen and Malenka, 2006). Still more recently, the scaling up of open-eye responses following light deprivation in visual cortex was shown to require TNF-alpha

(Kaneko et al., 2008). A particularly intriguing possibility is that the excitatory.inhibitory balance is coordinated via a few or even a single molecular control point. Indeed, increases to TNF-alpha signaling have been shown to coordinately increase AMPA receptor surface expression while simultaneously decreasing GABA receptor surface expression (Stellwagen et al., 2005).

Negative Feedback Regulation via CDK5 and Arc

What is responsible for the scaling down of excitability? One pathway that is emerging for rebalancing high levels of activity is CDK5.Polo-like kinase 2 (Plk2; Seeburg et al., 2008). Another likely possibility is the immediate-early gene Arc, the expression of which is regulated by activity, triggers AMPA receptor endocytosis (Chowdhury et al., 2006) and is required for synaptic scaling (Shepherd et al., 2005). Perhaps through its known homeostatic role, Arc has been found to be important for organizing representations in visual cortex (Wang et al., 2006) and has recently been found to underpin the loss of cortical territory that occurs during ocular dominance plasticity (McCurry et al., 2008). The scaling down of input strength mediated by Arc could also lead to the functional elimination of extraneous inputs during cortical refinement; indeed, mice that lack Arc exhibit visual cortical neurons that are less precisely tuned (Wang et al., 2006).

Inhibition as a Plasticity Gate

Inhibitory neurons are widespread in the cortex and may be even more diverse in morphology and function than excitatory neurons (Markram et al., 2004). The balance of excitation and inhibition appears to be dynamically maintained at the level of dendritic branches (Liu, 2004) and neurons (Cline, 2005). In cortical dynamics, stimuli that elicit maximal excitation to neurons also elicit maximal inhibition at those same neurons (Marino et al., 2005; Okun and Lampl, 2008), ensuring that functional responses always result from a precise balance of excitatory and inhibitory drive.

In addition to balancing the firing rates of circuits, inhibition may have a complementary role in controlling the plasticity of circuits. Preventing the activation of inhibition prevents the critical period of plasticity from happening until inhibition is enabled (Hensch et al., 1998). Conversely, augmenting inhibitory signaling prematurely launches the critical period prematurely (Iwai et al., 2003). Once inhibition is developed to adult levels, however, it may become an obstacle to cortical plasticity. Inhibition in the cortex has long been claimed to gate adult LTP, wherein robust LTP was only observable when suppressing inhibition pharmacologically with bicuculline (Artola and Singer, 1987). In the adult visual system of the rat, ocular dominance plasticity is greatly reduced

compared to juvenile levels but can be restored to juvenile levels by suppressing inhibition with the antidepressant fluoxetine (Maya Vetencourt et al., 2008).

The Role of Neurotrophins

Neurotrophins such as BDNF have emerged as an ideal candidate for communicating the status of activity across the circuit to regulate plasticity. Neuronal activity has a positive feedback relationship with the transcription of the BDNF gene, the transport of its protein into dendrites, and its secretion at synapses (Lu, 2003). At the cellular level, BDNF is known to support growth and strengthening of synapses during development (Cellerino and Maffei, 1996) and is critical for the proper establishment of excitatory synaptic transmission (Schuman, 1999).

BDNF also seems to play an instructive role in a host of processes relevant to circuit development. BDNF triggers the maturation of inhibition that initiates the critical period as described above (Huang et al., 1999), and expressing it prematurely accelerates the timing of the critical period (Hanover et al., 1999). BDNF also triggers the release of tPA (Fiumelli et al., 1999), which as described below is important for liberating structural plasticity. In homeostatic plasticity, BDNF has been identified as a signal that triggers the reactive scaling of

excitatory and inhibitory synapses to offset recent elevations in activity levels (Rutherford et al., 1998).

Extraneuronal Influences: Astrocytes and Perineuronal Nets

Astrocytes constitute more than half of all cortical cells (Nedergaard et al., 2003) and have now been shown to exhibit functional responses to stimuli and organize into maps that are just as exquisitely defined as those of the neurons (Schummers et al., 2008). Astrocytes receive synaptic inputs, express neurotransmitter receptors, and can directly modulate the reliability of neuronal synapses (Perea and Araque, 2007). Furthermore, many of the factors critical for circuit plasticity may be stored by astrocytes and released onto neurons in response to functional events. For example, the TNF alpha described above as a potentially pivotal homeostatic signal is expressed in and released by astrocytes (Stellwagen and Malenka, 2006).

Extraneuronal circuit changes are also reinforced by "perineuronal nets" (PNNs), which are lattice-like structures, comprised of chondroitin-sulfate proteoglycans (CSPGs) and other extracellular components, that condense and entangle cortical cells and synapses. These lattices restrict further movement and growth and provide an obstacle to structural and functional plasticity (Berardi et al., 2004). Compounds that degrade CSPGs, such as chondroitinase ABC, have

been shown to restore ocular dominance plasticity to adult mice (Pizzorusso et al., 2002). Similarly, the extracellular protease tissue-type plasminogen activator (tPA), which also target CSPGs, has been shown to be most highly expressed at periods of maximal plasticity (Mataga et al., 2004) and play a key permissive role in enabling circuit remodeling during ocular dominance plasticity (Muller and Griesinger, 1998; Mataga et al., 2002; Oray et al., 2004). Recently, it has been shown that fear memories in adult mice, which are typically permanent features that are resilient to erasure, can be made susceptible to erasure via degradation of PNNs (Gogolla et al., 2009). These studies suggest that PNNs provide a form of "hard wiring" that can be dissolved or strengthened in order to modulate circuit flexibility.

Together, these findings demonstrate a rich array of mechanisms by which changes in input activity lead to changes in the structure and function of synapses, cells, and circuits of the cortex. Some of these same mechanisms come into play during disorders of brain development—which can thus be understood as disorders of cortical plasticity.

Disorders of Brain Development

Rett Syndrome

Rett syndrome (RTT) is a subset of autism and an X-linked neurological disorder affecting 1 in every 10,000–15,000 live births (Chahrour and Zoghbi, 2007). Unlike many neurodevelopmental disorders, the basis of RTT is straightforward and in approximately 90% of patients suffering from RTT has been traced to a single gene coding for methyl CpG-binding protein 2 (*MeCP2*; Amir et al., 1999; Guy et al., 2001). Combining a molecular understanding of RTT with a circuit perspective that links activity levels to plasticity could help pave the way for effective treatments (Zoghbi, 2003).

RTT is characterized by a profound reduction in cortical circuit activity (Dani et al., 2005), owing to a negative tilt in the balance of excitatory and inhibitory transmission (Dani et al., 2005; Chao et al., 2007; Tropea et al., 2009). Neurons are smaller (Chen et al., 2001), dendrites exhibit reduced elaboration (Armstrong et al., 1998; Kishi and Macklis, 2004), and spine density is reduced in key areas (Chao et al., 2007; Tropea et al., 2009). Plasticity, meanwhile, remains in an immature state, with impairments to LTP (Moretti and Zoghbi, 2006), and

ocular dominance plasticity that aberrantly persist into adulthood (Tropea et al., 2009).

Viewed through this lens, RTT seems to arise from a failure of brain circuitry to mature or sustain a mature phenotype (Magee and Johnston, 1997; Moretti and Zoghbi, 2006). This failure has been shown to be reversible by driving pathways that promote circuit maturation and stabilization such as BDNF (Guy et al., 2007), which stimulates synaptic strengthening via PI3K.pAkt.PSD-95 and MAPK signaling (Carvalho et al., 2008). A similar stimulus to circuit maturation may also be derived through the systemic delivery of other neurotrophic factors such as insulin-like growth factor 1 (Tropea et al., 2009) that are capable of crossing the blood-brain barrier (Aberg et al., 2000; Lopez-Lopez et al., 2004; Jaworski et al., 2005) and which stimulate these same pathways (Zheng and Quirion, 2004; Tropea et al., 2006). Thus, RTT syndrome offers a prime example for how an understanding of circuit plasticity may aid in elucidating pathways for targeted intervention.

Tuberous Sclerosis

Tuberous sclerosis (TSC) is another neurodevelopmental disorder associated with cognitive impairment, seizures, perseverative behavior, and other disabilities similar to autism (Ehninger et al., 2008a). It has been linked to specific

heterozygous mutations in 2 genes—*TSC1* and *TSC2*. TSC may offer an excellent model for how too much synaptic potentiation can lead to cortical rigidity. Disruption of *TSC1.2* brings about a fundamental shift in spine morphology—converting numerous small spines into fewer large spines, with stronger excitatory transmission (Tavazoie et al., 2005). A likely reason for this is that TSC results in enhanced mTOR signaling (Ehninger et al., 2008a; Meikle et al., 2008), which lowers the threshold for plasticity and makes long-lasting LTP more likely to occur, thus pathologically stabilizing synaptic pathways (Hoeffer et al., 2008). Compatible with this interpretation, application of mTOR inhibitors in a mouse model of TSC suppresses seizures, rescues the aberrantly stable synaptic potentiation, and reverses neurocognitive deficits (Ehninger et al., 2008b).

Fragile X

Fragile X is a condition of moderate to severe mental retardation (Loesch et al., 2002) that has been methodically linked to pathologies in cortical circuits (Bear, 2005). In mouse models of the disorder, circuits are characterized by an increased spine density (Grossman et al., 2006), comprised of weaker spines (Hinton et al., 1991; Irwin et al., 2001) with fewer AMPA receptors (Li et al., 2002) that are functionally "hyperplastic" in terms of synaptic changes (Bear et al., 2004) and cortical plasticity (Dolen et al., 2007). According to one hypothesis, increased

translation of fragile X mental retardation protein (FMRP) underlies enhanced LTD in the mouse model for the disorder, and blockade of metabotropic glutamate receptors would act as a corrective. Indeed, a genetic rescue of multiple phenotypes of fragile X in the mouse model demonstrates the feasibility of this hypothesis (Dolen et al., 2007).

Conclusion and Future Directions

The development of effective interventions for disorders of cortical plasticity will require tools for rapidly assessing the plasticity status of a circuit in a manner that goes beyond single synapse measures to take into account the host of network influences described above. Promisingly, new imaging methods are allowing more subtle changes in circuit function to be measured optically, including in the intact animal (Grinvald and Hildesheim, 2004; Pologruto et al., 2004; Schummers et al., 2008). Another promising tool is the advent of optical probes of plasticity (Wang et al., 2006; Hayashi et al., 2009), which offer the potential of reporting either the plasticity event or the plasticity status of cells within a circuit. Assays are also becoming available that can detect changes in protein levels in response to specific activity paradigms or plasticity and connect those into functional pathways that might drive or be driven by the plasticity (Tropea et al., 2006). Finally, advances in virally mediated gene transfer and optogenetics continue to

provide increasingly pinpointed experimental control over specific cells' genetic makeup and electrical input (Zhang et al., 2007).

As these tools are brought into play, they are revealing that plasticity is not merely a synaptic phenomenon but one that results from the coordinated interplay of excitatory, inhibitory, and glial cells, operating in tandem via feedforward and feedback mechanisms to regulate the plasticity tone of the circuit. Perhaps the greatest challenge in the coming years will be to devise methods for selectively understanding these network components to comprehend how they give rise to the choreographed processes of development and disease.

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