



Published in final edited form as:

J Neurobiol. 1999 October ; 41(1): 135–147.

Molecular Analysis of Developmental Plasticity in Neocortex

Elly Nedivi

Department of Brain and Cognitive Sciences, Center for Learning and Memory, Massachusetts Institute of Technology, 45 Carleton St., E25-435, Cambridge, Massachusetts 02139

Abstract

Gene expression studies indicate that during activity-dependent developmental plasticity, *N*-methyl-D-aspartate receptor activation causes a Ca^{2+} -dependent increase in expression of transcription factors and their downstream targets. The products of these plasticity genes then operate collectively to bring about the structural and functional changes that underlie ocular dominance plasticity in visual cortex. Identifying and characterizing plasticity genes provides a tool for molecular dissection of the mechanisms involved. Members of second-messenger pathways identified in adult plasticity paradigms and elements of the transmission machinery are the first candidate plasticity genes tested for their role in activity-dependent developmental plasticity. Knockout mice with deletions of such genes have allowed analyzing their function in the context of different systems and in different paradigms. Studies of mutant mice reveal that activity-dependent plasticity is not necessarily a unified phenomenon. The relative importance of a gene can vary with the context of its expression during different forms of plasticity. Forward genetic screens provide additional new candidates for testing, some with well-defined cellular functions that provide insight into possible plasticity mechanisms.

Keywords

gene expression; development; cerebral cortex; activity-dependent plasticity; gene knockout

Since the groundbreaking work of Hubel and Wiesel in the 1960s and 1970s on how the environment influences development of the visual cortex (Wiesel, 1982), studies of ocular dominance column (ODC) formation have come to play a leading role in the field of developmental plasticity. Concepts emerging from these studies have been extended to other parts of the visual system and to other sensory and motor systems. True to precedent, the application of molecular tools toward elucidating mechanisms of developmental plasticity has also started predominantly in visual cortex. This review discusses gene expression studies and molecular genetic analysis of developmental plasticity in the neocortex, and how this complementary approach to electrophysiology and anatomy is providing new insight as to the components of cellular plasticity mechanisms and the level to which these components are essential.

DEVELOPMENTAL PLASTICITY

Developmental plasticity is typified by a critical period when manipulating input will cause dramatic changes in cortical connectivity (Hubel and Wiesel, 1970; Hubel et al., 1977; Jeanmonod et al., 1981). In the visual system, neural activity generated by both eyes during the critical period drives the final patterning of neuronal connections (reviewed in Constantine-Paton et al., 1990; Goodman and Shatz, 1993; Katz and Shatz, 1996; Shatz, 1990). Formation of eye-specific layers in the lateral geniculate nucleus (LGN) of the thalamus and ODCs in the cortex both occur through an activity-driven process of axon terminal remodeling (LeVay et al., 1978, 1980; Shatz, 1990; Shatz and Sretavan, 1986;

Shatz and Stryker, 1978). Inappropriate connections are gradually withdrawn, while appropriate ones develop extensive terminal arbors (Antonini and Stryker, 1993; Guillery, 1972; Sretavan and Shatz, 1986). In this context, an appropriate connection is defined as a connection where pre- and postsynaptic activity are correlated—in other words, a Hebbian synapse (Fregnac et al., 1988; Shulz and Fregnac, 1992; Stryker and Strickland, 1984).

In principle, the Hebbian synapse hypothesis provides a theoretical basis for linking developmental plasticity that occurs during ODC formation in visual cortex with adult plasticity that occurs in the hippocampus and neocortex (Constantine-Paton et al., 1990; Goodman and Shatz, 1993; Shatz, 1990). In the developing visual system there are correlated patterns of activity (Maffei and Galli-Resta, 1990; Meister et al., 1991; Schwartz et al., 1998; Yuste et al., 1992) and there are cortical synapses that are capable of detecting such activity and responding with functional changes (Kirkwood et al., 1993; Miller et al., 1989; Shulz and Fregnac, 1992). These Hebbian characteristics of visual cortical synapses during the critical period resemble those of synapses in the adult hippocampus that are capable of undergoing long-term potentiation (LTP) (Brown et al., 1990; Madison et al., 1991; Wigstrom and Gustafsson, 1985). Since its discovery in the hippocampus, LTP, the sustained increase in synaptic transmission resulting from high-frequency stimulation of excitatory pathways, has been the primary experimental model for studies of the synaptic basis of learning and memory in vertebrates (Bliss and Collingridge, 1993). The same type of stimulation protocols that elicit LTP in the CA1 region of a hippocampal slice can elicit LTP in layer III, when applied to the optic radiation or to layer IV of a visual cortical slice, (Artola and Singer, 1987; Kirkwood and Bear, 1994; Kirkwood et al., 1993). Another form of synaptic plasticity found in the hippocampus, long-term depression (LTD), can be elicited electrophysiologically in a visual cortical slice (Kirkwood and Bear, 1994) or *in vivo* in the developing visual cortex by monocular deprivation (Rittenhouse et al., 1999). Susceptibility to both LTP and LTD in visual cortical slices correlates with the critical period for development of ocular dominance (Dudek and Friedlander, 1996; Kirkwood et al., 1995). These and additional studies showing that visual experience can enhance or diminish LTP and LTD in visual cortical slices (Kirkwood et al., 1996) have lent support to the theory that the properties of synaptic LTP and LTD can account for many aspects of activity-dependent plasticity in the developing visual cortex (Bear et al., 1987).

DOWNSTREAM OF THE N-METHYL-D-ASPARTATE (NMDA) RECEPTOR

In visual cortex, as in the adult hippocampus, the ability of postsynaptic cells to detect coincident activity during LTP and LTD apparently resides in the NMDA receptor (Artola and Singer, 1987; Kirkwood and Bear, 1994a, b). The NMDA receptor is essential not only for LTP in hippocampal CA1 synapses and for spatial memory (Morris et al., 1986; Tsien et al., 1996), but also for ocular dominance plasticity that occurs in cortical neurons in response to visual manipulations during the critical period (Bear et al., 1990; Kleinschmidt et al., 1987). In hippocampal neurons, activation of the NMDA receptor causes a rise in intracellular Ca^{2+} , thereby triggering several second-messenger systems, among them cyclic adenosine monophosphate (cAMP) and a variety of kinases such as protein kinase A (PKA) and Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) (Bliss and Collingridge, 1993). Second messengers can have both short- and long-term effects within the postsynaptic cell. One of the long-term effects is activation of immediate early genes (IEGs). Tetanic stimulation that produces LTP in the hippocampus has been shown to cause an NMDA receptor-dependent increase in mRNA for the IEG *zif268* (Cole et al., 1989; Wisden et al., 1990). During the late phase of LTP and for hippocampal-dependent long-term memory, cAMP induces new gene transcription through another IEG: the cAMP-responsive element binding protein (CREB) (Bourtchuladze et al., 1994; Huang et al., 1994). Many IEGs such as *zif268* and CREB encode transcription factors that subsequently activate additional

downstream genes containing specific regulatory elements in their promoters. For example, CREB can induce transcription of any gene that contains a cAMP-responsive element (CRE). It has been suggested that activation of IEGs that are transcription factors provides a link between extracellular signals and synthesis of the mRNA and protein required for long-term changes in synaptic connections (Goelet et al., 1986; Sheng and Greenberg, 1990).

In cats and primates, the physiological plasticity manifested by cortical cells after monocular deprivations during the critical period for ODC formation is accompanied by clear activity-driven rearrangements of geniculocortical afferents (Antonini and Stryker, 1993, 1996; Shatz and Stryker, 1978). The obvious structural changes required for remodeling of axon arbors suggest that the underlying cellular processes involve new protein synthesis and therefore regulation at the level of gene expression. Indeed, visual manipulations during the critical period for ODC formation have been shown to regulate expression of transcription factor IEGs (Table 1). Brief visual experience after dark rearing induces expression of the IEGs *zif268*, *c-fos*, and *junB* specifically in visual cortex (Rosen et al., 1992).

Developmental and adult laminar distributions of the Zif268 and Fos proteins are responsive to visual manipulations that are correlated with plasticity rather than neural activity (Kaplan et al., 1996). Most conclusively, transgenic mice carrying a CRE-lacZ reporter were used to demonstrate that monocular deprivation leads to activation of CRE-mediated transcription (presumably through CREB binding) in visual cortex during the critical period (Pham et al., 1999).

Expression and regulation of IEG transcription factors during developmental plasticity in visual cortex implies that through their activity a cohort of downstream effector genes are being mobilized to execute long-term modification of neuronal properties. There are indications that IEG downstream targets are regulated in the developing visual cortex. For example, Ca²⁺-dependent regulation of brain-derived neurotrophic factor (BDNF) transcription in cortical neurons is mediated by CREB through a CRE in the BDNF gene promoter (Tao et al., 1998). Thus, BDNF, whose mRNA levels are regulated by visual activity in the developing and adult visual cortex (Castren et al., 1992; Schoups et al., 1995), is an IEG-activated effector molecule that can profoundly effect the morphology of developing cortical neurons (McAllister et al., 1995), and has been implicated in formation of ODCs (Cabelli et al., 1995). Other potential activity-regulated IEG targets are effector genes whose products such as BDNF are regulated in the developing visual system by sensory input (Table 1). One example is the NMDA receptor, whose level in layer 4 of visual cortex is regulated by activity during the critical period (Catalano et al., 1997). Others are GAP-43, CaMKII, and glutamic acid decarboxylase (GAD), whose mRNA levels are all regulated by visual input during early postnatal development (Mower and Rosen, 1993; Neve and Bear, 1989). Additional genes identified as induced by seizure activity in the hippocampus, *COX-2*, *Arc*, *Narp*, *homer* (identified in parallel as *cpg22*), and *cpg15*, were subsequently shown to be regulated by visual activity in the developing striate cortex (Table 1; discussed in more detail later in this review) (Brakeman et al., 1997; Corriveau et al., in preparation; Lyford et al., 1995; Tsui et al., 1996; Yamagata et al., 1993, 1994). The plenitude of IEGs and effector genes regulated by visual input in the developing neocortex makes it easy to imagine that the similarity between developmental plasticity and adult forms of plasticity such as LTP does not stop at the NMDA receptor. During development, similarly to the adult, synaptic modifications brought about by correlated activity may result from activation of gene expression via this receptor.

MOLECULAR GENETIC ANALYSIS OF DEVELOPMENTAL PLASTICITY

The cAMP second-messenger system and components thereof—CREB, PKA, and CaMKII—have been repeatedly shown in a variety of organisms to be involved in long-term

synaptic plasticity, during learning and memory as well as LTP (Frank and Greenberg, 1994; Martin and Kandel, 1996; Stevens, 1994). Recently transgenic and gene-transfer technologies in mice have allowed genetic manipulation of genes suspected to be involved in plasticity. Knockout mice lacking genes for CREB, PKA, α -CaMKII, PKC- γ , metabotropic glutamate receptor 1 (mGluR1), BDNF, and double mutants in endothelial and neuronal nitric-oxide synthase (eNOS and nNOS, respectively) have been generated and tested in adult forms of plasticity such as learning and memory and/or LTP (Abeliovich et al., 1993a, b; Aiba et al., 1994; Bourtchuladze et al., 1994; Brandon et al., 1995; Huang et al., 1995; Patterson et al., 1996; Silva et al., 1992a, b; Son et al., 1996). Some of these genes are responsive to activity in the visual system (Neve and Bear, 1989; Tighilet et al., 1998) and/or have been otherwise implicated in developmental plasticity (Cabelli et al., 1995; Cramer et al., 1996; Pham et al., 1999; Reid et al., 1996). It is therefore reasonable that candidate plasticity gene knockout mice were tested for a role not only in adult plasticity, but also during development of ocular dominance plasticity in visual cortex. Although in the rodent visual cortex there is no anatomical segregation of neurons according to function such as the orientation or ocular dominance columns seen in cats and primates, neurons in their visual cortex do have well-defined functional properties and a certain degree of eye preference (Fagiolini et al., 1994; Gordon and Stryker, 1996; Maffei et al., 1992; Parnavelas et al., 1981). Moreover, monocular deprivations during a critical period shift the responses of neurons in the binocular zone toward the open eye (Fagiolini et al., 1994; Gordon and Stryker, 1996). The beautiful quantitative studies by Gordon and Stryker defining a critical period for developmental plasticity in mouse visual cortex provide a basis for comparison when mutant mice are used to investigate the role of individual molecules in activity-dependent development (Gordon and Stryker, 1996).

Adult mice with an α -CaMKII knockout were used to confirm a role for this gene in certain forms of learning and memory (Bach et al., 1995; Silva et al., 1992), in the ability of adult synapses to undergo LTP in both hippocampus and neocortex (Bach et al., 1995; Hinds et al., 1998; Kirkwood et al., 1997; Silva et al., 1992), and in experience-dependent plasticity of barrel cortex (Glazewski et al., 1996). The α -CaMKII knockouts develop normal visual cortical responses, including receptive field properties, maximum response strength, orientation selectivity, and ocular dominance (Gordon et al., 1996). Recording field potentials in layer II/III evoked by stimulation of layer IV showed that in slices from visual cortex of young α -CaMKII knockout mice there is a reduced probability of obtaining LTP and a reduction in the magnitude of potentiation (Kirkwood et al., 1997). The LTP deficits are less drastic than in older mutants, since potentiation could be obtained in most slices. In monocular deprivation experiments, the α -CaMKII knockouts exhibit dramatically reduced but variable plasticity (Gordon et al., 1996). The shift in eye preference toward the open eye is significantly less in approximately half the α -CaMKII knockouts, the same fraction of animals severely impaired in a spatial learning task (Gordon et al., 1996). The finding that α -CaMKII knockouts display severe deficits in ocular dominance plasticity argues that α -CaMKII does play a role in activity-dependent aspects of visual cortex development. The variability of the *in vivo* deficits and the mildness of the *in vitro* ones argue that this role is not pivotal to the developmental plasticity occurring during establishment of eye preference; as in most cases, the system is capable of adequate performance in its absence.

The α -CaMKII knockouts are thus far the only plasticity gene knockouts that have been tested for involvement in both ocular dominance plasticity and developmental plasticity of somatosensory cortex. In experience-dependent plasticity of the somatosensory barrel cortex, when sensory input is restricted to a single whisker on the rodent snout, the cortical representation of this spared vibrissa is increased (Fox, 1992, 1994). Similarly to ODC plasticity, vibrissa deprivation plasticity in layer IV is restricted to the critical period, while layers 2/3 show a prolonged propensity to shift receptive field properties in response to

peripheral manipulations (Daw et al., 1992; Fox, 1994; Glazewski and Fox, 1996). In contrast to adult mice lacking the α -CaMKII gene, where there is a significant decrease in experience-dependent plasticity of the barrel cortex, plasticity in the developing barrel cortex seems wholly intact (Glazewski et al., 1996). Since development of eye preference is disrupted in approximately half the animals while vibrissa deprivation plasticity during development seems unaffected, α -CaMKII may not be required for activity-dependent development of somatosensory cortex, while it is necessary for some aspects, albeit noncrucial ones, of activity-dependent development of visual cortex.

Another study testing for the role of a plasticity molecule, nitric oxide (NO), in development of both visual and somatosensory cortex only partially involved the use of knockout mice (Finney and Shatz, 1998). NO has been a prime candidate for the role of retrograde messenger communicating between the post and the presynaptic cell during synaptic plasticity (Bliss and Collingridge, 1993). NO effects hippocampal LTP *in vivo* and *in vitro* (O'Dell et al., 1991; Schuman and Madison, 1991; Son et al., 1996). In the developing visual system, blockade of NOS activity inhibits segregation of retinogeniculate axons into ON-OFF sublaminae (Cramer et al., 1996), and NOS expression in the visual subplate and cortex of ferrets correlates well with ODC formation (Finney and Shatz, 1998). Nevertheless, NOS blockade in ferrets fails to prevent formation of ODCs, and pharmacological NOS blockade in NOS knockout mice fails to prevent formation of cortical barrels or barrel field plasticity induced by whisker ablation (Finney and Shatz, 1998). In this case, pharmacological and knockout analysis concur that NO is unlikely to be essential for developmental plasticity of thalamocortical connections in either visual or somatosensory systems, despite playing a role in hippocampal LTP.

Adult mice deficient for the $R1\beta$ regulatory subunit of another candidate-plasticity gene, PKA, display defective hippocampal LTD (Brandon et al., 1995) and mossy fiber LTP (Huang et al., 1995), but appear normal in spatial and contextual learning and long-term memory (Huang et al., 1995). Primary visual cortex in these mice develops with apparently normal receptive field size, retinotopy, and ocular dominance (Hensch et al., 1998). In monocular deprivation experiments, the shift in eye preference toward the open eye is significant and comparable to wild-type controls. In the mutants as in the wild-type mice, loss of responsiveness to stimulation of the originally deprived eye can be restored by reverse suture of eyelids during the critical period (Hensch et al., 1998). In contrast, in visual cortical slices from the mutant mice, profound deficiencies in synaptic plasticity are manifested by the total absence of theta burst-induced LTP, LTD, or paired pulse facilitation (Hensch et al., 1998).

The most severe disruption of ocular dominance plasticity *in vivo* is manifested in GAD65 knockout mice (Hensch et al., 1998). This is perhaps not surprising in light of the serious perturbations to ODC formation induced in kitten visual cortex by the GABA-A agonist muscimol (Hata and Stryker, 1994; Reiter and Stryker, 1988). In mice lacking the 65-kD isoform of GAD, cortical morphology and adult GABA concentrations are normal presumably owing to the presence of the constitutively expressed GAD67 isoform (Kash et al., 1997). GAD65 is normally localized to synaptic terminals (Fukuda et al., 1998) and serves as a reservoir recruited when additional GABA synthesis is required (Martin et al., 1991). In the GAD65 knockouts, extracellular GABA concentrations are similar to those in wild types but release in response to a brief depolarization with high potassium is significantly compromised, supporting the notion that the GAD65 isoform function may be specialized for a rapid response to intense neuronal activity (Hensch et al., 1998). Despite a tendency for prolonged discharge after visual stimulation, cortical cells in the binocular zone of visual cortex in these mutants appear to develop normally by all other visual parameters tested: spontaneous activity, habituation, retinotopic organization, orientation and direction

selectivity, and receptive field size. The distribution of ocular dominance within the binocular zone is identical in the GAD65 knockout and wild-type mice (Hensch et al., 1998). However, the GAD65 knockout mice do not show the shift in eye preference that normally occurs in response to monocular deprivation: they continue to show a preferred response to contralateral (deprived) eye input (Hensch et al., 1998). LTP and LTD in layers 2/3 of visual cortical slices from the mutant animals are indistinguishable from those in wild-type controls (Hensch et al., 1998).

In the α -CaMKII knockouts, deficits are significant in all cases of adult plasticity irrespective of whether the assay is behavioral or electrophysiological. Learning and memory are defective, as well as LTP and LTD in both hippocampus and neocortex. Developmental plasticity in these mutants, assayed *in vivo* and *in vitro*, is not impaired to the same degree. The severity of the deficits in different types of plasticity in these knockouts splits along developmental lines, demonstrating that a role for a specific molecule in adult plasticity does not necessarily have predictive value for its participation in activity-dependent aspects of development. The differential sensitivity of the developing visual cortex as opposed to somatosensory cortex in response to loss of CAMKII suggests that mechanisms of plasticity may not be totally overlapping in these two cortical regions. In the RI β -PKA knockouts the dividing line is not between adult and developmental plasticity, but between *in vivo* versus *in vitro* models of plasticity. Learning and memory in the adult and ocular dominance plasticity during development seem unaffected by the RI β -PKA knockout, while LTP and LTD in hippocampus and visual cortex are both impaired. Analysis of these particular knockouts provides evidence contrary to the growing consensus that the *in vitro* models of LTP and LTD faithfully represent *in vivo* synaptic mechanisms of plasticity that occur during ocular dominance development or, for that matter, during learning and memory in the adult. The predictive value of *in vitro* LTP and LTD paradigms is also undermined in the GAD65 knockouts, where conversely to the RI β -PKA knockouts, LTP and LTD are intact despite severe deficits in developmental ocular dominance plasticity.

The analysis of knockout mice demonstrating that the same gene may be involved to a different degree in paradigms of adult versus developmental plasticity, in behavioral versus electrophysiological paradigms, during development of visual versus somatosensory systems, or perhaps even in hippocampus versus neocortex, provides insight not only as to the mechanisms involved in each individual case, but also as to the extent of overlap between them. Such informative genetic experiments are possible only once genes of potential interest are identified. Elements of the basic transmission machinery or components of second-messenger pathways previously implicated in plasticity have been the first obvious candidates. However, discovery of unknown or unsuspected participants in neuronal plasticity can only be achieved through unprejudiced forward genetic screens.

SCREENS FOR CANDIDATE PLASTICITY-RELATED GENES (CPGS)

Screening for genes that are specifically expressed in cells that are undergoing activity-dependent plasticity is an individual example of a more general strategy for differential screening for genes that are expressed in one population of cells versus another. Differential screening is often combined with subtractive hybridization methods that are used to enrich the screened clones for sequences specific to the tissue from which one wants to isolate differentially expressed genes. The main difficulty in designing a differential screen is selecting the two tissue sources to be compared. The greater the number of differences between two tissue sources, the more difficult it is to select from the cloned genes those that are relevant to the specific difference of interest. The more complex a tissue source is, containing multiple cell types or multiple functional regions, the more differences will likely be detected. For these reasons, it is best to compare cell populations that are as similar and

homogenous as possible. In the case of plasticity during development, such a comparison is inherently confounded by the developmental changes unrelated to synaptic plasticity that are still occurring in the cortex between time points that may be compared. In addition, a complex tissue such as neocortex is not homogenous as to the timing of activity-dependent plasticity. Experience-dependent plasticity in rat barrel cortex precedes that of ocular dominance plasticity in visual cortex by approximately 2 weeks (Fox, 1992; Maffei et al., 1992). Even if one were to confine the screen to a functional region of neocortex such as striate cortex, all aspects of activity-dependent plasticity would not necessarily be temporally synchronized or spatially discrete. It is not clear that the critical period for ocular dominance plasticity overlaps critical periods for activity-dependent refinement of other visual properties. Experience-independent activity may guide development of orientation columns prior to the critical period for ODC formation (Chapman et al., 1996; Crair et al., 1998). Upper-layer organization may precede and guide thalamocortical organization (Chapman and Stryker, 1993; Crair et al., 1998), and in cat, persists past the critical period for ODC formation (Daw et al., 1992; Gilbert and Wiesel, 1992; Singer et al., 1981). Development and susceptibility of cells within a given layer to the effects of monocular deprivation are not uniform. A substantial fraction of layer 4 cells do not shift their eye preference in response to monocular deprivation, and weakening of deprived eye responses are far from homogenous across the superficial layers (Crair et al., 1997; Shatz and Stryker, 1978). In general, cells that are able to rearrange connections in response to correlated activity at any given time or place may be a minority within the general population of cortical cells. The dilution problem is more severe in rodents, where the binocular region is small and activity-dependent segregation of geniculocortical afferents has not been demonstrated. On the other hand, working in cats or primates would greatly restrict the amount of tissue available for cloning, imposing the use of amplification-based technologies that introduce bias problems and a higher percent of false positives. In addition, *in vivo* testing of feline or primate candidate plasticity genes would require isolation of their murine homologs. To make matters more complicated, if one were looking at developmental plasticity as that occurring at the geniculocortical synapse, the mRNA containing cell bodies of the presynaptic partners at this synapse would be located in the LGN. Using the cortex as a tissue source for a differential screen would limit the screen toward isolation of exclusively postsynaptic components.

The above considerations illustrate some of the difficulties in temporal and regional selection of tissue sources for a differential screen in a complex system where multiple variables are at play. Perhaps because of these difficulties, as yet there have been no screens devised for directly identifying candidate genes that may be specifically involved in neocortical developmental plasticity. The main premise of all searches for CPGs thus far has been that because activity is the driving force for plasticity, regulation by activity is a prerequisite for any gene involved in plasticity. Screens for identifying and isolating genes that are induced by activity have successfully generated a large pool of candidates. These candidates can now undergo secondary screens for expression during specific developmental or adult plasticity paradigms before ultimately being selected for testing in knockout or transgenic animals.

All but one of the CPGs (class I MHC; see below) have been generated by differential screens for activity-regulated genes that are induced by seizure activity in the adult rat hippocampus (Nedivi et al., 1993; Qian et al., 1993; Yamagata et al., 1993). The rationale of this approach is to simplify the cloning procedure in two important ways. The first is by specifying a well-defined differential selection criterion between two tissues that are as similar and homogenous as possible. Using adult tissue circumvents the problem of interference from developmental processes unrelated to activity. The hippocampus is a simpler tissue source than neocortex as far as cell types and circuitry, but it shares structural

similarities and common forms of synaptic plasticity with the neocortex (Kirkwood et al., 1993). It is reasonable to assume that the hippocampus, a region of the brain involved in learning and memory (Squire and Zola-Morgan, 1991), also shares with neocortex molecular mechanisms that underlie the ability to undergo change in response to activity. Seizures provide a strong, temporally synchronized activation of dentate gyrus neurons that result in prominent physiological and morphological changes (Ben-Ari and Represa, 1990; Sloviter, 1992; Tauck and Nadler, 1985) that are accompanied by activation of gene expression (Bugra et al., 1994; Gall et al., 1991; Morgan and Curran, 1991). The second practical simplification is that using relatively low investment stimulation protocols allows harvesting of the large amount of material necessary for subtractive technologies that are not polymerase chain reaction (PCR) based. Once candidate genes are cloned, they can then be further screened by *in situ* hybridization in a variety of specific plasticity paradigms by which it would be extremely difficult to clone. The expression of a specific gene in correlation with the critical period and in response to visual manipulations can be tested at various times in multiple locations in parallel without resorting to preconceptions about temporal and spatial regulation patterns.

A total of 362 different CPGs were isolated in a uniquely sensitive subtractive and differential cloning procedure that selected genes induced by the glutamate analog kainate in the rat hippocampal dentate gyrus (Hevroni et al., 1998; Nedivi et al., 1993). Partial sequence analysis showed that 70 of the cloned CPGs encode known proteins, while 292 are novel. Despite the large number of genes that are induced by seizure activity (approximately 5% of the genes expressed in dentate gyrus neurons) (Nedivi et al., 1993), induction is not random. The CPGs encoding known proteins can be classified into distinct functional categories: for example, IEGs, proteins participating in second-messenger pathways, growth factors, and structural proteins. Housekeeping genes related to ubiquitous metabolic functions are not induced (Hevroni et al., 1998; Nedivi et al., 1993).

Additional candidate plasticity genes have been isolated from the hippocampus in related approaches using metrazol (Qian et al., 1993) or electrically induced seizures (Yamagata et al., 1993) as the inducing stimulus. Since these screens were intended for identification of novel CPGs that were IEGs, the inducing stimulus was administered in the presence of the protein synthesis inhibitor cycloheximide. Some of the genes identified in these two screens encode transcription factors (Qian et al., 1993; Yamagata et al., 1994), but many encode IEGs that can directly affect synaptic structure or function (Brakeman et al., 1997; Link et al., 1995; Lyford et al., 1995; Qian et al., 1993; Tsui et al., 1996; Yamagata et al., 1994a, b). In all the above screens, the predominant category of known CPGs is that of membrane-, vesicle-, and synapse-related proteins. The constructive nature of these molecules suggests that seizure-induced gene expression is not necessarily related to excitotoxicity or cell death. Moreover, induction of molecules that could be used for synaptic restructuring provides molecular genetic support for the idea that morphological rearrangement may also play a role in activity-dependent plasticity in the adult (Bailey and Kandel, 1993; Merzenich, 1998). Structural reorganization is obviously less dramatic than that seen during development of ODCs, but there is anatomical evidence for mossy fiber growth in the hippocampus after seizure (Ben-Ari and Represa, 1990; Sloviter, 1992; Tauck and Nadler, 1985) and for extensive sprouting of horizontal connections during functional rearrangement of primary sensory maps in the adult cortex (Darian-Smith and Gilbert, 1994; Florence et al., 1998).

The one rather heroic attempt to directly identify genes regulated by activity in the developing visual system resulted in cloning of the previously characterized class I major histocompatibility antigen (class I MHC) (Corriveau et al., 1998). In this screen, differential display was used to compare gene expression in kitten LGN during the period of eye-

specific layer formation, in the presence or absence of action potential blockade with tetrodotoxin (TTX) (Corriveau et al., 1998). Identification of class I MHC in this screen is another example of how forward genetic screens can bring to attention in addition to new molecules also known ones not previously associated with nervous system function or plasticity. With class I MHC, as with the other CPGs, it remains to be shown that regulation by activity in correlation with activity-dependent plasticity is due to participation in these events.

SECONDARY SCREENS OF THE CPG POOL

A substantial fraction of candidate genes have been tested subsequent to their isolation by criteria designed to more closely correlate them with plasticity as a prelude to later *in vivo* testing in transgenic or knockout mice.

Since none of the CPGs were isolated from neocortex, and except MHC all had been isolated using a seizure protocol, it was important to show that these genes could be induced by a normal physiological stimulus in the neocortex. The first physiological test in all cases was whether these genes' expression could be regulated specifically in visual cortex by manipulating visual activity. In some cases, expression in visual cortex was monitored after activity blockade by intraocular injection of TTX (Brakeman et al., 1997; Lyford et al., 1995; Tsui et al., 1996; Worley et al., 1990; Yamagata et al., 1993, 1994), in others by exposure to light after dark adaptation (Brakeman et al., 1997; Nedivi et al., 1996). *zif268*, *COX-2*, *Egr3*, *Arc*, *Narp*, *cpg2*, *cpg22 (homer)*, *rheb*, *cpg15*, and *cpg29* were thus shown to be regulated by activity levels that are within the realm of everyday neocortical function (Table 1).

A similar although not totally overlapping set of CPGs could be induced when screened for induction in the hippocampal plasticity paradigm of LTP or by high-frequency stimulation that elicits LTP (Brakeman et al., 1997; Hevroni et al., 1998; Link et al., 1995; Lyford et al., 1995; Nedivi et al., 1993; Qian et al., 1993; Tsui et al., 1996; Yamagata et al., 1994).

A third screen of the CPG pool, and perhaps most relevant to the topic of this review, was for developmental expression in neocortex, specifically in correlation with the critical period for ocular dominance plasticity. The same CPGs that were tested for light induction in the adult neocortex were also analyzed by *in situ* hybridization for expression in the postnatally developing cortex. Approximately 70% of the CPGs tested were found to be transiently expressed in the developing cortex between postnatal days 1 and 21, at levels significantly higher than in normal adult rat cortex (Nedivi et al., 1996). Up-regulation of *COX-2*, *Arc*, *Narp*, *cpg22 (homer)*, *cpg2*, and *cpg15* during cortical development correlates with eye opening and the onset of the critical period for OD plasticity in rat (Brakeman et al., 1997; Lyford et al., 1995; Nedivi et al., 1996; Tsui et al., 1996; Yamagata et al., 1993), and MHC up-regulation is correlated with the critical period for OD plasticity in kittens (Corriveau et al., 1998) (Table 1). Of these, *COX-2*, *Arc*, *Narp*, *cpg22 (homer)*, and *cpg15* are regulated by visual activity at this time (Brakeman et al., 1997; Corriveau et al., in press; Lyford et al., 1995; Tsui et al., 1996; Yamagata et al., 1993) (Table 1).

These secondary screens using *in situ* hybridization as an assay show that the CPG pool generated by a seizure paradigm in the adult contains a subgroup of genes that is also regulated by visual activity during development, in correlation with critical period plasticity. As it turns out, class I MHC mRNA, identified in a developmental activity-based screen, can also be induced in the adult hippocampus and neocortex following kainate-induced seizure (Corriveau et al., 1998). The existence of an overlapping set of genes that are induced by seizure activity in the adult and also by normal action potential activity during development has several implications. Theoretically, the implication is that overlapping gene sets reflect

an overlap in activity-dependent mechanisms in the adult and during development. The practical implication is that the CPG pool, with appropriate subscreens, may provide useful candidates for testing in developmental plasticity paradigms.

Candidate plasticity-related genes passing at least two of the three above screens were partially or fully characterized. *COX-2* encodes an enzyme that catalyzes the first and rate-limiting step in prostaglandin synthesis. Since levels of prostanooids are determined mainly by their rate of synthesis, *COX-2* regulation by neuronal activity could dynamically regulate the level of these signaling proteins (Yamagata et al., 1993). *Arc* encodes a cytoskeletal-associated protein localized to neuronal dendrites (Link et al., 1995; Lyford et al., 1995). *Narp* encodes a secreted calcium-dependent lectin that promotes neuronal migration and dendritic outgrowth (Tsui et al., 1996). The activity-regulated form of *Homer* encodes an EVH domain protein that competes with constitutively regulated *Homer* for binding to the C-terminus of mGluR1 and mGluR5 (Brakeman et al., 1997; Xiao et al., 1998), thus interfering with their ability to activate the inositol triphosphate receptor (Tu et al., 1998). The EVH domain in *Homer* suggests that it may also interact with the actin-based cytoskeleton. *cpg15* encodes a small secreted protein that is bound to the extracellular membrane surface by a glycosylphosphatidylinositol (GPI) linkage (Naeve et al., 1997) and promotes growth of dendritic arbors in neighboring neurons through an intercellular signaling mechanism that requires its GPI link (Nedivi et al., 1998). CPG15 may therefore represent a new class of activity-regulated membrane-bound ligands that can permit exquisite temporal and spatial control of neuronal structure (Nedivi et al., 1998). Immunohistochemistry in the *Xenopus* retinotectal system shows intense CPG15 staining in axon tracts throughout the brain (Nedivi et al., in preparation). This, together with *cpg15* expression patterns and regulation in the developing kitten visual system, suggests that presynaptic CPG15 expression on axon arbors may function to promote growth of apposing postsynaptic dendritic partners (Corriveau et al., in press). These functions of new CPGs are consistent with those of the known ones in that they include both signaling elements and structural components that could assist synaptic remodeling.

CONCLUSION

Cloning of numerous candidate-plasticity genes provides an enormous opportunity to advance our understanding of plasticity mechanisms. As in the case of *homer* or *cpg15*, analysis of individual CPG functions can introduce us to hitherto unsuspected or unsubstantiated aspects of plasticity: for example, negative regulation of mGluR signaling by *homer*, or regulation of coordinated growth of pre- and postsynaptic elements by *cpg15*. An integrated picture of combined CPG functions can hint at the mechanisms they represent. For example, the preponderance of CPGs associated with structural remodeling both during development and in the adult implicates process outgrowth as a plasticity mechanism. In addition, as more candidate plasticity genes are analyzed, we can use them to address in a comprehensive way the extent of overlap between different manifestations of activity-dependent plasticity. Using gene expression studies and mouse knockout mutants, it should eventually be possible to form a picture of combinatorial gene sets that are regulated as groups during activity-dependent plasticity. Although some of the same genes may be involved in different cases, their combination in a discrete set would be unique to a specific system and stimulus and would define the underlying molecular mechanism.

Acknowledgments

The author thanks Dr. Hollis Cline for critical reading of the manuscript. Research in the author's laboratory is supported by NIH Grant EY11894, a Young Scholar Award from the Ellison Medical Foundation, and an Alfred P. Sloan Fellowship.

References

- Abeliovich A, Chen C, Goda Y, Silva AJ, Stevens CF, Tonegawa S. Modified hippocampal long-term potentiation in PKC gamma-mutant mice. *Cell*. 1993a; 75:1253–1262. [PubMed: 8269509]
- Abeliovich A, Paylor R, Chen C, Kim JJ, Wehner JM, Tonegawa S. PKC gamma mutant mice exhibit mild deficits in spatial and contextual learning. *Cell*. 1993b; 75:1263–1271. [PubMed: 8269510]
- Aiba A, Chen C, Herrup K, Rosenmund C, Stevens CF, Tonegawa S. Reduced hippocampal long-term potentiation and context-specific deficit in associative learning in mGluR1 mutant mice. *Cell*. 1994; 79:365–375. [PubMed: 7954802]
- Antonini A, Stryker MP. Development of individual geniculocortical arbors in cat striate cortex and effects of binocular impulse blockade. *J Neurosci*. 1993a; 13:3549–3573. [PubMed: 8340819]
- Antonini A, Stryker MP. Rapid remodeling of axonal arbors in the visual cortex. *Science*. 1993b; 260:1819–1821. [PubMed: 8511592]
- Antonini A, Stryker MP. Plasticity of geniculocortical afferents following brief or prolonged monocular occlusion in the cat. *J Comp Neurol*. 1996; 369:64–82. [PubMed: 8723703]
- Artola A, Singer W. Long-term potentiation and NMDA receptors in rat visual cortex. *Nature*. 1987; 330:649–652. [PubMed: 2446147]
- Bach ME, Hawkins RD, Osman M, Kandel ER, Mayford M. Impairment of spatial but not contextual memory in CaMKII mutant mice with a selective loss of hippocampal LTP in the range of the σ frequency. *Cell*. 1995; 81:905–915. [PubMed: 7781067]
- Bailey CH, Kandel ER. Structural changes accompanying memory storage. *Annu Rev Physiol*. 1993; 55:397–426. [PubMed: 8466181]
- Bear MF, Cooper LN, Ebner FF. A physiological basis for a theory of synapse modification. *Science*. 1987; 237:42–48. [PubMed: 3037696]
- Bear MF, Kleinschmidt A, Gu Q, Singer W. Disruption of experience-dependent synaptic modifications in striate cortex by infusion of an NMDA receptor antagonist. *J Neurosci*. 1990; 10:909–925. [PubMed: 1969466]
- Ben-Ari Y, Represa A. Brief seizure episodes induce long-term potentiation and mossy fibre sprouting in the hippocampus. *Trends Neurosci*. 1990; 13:312–318. [PubMed: 1699312]
- Bliss TVP, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*. 1993; 361:31–39. [PubMed: 8421494]
- Bourtchuladze R, Frenguelli B, Blendy J, Cioffi D, Schutz G, Silva A. Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. *Cell*. 1994; 79:59–68. [PubMed: 7923378]
- Brakeman PR, Lanahan AA, O'Brien R, Roche K, Barnes CA, Huganir RL, Worley PF. Homer: a protein that selectively binds metabotropic glutamate receptors. *Nature*. 1997; 386:284–288. [PubMed: 9069287]
- Brandon EP, Zhuo M, Huang Y-Y, Qi M, Gerhold KA, Burton KA, Kandel ER, McKnight GS, Idzerda RL. Hippocampal long-term depression and depotentiation are defective in mice carrying a targeted disruption of the gene encoding the RI β subunit of cAMP-dependent protein kinase. *Proc Natl Acad Sci USA*. 1995; 92:8851–8855. [PubMed: 7568030]
- Brown TH, Kairiss EW, Keenan C. Hebbian synapses: mechanisms and algorithms. *Annu Rev Neurosci*. 1990; 13:475–511. [PubMed: 2183685]
- Bugra K, Pollard H, Charton G, Moreau J, Ben-Ari Y, Khrestchatsky M. aFGF, bFGF and flg mRNAs show distinct patterns of induction in the hippocampus following kainate-induced seizures. *Eur J Neurosci*. 1994; 6:58–66. [PubMed: 7510570]
- Cabelli RJ, Andreas H, Shatz CJ. Inhibition of ocular dominance column formation by infusion of NT-4/5 or BDNF. *Science*. 1995; 267:1662–1666. [PubMed: 7886458]
- Castren E, Zafra F, Thoenen H, Lindholm D. Light regulates expression of brain-derived neurotrophic factor mRNA in rat visual cortex. *Proc Natl Acad Sci USA*. 1992; 89:9444–9448. [PubMed: 1409655]
- Catalano SM, Chang CK, Shatz CJ. Activity-dependent regulation of NMDAR1 immunoreactivity in the developing visual cortex. *J Neurosci*. 1997; 17:8376–8390. [PubMed: 9334411]

- Chapman B, Stryker MP. Development of orientation selectivity in ferret visual cortex and effects of deprivation. *J Neurosci.* 1993; 13:5251–5262. [PubMed: 8254372]
- Chapman B, Stryker MP, Bonhoeffer T. Development of orientation preference maps in ferret primary visual cortex. *J Neurosci.* 1996; 16:6443–6453. [PubMed: 8815923]
- Cole AJ, Saffen DW, Baraban JM, Worley PF. Rapid increase of an immediate early gene messenger RNA in hippocampal neurons by synaptic NMDA receptor activation. *Nature.* 1989; 340:474–476. [PubMed: 2547165]
- Constantine-Paton M, Cline HT, Debski E. Patterned activity, synaptic convergence, and the NMDA receptor in developing visual pathways. *Annu Rev Neurosci.* 1990; 13:129–154. [PubMed: 2183671]
- Corriveau RA, Huh GS, Shatz CJ. Regulation of class I MHC gene expression in the developing and mature CNS by neural activity. *Neuron.* 1998; 21:505–520. [PubMed: 9768838]
- Corriveau R, Shatz CJ, Nedivi E. Modulation of *cpg15* expression in the mammalian visual system by neural activity. *J Neurosci.* in press.
- Crair MC, Gillespie DC, Stryker MP. The role of visual experience in the development of columns in cat visual cortex. *Science.* 1998; 279:566–570. [PubMed: 9438851]
- Crair MC, Ruthazer ES, Gillespie DC, Stryker MP. Relationship between the ocular dominance and orientation maps in visual cortex of monocularly deprived cats. *Neuron.* 1997; 19:307–318. [PubMed: 9292721]
- Cramer KS, Angelucci A, Hahn J-O, Bogdanov MB, Sur M. A role for nitric oxide in the development of the ferret retinogeniculate projection. *J Neurosci.* 1996; 16:7995–8004. [PubMed: 8987826]
- Darian-Smith C, Gilbert CD. Axonal sprouting accompanies functional reorganization in adult cat striate cortex. *Nature.* 1994; 368:737–740. [PubMed: 8152484]
- Daw NW, Fox K, Sato H, Czepita D. Critical period for monocular deprivation in the cat visual cortex. *J Neurophysiol.* 1992; 67:197–202. [PubMed: 1552319]
- Dudek SM, Friedlander MJ. Developmental down-regulation of LTD in cortical layer IV and its independence of modulation by inhibition. *Neuron.* 1996; 16:1097–1106. [PubMed: 8663986]
- Fagiolini M, Pizzorusso T, Berardi N, Domenici L, Maffei L. Functional postnatal development of the rat primary visual cortex and the role of visual experience: dark rearing and monocular deprivation. *Vis Res.* 1994; 34:709–720. [PubMed: 8160387]
- Finney EM, Shatz CJ. Establishment of patterned thalamocortical connections does not require nitric oxide synthase. *J Neurosci.* 1998; 18:8826–8838. [PubMed: 9786989]
- Florence SL, Taub HB, Kaas JH. Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys. *Science.* 1998; 282:1117–1120. [PubMed: 9804549]
- Fox K. A critical period for experience-dependent synaptic plasticity in rat barrel cortex. *J Neurosci.* 1992; 12:1826–1838. [PubMed: 1578273]
- Fox K. The cortical component of experience-dependent synaptic plasticity in the rat barrel cortex. *J Neurosci.* 1994; 14:7665–7679. [PubMed: 7996202]
- Frank DA, Greenberg ME. CREB: A mediator of long-term memory from mollusks to mammals. *Cell.* 1994; 79:5–8. [PubMed: 7923377]
- Fregnac Y, Shulz D, Thorpe S, Bienenstock E. A cellular analogue of visual cortical plasticity. *Nature.* 1988; 333:367–370. [PubMed: 3374571]
- Fukuda T, Aika Y, Heizmann CW, Kosaka T. GABAergic axon terminals at perisomatic and dendritic inhibitory sites show different immunoreactivities against two GAD isoforms, GAD67 and GAD65, in the mouse hippocampus: a digitized quantitative analysis. *J Comp Neurol.* 1998; 395:177–194. [PubMed: 9603371]
- Gall CM, Murray K, Isackson PJ. Kainic acid-induced seizures stimulate increased expression of nerve growth factor mRNA in rat hippocampus. *Mol Brain Res.* 1991; 9:113–123. [PubMed: 1708074]
- Gilbert CD, Wiesel TN. Receptive field dynamics in adult primary visual cortex. *Nature.* 1992; 356:150–152. [PubMed: 1545866]
- Glazewski S, Chen C-M, Silva A, Fox K. Requirement for α -CaMKII in experience-dependent plasticity of the barrel cortex. *Science.* 1996; 272:421–423. [PubMed: 8602534]

- Glazewski S, Fox K. Time course of experience-dependent synaptic potentiation and depression in barrel cortex of adolescent rats. *J Neurophysiol.* 1996; 75:1714–1729. [PubMed: 8727408]
- Goelet P, Castellucci VF, Schacher S, Kandel ER. The long and the short of long-term memory: a molecular framework. *Nature.* 1986; 322:419–422. [PubMed: 2874497]
- Goodman CS, Shatz CJ. Developmental mechanisms that generate precise patterns of neuronal connectivity. *Cell.* 1993; 10:77–98. [PubMed: 8428376]
- Gordon JA, Cioffi D, Silva AJ, Stryker MP. Deficient plasticity in the primary visual cortex of α -calcium/calmodulin-dependent protein kinase II mutant mice. *Neuron.* 1996; 17:491–499. [PubMed: 8816712]
- Gordon JA, Stryker MP. Experience-dependent plasticity of binocular responses in the primary visual cortex of the mouse. *J Neurosci.* 1996; 16:3274–3286. [PubMed: 8627365]
- Guillery RW. Binocular competition in the control of geniculate cell growth. *J Comp Neurol.* 1972; 144:117–130. [PubMed: 5027758]
- Hata Y, Stryker MP. Control of thalamocortical afferent rearrangement by postsynaptic activity in developing visual cortex. *Science.* 1994; 265:1732–1735. [PubMed: 8085163]
- Hensch TK, Fagiolini M, Mataga N, Stryker MP, Baekkeskov S, Kash SF. Local GABA circuit control of experience-dependent plasticity in developing visual cortex. *Science.* 1998a; 282:504–508.
- Hensch TK, Gordon JA, Brandon EP, McKnight GS, Idzerda RL, Stryker MP. Comparison of plasticity in vivo and in vitro in the developing visual cortex of normal and protein kinase A RI β -deficient mice. *J Neurosci.* 1998b; 18:2108–2117. [PubMed: 9482797]
- Hevroni D, Rattner A, Bundman M, Lederfein D, Gbarah A, Mangelus M, Silverman M, Kedar H, Naor C, Kornuc M, Hanoch T, Seger R, Theill L, Nedivi E, Richter Levin G, Citri Y. Hippocampal plasticity involves extensive gene induction and multiple cellular mechanisms. *J Mol Neurosci.* 1998; 10:75–98. [PubMed: 9699150]
- Hinds HL, Tonegawa S, Malinow R. CA1 long-term potentiation is diminished but present in hippocampal slices from α -CaMKII mutant mice. *Learn Mem.* 1998; 5:344–354. [PubMed: 10454359]
- Huang Y-Y, Li X-C, Kandel ER. cAMP contributes to mossy fibers LTP by initiating both a covalently mediated early phase and macromolecular synthesis-dependent late phase. *Cell.* 1994; 79:69–79. [PubMed: 7923379]
- Huang YY, Kandel ER, Varshavsky L, Brandon EP, Qi M, Idzerda RL, McKnight GS, Bourchouladze R. A genetic test of the effects of mutations in PKA on mossy fiber LTP and its relation to spatial and contextual learning. *Cell.* 1995; 83:1211–1222. [PubMed: 8548807]
- Hubel DH, Wiesel TN. The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J Physiol.* 1970; 206:419–436. [PubMed: 5498493]
- Hubel DH, Wiesel TN, LeVay S. Plasticity of ocular dominance columns in monkey striate cortex. *Phil Trans R Soc Lond B.* 1977; 278:377–409. [PubMed: 19791]
- Jeanmonod D, Rice FL, Van der Loos H. Mouse somatosensory cortex: alterations in the barrelfield following receptor injury at different early postnatal ages. *Neuroscience.* 1981; 6:1503–1535. [PubMed: 7266876]
- Kaplan IV, Guo Y, Mower GD. Immediate early gene expression in cat visual cortex during and after the critical period: differences between EGR-1 and Fos proteins. *Mol Brain Res.* 1996; 36:12–22. [PubMed: 9011747]
- Kash SF, Johnson RS, Tecott LH, Noebels JL, Mayfield RD, Hanahan D, Baekkeskov S. Epilepsy in mice deficient in the 65-kDa isoform of glutamic acid decarboxylase. *Proc Natl Acad Sci USA.* 1997; 94:14060–14065. [PubMed: 9391152]
- Katz LC, Shatz CJ. Synaptic activity and the construction of cortical circuits. *Science.* 1996; 274:1133–1138. [PubMed: 8895456]
- Kirkwood A, Bear MF. Hebbian synapses in visual cortex. *J Neurosci.* 1994a; 14:1634–1645. [PubMed: 8126560]
- Kirkwood A, Bear MF. Homosynaptic long-term depression in the visual cortex. *J Neurosci.* 1994; 14:3404–3412. [PubMed: 8182481]
- Kirkwood A, Dudek SM, Gold JT, Aizenman CD, Bear MF. Common forms of synaptic plasticity in the hippocampus and neocortex in vitro. *Science.* 1993; 260:1518–1521. [PubMed: 8502997]

- Kirkwood A, Lee H-K, Bear MF. Co-regulation of long-term potentiation and experience-dependent synaptic plasticity in visual cortex by age and experience. *Nature*. 1995; 375:328–331. [PubMed: 7753198]
- Kirkwood A, Rioult MG, Bear MF. Experience-dependent modification of synaptic plasticity in visual cortex. *Nature*. 1996; 381:526–528. [PubMed: 8632826]
- Kirkwood A, Silva A, Bear MF. Age-dependent decrease of synaptic plasticity in the neocortex of α CaMKII mutant mice. *Proc Natl Acad Sci USA*. 1997; 94:3380–3383. [PubMed: 9096402]
- Kleinschmidt A, Bear MF, Singer W. Blockade of “NMDA” receptors disrupts experience-dependent plasticity of kitten striate cortex. *Science*. 1987; 238:355–358. [PubMed: 2443978]
- LeVay S, Stryker MP, Shatz CJ. Ocular dominance columns and their development in layer IV of the cat’s visual cortex. *J Comp Neurol*. 1978; 179:223–244. [PubMed: 8980725]
- LeVay S, Wiesel TN, Hubel DH. The development of ocular dominance columns in normal and visually deprived monkeys. *J Comp Neurol*. 1980; 191:1–51. [PubMed: 6772696]
- Link W, Konietzko U, Kauselmann G, Krug M, Schwanke B, Frey U, Kuhl D. Somatodendritic expression of an immediate early gene is regulated by synaptic activity. *Proc Natl Acad Sci USA*. 1995; 92:5734–5738. [PubMed: 7775777]
- Lyford GL, Yamagata K, Kaufmann WE, Barnes CA, Sanders LK, Copeland NG, Gilbert DJ, Jenkins NA, Lanahan A, Worley PF. *Arc*, a growth factor and activity-regulated gene encodes a novel cytoskeletal-associated protein that is enriched in neuronal dendrites. *Neuron*. 1995; 14:433–445. [PubMed: 7857651]
- Madison DV, Malenka R, Nicoll RA. Mechanisms underlying long-term potentiation of synaptic transmission. *Annu Rev Neurosci*. 1991; 14:379–397. [PubMed: 1851607]
- Maffei L, Berardi N, Domenici L, Parisi V, Pizzorusso T. Nerve growth factor (NGF) prevents the shift in ocular dominance distribution of visual cortical neurons in monocularly deprived rats. *J Neurosci*. 1992; 12:4651–4662. [PubMed: 1334503]
- Maffei L, Galli-Resta L. Correlation in the discharges of neighboring rat retinal ganglion cells during prenatal life. *Proc Natl Acad Sci USA*. 1990; 87:2861–2864. [PubMed: 2320593]
- Martin DL, Martin SB, Wu SJ, Espina N. Regulatory properties of brain glutamate decarboxylase (GAD): the apoenzyme of GAD is present principally as the smaller of two molecular forms of GAD in brain. *J Neurosci*. 1991; 11:2725–2731. [PubMed: 1880546]
- Martin KC, Kandel ER. Cell adhesion molecules, CREB, and the formation of new synaptic connections. *Neuron*. 1996; 17:567–570. [PubMed: 8893013]
- McAllister AK, Lo DC, Katz LC. Neurotrophins regulate dendritic growth in developing visual cortex. *Neuron*. 1995; 15:791–803. [PubMed: 7576629]
- Meister M, Wong ROL, Baylor DA, Shatz CJ. Synchronous bursts of action potentials in ganglion cells of the developing mammalian retina. *Science*. 1991; 252:939–943. [PubMed: 2035024]
- Merzenich M. Long-term change of mind. *Science*. 1998; 282:1062–1063. [PubMed: 9841454]
- Miller KD, Keller JB, Stryker MP. Ocular dominance column development: analysis and simulation. *Science*. 1989; 245:605–615. [PubMed: 2762813]
- Morgan JI, Curran T. Stimulus-transcription coupling in the nervous system: involvement of the inducible proto-oncogenes *fos* and *jun*. *Annu Rev Neurosci*. 1991; 14:421–451. [PubMed: 1903243]
- Morris RGM, Anderson E, Lynch GS, Baudry M. Selective impairment of learning and blockade of long-term potentiation by an *N*-methyl-D-aspartate receptor antagonist, AP5. *Nature*. 1986; 319:774–776. [PubMed: 2869411]
- Mower GD, Rosen KM. Developmental and environmental changes in GAP-43 gene expression in cat visual cortex. *Mol Brain Res*. 1993; 20:254–258. [PubMed: 8302163]
- Naeve GS, Ramakrishnan M, Rainer K, Hevroni D, Citri Y, Theill LE. Neuritin: a gene induced by neural activity and neurotrophins that promotes neurogenesis. *Proc Natl Acad Sci USA*. 1997; 94:2648–2653. [PubMed: 9122250]
- Nedivi E, Fieldust S, Theill L, Hevroni D. A set of genes expressed in response to light in the adult cerebral cortex and regulated during development. *Proc Natl Acad Sci USA*. 1996; 93:2048–2053. [PubMed: 8700883]

- Nedivi E, Hevroni D, Naot D, Israeli D, Citri Y. Numerous candidate plasticity-related genes revealed by differential cDNA cloning. *Nature*. 1993; 363:718–722. [PubMed: 8515813]
- Nedivi E, Javaherian A, Cline HT. Developmental regulation of dendritic growth rate *in vivo* by CPG15. (in preparation).
- Nedivi E, Wu GY, Cline H. Promotion of dendritic growth by CPG15, an activity-induced signaling molecule. *Science*. 1998; 281:1863–1866. [PubMed: 9743502]
- Neve RL, Bear MF. Visual experience regulates gene expression in the developing striate cortex. *Proc Natl Acad Sci USA*. 1989; 86:4781–4784. [PubMed: 2543986]
- O'Dell TJ, Hawkins RD, Kandel ER, Arancio O. Tests of the roles of two diffusible substances in long-term potentiation: evidence for nitric oxide as a possible early retrograde messenger. *Proc Natl Acad Sci USA*. 1991; 88:11285–11289. [PubMed: 1684863]
- Parnavelas JG, Burne RA, Lin CS. Receptive field properties of neurons in the visual cortex of the rat. *Neurosci Lett*. 1981; 27:291–296. [PubMed: 7329634]
- Patterson SL, Abel T, Deuel TAS, Martin KC, Rose JC, Kandel ER. Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. *Neuron*. 1996; 16:1137–1145. [PubMed: 8663990]
- Pham TA, Impey S, Storm DR, Stryker MP. CRE-mediated gene transcription in neocortical neuronal plasticity during the developmental critical period. *Neuron*. 1999; 22:63–72. [PubMed: 10027290]
- Qian Z, Gilbert ME, Colicos MA, Kandel ER, Kuhl D. Tissue-plasminogen activator is induced as an immediate-early gene during seizure, kindling and long-term potentiation. *Nature*. 1993; 361:453–457. [PubMed: 8429885]
- Reid SNM, Daw NW, Gregory DS, Flavin H. cAMP levels increased by activation of metabotropic glutamate receptors correlate with visual plasticity. *J Neurosci*. 1996; 16:7619–7626. [PubMed: 8922418]
- Reiter HO, Stryker MP. Neural plasticity without postsynaptic action potentials: less-active inputs become dominant when kitten visual cortical cells are pharmacologically inhibited. *Proc Natl Acad Sci USA*. 1988; 85:3623–3627. [PubMed: 3285347]
- Rittenhouse CD, Shouval HZ, Paradiso MA, Bear MF. Monocular deprivation induces homosynaptic long-term depression in visual cortex. *Nature*. 1999; 397:347–350. [PubMed: 9950426]
- Rosen KM, McCormack MA, Villa-Komaroff L, Mower GD. Brief visual experience induces immediate early gene expression in the cat visual cortex. *Proc Natl Acad Sci USA*. 1992; 89:5437–5441. [PubMed: 1376920]
- Schoups AA, Elliott RC, Friedman WJ, Black IB. NGF and BDNF are differentially modulated by visual experience in the developing geniculocortical pathway. *Brain Res Dev Brain Res*. 1995; 86:326–334.
- Schuman EM, Madison DV. A requirement for the intercellular messenger nitric oxide in long-term potentiation. *Science*. 1991; 254:1503–1506. [PubMed: 1720572]
- Schwartz TH, Rabinowitz D, Unni V, Kumar VS, Smetters DK, Tsiola A, Yuste R. Networks of coactive neurons in developing layer I. *Neuron*. 1998; 20:541–552. [PubMed: 9539127]
- Shatz CJ. Competitive interactions between retinal ganglion cells during prenatal development. *J Neurobiol*. 1990a; 21:197–211. [PubMed: 2181063]
- Shatz CJ. Impulse activity and the patterning of connections during CNS development. *Neuron*. 1990b; 5:745–756. [PubMed: 2148486]
- Shatz CJ, Sretavan DW. Interactions between ganglion cells during the development of the mammalian visual system. *Ann Rev Neurosci*. 1986; 9:171–207. [PubMed: 2423004]
- Shatz CJ, Stryker MP. Ocular dominance in layer IV of the cat's visual cortex and the effects of monocular deprivation. *J Physiol*. 1978; 281:267–283. [PubMed: 702379]
- Sheng M, Greenberg ME. The regulation and function of *c-fos* and other immediate early genes in the nervous system. *Neuron*. 1990; 4:477–485. [PubMed: 1969743]
- Shulz D, Fregnac Y. Cellular analogs of visual cortical epigenesis. II. Plasticity of binocular integration. *J Neurosci*. 1992; 12:1301–1318. [PubMed: 1556598]
- Silva AJ, Paylor R, Wehner JM, Tonegawa S. Impaired spatial learning in alpha-calcium-calmodulin kinase II mutant mice. *Science*. 1992a; 257:206–211. [PubMed: 1321493]

- Silva AJ, Stevens CF, Tonegawa S, Wang Y. Deficient hippocampal long-term potentiation in alpha-calcium-calmodulin kinase II mutant mice. *Science*. 1992b; 257:201–226. [PubMed: 1378648]
- Singer W, Freeman B, Rauschecker J. Restriction of visual experience to a single orientation affects the organization of orientation columns in cat visual cortex: a study with deoxyglucose. *Exp Brain Res*. 1981; 41:199–215. [PubMed: 7215484]
- Sloviter RS. Possible functional consequences of synaptic reorganization in the dentate gyrus of kainate-treated rats. *Neurosci Lett*. 1992; 137:91–96. [PubMed: 1625822]
- Son H, Hawkins RD, Martin K, Kiebler M, Huang PL, Fishman MC, Kandel ER. Long-term potentiation is reduced in mice that are doubly mutant in endothelial and neuronal nitric oxide synthase. *Cell*. 1996; 87:1015–1023. [PubMed: 8978606]
- Squire LR, Zola-Morgan S. The medial temporal lobe memory system. *Science*. 1991; 253:1380–1386. [PubMed: 1896849]
- Sretavan DW, Shatz CJ. Prenatal development of retinal ganglion cell axons: segregation into eye-specific layers. *J Neurosci*. 1986; 6:234–251. [PubMed: 3944621]
- Stevens CF. CREB and memory consolidation. *Neuron*. 1994; 13:769–770. [PubMed: 7946327]
- Stryker MP, Strickland SL. Physiological segregation of ocular dominance columns depends on the pattern of afferent electrical activity. *Invest Ophthalmol Vis Sci*. 1984; 25:278. [PubMed: 6321388]
- Tao X, Finkbeiner S, Arnold DB, Shaywitz AJ, Greenberg ME. Ca²⁺ influx regulates BDNF transcription by a CREB family transcription factor-dependent mechanism. *Neuron*. 1998; 20:709–726. [PubMed: 9581763]
- Tauk DL, Nadler VJ. Evidence for functional mossy fiber sprouting in hippocampal formation of kainic acid-treated rats. *J Neurosci*. 1985; 5:1016–1022. [PubMed: 3981241]
- Tighilet B, Hashikawa T, Jones EG. Cell- and lamina-specific expression and activity-dependent regulation of type II calcium/calmodulin-dependent protein kinase isoforms in monkey visual cortex. *J Neurosci*. 1998; 18:2129–2146. [PubMed: 9482799]
- Tsien JZ, Huerta PT, Tonegawa S. The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. *Cell*. 1996; 87:1327–1338. [PubMed: 8980238]
- Tsui CC, Copeland NG, Gilbert DJ, Jenkins NA, Barnes CA, Worley PF. *Narp*, a novel member of the pentraxin family, promotes neurite outgrowth and is dynamically regulated by neuronal activity. *J Neurosci*. 1996; 16:2463–2478. [PubMed: 8786423]
- Tu JC, Xiao B, Yuan JP, Lanahan AA, Loeffert K, Li M, Linden DJ, Worley PF. Homer binds a novel proline-rich motif and links group 1 metabotropic glutamate receptors with IP3 receptors. *Neuron*. 1998; 21:717–726. [PubMed: 9808459]
- Wiesel TN. Postnatal development of the visual cortex and the influence of environment. *Nature*. 1982; 299:583–591. [PubMed: 6811951]
- Wigstrom H, Gustafsson B. On long-lasting potentiation in the hippocampus: a proposed mechanism for its dependence on coincident pre- and post-synaptic activity. *Acta Physiol Scand*. 1985; 123:519–522. [PubMed: 2986416]
- Wisden W, Errington ML, Williams S, Dunnett SB, Waters C, Hitchcock D, Evans G, Bliss TVP, Hunt SP. Differential expression of immediate early genes in the hippocampus and spinal cord. *Neuron*. 1990; 4:603–614. [PubMed: 2108708]
- Worley PF, Cole AJ, Murphy TH, Christy BA, Nakabeppu Y, Baraban JM. Synaptic regulation of immediate-early genes in brain. *Cold Spring Harbor Symp Quant Biol*. 1990; 55:213–222. [PubMed: 2151923]
- Xiao B, Tu JC, Petralia RS, Yuan JP, Doan A, Breder CD, Ruggiero A, Lanahan AA, Wenthold RJ, Worley PF. Homer regulates the association of group 1 metabotropic glutamate receptors with multivalent complexes of homer-related, synaptic proteins. *Neuron*. 1998; 21:707–716. [PubMed: 9808458]
- Yamagata K, Andreasson KI, Kaufmann WE, Barnes CA, Worley PF. Expression of a mitogen-inducible cyclooxygenase in brain neurons: regulation by synaptic activity and glucocorticoids. *Neuron*. 1993; 11:371–386. [PubMed: 8352945]

- Yamagata K, Kaufmann WE, Lanahan A, Papapavlou M, Barnes CA, Andreasson KI, Worley PF. *Egr3/Pilot*, a zinc finger transcription factor, is rapidly regulated by activity in brain neurons and colocalizes with *Egr1/zif268*. *Learn Mem.* 1994a; 1:140–152. [PubMed: 10467592]
- Yamagata K, Sanders LK, Kaufmann WE, Yee W, Barnes CA, Nathans D, Worley PF. *rheb*, a growth factor-and activity-regulated gene, encodes a novel ras-related protein. *J Biol Chem.* 1994b; 269:16333–16339. [PubMed: 8206940]
- Yuste R, Peinado A, Katz LC. Neuronal domains in developing neocortex. *Science.* 1992; 257:665–669. [PubMed: 1496379]

Table 1

CPGs Implicated in Cortical Plasticity

Gene	Adult Expression		Developmental Expression		Protein
	Seizure Induced	Visually Induced	During CP for OD Plasticity	Activity-Dependent	
<i>zif268</i>	+	+	+	+	Transcription factor
<i>c-fos</i>	+	ND	+	+	Transcription factor
<i>jun B</i>	+	ND	+	+	Transcription factor
BDNF	+	+	+	+	Neurotrophin
<i>GAP-43</i>	+	+	+	+	Axon-specific growth-associated protein
<i>CaMKII</i>	-	+	+	+	Ca ²⁺ -calmodulin-dependent kinase
<i>GAD</i>	+	+	+	+	GABA synthetic enzyme
<i>COX-2</i>	+	+	+	+	Rate-limiting prostaglandin synthetic enzyme
<i>Egr3</i>	+	+	+	-	Transcription factor
<i>Arc</i>	+	+	+	+	Dendrite-specific cytoskeletal-associated protein
<i>Narp</i>	+	+	+	+	Ca ²⁺ -dependent lectin that promotes neuronal migration and dendrite growth
<i>cpg2</i>	+	+	+	ND	Structural protein
<i>cpg22 (homer)</i>	+	+	+	+	EVH domain protein that binds to mGluR c-terminus
<i>rheb</i>	+	+	+	-	Small G protein
<i>cpg15</i>	+	+	+	+	Membrane-bound extracellular signaling molecule that promotes dendritic growth
<i>cpg29</i>	+	+	+	ND	?
MHC	+	ND	+	+	Major histocompatibility protein