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The Role of Oscillations and Synchrony in the Development of the Nervous System

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Abstract

To orchestrate the stepwise assemblage of building blocks in a living system, effective developmental processes are required to establish precise relations among the organism's components. Particular challenges exist for the development of nervous systems, as their functionality depends critically on highly specific relations among individual neurons. To establish precise connections among neurons, these challenges are met by using both molecular signaling systems and the electrical activity of neurons. Exploiting the exquisite sensitivity of synaptic modification rules for the precise timing of discharge patterns, the temporal correlation structure of both self-generated and environmentally induced activity is used to encode relations, thereby specifying the functional architecture of neuronal networks. Among the multiple mechanisms implemented to generate temporally structured activity, the propensity of microcircuit networks to engage in oscillatory activity plays a prominent role: network oscillations permit precise timing relations between discharges of distributed neurons to be established through synchronization, systematic phase shifts, and cross-frequency coupling. Developmental mechanisms are reviewed that translate temporal relations among neuronal discharges into functional architectures.

Relations Matter

Advances in the identification of genes and their products have revealed that the building blocks of living systems are strikingly similar. This implies that the often marked differences in the organisms' organization are essentially due to differences in the arrangement of components. A considerable amount of information specifying the idiosyncratic nature of organisms is thus contained in the relations between their rather stereotyped components. This raises the question of how information about these relations is encoded and read out

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during the organism's development. With the advent of whole genome sequencing methods, it soon became evident that the information which defines the future relations between the building blocks is stored in complex interaction networks constituted by coding and, in particular, noncoding genes. It is the extremely complex and still poorly understood dynamics of these reciprocal gene–gene interactions, together with epigenetic signals from their environment, that orchestrate the sequence of gene expression and ultimately define how the building blocks will be assembled. As development of the organism unfolds, the complexity and the origin of the environmental signals modulating this self-organizing process change. Initially, these signals are provided essentially by the constituents of the egg, but as differentiation proceeds, the environment-influencing gene expression expands to cell assemblies and ultimately the whole environment in which the developing organism is embedded. During early developmental stages, signals are mainly conveyed by physical contact among cells, membrane-bound recognition molecules, and diffusible messengers. Later, when neuronal systems come into play, electrochemical signals assure fast distribution of orchestrating signals throughout the developing organism over large distances and with high topological specificity. Ultimately, with the maturation of exteroceptive sensory systems, even distant environmental factors become influential for the developmental process. Thus, the information required for the development of an organism resides in an exceedingly complex network of relations that extends across multiple scales.

Definition of Relations in the Developing Nervous System

For obvious reasons, the precise definition of relations among components is particularly important and challenging for the development of the nervous system, because functions depend crucially on extremely complex and specific interactions among neurons. In addition, the functional architecture of neuronal networks provides the storage space for data and programs. Knowledge about the conditions of the world, acquired through evolutionary selection, is stored in the genome and expressed during development in the functional architecture of nervous systems. This architecture is subsequently refined by experience: after structural development has come to an end, network interactions continue to be modified by learning to modulate the efficiency of connections. Thus, the internal model of the world required for predictive coding and the programs for adapted behavior reside in the functional architecture of the brain, and hence in the idiosyncratic relations between neurons.

During the early stages of development, the signaling systems that control cell differentiation, migration, and contact formation resemble those supporting the formation of other organs: diffusible molecules and cell-specific surface markers. These signaling systems suffice to support the differentiation of the various brain structures, the coarse specification of the connectome, and the

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formation of protomaps. However, once neurons become electrically excitable and sensitive to synaptic input, the ability of nerve cells to convey signals over large distances with high speed and spatial selectivity is used to further support the development of the nervous system. This not only enables establishment of relations among distant maturation processes but also permits the unique computational abilities of neuronal networks to be exploited for the specification of developmental steps. This process has profound implications, as it permits (a) the selection of connections and the formation of maps with a precision that goes well beyond that attainable with the other signaling systems, (b) the optimization of developing circuits according to functional criteria, and (c) the adaptation of functional architectures to the actual conditions of the embedding environment.

The Role of Neuronal Activity in Development

Neuronal activity fulfills several functions in the context of the development and maintenance of neuronal architectures:

- Neuronal discharges and related synaptic activity are associated with the release, uptake, and transport of trophic signals necessary for the survival of neurons, the motility of cells and their processes, and the maintenance of synaptic connections.
- Activity has a normalizing function by regulating the number and efficiency of excitatory and inhibitory synapses that converge on a particular neuron, so that the average activity of the cell is kept within the optimal dynamic range.
- Temporal relations between discharge patterns of converging inputs are evaluated and used for the selective stabilization and disruption of connections.
- Neuronal activity controls the degree of myelination and thus conduction velocity of axons, as suggested by recent evidence (Elbaz 2016). Thus, activity plays a crucial role in shaping not only the topology of neuronal networks but also the temporal dimension of interactions.

In this chapter, I will focus on the third mechanism—the activity-dependent stabilization and disruption of connections—as this mechanism is crucial for the development of complex nervous systems and the realization of higher cognitive and executive functions. The fourth mechanism—the activity-dependent regulation of conduction velocities—may be equally important for the specification of network dynamics and ensuing functions, but research in this domain is still at the very beginning. Excluded from this review are also the numerous other developmental changes that target critical functions of neuronal networks and have no direct relation with synaptic plasticity and circuit formation: developmental changes in the subunit composition and spatial

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distribution of transmitter and voltage-gated membrane channels, as well as the extensive structural modifications of developing neurons (differentiation of dendritic and axonal ramifications). These variables play a crucial role in the spatial and temporal integration of signals and the homeostasis of cell excitability.

My reason for focusing on activity-dependent synaptic modifications is that the underlying mechanisms exploit network dynamics for the detection and encoding of relations and their translation into lasting changes of the functional architecture of the brain.

Hebbian Mechanisms: Evaluation of Relations and Their Translation in Network Architectures

Mechanisms which support activity-dependent circuit selection during development and use-dependent long-term modifications of synaptic gain, thought to underlie learning in the adult, share numerous similarities. Major differences are that during development, functionally weakened synaptic connections eventually get physically and irreversibly removed while the pool of connections available for selection is permanently replenished by newly formed connections. The initial steps, however, that serve the evaluation of relations and their translation in selective modifications of synaptic gain seem to be based on very similar molecular mechanisms and to follow closely the rules proposed by Donald Hebb for establishing permanent relations between frequently co-occurring and hence statistically related events. Hebb postulated that connections among neurons should strengthen if the coupled neurons are repeatedly active in temporal contiguity (Hebb 1949). This prediction received experimental support through the seminal discovery of long-term potentiation (LTP) in the hippocampus by Bliss and Lomo (1973). These authors found that tetanic stimulation of excitatory pathways led to a long-lasting enhancement of the efficacy of the synapses between the activated fibers and the respective postsynaptic target cells. Later, it was shown in multiple studies that this increase in synaptic efficacy occurred only if the postsynaptic cells were actually responding with action potentials to the tetanic stimuli, thus fulfilling the criterion of contingent pre- and postsynaptic activation. If postsynaptic cells were prevented from responding, modifications either did not occur or had opposite polarity; that is, they consisted of a reduction of synaptic efficacy. This phenomenon has become known as long-term depression (LTD). It is now well established that both modifications depend on a surge of calcium in the subsynaptic space of the postsynaptic dendrites and that the polarity of the modifications depends on the rate of rise, amplitude, and sources of this Ca increase (Bröcher et al. 1992b; Hansel et al. 1996, 1997). Fast and strong increases lead to LTP, whereas slow and smaller increases trigger LTD. Moreover, the source of the Ca increase is of importance. Calcium entering through N-methyl-D-aspartate (NMDA) receptor-associated channels

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favors the induction of LTP, whereas Ca entering through voltage-dependent Ca channels is more likely to trigger LTD. Moreover, secondary release of Ca from intracellular stores plays an important role in gating polarity and duration of gain changes (Cho et al. 2012). Both modifications, however, can be obtained merely by raising intracellular Ca concentrations through the liberation of caged Ca in a concentration-dependent manner (Neveu and Zucker 1996). A vast number of studies have been performed to elucidate the site of change (pre- or postsynaptic) and the molecular cascades that mediate the respective changes. It is now well established that modifications involve changes of both transmitter release and the number and sensitivity of postsynaptic receptors. These molecular approaches have led to a deep understanding of the extremely complex regulatory processes that translate neuronal activity into lasting changes of synaptic transmission (for a review, see Morishita et al. 2005).

It has long been held that the polarity of use-dependent synaptic gain changes depends on the extent to which pre- and postsynaptic activity is correlated in time. The evidence that activation of NMDA receptors was one of the decisive variables agreed with this notion, because these channels function as coincidence detectors, becoming permeable for Ca ions only if glutamate is bound to the receptor and if the postsynaptic cell is sufficiently depolarized to remove the magnesium block (Nowak et al. 1984; Artola and Singer 1987; Kleinschmidt et al. 1987; Artola et al. 1990; Bear et al. 1990; Collingridge and Singer 1990). Since the level of depolarization of the postsynaptic membrane does not only depend on the activity of the local excitatory synapses, but also on all the other excitatory and inhibitory inputs, this mechanism also accounts for the cooperativity that characterizes use-dependent synaptic modifications. Even weak inputs can increase their gain if they are active in synchrony with other nearby excitatory inputs that contribute to depolarization and the removal of the magnesium block. With the advent of two-photon imaging technology it became possible to demonstrate *in vivo* that contingent activation of weak inputs converging onto the same dendritic branch could induce sufficient depolarization to activate regenerative dendritic responses (Na and Ca spikes) and to induce LTP (Grienberger et al. 2015). Conversely, concomitant activation of inhibitory inputs can prevent even strongly activated inputs from depolarizing the postsynaptic dendrite above LTP threshold. In this case, presynaptic activity that would normally induce LTP may either induce LTD or no change at all (Artola et al. 1990).

In conclusion, the net effect of these use-dependent synaptic modifications of excitatory connections include

- a strengthening of (reciprocal) connections among pairs of cells that are frequently activated in temporal contiguity,
- a strengthening of the gain of converging inputs that are frequently active in temporal contiguity,

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- a weakening of connections among pairs of cells whose activity is un- or anti-correlated,
- a weakening of inputs active in contiguity with inhibition of the postsynaptic cell, and
- a weakening of connections that are inactive while the postsynaptic cell is strongly activated by other inputs (heterosynaptic depression).

In this conceptual framework, the crucial variable that determines the occurrence and polarity of synaptic gain changes is the temporal coherence (contiguity) of the activity of converging presynaptic inputs and/or the activity of presynaptic afferents and the depolarization of the postsynaptic neuron.

The notion that the occurrence and polarity of use-dependent synaptic modifications depend crucially on precise timing relations between the discharges of converging inputs received further support from the demonstration that postsynaptic spikes can backpropagate into dendrites, and that the ensuing depolarization also contributes to the gating of synaptic plasticity (Markram et al. 1997; Bi and Poo 1998; Stuart and Häusser 2001; but see Stiefel et al. 2005). Varying the timing between a single excitatory postsynaptic potential (EPSP) and the backpropagating spike revealed that small changes in the temporal relation have a massive impact on synaptic modifications. No changes occurred when the interval between the EPSP and the back-propagating spike was longer than about 50 ms. When the EPSP preceded the backpropagating action potential, the probability of obtaining LTP increased with decreasing delays; once the EPSP occurred after the backpropagating spike, there was a sharp transition toward LTD. The underlying mechanism is the same as detailed above. If the backpropagating spike occurs shortly *before* the EPSP, it can contribute to lifting the Mg block, allowing LTP to occur; if it arrives *after* the EPSP, the repolarizing currents prevent NMDA receptor activation, and LTD is the likely result. This special case of a use-dependent synaptic modification, known as spike timing-dependent plasticity, has an important implication: It suggests that synaptic changes may not only be sensitive to the coherence of converging activity but also to causal relations. The gain of excitatory connections increases if their activity can be causally related to the activation of the postsynaptic neuron and weakens when this is not the case.

Temporal Relations among Neuronal Discharges Signal the Degree of Relatedness

Consistent temporal relations between events signal relatedness. Simultaneously occurring events usually have a common cause or are interdependent because of reciprocal interactions. If one event consistently precedes the other, the first is likely the cause of the latter; if there are no temporal correlations between the events, they are most likely unrelated. The learning rules adopted

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by evolution exploit these relations, thereby permitting internal models of the world to be generated that have considerable predictive power—a likely reason for the striking conservation of the mechanisms supporting use-dependent modifications of synaptic transmission.

The fact that the *learning rules* are exquisitely sensitive to *temporal relations* has several important consequences for the way nervous systems process information and attribute significance to temporal relations. One requirement is that the precise timing relations between events in the environment are reliably encoded in neuronal responses to permit learning of correct associations. This requirement is met in all sensory modalities by the implementation of transmission chains, commonly referred to as "phasic systems," which operate with high temporal resolution and accuracy. *In vivo* recordings from higher visual areas as well as the auditory and the somatosensory cortex revealed that the discharges of individual neurons signal the temporal structure of stimuli with extreme precision in the millisecond range. This proves that precise timing of discharges can be preserved despite numerous intervening synaptic transmission steps (Buracas et al. 1998; Reinagel and Reid 2002). Simulation studies, partly based on the concept of synfire chains proposed by Moshe Abeles (1991), confirmed that conventional integrate-and-fire neurons are capable of transmitting temporal information with the required precision (Mainen and Sejnowski 1995; Diesmann et al. 1999).

Additional mechanisms are required, however, when selective associations have to be established between neurons that represent features which lack temporal structure and just give rise to sustained responses, or when a particular set of neurons (out of many simultaneously active neurons) have to become selectively associated because they code for contents that should be bound together. These types of mechanisms are most likely required for the segmentation of stationary scenes or when associations have to be formed among contents stored in memory, as is the case during reasoning. To accommodate this, one possibility would be to implement mechanisms of synaptic plasticity that are insensitive to the relative timing of inputs but establish associations according to other than temporal criteria. To the best of my knowledge, such mechanisms have not yet been described. An alternative and parsimonious solution is to impose a temporal structure on neuronal responses that satisfies the contingency requirements of the classical plasticity rules and to utilize the existing mechanisms also for the association of signals that initially lack temporal structure. Responses that become associated would have to be made temporally coherent, whereas those that do not should remain uncorrelated.

Neuronal mechanisms responsible for the generation of temporally structured activity are diverse, abundant, and already implemented in simple nervous systems. A common and highly conserved strategy is the oscillatory patterning of activity, the basic principle of parsing time, used in virtually all clocks. Certain neurons are endowed with pacemaker currents that support oscillatory discharge patterns (Heyer and Lux 1976; Gray and McCormick

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1996). Networks which function as central pattern generators produce rhythmic activity for the coordination and synchronization of a large variety of effector systems (Grillner 2006). Neuronal networks endowed with reciprocal connections among their nodes engage spontaneously in temporally coordinated activity that manifests itself in traveling waves (Meister et al. 1991; Ermentrout and Kleinfeld 2001; Plenz and Thiagarajan 2007), especially during development when neurons often interact synaptically as well as through gap junctions. Finally, most neuronal networks share the motive of recurrent inhibition, which endows them with the propensity to engage in oscillatory activity, whereby the frequency of these oscillations is determined by the various time constants of the interacting elements and the conduction velocity of the coupling connections. Prominent examples are the septo-hippocampal circuits which generate the theta rhythm (Buzsáki 2006), the thalamocortical interactions responsible for the alpha rhythm (Steriade et al. 1993), and the cortical microcircuits which generate the gamma oscillations known as ING and PING circuits (Kopell et al. 2000; Börgers and Kopell 2008; for a review, see Buzsáki et al. 2013). These mechanisms provide ample opportunities to impose temporal structure on neuronal activity and to establish precise temporal relations among discharges. These relations can then be converted by the established mechanisms of time-sensitive synaptic plasticity into selective modifications of functional architectures.

The exquisite sensitivity of plasticity mechanisms for precise timing relations also constrains strategies for information processing in general. This implies that information about the relatedness of neuronal responses be expressed in precise temporal relations among the discharges of neurons. Indeed, there is ample evidence for mechanisms that render responses temporally coherent (if they need to be bound together) or which make them uncorrelated (if they represent unrelated contents). Most of these mechanisms are based on an oscillatory patterning of activity, and the resulting option is to synchronize responses with variable phase lags and across different oscillation frequencies for the definition of relations. These mechanisms are considered relevant for signal processing and the dynamic coordination of distributed neuronal processes in the context of feature binding, scene segmentation, the formation of Hebbian assemblies, selective routing of signals, interareal communication, and the specification of functional networks. These aspects of temporal coding have been discussed in numerous reviews (Singer 1999; Buzsáki 2006; Fries 2009; Uhlhaas et al. 2009a; von der Malsburg et al. 2010; Buzsáki et al. 2013) and will thus not be considered further here. Also excluded from review are mechanisms that influence and shape the sequence order of discharges at longer timescales (e.g., synfire chains) and more global synchronized fluctuations of excitability that occur, for example, during alternations between up- and down-states.

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The Role of Temporally Structured Activity in Embryonic Development

As soon as neurons become active, temporal relations between their firing patterns are exploited by developmental mechanisms to guide the selection of connections. A well-examined example involves the refinement of topological maps in the visual system. Because of the cooperative nature of the synaptic modification rules, afferents that convey well-correlated activity mutually support their consolidation on common target cells and repress afferents whose activity is less well correlated—neurons wire together if they fire together. The correlation structure of activity used to select circuits results from widely differing mechanisms, and these change during development. At early stages, before interactions with the environment become important, correlated discharge patterns result from interactions among spontaneously active neurons; that is, from self-generated activity. Slowly oscillating burst activity in thalamic and cortical structures leads to synchronized discharges of local clusters of neurons (Yang et al. 2009b), and in the retina, traveling waves cause sequential, highly synchronized volleys of activity whose sequence order or phase offset reflects precisely the neighborhood relationships among ganglion cells (Meister et al. 1991). While research on the role of the slow burst activity is still in an exploratory phase, evidence indicates that the traveling waves, through the synchronized discharges at the respective wave front, are causally involved in the formation and refinement of topographical maps. First proposed by Kohonen (1982) and Willshaw and von der Malsburg (1976), the neighborhood relations of the array of ganglion cells are encoded in the correlation structure of the activity of axonal projections and then reconstituted by selective stabilization and disruption of connections in the respective target structures such as the optic tectum, the lateral geniculate body, and to some extent the visual cortex (Penn et al. 1998). Although coarse maps have already formed by matching gradients of diffusible and membrane-bound molecules (Bonhoeffer and Gierer 1984), the refinement of topological correspondence required for high-resolution vision is achieved only through this activity-dependent sorting of axons. Self-generated activity patterns in the two eyes are—as far as is known—uncorrelated and thus the clustering of afferents from the same eye and the segregation of afferents from different eyes can be supported by activity-dependent pruning. Blocking retinal activity reduces clustering of afferents in the lateral geniculate nucleus and cortex into eye-specific domains and segregation of the afferents from the two eyes. However, there is a possible confound that is difficult to resolve: blocking activity altogether may also interfere with the transport and uptake of eye-specific marker molecules.

It is likely that temporally structured self-generated activity also plays a role in refining circuits responsible for the coordination of movements, because embryos exhibit coordinated movements at early stages of maturation. Here, however, evidence for causal relations is still sparse. Currently it is unknown to

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which extent traveling waves and synchronous low-frequency oscillations contribute to map formation in nonvisual sensory systems and the refinement of connections between subcortical nuclei or cortical areas. As demonstrated by Khazipov et al. (2004) and Minlebaev et al. (2011), correlated activity patterns occur in the somatomotor system, already at early stages of development, and likely contribute to the shaping of functional architectures. Because the mechanisms mediating use-dependent modifications of synaptic transmission are ubiquitous, it would be surprising if activity-dependent selection of circuits is restricted to the model systems investigated so far, but the critical experiments have not yet been conducted. Occasional observations indicate, however, that the capacity of central structures to adapt to their respective afferent input is astounding. In a routine scan of one of our subjects—a 14-year-old girl—we discovered that the subject lacked one cerebral hemisphere, including the striatum and the entire thalamus (Muckli et al. 2009). To our great surprise, the girl exhibited only minor distal apraxia of the hand, contralateral to the missing hemisphere, but had a close to normal visual field. Closer examination with structural scans and fMRI mapping of retinotopic representations revealed, however, that both the nasal and temporal retina of the ipsilateral eye projected to the intact hemisphere, and that two complementary retinotopic maps had developed in the primary visual cortex: one for the ipsilateral, the other for the contralateral hemifield. These maps met at the representation of the vertical meridian. Apparently, the normally crossing axons from the nasal retina were rerouted to the ipsilateral hemisphere because their natural target was missing, and the nasal and temporal afferents from the ipsilateral eye got sorted to form two independent maps that covered the two hemifields, respectively. To which extent these drastic rearrangements were mediated by molecular markers or structured activity patterns from the retina is unfortunately unresolved.

A recent study on the development of the entorhinal-hippocampal circuitry provides direct evidence for the crucial function of activity in promoting sequential maturation of functional networks. If activity in the respective feeding structures is blocked, the maturation of all elements constituting the subsequent processing stages is jeopardized (Donato et al. 2017).

The Role of Correlated Activity Patterns in Postnatal Development

Once sensory systems become responsive to stimulation from the outer world, the correlation structure of activity in sensory pathways reflects the correlation structure of (a) events in the embedding environment and (b) characteristic features of perceptual objects. The developmental mechanisms described above utilize these additional sources of information to refine microcircuits and maps and improve the inherited internal model of the world that is stored in the brain's functional architecture.

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Results from lesion and deprivation experiments clearly indicate that the formation of sensory maps is influenced by the activity conveyed by sensory afferents. This has been shown for the somatosensory system (Jenkins et al. 1990) and the somewhat special variant, the cortical representation of the whiskers in rodents (Jeanmonod et al. 1981; Petersen et al. 2004). Of particular relevance in the present context are findings that artificial synchronization of proprioceptive signals from different fingers or whiskers led to the fusion of the cortical representations that are normally well segregated. This suggests that the correlation structure of afferent activity is used to associate or segregate the territories occupied by the respective axonal arborizations.

Very similar results have been obtained in the visual system. For binocular vision and stereoscopic depth perception, it is imperative to assure that those afferents converge on common cortical target cells that convey signals from precisely corresponding loci in the two eyes. Genetic instructions alone do not suffice, because correspondence depends on variables such as interocular distance and size of the eyes—variables which are subject to epigenetic influences and cannot be anticipated with precision. For this reason, the correlation structure of afferent activity is again used for the refinement of circuitry. By definition, afferents from corresponding retinal loci convey precisely correlated activity when the two eyes are fixating an object. Thus, selective stabilization of these afferents will establish precise retinal correspondence. However, selection of afferents must be confined to epochs when the two eyes are actually fixating. This is one of the reasons why many experience-dependent refinement processes are supervised. In this particular case, synaptic plasticity is gated by nonretinal signals from extraocular muscles (Buisseret and Singer 1983) and additional "now print" systems capable of evaluating the adequacy of retinal activity in a more global behavioral context (for a review, see Singer 1995). This important issue will be addressed in more detail below. If activity from the two eyes is consistently de-correlated, as occurs with strabismus or monocular deprivation, afferents from different eyes compete with one another and a winner-take-all mechanism destroys binocular convergence.

From the visual cortex, causal evidence also indicates that correlated sensory signals play a role in shaping the dense network of recurrent tangential connections, which link feature-selective neurons with one another (Löwel and Singer 1992). In the mature cortex, these connections are particularly dense between columns that share similar functional properties, such as eye dominance and orientation preference (Gilbert and Wiesel 1989). However, when visual experience is withheld, this bias does not develop and connections distribute randomly across functional domains (Löwel and Singer 1992). This observation can be accounted for if one assumes that (a) connections stabilize selectively between columns that have a high probability of being active simultaneously and (b) the structure of the visual world favors coherent activation of columns responding to similar features. Both prerequisites are fulfilled. As demonstrated in numerous slice experiments, tangential connections are

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endowed with Hebbian synapses that obey the "fire and wire together" rule and "orientation" columns with similar preference—in particular if they have collinearly aligned receptive fields—have a high probability of being simultaneously activated, because elongated contours are prominent in natural scenes (Kayser et al. 2003). In essence, these findings indicate that the contingencies of features in the outside world get translated during development into the weight distributions of the myriads of connections that link neurons with corresponding feature preferences. Because these graded and selective weight distributions reflect the statistics of the outer world, it has been proposed that they serve as priors in predictive coding and, in fact, correspond to the Gestalt criteria applied for figure-ground segregation, perceptual grouping, and feature binding (Singer 2013; Singer and Lazar 2016). Strongly coupled neurons engage more likely in synchronous firing than weakly interacting neurons (Schillen and König 1991). Thus, as previously proposed (Singer and Gray 1995; Singer 1999), readout of the "learned" binding criteria would occur through enhanced synchronization of neurons coding for features that are related (e.g., features that co-occur in frequently observed objects). If experience is withheld during the critical period of development in which these architectural changes are induced, cognitive functions become irreversibly impeded. The likely reason is that sensory signals cannot be interpreted adequately if the priors reflecting meaningful relations among features have not been installed by experience-dependent shaping of intercolumnar connections. This interpretation agrees with reports of patients suffering from early-life visual deprivation, who have problems with figure-ground segregation and feature binding.

Although other sensory systems have been studied less extensively, it is very likely that their development follows the same principle and that the priors representing the statistical contingencies in the respective sensory environment become internalized by use-dependent adaptation of cortical circuits. Obvious examples are provided by the development of auditory functions, such as the acquisition of kin-specific songs in songbirds and the learning of the mother tongue in children (see Kaschube et al., this volume). In both cases, priors are installed that permit automatic parsing of sound streams into syllables, and there are critical periods for the development of these abilities (Tchernichovski et al. 2001; Ortiz-Mantilla et al. 2016). This suggests that the acquisition of the respective priors goes along with circuit changes that are only possible during development. In the case of auditory stimuli, the temporal patterning of activity is already inherent in the rhythmicity of the utterances, but it is unclear how exactly this information is used to fine-tune circuits for appropriate chunking of sounds.

It is not too surprising that activity-dependent development and learning rely on similar mechanisms because in both cases, relations between distributed neurons must be established, specified, and modified. For memory formation in the adult, the modifications of the interaction architecture seem to be confined to gain changes of synaptic transmission, whereas during development, such

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gain changes lead to either consolidation or disruption of connections, and thus to irreversible changes of anatomical architecture. In both cases, however, the critical variable determining the polarity of the respective changes appears to be the correlation structure of the activity displayed by the interacting elements—not only the level of activation but also the precise temporal relations among activation patterns.

The Need for Supervision

As mentioned above, in the context of the development of precise binocular correspondence, selection processes that rely on temporal correlations are often supervised. Activity-dependent changes of connectivity are permitted only when certain additional conditions are fulfilled. Experimental observations and theoretical arguments suggest that such gating of activity-dependent developmental processes may be a general strategy. Evidence from the visual system indicates that activity, even when it is strong and well structured, may alone not be sufficient to support use-dependent plasticity and circuit changes. The seminal experiment by Held and Hein (1963) demonstrated that development of normal visual abilities requires active exploration; passive exposure to a visual environment is insufficient. Likewise, when animals are anesthetized or eye movements abolished, ocular dominance changes do not occur in response to monocular stimulation, even when cortical neurons are strongly driven by the visual stimuli (Buisseret et al. 1978). Circuit modifications also fail to occur in freely behaving animals when the retinal signals are in conflict with inbuilt visuomotor reflexes; for example, when the retinal coordinates are rotated (Singer et al. 1982; for a review, see Singer 1995). These findings suggest that central gating systems can permit or veto activity-dependent circuit modifications. Some systems, whose activation is required for the induction of experience-dependent circuit changes, have been identified. These are the cholinergic, noradrenergic, and serotonergic projections originating in the brain stem and basal forebrain (Bear and Singer 1986; Gu and Singer 1995). The dopaminergic projections, prime candidates for the supervision of use-dependent synaptic plasticity, have not been investigated in this context. The more recent findings of a strong enhancement by locomotion of responses, even in primary visual cortex, might account for the early finding of Held and Hein (1963) that exploratory behavior is a necessary prerequisite for experience-dependent maturation of visual functions.

Using neuronal activity to optimize the development of architectures has obvious advantages: it permits the information-processing capacities of nervous systems to be exploited for their own development. This option is used not only to adapt sensory and motor systems to the constraints of the environment but also to coordinate developmental processes that assure cooperativity between the various subdivisions of the brain. One example is the adaptation of

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the auditory map to the visual map in the tectum (Knudsen and Knudsen 1989). Whether this strategy is applied ubiquitously to establish correspondence, and to which extent self-generated patterned activity may play a role, is still little explored.

Despite the obvious advantages of using experience (i.e., signals) from the environment to guide developmental processes, there is a price to be paid: abnormal activity patterns can have deleterious effects on development, as demonstrated by the often severe consequences of deprivation. One way to minimize these risks is to permit circuit changes to take place only when the respective activity patterns have been identified as consistent or appropriate in a more general context. Studies on the experience-dependent development of the visual system suggest that consistency criteria for sensory signals could be correct predictions about the effects of eye movements or locomotion on retinal image slip or the congruence of signals conveyed by different sensory systems.

How distinctions are made between internally generated activity patterns which should or should not induce circuit changes is unknown. This question is intimately related to the equally unresolved riddle of how the brain "knows" when it has arrived at a solution—or in other words, how activity patterns which result from computations during the search for a result differ from those representing the result. For development as well as for signal processing and learning, the brain needs to prevent spurious activity from changing neuronal architectures. As mentioned above, gating functions that prevent inappropriate activity from inducing changes in circuitry seem to be realized by globally organized modulatory systems whose activity facilitates synaptic plasticity, and thereby serves as a "now print" signal. These systems are activated as a function of arousal, attention, and reward expectancy (Tobler et al. 2005) and have been shown to facilitate activity-dependent synaptic modifications. They either control dendritic depolarization directly, by modulating the conductance of ion channels, or indirectly, by regulating the excitability of inhibitory networks. In addition, they act through metabotropic receptors on the second messenger cascades that mediate long-term changes of synaptic transmission. Through these complex actions, modulatory systems can veto or permit synaptic modifications as well as adjust the set points of synaptic plasticity. As *in vitro* and *in vivo* studies suggest, a given pattern of activity can lead to transient adaptation, long-term depression or potentiation, depending on the state of the modulatory systems. However, just how these modulatory systems are informed about activity constellations that warrant synaptic changes is by and large unknown.

Gating of Synaptic Plasticity by Local Circuit Dynamics

Considering the activity requirements for the induction of synaptic modifications, it is likely that gating of plasticity is not only mediated by globally organized modulatory systems but also by local computations. As summarized

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above, a favorable condition for the induction of circuit changes is strong dendritic depolarization: it results from cooperativity among converging excitatory inputs and/or coincidence between pre- and postsynaptic discharges. These two conditions are particularly well fulfilled if neuronal activity is synchronous. Since synchrony is, in turn, enhanced when neuronal groups engage in oscillations, there could be a relation between the occurrence of an oscillatory patterning of activity and plasticity, in particular in high-frequency oscillations, as these lead to high-precision synchrony. The prediction is that circuits which engage in synchronous high-frequency oscillations should be particularly susceptible to undergo use-dependent modifications of synaptic transmission. In actuality, there is a close correlation between the state of plasticity-enhancing modulatory systems, the propensity of microcircuits to engage in synchronous oscillations, and the occurrence of synaptic modifications. Synchronized high-frequency oscillations in the gamma-frequency range are facilitated by acetylcholine (Munk et al. 1996; Herculano-Houzel et al. 1999)—one of the neuromodulators proven to enhance synaptic plasticity *in vitro* (Bröcher et al. 1992a) and memory formation *in vivo* (Letzkus et al. 2011). High-frequency oscillations are also enhanced by attention (Fries et al. 2001), an important variable that controls learning processes. Thus, it is likely that synchronous oscillations contribute to the gating of synaptic plasticity, by means of enhancing the coincidence of discharges (cooperativity).

Direct support for this conjecture comes from experiments that relate the occurrence of oscillations to use-dependent modifications of neuronal response properties. The receptive fields of neurons in the visual cortex can be modified by appropriate visual stimulation, even in anesthetized preparations, if the brain is concomitantly activated by electrical stimulation of the mesencephalic reticular formation (Singer and Rauschecker 1982). Reticular stimulation increases the release of plasticity-enhancing neuromodulators while, at the same time, favoring the occurrence of gamma oscillations in response to the applied stimuli. Post hoc analysis of the neuronal responses to change-inducing light stimuli revealed that lasting changes in receptive field properties (in this case, orientation preference) occurred only in response to stimuli associated with a strong oscillatory modulation and synchronization of neuronal responses in the gamma band. Changes consisted in a shift of orientation tuning toward the stimuli used for conditioning. In the absence of gamma oscillations, the cells preserved their initial tuning properties although still vigorously driven by the light stimulus. However, in this case, the cells became less responsive to the change-inducing stimuli: they showed adaptation (Galuske, pers. comm.). A dependence of synaptic plasticity on oscillations, albeit in the theta-frequency range, has also been found in the hippocampus (Huerta and Lisman 1995). Here, the so-called theta-burst stimulation that entrains the hippocampus in the characteristic theta rhythm turned out to be particularly effective for the induction of long-lasting synaptic modifications. Other evidence for an instrumental role of synchronized oscillations in use-dependent changes of synaptic

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transmission comes from research on memory formation (Fell et al. 2001; Tallon-Baudry et al. 2001, 2004). In human subjects implanted with depth electrodes for the localization of epileptic foci, it was found that successful formation of episodic memories was accompanied by transient increases in gamma- and theta-oscillatory synchrony between the hippocampus and neighboring entorhinal cortex, structures known to be involved in memory formation. In trials in which memory formation was not successful, these increases in synchronization were not observed (Fell et al. 2001, 2003, 2011). Likewise, simultaneous recordings from limbic structures (amygdala and hippocampus) have shown that fear conditioning is associated with transient synchronization of oscillatory activity between the two structures (Seidenbecher et al. 2003; Narayanan et al. 2007; Liu et al. 2012a; Igarashi et al. 2014; Yamamoto et al. 2014). Finally, studies on memory consolidation during sleep have revealed correlations between an oscillatory patterning of neuronal activity and memory formation. Memory consolidation during sleep has been reported to be enhanced following induction of slow oscillations with direct-current stimulation in human subjects (Marshall et al. 2006).

If synchronous oscillations facilitate use-dependent synaptic modifications, they could indeed serve as local gates and enable activity to induce changes if this activity meets certain criteria of consistency. There are some indications that patterns elicit strong gamma oscillations if they match the prewired response properties (priors) of local cortical networks, if their structure is sufficiently regular to allow for predictions across different parts of the pattern, and if the stimulus is expected (Lima et al. 2011; Vinck and Bosman 2016; for a review, see Singer and Lazar 2016). Thus, synchronous oscillations (or, in other terms, high temporal coherence) could be signatures of consistent states that are worth being reinforced by synaptic modifications.

These considerations of mechanisms that relate neuronal plasticity and oscillatory activity have recently experienced an unexpected twist. Two independent studies indicate that the entrainment of circuits in narrow-band gamma oscillations triggers specific signaling systems that act upon the microglia and the extracellular matrix. Iaccarino et al. (2016) showed that entrainment of neuronal networks in synchronized narrow-band gamma oscillations reduces synthesis and accelerates degradation of Aß, the plaque-generating polypeptide in Alzheimer disease. These effects on metabolic processes were mediated by the activation of microglia and were surprisingly frequency specific. Entrainment of oscillations was ineffective in higher- or lower-frequency bands. As reported by Takao Hensch (see Kaschube et al., this volume), entrainment of cortical circuits in narrow-band gamma oscillations also has the unexpected effect of rendering adult visual cortex susceptible again to use-dependent synaptic plasticity that shares all characteristics of critical period plasticity. This effect appears to be mediated by changes in the extracellular matrix.

These new findings suggest the possibility that abnormalities in the ability of networks to generate well-synchronized narrow-band gamma oscillations

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impede developmental processes, such as pruning and stabilization of connections, due to the effects that reduced and imprecise synchrony has on Hebbian mechanisms as well as its direct effects on metabolism, glial cells, and the extracellular matrix. At present one can only speculate as to why there seems to be something special about gamma oscillations. When networks engage in well-synchronized narrow-band gamma oscillations, parvalbumin-containing inhibitory interneurons—the basket cells—exhibit a drastic change in their discharge pattern: they emit a burst of spikes in each cycle and show an overall increase in activity. Pyramidal cells, by contrast, show little change in overall activity because they skip cycles and do not burst. Their spikes become concentrated around the depolarizing peak of the oscillations, but their discharge rate does not signal engagement in an oscillatory process. The activity of the basket cells—the pacemakers of the gamma-generating PING circuit (Whittington et al. 2000)—is thus a reliable indicator for the transition of a network in the gamma mode. If, as suggested above, entering the gamma-processing mode is associated with an increased likelihood of ensuing synaptic modifications, entering the gamma mode would predict enhanced metabolic demands. During gamma oscillations, basket cells are likely to experience a massive influx of Ca ions, and this could be the trigger for the generation of metabolically relevant signals. Unlike pyramidal cells, they contain, for example, NO synthase, and nitrous oxide is a very potent diffusible messenger for a host of downstream processes. Support for this admittedly speculative scenario comes from the finding that entrainment of cortical circuits in gamma oscillations is particularly effective in increasing the hemodynamic response (Niessing et al. 2005).

Concluding Remarks and Outlook

Despite intensive research on the functional role of oscillatory activity and the concomitant synchronization of discharges in neuronal processing and its ubiquitous occurrence from the early stages of development throughout the rest of life, there is still only sparse evidence for a causal role of these phenomena in brain development. However, given the importance that relations play in defining mechanisms in development, the central role that oscillations and their propensity to synchronize play in the encoding of relations, and the special effects that synchronization has on synaptic cooperativity and plasticity, it seems highly likely that entrainment of networks into synchronous oscillatory activity plays an important role in the development of the nervous system.

Obtaining causal rather than solely correlative evidence for this conjecture is, however, notoriously difficult. Oscillations are nearly as fundamental a property of neuronal activity as discharge rate, and the two variables are closely intertwined. Hence, manipulating oscillatory patterning without simultaneously interfering with discharge rate is almost impossible. Still, this approach will have to be taken to obtain more direct evidence for a causal role of

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oscillatory activity in promoting developmental self-organization of neuronal networks.

Tools are now available that should permit us to selectively manipulate oscillating network components and to interfere with synchrony without affecting discharge rates. Still, the epistemic mandate to provide causal evidence may well encounter insurmountable methodological hurdles which may need to be relaxed as we investigate these extremely complex systems that exhibit nonstationary, nonlinear high-dimensional dynamics. The classical approach of manipulating an *independent* variable and investigating the consequences is likely to fail because of inherent circularities. Thus in certain domains of systems neuroscience, we may have to be content with correlative evidence, inductive reasoning, arguments of plausibility, and consistency of simulation results. This epistemic challenge is not unique to brain research. Other domains in the natural sciences face similar problems, either because it is impossible to manipulate the independent variables, as in evolutionary anthropology or cosmology, or because the systems are simply too complex and nonlinear, as in the Earth sciences and climatology.

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