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Neuroplasticity: From Bench to Bedside
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Chapter 1

Defining neuroplasticity

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Abstract

Neuroplasticity, i.e., the modifiability of the brain, is different in development and adulthood. The first includes changes in: (i) neurogenesis and control of neuron number; (ii) neuronal migration; (iii) differentiation of the somato-dendritic and axonal phenotypes; (iv) formation of connections; (v) cytoarchitectonic differentiation. These changes are often interrelated and can lead to: (vi) system-wide modifications of brain structure as well as to (vii) acquisition of specific functions such as ocular dominance or language. Myelination appears to be plastic both in development and adulthood, at least, in rodents. Adult neuroplasticity is limited, and is mainly expressed as changes in the strength of excitatory and inhibitory synapses while the attempts to regenerate connections have met with limited success. The outcomes of neuroplasticity are not necessarily adaptive, but can also be the cause of neurological and psychiatric pathologies.

INTRODUCTION

The term "plasticity" referred to the nervous system is often used, but rarely defined. It includes changes in neural structure and/or function often pooled together as "brain remodeling" (Merzenich et al., 2014). Therefore, the term has unclear boundaries that I will try to sharpen in this chapter.

Neuroplasticity is at the roots of why the nervous system exists at all. Indeed, the nervous system exists so that an input from the environment is transformed into an output by the animal. Neuroplasticity however exceeds the normal, more, or less reflexive elaboration of the response to a stimulus in that the nervous system is modified by the environmental input. This is precisely what happens when the animal learns, but l will keep learning at the periphery of the present chapter (see Chapter 2 by Mancini et al.).

Neuroplasticity includes a broad variety of phenomena spanning from development to adulthood. Therefore, it should not be surprising that it might be difficult to ascribe the origin of the concept unequivocally to one of the founders of our discipline (discussed in Jones, 2000, 2004; Berlucchi and Buchtel, 2009). The many facets of neuroplasticity will be dealt briefly here; each of them would be worth a full chapter. Most of the data are derived from animal studies where it is easier to identify the underlying mechanisms and therefore might guide the interpretation of human cases. Other reviews exist which detail different aspects of neuroplasticity (e.g., Williams, 1988; Sur and Leamey, 2001; Rouiller and Olivier, 2004; Voss and Zatorre, 2012; Sur et al., 2013; Medini, 2014; Merzenich et al., 2014; Castaldi et al., 2020; La Rosa et al., 2020; Magee and Grienberger, 2020; Pan and Monje, 2020).

DEVELOPMENTAL PLASTICITY

The developing brain is exquisitely plastic and this provides an exaggerated image of mechanisms some of which still exist in the adult. Developmental plasticity

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is restricted to epochs in the life of the brain usually called "critical periods" or "sensitive periods". Since different aspects of brain development can be modified, several sensitive periods exist whose temporal boundaries can be modified as well, i.e., terminated precociously (e.g., Innocenti et al., 1985; Zufferey et al., 1999) or extended (below).

Sources of developmental neuroplasticity relate to the following

Neurogenesis and the control of neuronal number

Neuronal number can be manipulated either by preventing the regular neuronal death which occurs after neurogenesis or by exaggerating it. This aspect of neuronal plasticity has a time-honored history. In the first half of the last century observations by the fathers of experimental embryology including Detwiler, Shorey, Hamburger, and Levi-Montalcini demonstrated that limb excision caused loss in the number of motor neurons and spinal ganglia neurons in amphibia and chicks while peripheral grafts had the opposite effect. This line of work led to the concept that neuronal death occurs in normal development and that the competitive success for the innervation of the peripheral territory (skin or muscle) is necessary for neuronal survival. This concept eventually led to the discovery of neurotrophins (reviewed in Hamburger, 1988). The view that the mere competition for trophic factors in the periphery regulates neuronal survival was challenged by the discovery of intrinsically different fitness of spinal ganglia neurons.

In the cerebral cortex, cell number is regulated by two factors: (i) the number of cells leaving the cell cycle (the Q fraction) vs that of the reentering the cell cycle (the P fraction), in the proliferative ventricular zone, and (ii) the developmental death of neurons and neuronal precursors (apoptosis). Manipulating the first factor by acting on the mitotic inhibitor p27 led to either increase or decrease of cortical layers thickness indicating changes in neuron number (Caviness et al., 2003). Interfering with apoptosis in caspase-3 orEphA7knock out mice led to enlarged cerebral cortex with a tendency to gyration (Roth et al., 2000; Depaepe et al., 2005).

Microcephaly is a human condition characterized by decreased neuronal numbers. The causes include infections (Devakumar et al., 2018) but the pathogenesis, arrested neuronal production, or excessive neuronal death, is uncertain.

Neuronal migration

The journey leading neurons from the site of generation in the periventricular proliferative zone to their final location in cortex is a well-regulated series of events, which normally leads the earliest generated neurons to the bottom of the cortex and the later generated neurons to the top (Rakic, 1974). This journey can be dramatically altered in the "reeler" mouse where the absence of the extracellular matrix protein reelin leads to a reversed and somewhat scrambled distribution of neuronal birthday in cortex, with the early generated neurons at the top and the later neurons below (Caviness, 1976; Prume et al., 2018). Incoming thalamocortical axons, which normally are guided into the cortex by the early generated neurons at the bottom of the cortex take an abnormal trajectory to the top of the cortex, before diving down (Caviness, 1976). They are accompanied by oligodendrocytes which are not seen in the wild type mouse (Prume et al., 2018).

Other connections, including callosal connections are preserved in the "reeler" (Simmons et al., 1982). Some visual functions and receptive field properties are preserved as well (Sinex et al., 1979; Dräger, 1981; Simmons and Pearlman, 1983). Somatosensory functions are preserved (Guy and Staiger, 2017). On the whole the "reeler" and the experimentally induced microgyria (below) are examples of functional resilience of cerebral cortex against severe anatomical alterations.

Less dramatic alterations of neuronal migration were described in hypothyroidism (Berbel et al., 1993) or as neuronal ectopias of various origin sometimes associated with epilepsy (reviewed in Luhmann, 2016).

Neuronal differentiation

The acquisition of neuronal phenotype involves changes at the soma-dendritic complex and at the axon. These changes are related to the genetic makeup of the neuron but require interaction with the cellular environment, which in turn might mediate interaction with the environment of the animal. The acquisition of both the dendritic and the axonal phenotype involves progressive and regressive events. The progressive events comprise elongation, mediated by growth cones, radial growth, formation of spines or synaptic boutons and branching. The regressive events, are extremely common across structures, systems, and species and involve elimination of part of the dendritic arbor (Leuba and Garey, 1984; McMullen et al., 1988; Ramoa et al., 1988; Ulfhake et al., 1988; Koester and O'Leary, 1992). In extreme cases the regressive events can change the overall neuronal morphology from the pyramidal to the spiny stellate typology (Vercelli et al., 1992; Callaway and Borrell, 2011). The dendritic changes involve modifications of the dendritic microtubules (Khatri et al., 2018; Parcerisas et al., 2020) under the control of dendritic competition (Linden and Serfaty, 1985), activity (Callaway and Borrell, 2011; Skelton et al., 2020), experience

(Breach et al., 2019; Villanueva Espino et al., 2020). The areal location of cortical neurons, not their target, was found to be related to the morphology of dendritic arbors (Vercelli and Innocenti, 1993).

Formation of connections

Axonal differentiation involves elongation to target, guided by environmental cues, target recognition, target ingrowth, synaptogenesis (reviewed by Kolodkin and Tessier-lavigne, 2011; Zhang et al., 2017; Balaskas et al., 2019). The formation of connections is characterized both by progressive and regressive events. The latter consist in the massive elimination of long transient axons, initially described for the callosal connections of the cat (Innocenti et al., 1977; Innocenti, 1981; Berbel and Innocenti, 1988; LaMantia and Rakic, 1990) and later generalized to several systems and species, particularly intra-hemispheric and corticospinal projections (O'Leary and Stanfield, 1986; De León Reyes et al., 2019; reviewed in Innocenti and Price, 2005). Axonal selection occurs near the target (reviewed in Innocenti, 2020). At the time of cortical ingrowth transient short branches and synapses are generated mainly in the white matter while the distribution of intracortical branches and boutons is as in the adult, although it undergoes a phase of exuberant synaptogenesis (Innocenti and Price, 2005; Innocenti, 2020). Subsequent radial axonal growth paralleled by cytoskeletal changes (Guadano-Ferraz et al., 1990; Riederer et al., 1990) leads to myelination of axons whose diameter exceeds the threshold of 0.2 µm (Berbel and Innocenti, 1988). Continuing growth leads to cohorts of different axonal diameters in various CNS pathways, notably those leaving different cortical areas (Tomasi et al., 2012; Innocenti et al., 2014).

Activity dependent formation of connections: Ocular dominance

The final acquisition of the axonal phenotype is expressed in the formation of interneuronal connections. This step is controlled by activity. The best studied example is the shift of ocular dominance in the primary visual areas. The field was initiated by the findings that closing one eye during early life led to loss of the responses to that eye in visual area 17 (V1) of the cat and signs of neuronal atrophy in LGN neurons. Raising the kitten with artificially induced strabismus led to loss of binocularly responsive neurons (Hubel and Wiesel, 1965; Wiesel and Hubel, 1965). The work was later generalized to the macaque monkey where the loss of responses to the deprived eye could be ascribed to the loss of geniculocortical projection concerned with that eye (Hubel et al., 1977). These findings had an enormous resonance, which continues to this day. Subsequent work was performed in rodents with improved anatomical resolution. Neurons receiving from the deprived eye were found to lose synaptic spines (Coleman et al., 2010; Yu et al., 2011; Sun et al., 2019). Studies aimed at defining the conditions which terminated the critical period discovered the role of GABAergic transmission (Huang et al., 1999; Fagiolini and Hensch, 2000), specified the role of perineuronal extracellular matrix and the behavior of geniculo-cortical terminations (reviewed in Hensch, 2005; see also Berardi et al., 2004). Studies succeeded at reopening the critical period in mature animals by locally infused norepinephrine (Kasamatsu et al., 1979), reducing intracortical inhibition (Harauzov et al., 2010; Cisneros-Franco and De Villers-Sidani, 2019), deleting proteins of the Major Histocompatibility Complex (Adelson et al., 2016), grafting embryonic inhibitory neurons (Davis et al., 2017), subministering the antidepressant fluoxetine (Steinzeig et al., 2019), injuring the optic nerve (Vasalauskaite et al., 2019), depriving the animal of somatosensory and auditory input (Teichert et al., 2019). These studies raise the hope that recovering juvenile plasticity might be used to counteract pathologies of the adult brain (Hübener and Bonhoeffer, 2014).

A different concept of plasticity: homeostatic plasticity was put forth (reviewed in Turrigiano and Nelson, 2004). It signifies that neurons deprived of input tend to increase their firing. Confirming this concept, after short (2 h) periods of monocular deprivation, in adult humans, the BOLD signal was boosted for the deprived eye in V1, V2, V3 and V4, specifically for high spatial frequency of the stimulus, consistent with the involvement of the parvocellular input to the cortex (Binda et al., 2018).

Plasticity of cortical connections

The selection of juvenile cortico-cortical connections from the exuberant stock mentioned above is modulated by different conditions. One is the peripheral input in the form of organized thalamocortical input (Shatz, 1977) or retinal input. Two changes were caused by these manipulations: loss of projections which would normally be maintained (Innocenti and Frost, 1980; Zufferey et al., 1999) and maintenance of projections which would normally be eliminated (Shatz, 1977; Callaway and Katz, 1991; Zufferey et al., 1999; De León Reyes et al., 2019). These results suggested that cortical axons are labile at birth and require activity for their stabilization and maintenance. Short periods of normal vision are sufficient to stabilize the connections and trigger their further differentiation (Innocenti et al., 1985; Zufferey

et al., 1999; Box 1.1). Modification of cortical connections in development, with stabilization of connections normally deleted, were also caused by hypothyroidism (Berbel et al., 1993) and early cortical lesions (Restrepo et al., 2003).

Pietrasanta et al. (2012) have reviewed the consequences of deprivation on the development of callosal connections in rats and their role in the binocularity of cortical responses.

In humans, Friston has over the years supported the view of schizophrenia as a disconnection syndrome presumably caused by failed stabilization of connections in development (reviewed in Friston et al., 2016). Impaired development of middle and posterior sector of the Corpus Callosum where described in 6-16 year old children with early-onset bipolar disorder (Lopez-larson et al., 2013) and in congenitally blind children (Ptito et al., 2008; Cavaliere et al., 2020, and below).

BOX 1.1. THE DEVELOPMENT OF CALLOSAL AXONS BETWEEN VISUAL AREAS 17 AND 18 IN CATS BINOCULARLY DEPRIVED OF VISION WITH EYELID SUTURE.

Binocular eyelid suture prevents pattern vision, resembling bilateral cataract. It massively reduces the number of axons interconnecting the primary visual areas of the two hemispheres and the loss appears to be irreversible (Innocenti and Frost, 1980; Innocenti et al., 1985). The majority of the remaining axons are severely stunted; they are thinner and exhibit fewer branches, and synaptic boutons (Figs. 1.1 and 1.2). The effects are already seen after 1 month of deprivation. However, 10 days of normal visual experience after natural eye opening (at around 7 days) prevent the loss of callosal axons (Innocenti et al., 1985) and after 8 days of normal visual experience the arbors developed nearly normally in spite of binocular deprivation (Fig. 1.3). This suggests that even a limited amount of normal visual experience can stabilize the juvenile axon and triggers its normal development. Intrareal connections are similarly affected. They lose the normal patchy distribution of terminals and single axons are severely stunted (Figs. 1.4 and 1.5). These concepts might apply to other conditions where deprivation has deleterious consequences, in particular to the acquisition of language (Innocenti, 2007). Interestingly the distributions of CC axon diameters from areas 17 and 18 in the cat (Houzel et al., 1994) and in the monkey (Tomasi et al., 2012) were never previously compared and appear to be similar.

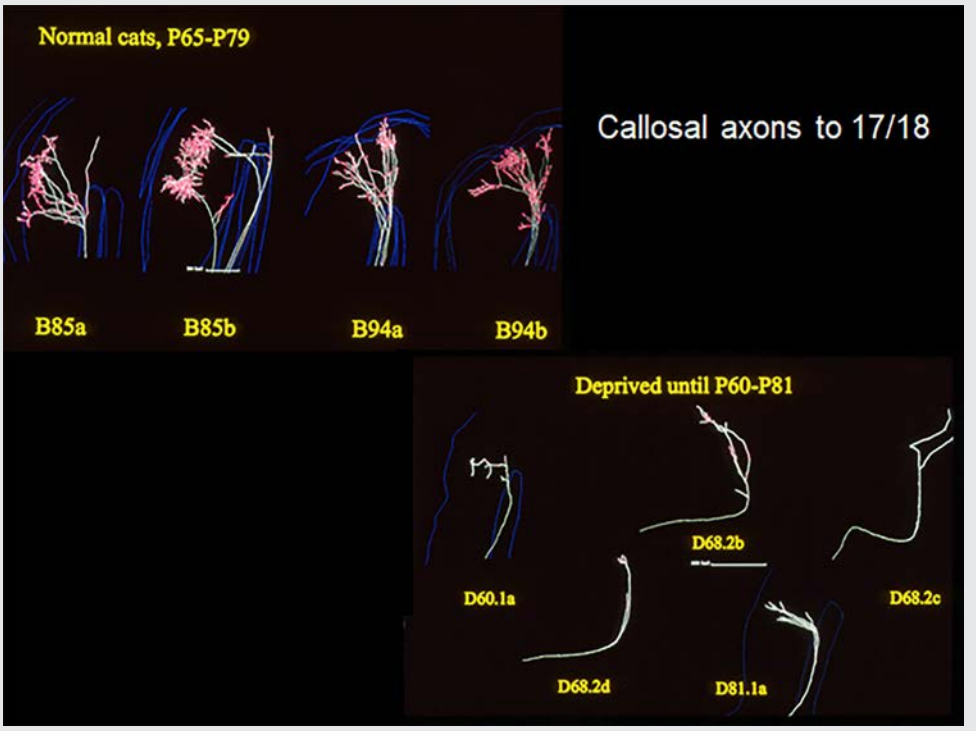

Fig. 1.1. Binocular deprivation by eyelid suture for at least 60 months stunts the development of callosal axons interconnecting areas 17 and 18 in the cat (D axons). The B axons are from normally reared adult cats. From Zufferey, P.D., et al., 1999. The role of pattern vision in the development of cortico-cortical connections. Eur J Neurosci 11, 2669–2688. doi: 10.1046/j.1460-9568.1999.00683.x, modified.

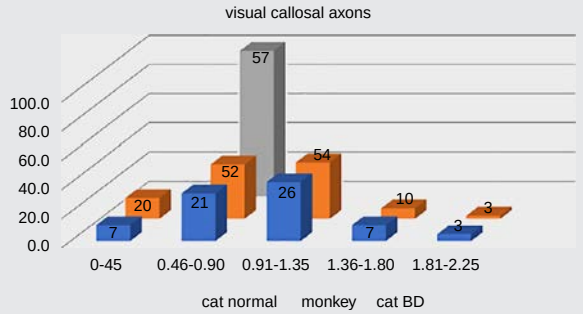

Fig. 1.2. Binocular deprivation results in thinner callosal axons interconnecting the visual areas 17 and 18 in the cat. Notice the previously unknown similar distribution of diameters of visual callosal axons in cats (Houzel et al., 1994) and monkey (Tomasi et al., 2012). The number of axons in each class of diameters is on the corresponding column.

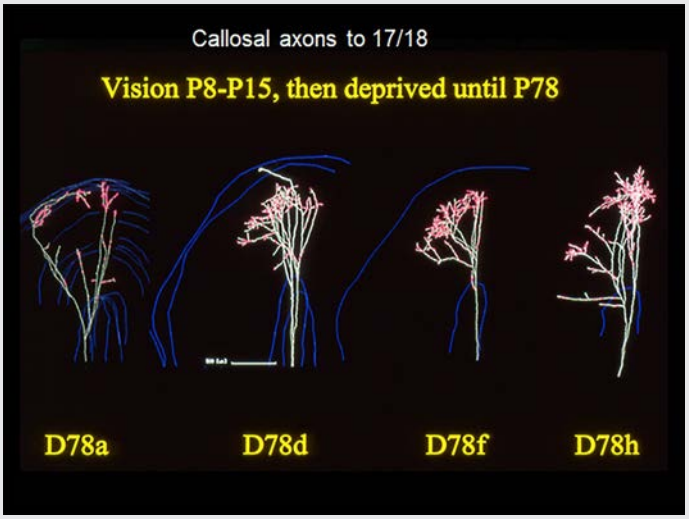

Fig. 1.3. A short period of normal vision followed by binocular deprivation triggers a nearly normal development of callosal axons. From Zufferey, P.D., et al., 1999. The role of pattern vision in the development of cortico-cortical connections. Eur J Neurosci 11, 2669–2688. doi: 10.1046/j.1460-9568.1999.00683.x, modified.

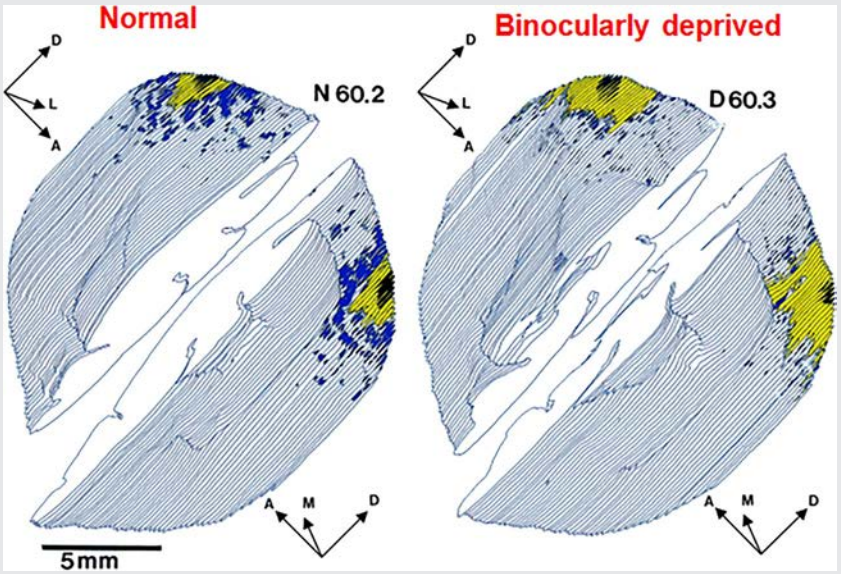

Fig. 1.4. Binocular deprivation prevents the clustered distribution of local connections in the primary visual areas of the cat. Three-dimensional reconstruction of the occipital pole of two representative P60 animals. The concentric regions on the dorsal surface of the brains represent the core of injection, containing densely packed biocytin-labelled cell bodies (*black*), the region of diffusely distributed (*yellow*) and clustered (*blue*) axons. From Zufferey, P.D., et al., 1999. The role of pattern vision in the development of cortico-cortical connections. Eur J Neurosci 11, 2669–2688. doi: 10.1046/j.1460-9568.1999.00683.x, modified.

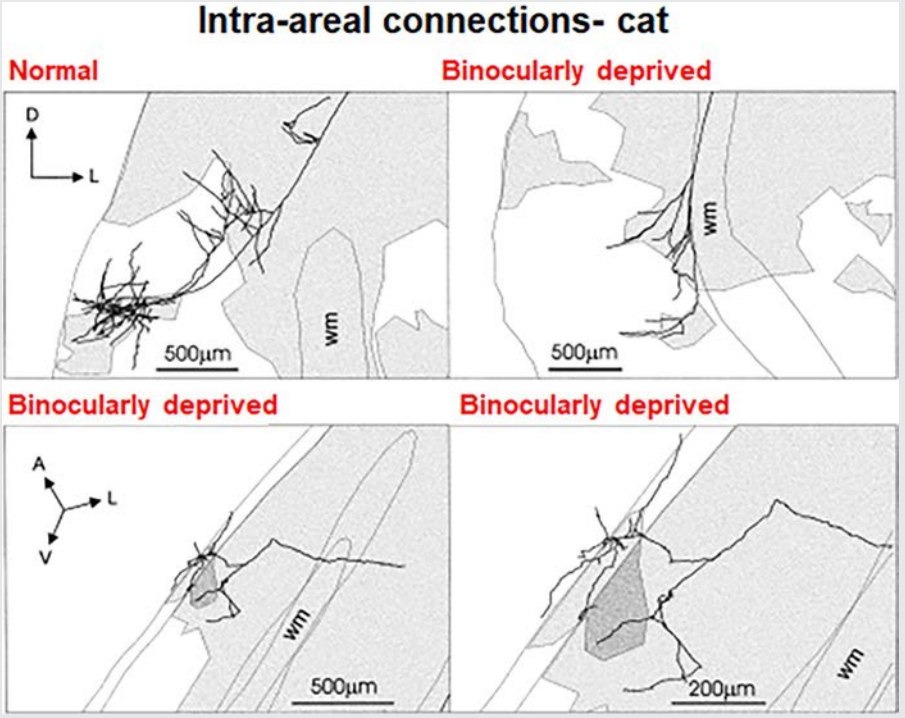

Fig. 1.5. Binocular deprivation by eyelid suture stunts the development of local axons in area 17 of the cat. From Zufferey, P.D., et al., 1999. The role of pattern vision in the development of cortico-cortical connections. Eur J Neurosci 11, 2669–2688. doi: 10.1046/j.1460-9568.1999.00683.x, modified.

Cytoarchitectonic/areal specializations

In the somatosensory cortex of rodents, the mystacial vibrissae (whiskers) are represented at the cortical level by "barrels," that is, cytoarchitectonic specializations in layer iv consisting, in the mouse, of a cellular rich wall and cellular poor hollow (Woolsey and Van der Loos, 1970). These specializations are exquisitely plastic in development. Cauterization of the whiskers in newborn mice leads to the disappearance of the corresponding "barrel" (Van Der Loos and Woolsey, 1973). In contrast, supernumerary vibrissae cause the appearance of supernumerary barrels (Van der Loos et al., 1984). A threshold number of axons are required to innervate the vibrissa follicle for the supernumerary barrel to appear and there is a linear correlation between the number of axons and the size of the barrel (Welker and Van der Loos, 1986). These findings spurred the powerful hypothesis that the sensory periphery has a direct control of cortical cytoarchitectonics (van der Loos and Dörfl, 1978). The concept was confirmed by the finding that retinal ablation in fetal monkey gave rise to a new cytoarchitectonic field between areas 17 and 18 (Rakic et al., 1991; Magrou et al., 2019). The mechanisms involved in the thalamic specification of barrel field architecture were reviewed (Dimou and Götz, 2012; Martini et al., 2018). Prenatal alcohol exposure decreased the size of the barrel field (Chappell et al., 2008).

Some degree of columnar organization of cell bodies is a feature of cortical cytoarchitecture noticed and discussed for more than 50 years (Bonin and Mehler, 1971 and quotations therein). The concept of "minicolumns" was revived recently (reviewed in Buxhoeveden and Casanova, 2002) as it appears to be at the crossroad between the developmental concept of "radial unit" (Rakic, 1988) and the physiologically defined "cortical columns" (reviewed in Mountcastle, 1997). The radial arrangement of cortical neurons varies across species which, sometimes, requires sophisticated morphometric methods (Rafati et al., 2016). Nevertheless, it was claimed to be altered in psychiatric conditions, including autism (Casanova et al., 2006; Casanova and Casanova, 2019).

Microgyria refers to the occurrence of abnormally small gyri at selective cortical sites, with abnormal lamination whereby mainly superficial layers are maintained while deep layers are mostly deleted. This defect appears spontaneously due to ischemic insults which interfere

with neuronal survival and migration in development. It can be induced in developing animals by different methods including the application of ibotenic acid which mimics the ischemic insult (Innocenti and Berbel, 1991). For methods to induce cortical malformations see Luhmann (2016). Interestingly many neurophysiological properties of the microgyric cortex were preserved (Innocenti et al., 1993). This was also the case in a human case of microgyria (Innocenti et al., 2001) and in a monkey case of spontaneous microgyria in the motor cortex (Schmidlin et al., 2009). However abnormal excitability and auditory perceptions were described in animal work (Luhmann, 1998; Escabí et al., 2007).

System-wide changes in development

Many, perhaps most of the changes in the developmental events mentioned above are not restricted to the topical modifications identified but are rather the expression of more widespread changes in brain structure. This is due to the fact that different brain parts influence each other's development via trophic interactions and/or activity.

The late Bertram Payne reviewed several years of work in his laboratory on the consequences of lesions of areas 17 and 18 in the cat at birth, 30 days and adulthood (Payne, 1999). In summary, the anatomical consequences of the lesion differed at each age. They involved differential degeneration of retinal ganglion cells classes, maintenance or elimination of geniculocortical projections, reorganization of projections among peristriate visual areas and enhanced projections from extrastriate visual areas to superior colliculus. The lesions, therefore, caused a complete rewiring of visual areas, accompanied by some degree of sparing of visuomotor behavior.

We investigated two cases of patients with early lesions of primary visual areas (MS and FJ; Kiper et al., 2002; Knyazeva et al., 2002). The patient with the earliest lesion (MS) improved with age in some visual tests but both patients remained impaired in tasks of figure-ground discrimination. The patients were studied with fMRI and EEG but the answers obtained with these methods were insufficient. Therefore, we developed an animal model consisting of early lesion of primary visual areas in the ferret (Restrepo et al., 2003). In this model the residual visually responsive portion of cortex showed scrambled retinotopy and the visual callosal connections were altered. It remains to be investigated if the patients MS and FJ mentioned above had scrambled retinotopy in their visually responsive cortical regions and if this was the cause for their impaired figure ground discrimination. Scrambled retinotopy was also reported in a case of early cortical lesion (Mikellidou et al., 2019), who however, was apparently not tested for figure-ground discrimination.

A particularly dramatic re-routing of visual projections to the auditory and somatosensory thalamus was obtained in the hamster with early lesions (Frost, 1981). Consequent to the lesion visual responses could be obtained in auditory cortex, (Ptito et al., 2001). Comparable results were obtained in the ferret (Sharma et al., 2000). Magrou et al. (2019) reported, in the monkey, changes in the thalamic projection to the cortex abnormally developed between areas 17 and 18 after early enucleation (above). Joint reduction of excitatory-inhibitory balance is expected to cause circuit-wide changes in an animal model of Rett syndrome (Banerjee et al., 2016). Conversely, multiple factors impact the development of prefrontal cortex in rodents (Kolb et al., 2012).

Studies on the consequences of early, or congenital visual deprivation have revealed widespread changes in connections including, in humans, atrophy of the geniculostriate system, pulvinar and corticocortical pathways including, as expected from the animal work (above), the posterior sectors of the Corpus Callosum (Ptito et al., 2008; Reislev et al., 2016; Cavaliere et al., 2020). The same deprivations in animals and in humans have provided evidence of cross-modal plasticity with the visual cortex becoming activated by somatosensory or auditory stimuli (Rauschecker, 1995; Watkins et al., 2013). Which pathways might be responsible for cross-modal plasticity is unclear. In development, exuberant, transient projections are formed from auditory and somatosensory areas to visual areas in the cat (Innocenti and Clarke, 1984; Dehay et al., 1988; Innocenti et al., 1988). Some of these projections remain in the adult cat and monkey (Innocenti et al., 1988; Falchier et al., 2002; Rockland and Ojima, 2003) and could be responsible for the cross-modal plasticity. In addition, somatosensory information could be carried by thalamocortical afferents (Müller et al., 2019).

In congenitally deaf cats different sectors of the auditory cortex were found to improve visual localization and visual motion detection (Lomber et al., 2010). Butler and Lomber (2013) have reviewed the system-wide changes caused by early deafness.

Language learning

Provides a fascinating example of functional plasticity in development probably exploiting some of the mechanisms above, in particular, the selection and functional validation of juvenile, labile cortical connections. The best explored feature is the development of phonemic boundaries (Kuhl, 2010) (e.g., the l/r contrast) which characterizes Indo-European languages but is absent in Japanese. Initially Japanese children can discriminate both phonemes but their subsequent exposure to their native language erases the boundary. Phonetic learning

occurs within the first year while syntactic learning, between 18 and 36 months (Kuhl, 2010). Phonemic learning is enhanced by social interaction as if a "social gating" exists for language learning. Top-down language processing occurs between 3 and over 10 years (Skeide and Friederici 2016).

Word learning revealed changes in Fractional Anisotropy (FA) in the left precentral gyrus, postcentral gyrus and middle-temporal white matter of preschool children, suggestive of some kind of white matter plasticity (Ekerdt et al., 2020).

A critical period might exist for the later developing aspects of language acquisition since children raised in isolation seem to have acquired, at best, rudimentary language, a striking similarity with the consequences of visual deprivation in animals (reviewed in Innocenti, 2007).

MYELIN PLASTICITY

The view that axons are cables faithfully conducting information between neurons has been superseded by the evidence that they participate in information processing by performing three kinds of computational operations: mapping, differential amplification and temporal transformations (Innocenti et al., 1994, 2016). The latter operation depends on axonal conduction velocity which in turn depends on axon diameter. These two parameters and axon length determine the conduction time (delay) between neurons. Myelin thickness keeps a nearly stable relation with axon diameter whereby the g ratio, the ratio between inner and outer axon diameter, stabilizes around 0.6–0.7, for optimal axonal conduction (Rushton, 1953; Smith and Koles, 1970; Drakesmith and Jones, 2018). It follows that myelin thickness tracks whichever changes in axon diameter are imposed by axonal plasticity in development. The existence of neurotransmitter receptors on oligodendrocytes and neurotransmitter release from axons are attractive conditions for the existence of direct coupling between axonal spiking and myelination (reviewed by Micu et al., 2018). This evidence probably clarifies how axonal conduction can be adjusted to pathway length in development in order to obtain synchronous activation of targets as in the auditory system (Seidl et al., 2010; Seidl and Rubel, 2016) or in visual callosal connections (Innocenti et al., 1994). In the auditory system axons of the trapezoid body remain thinner and less myelinated in animals raised with ear plugs (Sinclair et al., 2017) a finding resampling the consequences of binocular deprivation on visual callosal connections (Box 1.1).

In development, myelination is also under the control of thyroid hormones and is seriously impaired by hypothyroidism (Lucia et al., 2018 and references therein). Social interaction within a critical period is required for the development of normal myelination in medial prefrontal cortex axons (Makinodan et al., 2012) and for the development of normal social interactions, an effect which recalls that of visual experience on the development of visual callosal connections (Box 1.1).

In recent years the relations between axons and oligodendrocytes or oligodendrocytes precursor cells (OPCs) have revealed high degrees of complexity. Oligodendrocytes are not only involved in producing myelin, but also in supporting axonal metabolism, probably via transport of lactate (Fünfschilling et al., 2012; Lee et al., 2012).

An impressive body of evidence has documented the occurrence of myelin plasticity in the adult rodent, linked to the continuous production of OPCs (Rivers et al., 2008; Kang et al., 2010; Emery, 2010; Hill et al., 2018; Hughes et al., 2018; see Chang et al., 2016, for review). Fields (2015) has collected over several years evidence that myelination is modifiable by activity, hence might provide a basis for plasticity (memory) in addition to synaptic modifications (reviewed in Fields and Bukalo, 2020). Not only OPCs might be involved in adult myelin plasticity, but perinodal astrocytes as well (Dutta et al., 2018). Myelin plasticity in the adult is required for the acquisition of motor skills in mice (Xiao et al., 2017) and neuronal activity is required for oligodendrogenesis and adaptive myelination (Gibson et al., 2014). However, Yeung et al. (2014) have excluded adult genesis of oligodendrocytes in the adult human brain by studying the incorporation of ^{14}C. Some degree of remyelination may occur in MS patients (Kipp et al., 2012) and in some severe cases production of oligodendrocytes has been documented as well (Yeung et al., 2019).

It is unclear what enhanced myelination might achieve in the normal adult brain since the g ratio in most axons is close to the optimal 0.7 value (above). An increase in myelin could occur in two situations (i) myelination of unmyelinated or incompletely myelinated axons (Tomassy et al., 2014), of which a large number exists in the rodent brain, where most experiments have been performed and (ii) increased axon diameter which causes an increase in myelin thickness keeping the axon in the $g = 0.7$ range. In this second case myelination would rather be an epiphenomenon of the increased radial dimension of axons. In truth, the evidence for increased myelination in humans is scanty (Scholz et al., 2009; Sampaio-Baptista et al., 2018).

ADULT PLASTICITY

There seems to be a limited amount of neurogenesis in the adult brain and, particularly in humans, the concept is controversial (Lucassen et al., 2019). Axonal growth

in also limited in the adult brain and the expression of plasticity has been restricted to changes in response properties, whose nature is in general unknown. This is not to say that the adult brain is devoid of plasticity. Although some mechanisms supporting brain plasticity may continue through life, for example myelination (Wang and Young, 2014 and above), and synaptogenesis, the basis of adult plasticity is different and largely discussed in this volume. Changes in synaptic strength, including both increase and decrease, based on Hebbian-like rules or other principles (Magee and Grienberger, 2020), are clearly possible at any age (Merzenich et al., 2014) and also provide the basis for memory (Kandel, 2001; see Chapter 2 by Mancini et al.). This kind of plasticity is typically reversible. Local axonal sprouting and changes in dendritic spines and synapses which might alter excitatory-inhibitory balance are another mechanism of adult plasticity (Knott et al., 2002, 2006; El-Boustani et al., 2018). Ketamine administration was found to increase synapses in the adult brain (Pryazhnikov et al., 2018 and references therein) with therapeutic perspectives for the treatment of depression. The role of astrocytes in synaptic plasticity has been advocated (Singh and Abraham, 2017). Changes in neural network whose structural and functional complexity might escape us for a long time (Innocenti, 2017) can lead to unpredictable shifts in processing simulating a holistic behavior of brain function.

Kaas et al. (1983) and Merzenich et al. (1984) were probably the first to report that in the adult animal "When a restricted sector of somatosensory cortex is deprived of its normal pattern of activation in adult mammals by sectioning peripheral nerves or dorsal roots, or by amputation of a body part, the affected cortex rapidly becomes largely or completely reactivated by inputs from adjoining and nearby skin fields." The result was ascribed to unmasking and potentiation of pre-existing sub-threshold afferents as well as to sprouting of local connections. The first mechanism was supported by the finding that in the adult monkey which underwent lesion of the primary motor cortex improved function was sustained by enhanced activity in premotor cortex, supplementary motor and cingulate motor cortex (Rouiller and Olivier, 2004). The second mechanism was validated by work in the visual system where a cortical site corresponding to an artificial scotoma caused by retinal lesion was found to be invaded by axons sprouting from the surrounding intact cortex (Darian-Smith and Gilbert, 1994). Remodeling of intrinsic axons in V1 was reported in monkeys trained to identify collinear contours; changes consisted in addition as well as elimination of axonal segments imaged in-vivo (Van Kerkoerle et al., 2018).

Caleo (2018) has reviewed several studies demonstrating either enhanced or decreased callosal input after adult cortical lesions in animals and in humans.

Several studies aimed at exploring the potential of adult plasticity in regenerating long projections, in particular the corticospinal projections were initiated by the finding that myelin associated proteins impair the regeneration long projections in the adult and the inhibition can be overcome by anti-myelin antibody (Caroni and Schwab, 1988; Schwab 1990). These efforts have met with some success (Freund et al., 2009) although they still encounter some unknown obstacles (Beaud et al., 2020) as documented also by preliminary clinical trials (Kucher et al., 2018). Other attempts to repristinate growth of long connections in the adult included the use of peripheral nerve grafts (David and Aguayo, 1981) bulbar olfactory ensheathing cells (Tabakow et al., 2014) and other means (Endo et al., 2009). It is probable that attempt to repristinate growth of long axons in the adult by local action on the adult axons will not be able to repristinate the conditions which have allowed the precisely orchestrated axonal growth to target in development.

ADAPTIVE VS MALADAPTIVE PLASTICITY

Although, as mentioned in the introduction, the evolutionary goal of neuroplasticity may be that of favoring adaptation of the animal to the environment, evidence of neuroplasticity in pathological cases, including, autism, schizophrenia and Alzheimer disease have been reported (Oberman and Pascual-Leone, 2013). Some of the changes may be caused by abnormal developmental trajectories including neuronal migration (Ayoub and Rakic, 2015), maintenance of projections which should have been eliminated or other developmentally based abnormalities in connections (e.g., Innocenti et al., 2003; Herbert et al., 2004; Zikopoulos and Barbas, 2010). Transcranial Magnetic Stimulation can alleviate the symptomatology in some cases (Oberman and Pascual-Leone, 2013; see for instance Chapter 5). Behavioral training successfully recovered cortical network dysfunctions in a rodent model of autism (Zhou et al., 2015). Attentional training has been found to improve working memory (reviewed in Spencer-Smith and Klingberg, 2015).

CONCLUSIONS

I have suggested that neuroplasticity is at the roots of why the nervous system exists at all. That is, the nervous system exists so that an input from the environment is transformed into an output by the animal. In a cursory way, I have described many aspects of neuroplasticity which support this view. Changes in the brain, particularly striking in development, are caused by sensory

inputs, through the eyes, ears, skin, and probably muscles. Other aspects of neuroplasticity seem to be related to the adaptation of the brain to its body. The survival of neuron number in development depends on the size of the periphery, and cytoarchitectonic modifications are related to the structure of sensory organs, were they skin or retina. These adaptations might assist the brain to implement the sense of body ownership, a non-trivial operation which can be manipulated in adulthood (Ehrsson et al., 2004; Blanke et al., 2015).

But is the response to the environment the only cause of neuroplasticity? Or, is it because the manipulation of sensory inputs are the only conditions easily amenable to experiment and observation? Can one think of instances of neuroplasticity other than those driven by peripheral inputs? Perhaps one can, if one considers the brain a machine whose overall performance can be improved by tinkering. Therefore, one could consider changes in the brain which decrease energy costs and/or improve speed of information transfer (Wang et al., 2008). Also, neuron number increases along the mammalian radiation (Gabi et al., 2016) as does the number of cortical areas (Kaas, 2013; Halley and Krubitzer, 2019). Finally, it can be seen that morphological and functional hemispheric lateralization are distinctive features of the human brain. All these changes occur along the lines of increased differentiation and improve brain performance; but this kind of neuroplasticity is in the hands of evolution and of its fiddling with developmental mechanisms (Innocenti, 2011; Finlay and Uchiyama, 2015; Finlay and Huang, 2020), and fall beyond the scope of the present chapter.

It is in no way clear that the kind and degree of neuroplasticity should remain the same across the mammalian radiation. The case of myelin, in particular, seems to show decreased plasticity in the human vs the rodent brain. This calls for the emergence of a new discipline comparing the various aspects of neuroplasticity across fila.

What can be said by now is that the far more robust neuroplasticity of the developing compared to the adult brain imposes the search and implementation of strategies that might protect the brain of the child.

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