Introduction

1

"If the human brain were so simple we could understand it, we would be so simple we couldn't" (Emerson M. Pugh)

The human brain contains an estimated 100 billion neurons, connected by 10^{14} synapses. The requirement for such a complex organisation becomes understandable when we realise this one single organ in our body is responsible for basic functions such as breathing, for senses such as sight, hearing, smell and taste, for allowing us to recognise both others and ourselves, for making plans and carrying them out physically in the form of movement, as well as for emotions such as happiness, sadness, love and fear.

Plasticity

A vital property of the brain is the ability to learn, or to undergo changes in response to environmental influences. In neuroscience, the degree to which the brain is able to undergo changes is referred to as plasticity. Functionally, plasticity is at the basis of learning to play the guitar, learning to speak Spanish, recognising certain faces or learning and remembering the multiplication table of four. Our ability to learn relies on the potential of the brain, and most of all the neocortex, to change its neuronal connectivity through experience. Neurons in the neocortex are connected with one another by means of anatomical subcellular specialisations called synapses, locations where information is conveyed from one neuron to another. Synapses may be electrical, in which case the cytoplasm of the neurons is connected, or chemical, when information is conveyed using neurotransmitters, substances excreted by one neuron and bound by receptors on the synaptic membrane of the postsynaptic neuron. The most common excitatory neurotransmitter is glutamate, released by excitatory neurons such as the neocortical pyramidal cell. Within the cortex, most excitatory synapses are found between axonal en passant boutons and postsynaptic dendritic spines, small protrusions on dendritic shafts.

Dendritic spines come in different sizes and shapes, ranging from mushroom spines, characterised by a big spine head and a clear neck, to filopodia, long thin protrusions with a high motility and low stability. The morphology of the spine tells a great deal about the synapse the spine carries. A large spine head is indicative of a big synapse, reflecting the amount of glutamate receptors, which in turn corresponds directly with synapse strength. Spines with clear spine heads, such as mushroom spines, tend to

be more stable than spines lacking a spine head and are long-lived, persisting for months or longer.

Functional and structural activity-dependent synaptic plasticity is thought to be at the basis of learning and memory by changing neuronal connectivity. This may be accomplished by strengthening or weakening of existing synapses, by local synapse turnover in which synapses may be lost or formed, or by more extensive rewiring in the form of neurite outgrowth and retraction (figure 1).
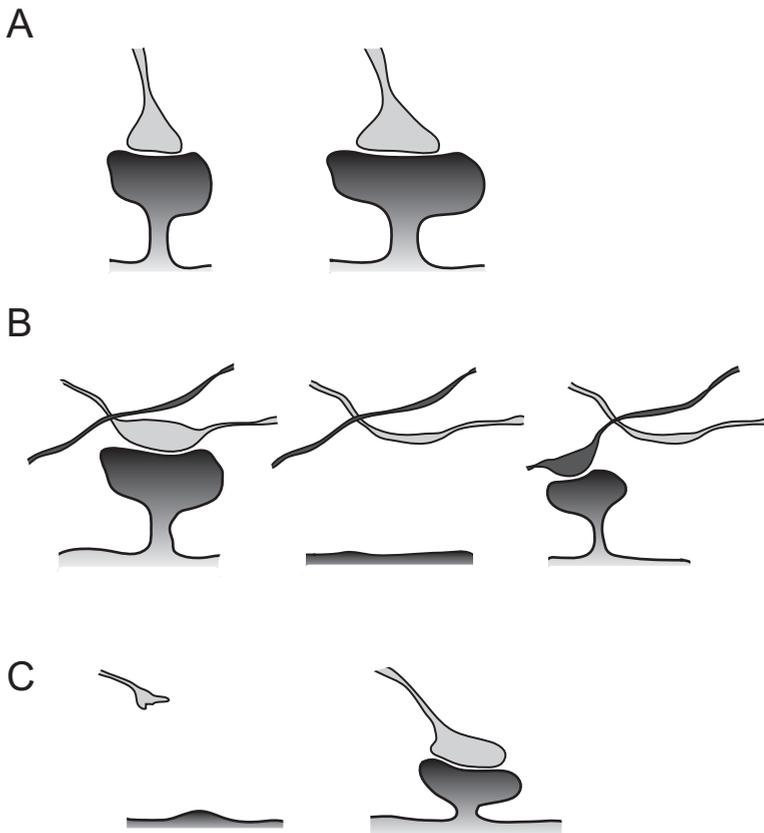

Figure 1. Three ways to change neuronal connectivity. a) Synaptic strengthening or weakening. Existing synapses are maintained but their efficacy is altered. b) Local synapse turnover. Existing synapses are lost and new synapses formed between neurons that contact each other. This results in the rewiring of neuronal connections. c) Neurite outgrowth to form a new synaptic connection. More extensive rewiring can be achieved by neurite outgrowth, allowing synapse formation between neurons that did not previously contact each other. A colour version of this figure is available in chapter 12.

Critical periods of plasticity during life

Plasticity in the neocortex is a cornerstone of our ability to learn and adapt to our environment. It occurs with active training, passive exposure and after lesions. Any adult will acknowledge that the ability to learn does not remain constant as time proceeds and we grow older; while learning to speak a foreign language is child's play when we are young, the same task may prove too difficult once we have reached a certain age. During critical periods in our childhood and adolescence, the neocortex shows greatly enhanced plasticity that facilitates the acquisition of skills and knowledge that we use and build on for the rest of our lives.

Anatomically, enhanced plasticity of the cortex during critical periods in development is reflected by a higher turnover of dendritic spines, axon growth and axon retraction during this period, allowing more rapid adjustments of synaptic connectivity. In contrast, the majority of dendritic spines in the adult animal are stable for long periods of time, and the turnover rate is low. This has been observed in different cortical areas [Grutzendler et al., 2002; Trachtenberg et al., 2002; Holtmaat et al., 2005; Holtmaat et al., 2006].

In the last decades, neocortical plasticity has been studied extensively in a range of cortical systems, such as the somatosensory barrel cortex and the primary visual cortex. These efforts have contributed significantly to our understanding of how the neocortex is organised, how experience alters neuronal responses, and why it is that neocortical plasticity is enhanced during certain 'critical periods' in development. A proper understanding of the molecular mechanisms regulating critical period plasticity is important, since dysregulation of neocortical plasticity and wiring during development is at the heart of many disorders of the brain, ranging from a lazy eye to schizophrenia and from epilepsy to different types of mental retardation. Knowledge about the molecular events regulating plasticity may ultimately allow us to control neocortical plasticity during development or to reactivate it in adulthood for clinical purposes.

The primary visual cortex as a model system

In our efforts to understand how neuronal circuits in the neocortex are altered under the influence of experience, plasticity in the primary visual cortex (V1) has become the most popular model system. The main reason for this popularity is the correlation between the anatomical and functional organisation of V1. In addition, visual

experience can easily be experimentally manipulated, and the effects are measurable molecularly, physiologically, as well as anatomically. Adding to this, the way in which plasticity of the visual cortex is regulated with age is similar to the way our ability to learn is, thus providing an excellent model for studying the biological and physiological mechanisms that underlie regulation of critical periods in cortical development.

Area V1 is located caudally in the brain, in the occipital neocortex. Visual information from our environment enters the central nervous system at the level of the eyes, from where it is relayed to the visual cortex via the lateral geniculate nucleus (LGN) of the thalamus [Hubener, 2003] (figure 2). The visual cortex is built up of six cortical layers. Information from the thalamus enters the visual cortex predominantly in layer 4 to then be passed on to layer 2/3, this is the first site within the visual system where visual information from the two eyes converges onto single neurons.

In the 1960s, Hubel and Wiesel demonstrated that V1 shows an intriguing correlation between its anatomical and functional layouts [Hubel et al., 1962]. Neurons in V1 respond to specific features of visual input, such as stimulus orientation, direction, spatial frequency, location in visual space and the eye providing the visual input. Responsiveness to these features is anatomically organised: neurons responding to the left or right eye are clustered in respective ocular dominance (OD) columns [Hubel et al., 1963]. In addition, they are organised in pinwheels according to the stimulus orientation they respond to best [Bonhoeffer et al., 1991]. From the retina through the primary visual cortex a retinotopic organisation is maintained, meaning that neurons responding to a neighbouring location in the visual field are located in a neighbouring position in the visual cortex [Talbot and Marshall, 1941]. These functional arrangements are underpinned by thalamocortical and intracortical axonal projections that link neurons with similar functional properties [Gilbert et al., 1989].

The initial development of neuronal circuitry of the visual system commences before the onset of vision. During early development, eye-specific thalamocortical axons form connections with their respective targets in V1 [Crowley et al., 1999; Sur et al., 2001; Sur et al., 2005]. Convergence of retinotopically matched input onto common postsynaptic neurons the visual cortex is the substrate for binocular vision, and proper visual input is essential for development, fine-tuning and maintenance of these binocular connections.
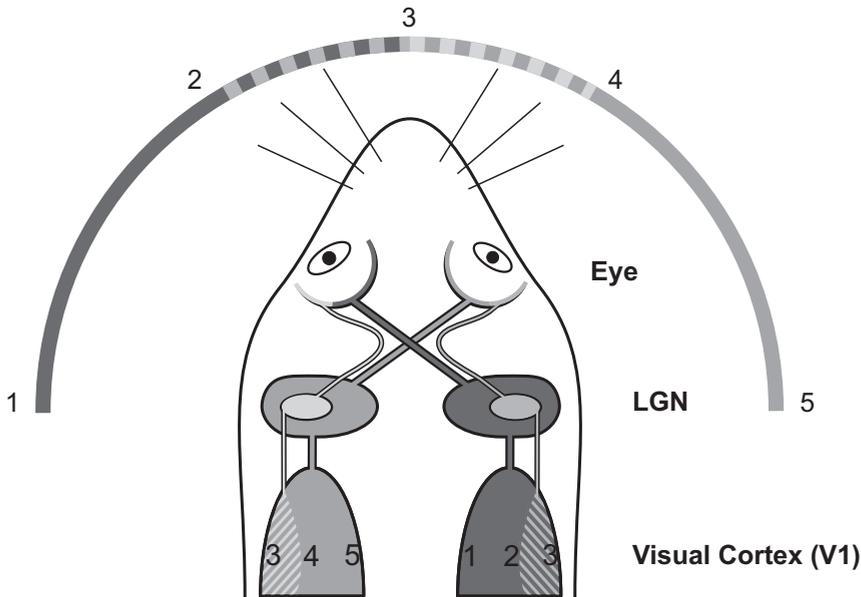
Figure 2. Schematic overview of the mouse visual system. The left and right visual hemifields and their representation throughout the visual system are colour-coded in red and green, respectively. The temporal parts of the retinas of both eyes see the small binocular part of the visual field directly in front of the mouse. Projections from the most temporal region of each retina (coded in light red and light green) innervate the ipsilateral lateral geniculate nucleus (LGN) in the thalamus. Axons of the majority of retinal ganglion cells (over 90%, reflecting the lateral position of the eyes) cross over at the optic chiasm to the contralateral hemisphere. In V1, binocular responses can be found in the lateral portion of this area, making up about one third of V1. The numbers in the visual cortex refer to the corresponding numbers in the visual field, illustrating the retinotopic organisation of the visual system. The '3' in the middle of the visual field is covered by both hemispheres, as in the mouse the primary visual cortex contains a small ipsilateral visual field representation (figure based on [Hubener, 2003], reprinted with kind permission from the author). A colour version of this figure is available in chapter 12.

Ocular dominance plasticity and the critical period for visual cortex plasticity

During the critical period, plasticity in the cortex occurs readily in response to environmental stimuli. Proper sensory experience and plasticity mechanisms during these critical periods are essential, as they facilitate fine-tuning and maintenance of the appropriate synaptic connections under the influence of sensory activity. In this way, sensory experience allows neuronal response properties such as visual acuity and binocular matching of orientation preference to reach adult levels [Fagiolini et al., 1994; Wang et al., 2010]. Visual acuity, an indication for the spatial resolution of

the visual system, is low at the start of the critical period and matures rapidly towards adult values during the critical period [Fagiolini et al., 1994].

Response properties and the anatomical organisation of neurons in V1 can be altered by manipulating visual input, for example by monocular deprivation [Hubel et al., 1964], misalignment of the optical axes [Hubel et al., 1965] or stripe rearing [Sengpiel et al., 1999].

Monocular deprivation, the closure of one of the two eyes, during development results in a loss of visual acuity in the deprived eye. A classic form of plasticity used as an experimental paradigm for understanding how activity shapes neuronal connectivity is ocular dominance plasticity: the rapid changes that occur in the circuitry of the primary visual cortex, resulting from imbalanced inputs from the two eyes. This artificial induction of amblyopia, or a lazy eye, by means of monocular deprivation, leads to a loss of physiological responses to the deprived eye, with neurons in the visual cortex shifting their responsiveness from the closed eye to the eye that had been open [Wiesel et al., 1963; Heimel et al., 2007] (figure 3).
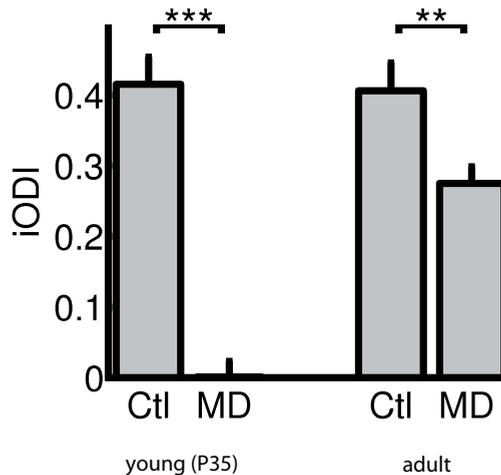

Figure 3. Ocular dominance plasticity in young and adult mice. Imaged ocular dominance index (iODI; contralateral eye response minus ipsilateral eye response divided by the sum of the responses) for young and adult B6 mice. An iODI of 1.0 corresponds to a response to contralateral eye input only, an iODI of −1.0 corresponds to a response to ipsilateral eye input only, whereas an iODI of 0.0 means equal responsiveness to both eyes. Monocular deprivation of the contralateral eye for 7 days from P28 results in an ocular dominance shift in the direction of the open eye. A much smaller shift is detectable in animals deprived in adulthood (figure based on [Heimel et al., 2007], reprinted with kind permission from the author).

Anatomically, this is reflected by retraction of thalamocortical projections conveying input from the deprived eye and growth of projections serving the non-deprived eye, resulting in an expansion of OD columns serving the open eye, at the cost of those serving the closed eye [Hubel et al., 1977; Stryker et al., 1986]. Thalamocortical axons representing the non-deprived eye have been shown to be more branched and have an increased total length. Conversely, axons carrying input from the deprived eye are less branched and have a reduced total length. Monocular deprivation also causes a reduction in axonal bouton size, as well as in the fraction of boutons containing mitochondria [Tieman, 1984].

Clearly, not only the acquisition of skills, knowledge and the maturation of neuronal response properties are easier when we are young. Amblyopia is a developmental disorder of the visual cortex in which vision through one of the eyes is impaired, with the eye itself appearing normal. Potential causes include strabismus, in which the optical axes of the eyes are misaligned, anisometropia, in which the two eyes do not have the same refractive power, and sensory deprivation. If left untreated, it may result in alterations in the visual cortex with permanent impairment of vision, in the form of a reduced visual acuity. Enhanced plasticity during the critical period, and as such enhanced sensitivity to sensory information, is exemplified by the easy inducibility of amblyopia in the lab, but also by the fact that treatment of amblyopia is generally successful in young children using an adhesive eye patch to cover the good eye, whereas in adults this therapy is not effective.

OD plasticity then is especially pronounced during the developmental critical period, a finding observed across a wide range of animal species [Berardi et al., 2000] including ferrets [Issa et al., 1999], monkeys [Horton et al., 1997] and rodents [Heimel et al., 2007] (figure 3). It should be noted that mice display a higher degree of adult plasticity [Sawtell et al., 2003; Hofer et al., 2006; He et al., 2006] than other animals including rats. For this reason, the period of heightened plasticity during development is usually referred to as a 'sensitive' period in mice.

Traditionally, visual plasticity has been studied in animals with good binocular vision such as cats, ferrets and primates [Dahlhaus et al., 2010]. More recently, molecular biological approaches have made the rodent visual cortex a more popular model system [Gordon et al., 1996]. Because of the lateral position of the eyes in mice, the binocular field of vision is relatively limited in size in these animals. Within the binocular region, which makes up about one third of the mouse visual cortex, the

vast majority of the neurons is responsive to input from both eyes. Still, there is a significant contralateral bias in the OD, implying the dominance of contralateral eye input over ipsilateral eye input, which is reflected by the majority of axons from the two eyes crossing over at the optic chiasm.

Although V1 in mice lacks a columnar organisation and OD columns, many fundamental aspects of visual function are similar to the way they are in higher animals. Also, similar effects of manipulation of visual input have been described, such as a reduced visual acuity in the deprived eye following monocular deprivation [Prusky et al., 2003]. OD plasticity can be induced in rodents as well [Maffei et al., 1992; Gordon et al., 1996] and many of its functional and anatomical aspects are very similar [Antonini et al., 1999]. A brief period of monocular deprivation during the sensitive period affects binocular response properties of neurons in the binocular zone of the visual cortex in a similar way as it does in higher animals such as cats and monkeys. Initially, after two to three days of monocular deprivation, the response to the deprived (generally the contralateral) eye input decreases, due to a reversible weakening of deprived-eye connections and reorganization of intracortical connections in the superficial layers [Trachtenberg et al., 2000; Trachtenberg et al., 2001]. Subsequently, after about seven days of deprivation, this is followed by an increased response to input from the non-deprived (ipsilateral) eye, accompanied by anatomical reorganization of thalamacortical afferents [Shatz et al., 1978; Antonini et al., 1993; Antonini et al., 1999; Frenkel et al., 2004].

The anatomical changes observed during ocular dominance plasticity in rodents match those underlying the shrinking and expansion of columns in higher animals, with thalamocortical axons serving the open eye expanding, while those serving the deprived eye stop growing [Antonini et al., 1999]. This similarity has facilitated a change in animal models and has made a set of genetic tools available for studying visual plasticity, resulting in the elucidation of molecular and cellular mechanisms underlying visual plasticity [Nedivi, 1999; Berardi et al., 2003; Tropea et al., 2009].

Dark rearing

The importance of visual experience, and thus of proper binocular vision during the sensitive period is emphasised by the effects of disturbed visual input, but also by the effects of an entire absence of sensory input. In dark-reared animals, grown up in total darkness from birth, cortical neurons display immature properties, such as reduced orientation and direction tuning, larger receptive field sizes, as well as

lower visual acuity. These are all immature neuronal properties typically observed at the time of eye-opening [Fregnac et al., 1978; Timney et al., 1978; Fagiolini et al., 1994]. In addition, dark rearing results in a postponement of the sensitive period for OD plasticity. A total lack of visual experience also affects the fine structure of neurons in V1, measured as changes in the size and density of dendritic spines, the post-synaptic elements for most excitatory connections [Wallace et al., 2004]. Normal developmental processes appear to be restored once the animals are exposed to light, allowing the recovery of neuronal response properties [Timney et al., 1978; Buisseret et al., 1982]. The effects of dark rearing have given rise to the belief that the dark reared visual cortex is merely a mirror image of an immature young cortex. To what extent the two are really the same remains to be determined.

Notch signalling

Great efforts have been put into elucidating the proteins and mechanisms underlying visual cortex plasticity. The model of ocular dominance plasticity allows us to investigate the influence and role of different proteins and factors in cortical plasticity. Instrumental in the identification of genes and proteins as regulators of cortical plasticity has been the use of both forward [Heimel et al., 2008] and reverse [Huang et al., 1999; Nedivi, 1999; Taha et al., 2002; Yang et al., 2005; Heimel et al., 2010] genetics.

The functional changes in ocular dominance plasticity are accompanied by structural rearrangement of thalamocortical and intracortical axons, as well as dendritic spine turnover. Naturally, signalling pathways regulating neuronal morphology and connectivity are prone to play an important role in visual plasticity [Tropea et al., 2009]. Examples of such signalling pathways and proteins that have been shown to affect both neuronal morphology and cortical plasticity include insuline-like growth factor 1 (IGF1) [Tropea et al., 2006] and neurotrophins such as Brain-Derived Neurotrophic Factor (BDNF) [Huang et al., 1999; Lodovichi et al., 2000; Gianfranceschi et al., 2003], myelin-related receptors [McGee et al., 2005] and PirB [Syken et al., 2006], as well as chondroitin sulphate proteoglycans (CSPGs) [Pizzorusso et al., 2006], a constituent of the extracellular matrix (ECM), and tissue plasminogen activator (tPA), an enzyme used to break down the ECM [Mataga et al., 2004; Oray et al., 2004]. The involvement of proteins and pathways related to the ECM reflects the important role of perineuronal nets in functioning of parvalbumin-expressing interneurons.

One interesting new candidate pathway is signalling through Notch1, a transmembrane receptor embedded within the neuronal plasma membrane [Bray, 2006] (figure 4).
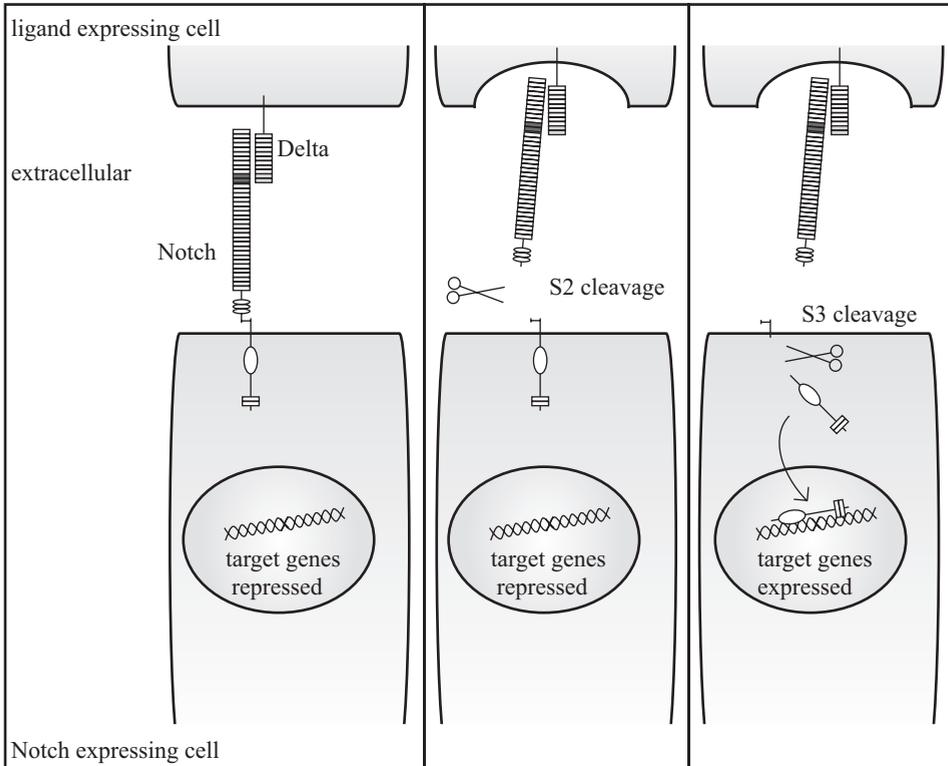

Figure 4. Canonical Notch pathway signalling. Binding of the ligand Delta ligand on one cell to Notch on another cell results in two proteolytic cleavages of Notch. S2 cleavage by ADAM10 generates a substrate for subsequent S3 cleavage by the γ-secretase complex containing presenilin. This last step results in release of the Notch intracellular domain (NICD), which enters the nucleus and interacts with the DNA-binding protein CBF1. Upon binding of Notch to CBF1, co-repressors are released and co-activators are recruited, resulting in transcription of target genes. A colour version of this figure is available in chapter 12.

The external domain of Notch (NED) contains a binding site for ligands. In mammals these are Jagged and Delta. Jagged and Delta are transmembrane proteins themselves, generally located in the cell membrane of neighbouring cells. Interaction of Notch with either of these ligands initially results in the NED being cleaved off and endocytosed by the ligand-bearing cell, together with the ligand to which it is bound. This allows subsequent cleavage of the remaining part of Notch near the plasma

membrane by presenilin [de Strooper et al., 1999], releasing the Notch Intracellular Domain (NICD), after which the NICD translocates to the nucleus. Previous work has demonstrated that cell-cell contact is required for Notch activation [Sestan et al., 1999]. In the cell nucleus, the NICD binds the transcriptional repressor C-promoter binding factor (CBF1/RBP-Jκ), turning it into a transcriptional activator, and in this way inducing transcription of target genes [Lu et al., 1996]. Notch1 is mostly known for its role in cell-fate determination and proliferation during development, but its expression in the central nervous system continues into adulthood, albeit at reduced levels [Sestan et al., 1999; Stump et al., 2002].

In the last decade, it has become clear that Notch regulates structural changes in developing neurons. Activation of the Notch1 signalling pathway results in enhanced neurite branching as well as reduced neurite outgrowth in postmitotic neurons [Berezovska et al., 1999; Sestan et al., 1999; Redmond et al., 2000], neuroblastoma cells [Franklin et al., 1999] and newborn neurons of the dentate gyrus [Breunig et al., 2007]. Also Hes1, the primary transcriptional target of Notch, has been shown to influence neurite morphology [Jessen et al., 2003]. The activation of Notch signalling upon cell-cell contact and the subsequent effects on neuronal morphology, suggest a negative feedback mechanism by which Notch regulates synaptic connectivity.
The idea that Notch may be an interesting protein from a perspective of cortical plasticity is supported by studies looking into in vitro plasticity and memory formation. Mice with reduced hippocampal Notch signalling display impaired long-term potentiation at CA1 synapses [Wang et al., 2004]. Interfering with Notch signalling also negatively affects certain types of learning and long-term memory in mice and Drosophila [Costa et al., 2003; Presente et al., 2004; Ge et al., 2004].
In addition, interactions between Notch1 and amyloid precursor protein (APP) processing have been described [Song et al., 1999; Fischer et al., 2005; Fassa et al., 2005]. APP is the protein that, when cleaved by presenilin, may give rise to the beta amyloid plaques in the brain that are characteristic hallmarks of Alzheimer's disease. Both Notch1 and APP are transmembrane proteins, both are substrates for the gamma-secretase activity of presenilin, and the two have been shown to interact physically. Expression of Notch is increased in Alzheimer's disease [Selkoe, 2001] and other brain disorders [Berezovska et al., 1998; Fischer et al., 2005; Ishikura et al., 2005; Nagarsheth et al., 2006], suggesting it may play a role in neurodegeneration.

Altogether, this renders Notch1 an interesting candidate protein when studying the molecular pathways regulating cortical plasticity.

Screening for new candidate proteins in cortical plasticity

Clearly, the number of genes and proteins potentially involved in cortical plasticity is vast. In order to obtain a coherent overview into those molecules without having to test them one by one, an approach adopted in the last decade is to study the broad-scale changes in gene expression resulting from plasticity-manipulating experimental paradigms such as monocular deprivation. Microarray studies have provided insight into the gene networks and signalling cascades potentially underlying visual cortex plasticity [Tropea et al., 2006; Majdan et al., 2006] and have resulted in many new candidate genes for closer examination.

Importantly, rather than studying the synapse, microarray studies have made use of mRNA isolated from entire pieces of cortex, thus including mRNA from any subcellular location in the cortical cells, and including non-neuronal cells in the cortex. Additionally, these studies analyse mRNA levels, rather than levels of the proteins which have more direct functional implications. If we are to study the molecular events intrinsic to the synapse, it is essential to directly and quantitatively assess the synaptic proteome. Such an approach has the important advantage that localised events can be revealed that are otherwise hidden in the complexity of molecular changes occurring in other subcellular compartments or in non-neuronal cell types. Proteomics approaches have recently been adopted [Van den Bergh et al., 2006] in order to directly screen for proteins potentially involved in cortical plasticity. Yet, a broad-scale study with a scope similar to microarray studies, allowing simultaneous comparisons between for example the plastic and less-plastic cortex, as well as the dark reared and monocularly deprived cortex has not been conducted yet. This will certainly provide valuable insights into the synaptic proteome and into the cascades of proteins involved in regulating cortical plasticity, as well as new endeavours in the form of proteins to be examined more closely.

Scope of this thesis

This thesis aims to extend current knowledge on plasticity of the primary visual cortex, and more specifically on the proteins and molecular mechanisms underlying it. The next chapters describe our studies addressing the following questions:

- What is the role of neuronal Notch signalling in vivo when it comes to synaptic morphology and plasticity? We address this question in chapter 2, and include the behavioural consequences in the form of visual acuity of the effects of Notch signalling.

- What does the molecular signalling downstream of neuronal Notch activation look like? And what might be the mediators of the effects of Notch signalling in neurons? In chapter 3 we describe the results of our microarray-based study into the effects of neuronal Notch signalling on downstream gene expression.

- What are the proteins that play a role at the synapse, in mediating the synaptic effects of visual cortex plasticity? How do monocular deprivation and dark rearing affect expression of these proteins? And how is this expression different between a plastic visual cortex during the critical period, and a less plastic cortex in adulthood? In chapter 4 we address these questions by means of a large-scale proteomics analysis of visual cortex plasticity.

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