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Neurotrophic receptor TrkB activation as an orchestrator of neuronal plasticity

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DOCTORAL DISSERTATION

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ABSTRACT

Structural brain plasticity is an essential process to adjust maladapted networks, but it dramatically declines after closure of the critical periods during early postnatal life. Growing evidence suggests, however, that certain interventions, such as environmental enrichment and antidepressant treatment, can reinstate a network plasticity that is similar to that observed during the critical periods. Chronic treatment with the antidepressant fluoxetine, for example, can reopen visual cortex plasticity and, when combined with monocular deprivation, can promote a shift in ocular dominance. Further, it promotes the erasure of previously acquired fear memory when combined with extinction training. Fluoxetine can bind to and activate the neurotrophic TrkB receptor and can therefore regulate the downstream pathway to induce synaptic plasticity. Considering that TrkB receptors are expressed in essentially all neurons, the question to be answered is through which neuronal subpopulation are the plasticity effects regulated within these two circuitries.

Visual cortex plasticity is tightly regulated by the inhibitory Parvalbumin (PV)-specific GABAergic network, which highly expresses TrkB receptors. During the critical periods TrkB's ligand Brain-Derived Neurotrophic Factor (BDNF) promotes the maturation of PV interneurons, thereby stimulating a precocious closure of critical periods. Hence, our first aim was to understand TrkB actions specifically in PV interneurons and their subsequent effects on visual cortex plasticity during adulthood. We used optically activated TrkB (optoTrkB) expressed only in PV interneurons of the visual cortex and found that optoTrkB activation by light combined with monocular deprivation is sufficient to induce ocular dominance plasticity. Strikingly, optoTrkB activation rapidly induces LTP in layer II/III of the visual cortex after theta burst stimulation (TBS). This potentiation in excitatory transmission is mediated by rapid decreases in the intrinsic excitability of PV regulated by reduced expressions of Kv3.1 and Kv3.2 mRNA. In addition, optoTrkB activation promotes the removal of perineuronal nets (PNNs) and shifts the PV and PNN networks into a plastic, immature configuration. Conversely, deleting TrkB from PV interneurons and using chronic fluoxetine treatment to pharmacologically induce plasticity prevented the effects of fluoxetine treatment.

Our second aim was to identify the effects of optoTrkB activation expressed specifically in pyramidal neurons of the ventral hippocampus on the fear circuitry. We therefore directed the expression of optoTrkB to pyramidal neurons of the ventral hippocampus. During fear extinction optoTrkB was activated with light, and spontaneous recovery and fear renewal were tested one and three (remote memory) weeks after extinction training. We found that optoTrkB activation during extinction training promoted the erasure of remote fear memory. This effect was accompanied by increased LTP expression after brief TBS stimulation.

Finally, fluoxetine and methylmercury (MeHg) are a common intervention and stressor, respectively, in our society, and exposure to either during pregnancy is known to impact brain development and functioning. An altered critical period can result in impairments that are retained into adulthood. Our aim was to understand how perinatal exposure to fluoxetine or MeHg affects the development of PV and PNNs, two well-established markers for the time course of critical periods, in the hippocampus and basolateral amygdala. We found that upon closure of the normal critical periods (P24) the number of PV and PNNs, and PV cell intensity increase. Perinatal fluoxetine treatment resulted in reduced expression of PNNs throughout critical periods, indicating a delayed closure. In contrast, perinatal MeHg exposure impaired the development of PV interneurons and PV expression at the onset of critical periods (P17), which were, however, restored upon critical period closure (P24), suggesting a delayed onset.

Our results provide new evidence that TrkB activation in PV interneurons rapidly orchestrates cortical networks by reducing the intrinsic excitability of PV cells regulated by decreased expression of Kv3.1 and Kv3.2 channels, subsequently promoting excitatory transmission. In contrast, TrkB activation in pyramidal neurons of the ventral hippocampus also potentiates excitatory transmission. These opposite findings demonstrate that TrkB employs different mechanisms to increase the excitability of the neuronal network to induce plasticity. We propose that TrkB is a promising therapeutic target for the treatment of neuropsychiatric diseases that benefit from high plasticity modes.

We further shed light on the effects of fluoxetine and MeHg exposure during pregnancy on the time course of the critical periods, which can help in developing better guidelines for the use and consumption of both during pregnancy.

ABBREVIATIONS

ACh	Acetylcholine
AchE	Acetylcholineesterase
Akt	Protein kinase B
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
AP	Action potential
BDNF	Brain-derived neurotrophic factor
CaMKII	Calcium/Calmodulin-dependent protein kinase II
ChABC	Chondroitinase ABC
CNS	Central nervous system
CREB	Cyclic AMP response element-binding protein
CSPG	Chondroitin sulfate proteoglycan
DAG	Diacylglycerol
DG	Dentate Gyrus
ECM	Extracellular matrix
EPSC	Extracellular postsynaptic currents
EPSP	Excitatory postsynaptic potential
ERK	Extracellular signal-regulated kinase
Frs2	Fibroblast growth factor receptor substrate 2
GABA	Gamma-aminobutyric acid
GAD65	Glutamic acid decarboxylase 65
Grb2	Growth factor receptor-bound protein 2
HA	Hyaluronic acid
HDAC	Histone deacetylase
IP3	Inositol triphosphate
LAR	Leukocyte common antigen-related phosphatase
LGN	Lateral geniculate nucleus
LTD	Long-term depression
LTP	Long-term plasticity
MAG	Myelin-associated glycoprotein
MAO	Monoamine oxidase
mRNA	Messenger ribonucleic acid
mTOR	Mammalian target of rapamycin
NGF	Nerve growth factor
NMDA	N-methyl-D-aspartate receptor
NSC	Neural stem cell
NT-3	Neurotrophin-3
NT-4/5	Neurotrophin-4/5
OMgp	Oligodendrocyte myelin glycoprotein
p75NTR	P75 neurotrophin receptor
PI3k	Phosphoinositide 3 kinase
PIP2	Phosphatidyl(4,5)inositolbisphosphate
PirB	Paired immunoglobulin-like receptor B
PKA	Protein kinase A
PKC	Protein kinase C

PLCγ	Phospholipase C gamma
PNN	Perineuronal net
Pten	Phosphatase and tensin homolog
PTSD	Post-traumatic stress disorder
PV	Parvalbumin
Ras	Rat sarcoma
RPTPσ	Receptor protein tyrosine phosphatase sigma
SGZ	Subgranular zone
SH2	Src homology 2
Shc	Src homology 2 domain-containing
Shp2	SH2 domain-containing protein-tyrosine phosphatase
SSRI	Selective serotonin reuptake inhibitor
STP	Short-term plasticity
SVZ	Subventricular zone
TBS	Theta burst stimulation
Trk	Tropomyosin receptor kinase
VIP	Vasoactive intestinal peptide

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications referred to in the text by their Roman numerals:

I. **Frederike Winkel**, Giuliano Didio, Maria Llach Pou, Anna Steinzeig, Maria Ryazantseva, Juliana Harkki, Jonas Englund, Tomi Taira, Sari Lauri, Juzoh Umemori, & Eero Castrén. *TrkB activation in Parvalbumin interneurons orchestrates cortical network plasticity* (submitted manuscript).

II. Juzoh Umemori, Giuliano Didio, **Frederike Winkel**, Maria Llach Pou, Juliana Harkki, Hanna Antila, Chloe Buj, Guirado Ramon, Tomi Taira, Sari Lauri, & Eero Castrén. *Optic activation of TrkB attenuates fear memory combined with fear extinction training* (submitted manuscript).

III. Juzoh Umemori*, **Frederike Winkel***, Eero Castrén, & Nina N. Karpova (2015). Distinct effects of perinatal exposure to fluoxetine or methylmercury on parvalbumin and perineuronal nets, the markers of critical periods in brain development. *International Journal of Developmental Neuroscience*, *44*, 55-64. *authors contributed equally.

IV. Juzoh Umemori, **Frederike Winkel**, Giuliano Didio, Maria Llach Pou, & Eero Castrén (2018). iPlasticity: Induced juvenile-like plasticity in the adult brain as a mechanism of antidepressants. *Psychiatry and clinical neurosciences*, *72*(9), 633-653.

These publications were reprinted with the permission of their copyright holders. In addition, some unpublished material is presented.

The doctoral candidate's contributions (the Roman numerals refer to the publications outlined above):

I. The candidate performed and analyzed the experiments, prepared the figures of the manuscript, planned the study, and wrote the manuscript together with EC and JU.

II. The candidate performed the electrophysiological recordings and participated in the virus infection and the writing of the manuscript.

III. The candidate performed and analyzed the immunohistochemical experiments.

IV. The candidate participated in the writing of the review, particularly the visual cortex part.

INTRODUCTION

In the mammalian brain, neuronal plasticity is necessary for the brain network to adapt and respond to external and internal stimuli not only to ensure survival but also to improve and optimize ones' fitness in the environment. External stimuli can include situations, such as threat, pain, or sensory deprivation, which trigger coping processes through learning and adaptation. Internal stimuli, in turn, are factors within the brain itself that initiate a cascade of processes signaling the need for change, such as the release of neurotrophic factors.

Plasticity processes can be defined on different levels starting from molecular plasticity taking place within a neuron itself to synaptic plasticity involving the strengthening of contacts between synapses, and extending to network plasticity, where structural changes take place between and within different neuronal subpopulations. It has been long appreciated that the family of neurotrophic factors is key in regulating these mechanisms. The brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin kinase B (TrkB) are members of this family, regulating plasticity processes in an activity-dependent manner.

The brain's ability to undergo wide structural changes decreases dramatically after the early postnatal days, when only active cells are selected and kept alive. Upon maturation, the brain network becomes stable and only minor brain plasticity can take place. A stable network is favorable during adulthood to ensure an efficient neural architecture; maladapted networks require major restructuring to reshape the neuronal network. This has been a challenge until recent discoveries of interventions that can reopen a juvenile-like network state, one being antidepressant treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine. Fluoxetine can activate TrkB receptors, thereby stimulating its downstream signaling pathway to induce gene transcription, ultimately regulating neurogenesis, neuronal differentiation, and survival.

This thesis investigates the role of TrkB receptors in reopening of juvenile-like plasticity in the adult brain, with a major focus on the visual cortex but also including studies from the hippocampus. TrkB receptors are widely expressed throughout the brain and different neuron subtypes. We evaluate how TrkB acts in different cell types to regulate plasticity in the adult brain. Finally, we examine the effects of perinatal exposure to fluoxetine, a widely prescribed antidepressant, and methylmercury, an environmental stressor, on plasticity markers during early postnatal days in the brain of the offspring. This information will facilitate identification of better targets and treatments for diseases that benefit from brain rewiring.

REVIEW OF THE LITERATURE

1. NEURONAL PLASTICITY

Neuronal circuits are defined by structures of axons and dendrites and the synapses that connect them (Bailey & Kandel, 1993; Holtmaat & Svoboda, 2009). Axons mediate a neuron's output to target regions that can span widely across the brain, while dendrites integrate inputs from several sources. These circuits are assembled during development by the formation of synaptic connections between hundreds of thousands of neurons. The initial patterning is followed by a prolonged period during which massive numbers of new synapses are added and pruned (Goodman & Shatz, 1993; Katz & Shatz, 1996). Neural activity is essential in guiding the synapse formation, elimination, and rearrangements to establish adult patterns of connectivity (Tessier-Lavigne & Goodman, 1996). Hence, circuit changes occur as plasticity, which is accompanied by synapse formation and the elimination/alteration in the structure of pre-existing synaptic connections thought to underlie long-term memory formation (Greenough, 1984; Greenough & Bailey, 1988; Holtmaat & Svoboda, 2009).

Synaptic plasticity in adult neuronal circuits may involve the strengthening or weakening of existing synapses, commonly referred to as long-term potentiation (LTP), but also structural plasticity, which includes the formation and elimination of newly formed synapses (Holtmaat & Svoboda, 2009) (Fig. 1). It is important to note that plasticity processes in the brain are experience-dependent; hence, they require synaptic activity to occur (Holtmaat & Svoboda, 2009; Katz & Shatz, 1996).

1.1. Neurogenesis

Neurogenesis in the adult brain has long been a matter of debate, but increasing evidence suggests that new neurons can be born in two locations of the mammalian brain: the subventricular zone (SVZ) of lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus. Neurons born in the adult SVZ migrate through the rostral migratory stream to become granule neurons and periglomerular neurons in the olfactory bulb (Zhao, Deng, & Gage, 2008). Neurons born in the adult SGZ migrate into the granule cell layer of the DG to become dentate granule cells. The newborn neurons then integrate into the existing circuitry and receive functional input (Zhao et al., 2008).

Adult neurogenesis is regulated by physiological and pathological activities at all levels, including the proliferation of adult neural stem cells (NSCs) or progenitors, the differentiation and fate determination of progenitors, and the survival, maturation, and integration of newborn neurons. In general, adult NSCs is a term to describe cells that can self-renew and differentiate into all types of neural cells, including neurons, astrocytes, and oligodendrocytes (Gage, 2000) (Fig. 1a).

Neurogenesis decreases during aging, but considering that interventions such as voluntary exercise can restore neurogenesis to a certain extent, it seems that the cells still have the capability to respond to extrinsic stimuli (Van Praag, Shubert, Zhao, & Gage, 2005). Numerous molecular pathways have been identified to participate in the regulation of adult neurogenesis. Among influences of neurotransmitters, extrinsic factors, and intracellular mechanisms, also growth factors, including BDNF, contribute substantially.

1.2. Structural plasticity

Structural plasticity appears as changes in synaptic connectivity and includes experience-driven alterations in the reorganization of pre-existing active zones to change the synaptic effectiveness as well as de novo growth and retraction of dendritic spines and axonal boutons (Couteaux, 1970; Heuser et al., 1979; Landis, Hall, Weinstein, & Reese, 1988). The axons are highly dynamic and axonal growth can be observed in brain injury or lesions of sensory periphery (Buonomano & Merzenich, 1998; Florence, Taub, & Kaas, 1998; Sutula, He, Cavazos, & Scott, 1988). Axonal branches in the cortex can undergo structural rearrangements by retractions and elongations associated with the turnover of numerous boutons, which is likely correlated with synapse formation and elimination (De Paola et al., 2006) (Fig. 1b). Therefore, structural plasticity might also be involved in recovery from brain injury (Brown, Li, Boyd, Delaney, & Murphy, 2007; Dancause et al., 2005).

Also, dendrites can undergo plasticity, such as changes in the complexity of dendritic arbors in some cortical areas observed, for instance, after environmental enrichment (Sirevaag & Greenough, 1987), extensive training (Kolb, Cioe, & Comeau, 2008), stress levels (Magariños, McEwen, Flügge, & Fuchs, 1996), and drugs of abuse (Robinson, Gorny, Mitton, & Kolb, 2001; Robinson & Kolb, 1999) (Fig. 1b).

Finally, the synapses are of dynamic nature (Fig. 1c). Synapse dynamics may include alterations in the size and vesicle complement (Applegate & Landfield, 1988; Applegate, Kerr, & Landfield, 1987; Atwood & Lnenicka, 1986; Bailey & Chen, 1983, 1988), modifications in the total number of vesicles per presynaptic terminal (Devoogd, Nixdorf, & Nottebohm, 1985; Garey & Pettigrew, 1974), adjustments in the geometry of position between pre- and postsynaptic components (Desmond & Levy, 1983, 1986b, 1986a), and structural modifications in postsynaptic dendritic spines (Chang & Greenough, 1984; Desmond & Levy, 1988, 1990) (Fig. 1c). In fact, spines show a high degree of motility, as the actin cytoskeleton of dendritic spines constantly rearranges (Fischer, Kaech, Knutti, & Matus, 1998; Matus, 2000).

The most consistent structural feature as a potential substrate for the storage of long-term memory is the alteration in the number of synapses or pattern of synaptic connections (Greenough, 1984; Greenough & Bailey, 1988). In the visual cortex, morphological and physiological changes are consistent with alteration in the number and pattern of synaptic connections (Hubel, Wiesel, & LeVay, 1977; David Hubel & Wiesel, 1963; LeVay, Wiesel, & Hubel, 1980). Long-term potentiation in the hippocampus is also associated with increases in synaptic number (Lee, Schottler, Oliver, & Lynch, 1980) and can be induced, for example, by environmental enrichment and spatial learning (Holahan, Rekart, Sandoval, & Routtenberg, 2006; Ramírez-Amaya, Balderas, Sandoval, Escobar, & Bermúdez-Rattoni, 2001).

Structural plasticity is not restricted to specific neuronal subtypes. For example, Lee et al. demonstrated that visual cortical GABAergic interneurons, which provide inhibitory control over a large repertoire of excitatory pyramidal neurons, were extending and retracting existing branches over a period of months, even adding new branch tips in rare cases, while pyramidal cells remained stable (Lee et al., 2005). In a follow-up study, Chen et al. (2011) provided evidence that experience drives structural remodeling of superficial layer 2/3 interneurons in the adult visual cortex, as visual deprivation induced dendritic branch retractions accompanied by a loss of inhibitory inputs onto neighboring pyramidal cells.

In addition, Chow et al. (2009) provided evidence of dendritic growth of pyramidal neurons, which is restricted to layer 2/3 of the mature cortex and regulated in a Pten/mTor-dependent manner.

1.3. *Long-term potentiation (LTP)*

Changes in synaptic strength and efficacy in terms of LTP are another mechanism underlying synaptic plasticity (Fig. 1d). LTP is a form of synaptic plasticity thought to underlie storage of long-term memory. Ramón y Cajal postulated that networks of neurons are not in cytoplasmic continuity, but communicate with each other at specialized junctions, which Sherrington called synapses. In the 1940s, Hebb (1949) and Konorski (1948) predicted that learning and memory would involve synaptic strengthening elicited by coordinated firing of pre- and postsynaptic cells, which later was called the coincidence-detection rule: a synapse that links two cells is strengthened if the cells are active at the same time (Bliss & Collingridge, 1993; Malenka, 2003).

LTP was first observed and continues to be the most easily studied in the hippocampus, but it is not exclusive for that brain region, as it is a ubiquitous property of excitatory synapses throughout the brain such as in the visual cortex and amygdala (Bliss & Collingridge, 1993; Huang & Kandel, 1998; Kirkwood, Rioult, & Bear, 1996). The first LTP was initiated by sustained high frequency firing that causes an abrupt increase in the efficiency of synaptic transmission (Bliss & Lømo, 1973). However, not only high frequency stimulation, commonly known as tetanus stimulation, can induce LTP but also theta burst stimulation, which has been suggested to represent a more physiological condition resembling spike discharge patterns of hippocampal neurons in animals in exploratory situations (Larson, Wong, & Lynch, 1986).

The basic properties of LTP are cooperativity, associativity, and input-specificity (Bliss & Collingridge, 1993). Cooperativity describes existence of an intensity threshold for induction, meaning that a crucial number of presynaptic fibers must be activated simultaneously, thus, they must "cooperate" (McNaughton, Douglas, & Goddard, 1978). Associativity means that a weak input stimulation can be potentiated if it is active at the same time as a strong tetanus. This occurs because the strong tetanus provides the depolarization, which is rapidly transmitted through the dendritic tree (Levy & Steward, 1979; McNaughton et al., 1978). Input-specificity refers to the property that inputs that are not active at the same time do not share in the potentiation, which is a cellular analog of classical conditioning (Andersen, Sundberg, Sveen, & Wigström, 1977; Lynch, Dunwiddie, & Gribkoff, 1977); a synapse will only be potentiated if it is active at a time that the region of the dendrite on which it terminates is sufficiently depolarized. The voltage-dependent block by Mg^{2+} makes NMDA receptors a coincidence detector. It requires depolarization of the membrane and the binding of glutamate. It therefore is input-specific since the presynaptic terminal needs to provide glutamate; it is cooperative since it requires sufficient depolarization; and it is associative since the depolarization is provided by different sets of afferent fibers (Ascher & Nowak, 1988).

LTP can be generated by presynaptic modifications resulting in increased release of glutamate; postsynaptic modifications, such as increased numbers of postsynaptic receptors or change in their functional characteristics; extrasynaptic modifications, such as reduced uptake of glutamate by glia cells, which results in increased neurotransmitter availability at receptors; and by morphological modifications, as LTP induces dendritic spine formation (Bliss, & Collingridge, 1993; Engert & Bonhoeffer, 1999). These properties of LTP distinguish it from short-term potentiation (STP), as LTP requires the induction of gene transcription/translation to enable protein synthesis, which is necessary for the presynaptic, extrasynaptic, and morphological modifications (Malenka & Nicoll, 1993) (Fig. 1e). If the increases in NMDA-dependent postsynaptic Ca^{2+} do not reach the threshold for LTP, it can generate either STP, which decays to baseline within minutes, or long-term depression

(LTD), which is a long-lasting decrease in synaptic strength (Artola & Singer, 1993; Malenka & Nicoll, 1993) (Fig. 1d). Hence, the magnitude and dynamics of Ca^{2+} increases within dendritic spines profoundly influence the resulting form of synaptic plasticity.

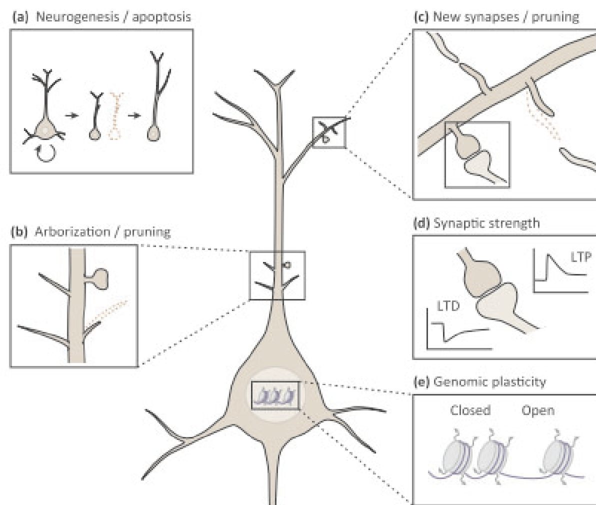

Fig. 1. Model for levels of plasticity. (a) Neurogenesis and selective apoptosis. Neurons that fail to functionally integrate into the circuitry are eliminated through apoptosis. (b) Arborization and pruning of axonal and dendritic branches. The increased dynamics of nascent branches promotes the stabilization of branches containing synapses that are active, whereas arbors without active synapses remain short-lived and are pruned. (c) Synaptogenesis and pruning. Synapses that are successfully activated during the trial period are preferentially selected for stabilization, whereas contacts that fail to mediate activity collapse and are eliminated. (d) Plastic regulation of synaptic strength. Information transfer through active synapses is potentiated through the process of long-term potentiation (LTP), whereas inactive or inappropriately active synapses are suppressed through long-term depression (LTD). (e) Environmental activity regulates the transcription and translation of effector genes involved in neuronal plasticity through transcriptional control and epigenetic mechanisms such as remodeling of chromatin structure from a closed to an open state. Reprinted Castrén, Eero, and René Hen. "Neuronal plasticity and antidepressant actions." Trends in neurosciences 36.5 (2013): 259-267 with permission of Elsevier.

1.4. Relevance of plasticity

As mentioned, plasticity processes in the brain are fundamental for our brain to undergo the changes required for learning and memory. However, the capacity of our brain to engage in synaptic plasticity becomes restricted in adulthood. This has significant implications for neuropsychiatric conditions, such as amblyopia (Campos, 1995), post-traumatic stress disorder (PTSD) (Mahan & Ressler, 2012), functional rehabilitation after cortical damage (Dancause et al., 2005), and lifelong learning, where synaptic plasticity is highly needed. While in these cases enhanced plasticity is desirable, one should take into account that exaggerated plasticity also leads to neuropsychiatric disorders, such as epilepsy, where a decrease in inhibitory control leads to seizures mediated by excessive excitatory transmission (Scharfman, 2002).

As for every part of the mammalian organism, stabilizing the neuronal network serves a biological purpose (Hensch, 2012). Our brains would be in a constant state of information flux and it would be impossible to retain lessons learnt or memory if the brain would continuously restructure as a result of plasticity. Hence, we would be unable to form a long-term memory or ensure efficient neural architecture to known conditions during adulthood, such as learning from past mistakes, therefore reducing biological fitness.

2. CRITICAL PERIOD PLASTICITY

Critical periods are time windows of heightened plasticity during early postnatal life during which the brain is particularly sensitive to environmental signals and adequate input is required for proper development of the neuronal system (Hensch & Bilimoria, 2012). Critical periods have been clearly demonstrated for visual, auditory, and somatosensory systems (Buonomano & Merzenich, 1998; Doupe & Kuhl, 1999; King & Moore, 1991) and are present in virtually all species. In humans, there are critical periods for seeing, hearing, receptive language, speech production, and higher cognitive functions (J. P. Shonkoff, 2007; Jack P. Shonkoff, Phillips, & National Research Council (U.S.). Committee on Integrating the Science of Early Childhood Development., 2000). It seems that the longer the life span, the longer the critical period. There also seems to be a relation between critical periods and brain weight (Berardi, Pizzorusso, & Maffei, 2000). If the brain weight is a rough measure for brain complexity, it means that the more complex the brain is the longer the critical period. Manipulations during critical periods have effects into adulthood, while the same manipulations during adulthood have minor to no effect (Berardi et al., 2000). However, some aspects of cortical organization remain modifiable in the adult, for example, the frequency map in the auditory cortex (Rauschecker, 1999) or the somatotopic map in the somatosensory cortex (Buonomano & Merzenich, 1998; Glazewski & Fox, 1996).

The best-studied critical period is that of the visual cortex, which is characterized in the monkey, cat, rat, mouse, ferret, and human (Banks, Aslin, & Letson, 1975;Fagiolini, Pizzorusso, Berardi, Domenici, & Maffei, 1994; Harwerther, Smith, Duncan, Crawford, & Noorden, 1983;Huang et al., 1999; Issa, Trachtenberg, Chapman, Zahs, & Stryker, 1999; Olson & Freeman, 1980), and it is also the focus of this thesis.

The onset, closure, and duration of the critical period are determined by sensory experience, and lack of experience through, for example, dark rearing extends the visual critical period (Rauschecker, 1999). An important question has been whether sensory experience is instructive or permissive or both (Berardi et al., 2000). Permissive sensory experience is supported by the finding that even brief light exposure during dark rearing triggers visual development. In addition, binocularly deprived cats proceed to develop ocular dominance columns and cortical orientation, initially, even without patterned visual inputs (Crair, Gillespie, & Stryker, 1998). Instructive sensory experience is supported by the findings that if the pattern of afferent electrical activity is artificially modified (Weliky & Katz, 1997) the sensory inputs from one modality are forcibly rerouted to cortical areas devoted to other modalities (Angelucci, Clascá, Bricolo, Cramer, & Sur, 1997) and that animals reared in particular restricted environments shift their orientation preference towards the experienced orientation (Sengpiel, Stawinski, & Bonhoeffer, 1999). Some aspects of cortical development are independent of sensory experience, but that does not imply that they are independent of electrical activity, as spontaneous activity early in life could play an instructive role (Crair, 1999).

Determinants of critical periods

Certain determinants of critical periods in sensory development, such as NMDA receptors, the inhibitory circuitry, and neurotrophins, have been identified (Berardi et al., 2000).

NMDA receptors

NMDA receptors are involved in the somatosensory (Schlaggar, Fox, & O'Leary, 1993), auditory (Feldman, Brainard, & Knudsen, 1991), and visual systems (Roberts, Meredith, & Ramoa, 1998). The characteristics of NMDA-mediated transmission are developmentally regulated and their expression is modified by electrical activity (Catalano, Chang, & Shatz, 1997; Livingston & Mooney, 1997). In general, NMDA receptors are heteromeric ion channels composed of NR1 and NR2 subunits. The NR2 subunit has four subtypes: NR2A, NR2B, NR2C, and NR2D with distinct functional properties (Ishii et al., 1993; Moriyoshi et al., 1991). In the cerebral cortex, however, NR1, NR2A, and NR2B are the dominant subunits (Monyer, Burnashev, Laurie, Sakmann, & Seeburg, 1994; Sheng, Cummings, Roldan& Jan, 1994). During early postnatal life the subunit composition shifts from dominantly NR2B to NR2A with a time course that parallels critical period (Catalano et al., 1997) and that also results in shortening of the NMDA current (Flint, Maisch, Weishaupt, Kriegstein, & Monyer, 1997).

Animals reared in darkness have a delay in the developmental shortening of NMDA current, suggesting that the increase in NR2A/NR2B ratio is related to visual cortex development and possibly closure of critical periods (Roberts & Ramoa, 1999). Dark-reared animals have lower NR2A subunit expression, and very brief light exposure is sufficient to trigger a rapid increase in NR2A expression (Quinlan, Philpot, Huganir, & Bear, 1999). As mentioned, NMDA receptors are crucial for synaptic plasticity that relies on NMDA-dependent modifications of synaptic efficiency such as LTP. In the somatosensory cortex, the critical period for LTP induction closely matches the developmental changes in NMDA properties and the critical period for sensory deprivation (Fox, 1995). In the visual cortex, LTP induction coincides with the critical period, and the closure of critical periods also correlates with a reduction in the ability to induce LTP (Kirkwood, Lee, & Bear, 1995).

Inhibitory network

Substantial research has been done on the role of the inhibitory circuitry, as experience-dependent plasticity is not restricted to the excitatory circuitry. At excitatory synapses, the release of neurotransmitters or chemical messengers intensifies the electrical activity at the receiving end (Hensch & Bilimoria, 2012). During development the inhibitory network, where the release of neurotransmitters from a neuron dampens the electrical activity at the receiving partners, evolves after the establishment of the excitatory network, creating a developmental mismatch between excitation and inhibition (Hensch & Bilimoria, 2012). This mismatch could provide a time window during which the organization of the cortical circuitry can be influenced by sensory experience.

In fact, the inhibitory cortical network tightly regulates the time course of the visual critical period. In mice in which glutamic acid decarboxylase (GAD) 65 is knocked out, the shift in ocular dominance induced by monocular deprivation during the critical period is absent (Hensch et al., 1998). Interestingly, local infusion of diazepam restores the ability of neurons to undergo ocular dominance plasticity in response to monocular deprivation, and this rescue is possible at any age, indicating that the onset of the visual critical period is dependent on an adequate level of cortical inhibitory transmission. Conversely, increasing intracortical inhibition prematurely in wild-type mice using diazepam just after eye opening triggers the onset of a precocious critical period (Fagiolini & Hensch, 2000). Using knock-in mice expressing a diazepam-resistant $GABA_A$ receptor α1 subunit, Fagiolini et

al. (2004) elegantly demonstrated that only α1-containing circuits drive cortical plasticity. Since α1-containing receptors mediate the synaptic input from PV basket cells, those cells may have an important role in opening the critical period. These findings provide strong evidence that increased intracortical inhibition is a major trigger for the initial onset of critical periods. The changes are likely to be linked to morphological alterations of the intracortical circuitry, as diazepam infusion into the visual cortex widens column spacing, while partial block of $GABA_A$ receptors exerts the opposite effects (Hensch & Stryker, 2004). Further evidence is provided using BDNF-overexpressing mice (Hanover, Huang, Tonegawa, & Stryker, 1999). In these mice, the development of interneurons is accelerated and increased levels of cortical inhibition are expressed. This increased inhibition is accompanied by both accelerated maturation of visual acuity and the time course of the visual critical period (Hanover et al., 1999;Huang et al., 1999).

These findings strongly suggest that the inhibitory transmission passes two functional thresholds during the development of critical periods: the first one enables the opening of critical periods, hence, a critical level of inhibition seems to be necessary to detect activity differences between the two eyes; and the second one causes the closure of critical periods.

This is not only the case for the visual system. In the tectum of young barn owls, the formation of new auditory maps in response to visual input displacement is accompanied by the development of selective inhibitory inputs. These inputs block the excitation of the old map, while leaving the neural circuitry in place. The inhibitory input is crucial for the emergence of new, appropriate visual-audio coordination (Zheng & Knudsen, 1999). The capacity for plasticity in adult owls is greater if they have experienced map rearrangements during the critical period (Knudsen, 1998): the old maps leave an enduring trace, which can be reactivated during adulthood.

Neurotrophins

Neurotrophins control the duration of the critical period and are the first molecules for which a causal correlation has been established between their action and the duration. Neurotrophins can modulate synaptic transmission, and their expression is developmentally regulated and dependent on electrical activity, hence, active neuronal connections are actively strengthened (Berardi & Maffei, 1999; McAllister, Katz, & Lo, 1999). The role of neurotrophins has been particularly studied in the critical period of the visual system and will be discussed in detail later. Alterations in the timing of sensitive periods (such as accelerated or delayed onset, or stalled, synchronized, or uncoupled progression) could underlie neurodevelopmental disorders, including autism and schizophrenia (Do, Cuenod, & Hensch, 2015), and understanding the underlying mechanisms is therefore of particular clinical interest.

3. VISUAL CORTEX PLASTICITY

3.1. Circuit formation

Sensory experience-driven development of the visual circuitry

The role of sensory experience in the formation of neural circuits has been extensively studied in the mammalian visual cortex based on the concept of the development of ocular dominance columns. In carnivores and primates, thalamic inputs to the cortex arise from the lateral geniculate

nucleus (LGN) and segregate by eye within cortical layer IV into a series of alternating stripes. These eye-specific structural stripes form the basis of the functionally defined system of ocular dominance columns. Early in development, the ocular dominance stripes in layer IV are absent and the LGN axons representing each eye are sparse and overlapping within layer IV (Rakig, Barlow, & Gaze, 1977; Shatz, 1990) (Fig. 2A). By adding large numbers of branches and synapses within the appropriate regions and eliminating sparse collaterals that are initially within the inappropriate regions, LGN axons gradually form dense, eye-specific patches (Antonini & Stryker, 1993a) (Fig. 2B). These structural rearrangements are accompanied by corresponding functional changes in the synaptic physiology of layer IV neurons. Initially, the majority of neurons are activated by stimuli presented to either eye, but finally become responsive to visual stimulation through one preferred eye (Levay, Stryker, & Shatz, 1978) (Fig. 2B). David Hubel and Torsten Wiesel demonstrated the important role of visual experience in determining the organization of ocular dominance columns (Hubel et al., 1977) for which they received the Nobel Prize in 1981. If one eye is deprived of vision in neonatal life, most of the mature visual cortical neurons are only responsive to stimuli presented to the eye that remained open. The patches of input from LGN axons in layer IV representing the open eye greatly expand, whereas the patches representing the closed eye shrink to very small regions (Hubel et al., 1977; Shatz & Strykert, 1978) (Fig. 2C). In rodents, ocular dominance columns are absent, but they have a small region of visual cortex in which neurons are binocularly responsive.

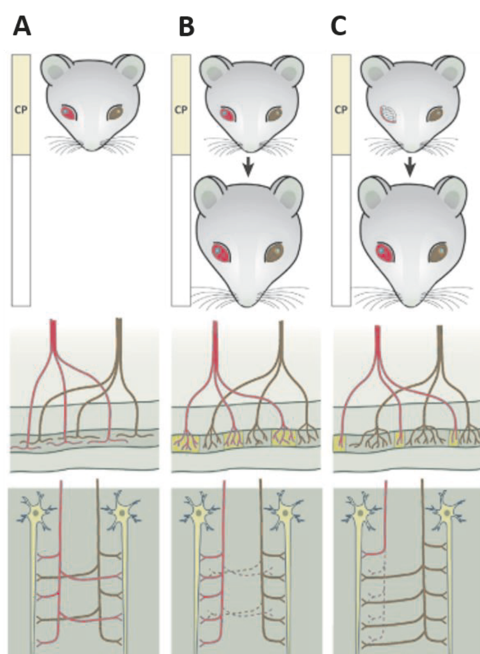

Fig. 2. Development of visual cortex circuitry and ocular dominance columns. (A) During early development the axons from both eyes sparsely innervate layer IV of the visual cortex. (B) Upon maturation, inputs to appropriate regions are maintained, while inputs to inappropriate regions are eliminated to form eye-specific stripes. (C) Manipulations of the visual input during early development results in changes in the circuit formation. The inputs from the open eye expand and the inputs from the closed eye shrink. Modified from Castrén & Hen (2013) with permission of Elsevier.

Spontaneous neural activity during early steps in circuit formation

Visual experience alone cannot account for early circuit formation. In nonhuman primates, the ocular dominance columns are formed in utero and are fully formed by birth (Katz & Shatz, 1996; Rakig et al., 1977). Hence, visual experience can modify existing columns, but is not required for the initial formation. Other features of the cortical architecture are also present before birth such as orientation tuning, orientation columns, and clustered horizontal cortical connections (Gödecke & Bonhoeffer, 1996). Therefore, early activity-dependent processes must operate before the onset of visually evoked activity. One source is likely to be spontaneously generated waves of action potentials that are generated in the retina before the onset of vision. Several weeks before eye opening and before the maturation of photoreceptors, ganglion cells spontaneously fire periodic bursts (Galli & Maffei, 1988). These bursts are correlated between neighboring cells and contribute to waves of neural activity that spread across domains of the retina (Feller, Wellis, Stellwagen, Werblin, & Shatz, 1996). These endogenously generated activity patterns may direct activity-dependent development of eye-specific layers in the visual thalamus (Katz & Shatz, 1996).

Similarly as in the formation of cortical ocular dominance columns, the inputs from the two eyes are initially intermixed in the developing LGN. The layers in the LGN form when ganglion cell axons remodel their branches and become restricted to appropriate layers (Sretavan & Shatz, 1986). This process requires neural activity provided by the retinal pathways (Meister, Wong, Baylor, & Shatz, 1991). When development proceeds, different functional classes of ganglion cells (ON and OFF cells) are recruited into the waves with distinct firing patterns (Wong & Oakley, 1996). Spontaneously generated retinal activity drives LGN neurons to fire periodic bursts and could therefore account for the segregation of LGN axons in the visual cortex, which occurs in utero in primates (Mooney, Penn, Gallego, & Shatz, 1996).

The formation of adult connectivity patterns involves morphological changes, namely the elimination of a limited number of immature connections in inappropriate layers, coupled with the elaboration and addition of many new connections in the appropriate layers. This means that the system does not invest largely in building stable synaptic structures before deciding whether to eliminate or retain a functional connection (Katz & Shatz, 1996). Hence, neural activity likely provides cues that drive the formation of new synapses and axon branches, and cues that act to select and stabilize existing ones (Antonini & Stryker, 1993b).

A possible mechanism for translating patterns of activity into patterns of synaptogenesis and growth is the local release of neurotrophic factors that act as retrograde signals in activity-dependent synaptic remodeling (reviewed in Thoenen, 1995). Neurotrophic factors control neuronal survival and differentiation during early development (Lindholm, Castrén, Berzaghi, Blöchl, & Thoenen, 1994), but also modulate synaptic strength within minutes.

3.2. Amblyopia/"lazy eye"

Children who suffer early visual deprivation due to refractory errors, strabismus, or cataracts can have lifelong visual impairments. If one eye is deprived early in life, they will develop amblyopia, which is poor vision in that eye, even though the eye itself is perfectly healthy. This is due to structural rewiring in the brain, where brain structures serving the deprived eye shrink and are taken over by cells favoring the open eye. Patching the better eye can restore the quality of vision through the lazy eye, but only during the critical period. This condition has been used as a classical model for

investigating critical period plasticity by inducing an amblyopic condition through monocular deprivation. The strength of the model is that it simulates a common condition in humans, affecting 2-5% of the population.

3.3. Molecular breaks

In the visual system, several molecular brakes have been identified that contribute to the closure of the visual critical period. These can be structural brakes (PNN and myelin-related factors: NogoR, PirB) that limit plasticity by altering local connectivity; and functional brakes (Lynx1) that limit plasticity by altering the excitatory and inhibitory neurotransmission between connections that have been formed to facilitate plasticity (Fig. 3).

PNN

Perineuronal nets (PNNs) are extracellular macromolecular aggregates associated with several subclasses of chondroitin sulfate proteoglycans (CSPGs) and preferentially enwrap Parvalbumin (PV)-expressing GABAergic interneurons (Ye & Miao, 2013). The formation of PNNs seems to be developmentally regulated and corresponds to the closure of critical periods, suggesting that their formation and the maturation of the nervous system depend on neuronal activity. Normal patterns of neuronal activity during early postnatal development are critical for the animal to express normal levels of aggrecan, a major constituent of PNNs, in the visual system, as well as for the establishment of mature anatomical and physiological features and the closure of the visual critical period (Guimarães, Zaremba, & Hockfield, 1990; Sur, Frost, & Hockfield, 1988).

NogoR and PirB

Increased myelin formation results in the promotion of intercellular communication by wrapping the axons in white, fatty insulation. Like PNNs, myelin can strongly inhibit axon growth, and increased myelin and its associated proteins are the main reason why neural circuits fail to regenerate with age (McKerracher et al., 1994). The key mediator of myelin signaling is Nogo receptors and its binding proteins, including NogoA, MAG, and OMgp (Akbik, Cafferty, & Strittmatter, 2012). The deletion of NogoR results in continued ocular dominance plasticity after the critical period (McGee, Yang, Fischer, Daw, & Strittmatter, 2005). Additionally, paired immunoglobulin-like receptor B (PirB) has high affinity for Nogo and has been found to restrict ocular dominance plasticity (Syken, Grandpre, Kanold, & Shatz, 2006). Mice lacking functional PirB expression have preserved visual plasticity after the closure of critical periods (Syken et al., 2006), and by blocking PirB, spines and functional synapses are upregulated (Bochner et al., 2014; Djurisic et al., 2013).

Lynx1

Early studies in visual cortex plasticity have indicated the importance of the neuromodulators acetylcholine (ACh) and noradrenaline (Bear & Singer, 1986). Lynx1, an endogenous prototoxin similar to α-bungarotoxin in snake venom, accumulates as the brain matures. Lynx1 acts by binding

to nicotinic ACh receptor, which is also the receptor for nicotine in cigarettes, and reduces the sensitivity to ACh itself (Morishita, Miwa, Heintz, & Hensch, 2010). Deletion of Lynx1 in mice results in amplified nicotinic ACh receptor signaling, and the mice can recover from amblyopia spontaneously (Morishita et al., 2010). Similar effects were obtained through pharmacological enhancement of ACh signaling using an inhibitor of acetylcholinesterase to degrade ACh (Furey, Pietrini, & Haxby, 2000; Silver, Shenhav, & D'Esposito, 2008). In fact, acetylcholinesterase inhibitors are already safely prescribed to improve symptoms of cognitive decline, such as Alzheimer's disease, in humans (Munoz-Torrero, 2008). A clinical study using Donezepil as treatment for amblyopia in young adults who are past their critical period is already underway (ClinicalTrials, 2012).

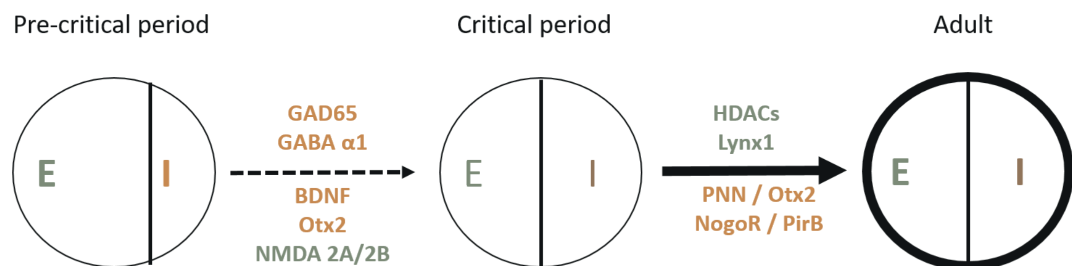

Fig. 3. Proposed model for circuit maturation. Excitatory transmission dominates during early development. Increased expression of GAD65, the GABA α1 subunit, BDNF, and ratio of NMDA 2A/2B subunits, as well as Otx2 transfer into the visual cortex promote the opening of the critical period by raising the inhibitory transmission to a critical threshold. The closure of critical periods is then promoted by the expression of the molecular brakes HDAC, Lynx1, PNNs, and NogoR. Modified from Morishita & Hensch (2008).

4. BDNF AND TrkB

4.1. Introduction

The first neurotrophin discovered was nerve growth factor (NGF) in the late 1940s and early 1950s by Rita Levi-Montalcini, Victor Hamburger, and Stanley Cohen (Levi-Montalcini, 1997). The initial findings suggested that non-neuronal tissue could release diffusible agents that could support survival and differentiation of developing nerve cells. This was a seminal finding in the history of developmental neurobiology and led to the formulation of the neurotrophic hypothesis (Bothwell, 2014), which quickly was supported by numerous data and follow-up experiments. According to the hypothesis, neurotrophins are released from cells in limited amounts to allow the survival of a restricted number of neurons during early development (Bothwell, 2014). This provided important insights into the way that neurons communicate during development and into neuroplasticity, memory, and learning in the adult nervous system. These findings motivated experiments leading to the discovery of brain-derived neurotrophic factor (BDNF) (Barde, Edgar, & Thoenen, 1982), which was isolated from pig brain, thereby resulting in its name. The two most recent members discovered were neurotrophin-3 (NT-3) (Hohn, Leibrock, Bailey, & Barde, 1990) and neurotrophin-4/5 (NT-4/5) (Berkemeier et al., 1991; Hallböök, Ibáñez, & Persson, 1991).

The four mammalian neurotrophins exert their actions by interacting with four receptors: $p75^{NTR}$, TrkA, TrkB, and TrkC. All four neurotrophins can bind and activate the signaling of the $p75^{NTR}$ receptor as pro-neurotrophins and as mature neurotrophins (Rodriguez-Tebar, Dechant, & Barde, 1990; Rodríguez-Tébar, Dechant, Götz, & Barde, 1992), whereas the Trk receptors preferentially bind the mature neurotrophins and are selective for particular neurotrophins. NGF binds and activates TrkA, NT-3 binds and activates TrkC, and BDNF and NT-4 bind and activate TrkB (Klein, Jing, Nanduri, O'Rourke, & Barbacid, 1991;Klein, Nanduri, et al., 1991; Lamballe, Klein, & Barbacid, 1991).

Neurotrophins regulate the survival and differentiation of neurons during embryonic development and maintenance of these neurons in adulthood (reviewed by Barde, 1990; Davies, 1994). While the effects of neurotrophin knockout are impressively apparent in the peripheral nervous system, the effects in the central nervous system are not as dramatic due to the overlapping and compensatory trophic support provided by the other members of the neurotrophin family (Crowley et al., 1994; Ernfors, Lee, & Jaenisch, 1994; Fariñas, Jones, Backus, Wang, & Reichardt, 1994). Although the lack of severe effects of gene-targeted deletion of neurotrophins might seem disappointing, it offers the possibility to identify subtle effects that refine neuronal functions such as activity-dependent neuronal plasticity (Thoenen, 1995).

The effects of overexpression of neurotrophins are similarly apparent in the peripheral nervous system (Davis et al., 1996; LeMaster et al., 1999), but the effects in the central nervous system seem to be controversial. While some evidence suggests that BDNF overexpression results in increased dendritic complexity in the hippocampal dentate gyrus (Tolwani et al., 2002), other studies indicate that overexpression of BDNF results in learning and memory impairments, anxiety-like traits, and seizure susceptibility (Cunha et al., 2009; Papaleo et al., 2011).

BDNF is widely expressed in the brain and while it was initially thought that the expression is restricted to neurons, it has been recently demonstrated that brain microglia – especially activated microglia – can take up and release BDNF as well (Parkhurst et al., 2013). BDNF seems to be mainly expressed in glutamatergic neurons and not in inhibitory interneurons, but this is not the case for TrkB receptors, which are expressed in essentially all neurons (Gorba & Wahle, 1999; Kuczewski, Porcher, Lessmann, Medina, & Gaiarsa, 2009).

4.2. Activity-dependent regulation of neurotrophin synthesis

The amount of BDNF mRNA synthesis is regulated by neuronal activity (Ballarín, Ernfors, Lindefors, & Persson, 1991; Zafra, Hengerer, Leibrock, Thoenen, & Lindholm, 1990), which in turn is mediated by classical neurotransmitters. Upregulation is regulated by glutamate binding to NMDA and non-NMDA receptors, and during development also by acetylcholine via muscarinic receptors (Zafra, Castrén, Thoenen, & Lindholm, 1991). Downregulation is predominantly mediated via GABA and GABA receptors (Zafra et al., 1991).

The synthesis of BDNF is regulated by physiological stimuli such as visual input (Castrén, Zafra, Thoenen, & Lindholm, 1992). Blocking sensory input to the visual cortex by intraocular injection of tetrodotoxin or by dark rearing results in rapid downregulation of BDNF mRNA levels. Dark rearing is particularly interesting since it dramatically regulates the functional development of the visual cortex (Frégnac & Imbert, 1978) and it reduces the developmental increase in BDNF, indicating that visual input is essential for the developmental regulation of BDNF.

4.3. *Activity-dependent secretion of neurotrophins and sites of release*

In the periphery, NGF is synthesized by a great variety of non-neuronal cells (Heumann, Korsching, Bandtlow, & Thoenen, 1987) and the regulation of synthesis and release is independent of neuronal input (Rohrer, Heumann, & Thoenen, 1988). In the CNS, BDNF and NGF are secreted by neurons in both constitutive and activity-dependent pathways (Griesbeck et al., 1999). The activity-dependent secretion depends on extracellular Na^{+}, but is independent of extracellular Ca^{2+}. However, intact intracellular Ca^{2+} stores are required; otherwise, the activity-dependent neurotrophin release is dramatically reduced. These characteristics of activity-mediated Na^{+}-dependent secretion of BDNF and NGF are unusual and distinctly different from those of the secretion of neurotransmitters and neuropeptides and of the activity-dependent secretion of other proteins such as acetylcholinesterase (Greenfield, 1985).

4.4. *TrkB structure*

TrkB receptors, the target of BDNF, was first cloned from mouse brain due to its high sequence homology to NGF receptor TrkA (Klein, Parada, Coulier, & Barbacid, 1989). The TrkB gene codes for the full-length catalytic tyrosine kinase receptor, but also produces multiple transcript variants that lack the catalytic kinase domain (Middlemas, Lindberg, & Hunter, 1991). The full-length TrkB receptor contains an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain, including the catalytic kinase domain that is essential for downstream signaling (Klein, Conway, Parada, & Barbacid, 1990). The truncated TrkB receptors (TrkB.T1 and TrkB.T2) share similar extracellular and transmembrane domains as the full-length receptor, but contain only a short intracellular domain consisting of a unique sequence of amino acid residues.

The human TrkB gene is unusually large, spanning 590 kbp, and contains 24 exons that can produce multiple mRNAs, which in turn can result in up to 10 different protein isoforms (Stoilov, Castren, & Stamm, 2002). The predominantly expressed isoforms at the protein level are TrkB.FL, TrkB.T1, and TrkB.T2. Exons 6-15 encode the extracellular part of the protein, the transmembrane region, and part of the juxtamembrane. Exon 16 encodes a stop codon and is used in the TrkB.T1 isoform. The third cluster of exons is composed of exons 17-19. Exons 17 and 18 encode the intracellular juxtamembrane part, and exon 19 is an alternative terminating exon part of TrkB.Shc, which lacks the tyrosine kinase domain but contains the intracellular Shc site. The fourth exon cluster comprises exons 20-24 encoding the tyrosine kinase domain and PLCγ site of the receptor (Stoilov et al., 2002).

The full-length TrkB receptors can be part of the postsynaptic densities (Wu et al., 1996) and can be found intracellularly in axons and dendrites and on the cell surface throughout development, thereby playing a key role in synapse formation (Gomes, Hampton, El-Sabeawy, Sabo, & McAllister, 2006). During maturation of cortical neurons TrkB receptors localize to excitatory synapses, while the expression pattern in interneurons and their responsiveness to neurotrophins vary (Gorba & Wahle, 1999).

TrkB surface expression is strongly regulated by BDNF. In cultured neurons, BDNF treatment rapidly increased TrkB surface expression, whereas treatment with BDNF for a longer time decreased TrkB surface levels, indicating that TrkB is predominantly located inside the cell (Haapasalo et al., 2002). Neuronal activity is another key regulator of TrkB synthesis, expression, and intracellular transport, and also results in increased synthesis and expression of BDNF (Merlio et al., 1993).

4.5. *Signaling cascade*

TrkB receptors belong to the family of tyrosine kinase receptors, which involves the phosphorylation of a tyrosine and subsequent catalyzation. Binding of the BDNF promotes the dimerization of TrkB receptors and results in the phosphorylation of the catalytic domains of tyrosines Y706 and Y707, leading to increased kinase activity of TrkB (Reichardt, 2006) (Fig. 4).

In addition to the catalytic domain, other tyrosine sites can be phosphorylated, namely Y515 and Y816 (Middlemas, Meisenhelder, & Hunter, 1994; Segal et al., 1996). Phosphorylation of these sites provides a docking site for Src homology 2 (SH2) adaptor proteins and phosphotyrosine binding domain-containing proteins (Fig. 4). The main interacting proteins binding to TrkB receptors are Shc, Frs2 (fibroblast growth factor receptor substrate 2), and PLCγ, activating Trk-associated signaling pathways Ras, PI_3k, and PLCγ1 (Obermeiert et al., 1993) (Fig. 4).

The binding of Shc to pY515 promotes signaling via PI_3K and Ras, thereby inducing a signaling cascade of protein-protein interactions to recruit serine/threonine kinases Akt and ERK (Obermeier et al., 1994) (Fig. 4). The latter can also be activated by a signaling cascade initiated by PLCγ binding to pY816 (Kaplan & Stephens, 1994) (Fig. 4). In general, signaling via the Shc binding site is associated with survival, differentiation, and axon outgrowth (Atwal, Massie, Miller, & Kaplan, 2000). Also, Frs2 can bind to pY515, subsequently interacting with Shp2 and Grb2 to induce ERK signaling (Easton, Royer, & Middlemas, 2006), which mediates inhibition of pro-apoptotic factors and increases the transcription of pro-survival factors, thus promoting survival (Bonni et al., 1999). The PI_3K-Akt pathway also activates mTOR, which regulates P70S6k and 4eBP1 to promote the translation of proteins that mediate cell survival, proliferation, differentiation, and dendritic growth (Kumar, Zhang, Swank, Kunz, & Wu, 2005; Takei et al., 2004).

BDNF-TrkB signaling also promotes the translocation of ERK to the nucleus, thereby mediating transcription factors such as cyclic AMP response element-binding protein (CREB) (Patterson et al., 2001) (Fig. 4). CREB is associated with the transcription of genes induced during late-phase LTP and cell survival (Minichiello et al., 2002; Watson et al., 2001). Importantly, besides TrkB activation, many other intracellular signaling cascades regulate CREB activity, including protein kinase A (PKA) or Calcium Calmodulin Kinase II (CaMKII), which can converge simultaneously and thereby potentiate CREB-mediated gene expression, demonstrating the activity-dependent nature of CREB (Shaywitz & Greenberg, 1999).

The phosphorylation of Y816 upon BDNF binding activates PLCγ1, which hydrolyzes phosphatidyl(4,5)inositolbisphoshate (PIP2) to second messengers diacylglycerol (DAG) and IP_3 (Carpenter & Ji, 1999). Considering that DAG is a lipid and cannot diffuse into the cytoplasm, it stays in the plasma membrane to activate protein kinase C signaling (PKC). IP_3 increases intracellular Ca^{2+} concentrations by stimulating the release from intracellular compartments and subsequent activation of a variety of Ca^{2+}-dependent intracellular molecules such as CaKMIV. DAG activates DAG-dependent PKC. PKC activation and Ca^{2+} release can result in the activation of ERK, CaMKIV, and CREB and can promote the release of neurotrophins (Finkbeiner et al., 1997; Saarelainen, Vaittinen, & Castrén, 2001; West et al., 2001). TrkB activation by BDNF can potentiate excitatory synaptic transmission via the PLCγ1 docking site of TrkB and is required for the induction of LTP, which is in contrast to the signaling via the Shc docking site (Minichiello et al., 2002).

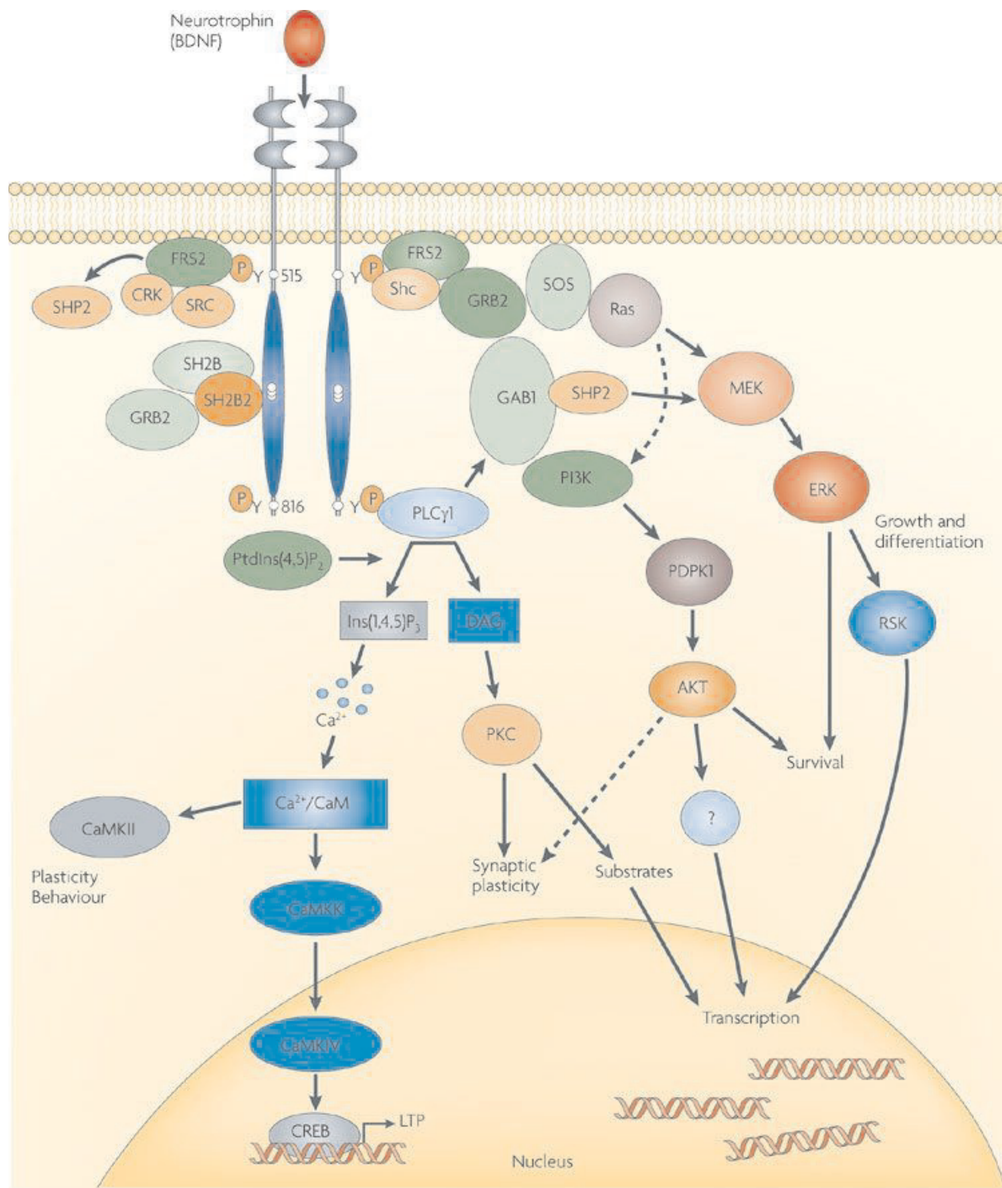

Fig. 4. TrkB signaling pathways. BDNF binding induces TrkB signaling via the catalytic domain Y706/7, the Shc binding site Y515, and the PLCγ binding site Y816. The main downstream pathways include Shc-PI$_3$K-Akt, Shc-PI$_3$K-Ras-Raf-ERK, and PLCγ-IP$_3$-PKC-CAMKIV, promoting cell survival, differentiation, Ca^{2+} release, and gene transcription and translation. Reprinted from Minichiello, Liliana. "TrkB signalling pathways in LTP and learning." Nature Reviews Neuroscience 10.12 (2009): 850 with permission from Elsevier

4.6. *TrkB-regulated plasticity*

Regulation of neurogenesis

Adult neurogenesis in the SGZ is strongly regulated through experience and activity. For example, modulators that promote neurogenesis are enriched environment and voluntary running (Olson, Eadie, Ernst, & Christie, 2006). In contrast, aging and stress impair neurogenesis (Klempin & Kempermann, 2007; Mirescu & Gould, 2006). BDNF plays a central role in regulating adult neurogenesis. For example, BDNF expression levels and SGZ neurogenesis are co-regulated by stress (Duman & Monteggia, 2006). Infusion of BDNF into the dentate gyrus increases neurogenesis in several brain areas (Pencea, Bingaman, Wiegand, & Luskin, 2001). Voluntary exercise and environmental enrichment, both of which increase BDNF expression levels, also increase neurogenesis. Mice heterozygous for the expression of BDNF fail to upregulate neurogenesis in response to an enriched environment (Rossi et al., 2006). Conditional ablation of BDNF expression in the hippocampus does not result in differences in cell proliferation and neuronal fate differentiation when housed in an enriched environment; however, reduced BDNF levels impair the survival of newborn cells (Choi, Li, Parada, & Sisodia, 2009).

The effects of BDNF on adult neurogenesis could, at least in part, be regulated through GABAergic transmission. BDNF knockout mice that exhibit reduced expression of GAD65 have increased proliferation of progenitor cells and impaired differentiation and maturation of newborn SGZ neurons. Pharmacological increase of $GABA_A$ activity rescues the deficits. Similar deficits in neurogenesis were also observed when selectively deleting TrkB in PV interneurons, indicating that locally synthesized BDNF promotes the differentiation and maturation of progenitor cells by enhancing GABA release from PV neurons (Waterhouse et al., 2012).

Regulation of LTP

The role of neurotrophins in LTP has been extensively studied, particularly in the hippocampus. Exogenous BDNF application to acute hippocampal slices promotes the induction of LTP, while TrkB-IgG fusion protein, which scavenges endogenous BDNF, reduces synaptic responses and the magnitude of LTP (Figurov, Pozzo-Miller, Olafsson, Wang, & Lu, 1996; Kang & Schuman, 1994). In acute hippocampal slices of BDNF knockout mice, synaptic function and LTP are strongly impaired. Treatment with recombinant BDNF, however, completely reverses the deficits in LTP and improves the deficits in basal synaptic transmission (Patterson et al., 1996). The induction of LTP itself increases the expression of BDNF and TrkB mRNA (Bramham, Southard, Sarvey, Herkenham, & Brady, 1996; E Castrén et al., 1993). In homozygous mutant mice, where TrkB is conditionally deleted in the forebrain, hippocampal LTP is impaired, and in heterozygous mutants substantially reduced (Minichiello et al., 1999). TrkB seems to mediate LTP particularly through the PLCγ docking site, as targeted mutation of that site impaired hippocampal LTP, while targeted mutation of the Shc binding site had no effect (Korte, Minichiello, Klein, & Bonhoeffer, 2000; Minichiello et al., 2002).

Neurotrophins in visual cortex plasticity

There is also a substantial role of neurotrophins in the regulation of visual critical periods. Intraventricular administration of NGF prevents a shift in ocular dominance in favor of the non-deprived eye (Carmignoto, Canella, Candeo, Comelli, & Maffei, 1993; Maffei, Berardi, Domenici,

Parisi, & Pizzorusso, 1992) and blocks the anatomical shrinkage of cell bodies of LGN neurons receiving inputs from the deprived eye (Domenici, Cellerino, Berardi, Cattaneo, & Maffei, 1994).

Ligands of TrkB (BDNF and NT-4) are involved in the activity-dependent control of LGN axon branching during development. Intracortical infusion of BDNF or NT4 prevents the formation of ocular dominance columns (Cabelli, Hohn, & Shatz, 1995), while a limited amount of either is necessary for its formation (Cabelli, Shelton, Segal, & Shatz, 1997). Infusion of BDNF alters the effects of monocular deprivation on ocular dominance distribution of cortical neurons (Galuske, Kim, Castrén, Thoenen, & Singer, 1996), and exogenous NT-4 attenuates the shrinkage of cell bodies of LGN neurons receiving input from the deprived eye during the critical period (Riddle, Lo, & Katz, 1995). In in vitro slices, BDNF elicits robust dendritic growth of postsynaptic cells in layer IV but only in the presence of spontaneous activity (McAllister, Lo, & Katz, 1995), and BDNF mRNA expression is regulated by neural activity (Castrén et al., 1992), indicating positive feedback.

As mentioned earlier, overexpression of BDNF results in a precocious critical period in the visual cortex (Hanover et al., 1999) and counteracts the effects of dark rearing, which prolongs the visual critical period (Gianfranceschi et al., 2003). In mice in which the postnatal rise of BDNF is accelerated, the GABAergic innervation and inhibition are also accelerated. These effects are associated with a precocious age-dependent decline of cortical LTP and closure of critical periods, indicating that BDNF promotes the closure of critical periods by enhancing the maturation of cortical inhibition (Huang et al., 1999). In turn, BDNF and NGF both potentiate excitatory synaptic transmission in acute slices of the rat visual cortex by potentiating AMPA and NMDA receptor-mediated components of the EPSC amplitude (Carmignoto, Pizzorusso, Tia, & Vicini, 1997).

Hence, neurotrophins play a pivotal role in mediating the time course of the visual critical period, and small alterations in their expression can have long-lasting dramatic effects.

5. PV INTERNEURONS

5.1. Introduction

From a reductionist's point of view, the neuronal network is composed of two types of neurons: glutamatergic pyramidal neurons and GABAergic interneurons. While glutamatergic neurons comprise 80-90% of the neuronal population, GABAergic interneurons form the remaining 10-20%. Hence, interneurons represent only a minority of the neuronal population (Freund & Buzsáki, 1998). However, their function is critical for normal brain functioning since they control the activity level of pyramidal neurons in the entire brain; if their function breaks down and excitation takes over, seizures and failure of higher brain functions, i.e. features of epilepsy, are the consequences (Scharfman, 2002).

An interesting hallmark of interneurons is their structural and functional diversity. Recently, 61 GABAergic cell types have been identified in the neocortex of mice (Tasic et al., 2018). Classically, these interneurons can be distinguished based on three criteria: (I) their morphological properties and particularly the axonal target selectivity; (II) the expression of molecular markers, including neuropeptides (somatostatin, cholecystokinin, vasoactive intestinal peptide, and neuropeptide-Y) and Ca^{2+}-binding proteins (PV, calretinin, and calbindin); and (III) the functional characteristics, particularly the action potential phenotype (Rudy & McBain, 2001).

In the 1990s, Celio proposed that PV interneurons are expressed in the majority of GABAergic neurons in the cortex (Celio, 1986). However, it quickly became apparent that although PV interneurons comprise about 24% of the GABAergic population they form only 2.6% of the total neuronal population (Bezaire & Soltesz, 2013). A significant characteristic of PV cells is their fast-spiking phenotype (Kawaguchi, Katsumaru, Kosaka, Heizmann, & Hama, 1987) and the selective expression of the Ca^{2+}-binding protein PV allows reliable post-hoc labeling with highly specific antibodies. Further, the high selectivity of the promoter of the PV gene allowed the genetic targeting of these cells and the generation of a PV-cre mouse line (Hippenmeyer et al., 2005) that specifically expresses Cre recombinase in PV interneurons. This mouse line opened the door for selective fluorescent labeling (Fig. 5A) and transgenic and optogenetic manipulations (Lucas, Jegarl, & Clem, 2014; Sohal, Zhang, Yizhar, & Deisseroth, 2009). PV interneurons are born in the medial ganglionic eminence and depend on specific transcription factors, such as Nkx2-1 and Lhx6, and thus, their developmental trajectory can be followed by labeling (Bartolini, Ciceri, & Marín, 2013; Taniguchi, Lu, & Huang, 2010; Tricoire et al., 2011).

PV interneurons can be distinguished by their morphological structure into large basket cells (the classical PV interneuron), which are characterized by their long-range axons that extend horizontally to target the perikaryon of pyramidal cells (DeFelipe, 1997; Lund & Lewis, 1993), and chandelier cells, which make synaptic connections with the axon initial segment of pyramidal cells (DeFelipe, 1997) (Fig. 5B). PV interneurons have multiple dendrites that can cross layers, permitting the cells to receive input from different afferent pathways, including feedforward and feedback (Gulyás, Megías, Emri, & Freund, 1999; Kubota et al., 2011; Nörenberg, Hu, Vida, Bartos, & Jonas, 2010). Considering the long cumulative dendritic length, which can span from 3.1 mm to 9 mm, and the dense coverage with synapses, PV interneurons sample input from a large population of principal cells (Gulyás et al., 1999; Kubota et al., 2011; Nörenberg et al., 2010). The morphological properties of the axon of PV interneurons are also impressive, as they show extensive arborization and a cumulative axonal length of 20-24 mm in the frontal cortex (Karube, Kubota, & Kawaguchi, 2004). From the extensive axonal arbor, a huge number of “en passant” terminals emerge, generating a massive inhibitory output of PV cells (Bezaire & Soltesz, 2013).

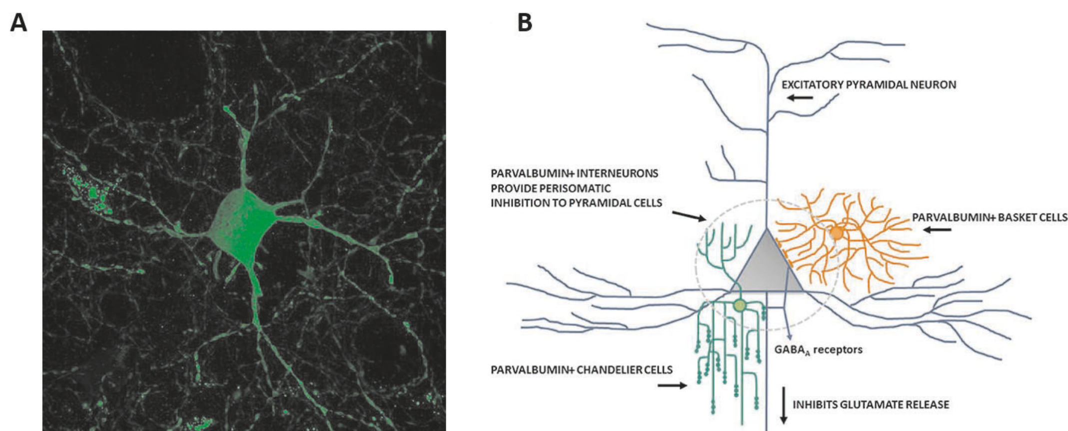

Fig. 5. Structure of PV interneurons. (A) Fluorescent labeling of a PV interneuron. (B) Perisomatic inhibition is provided by PV basket cells, which target the soma of pyramidal cells, and chandelier cells, which make synaptic contacts with the axon initial segment. Modified from MacKay (2018).

5.2. The dendrites

With direct dendritic recordings, the subcellular physiology of PV cells could be characterized as follows: (i) backpropagation of action potentials is highly decremental (Nörenberg et al., 2010); (ii) dendritic spikes cannot be initiated (Nörenberg et al., 2010); (iii) PV interneurons express only a low density of voltage-gated Na^+ cannels in their dendrites (Nörenberg et al., 2010); (iv) PV interneurons contain a high density of voltage-gated K^+ channels (Du, Zhang, Weiser, Rudy, & McBain, 1996); and (v) these channels are mainly of the Kv3 subtype, one of the four main subfamilies of voltage-gated K^+ channels, and show high activation threshold, fast activation, and fast de-activation (Rudy & McBain, 2001). The high expression of Kv3 channels in the dendrites of PV interneurons has profound functional consequences; their activation accelerates the decay time course of excitatory postsynaptic potentials (EPSPs), shortening the time of temporal summation, and promotes action potential (AP) initiation with high speed and precision (Fricker & Miles, 2000; Nörenberg et al., 2010). In addition, the dendrites of PV cells are highly interconnected by gap junctions (Galarreta & Hestrin, 1999; Gibson, Beierlein, & Connors, 1999), resulting in speeding of the EPSP time course since excitatory charge can escape into adjacent dendrites. Further, gap junctions can widen the spatial detection range of pyramidal neuron activity and could boost the efficacy of distal inputs and increase the average AP frequency upon repetitive synaptic stimulation of distal synapses (Galarreta & Hestrin, 2001; Vervaeke, Lorincz, Nusser, & Silver, 2012).

5.3. The axons

Recordings from axons of PV interneurons also revealed some surprising properties: (i) the APs are initiated very proximal from the soma (Hu, Gan, & Jonas, 2014);. (ii) AP propagation is highly reliable; (iii) the velocity propagation is faster than that of axons of pyramidal neurons (Meeks & Mennerick, 2007); (iv) the Na^+ channel distribution shows a stepwise increase in density from the soma to the proximal axon, followed by a further gradual increase to the distal axon (Hu & Jonas, 2014; Martina & Jonas, 1997). Hence, PV interneurons have a weakly excitable somatodendritic domain and a highly excitable axonal domain, separated by a steep transition zone; and (v) The axons express K^+ channels with similar properties to those in the dendrites (Goldberg et al., 2005; Hu et al., 2014). The expression of Na^+ channels in a “supercritical” density contributes to the rapid signaling in PV interneurons, hence, the unique and distinct properties of PV cells are specialized for rapid signaling.

5.4. Neurotransmitter release

Also the factors contributing to the conversion of the electrical signal to GABA release are optimized for speed. Axonal APs are brief, which translates into fast and synchronous transmitter release. While several types of synapses employ a mixture of P/Q-, N-, and R-type Ca^{2+} channels to induce transmitter release (Li, Bischofberger, & Jonas, 2007), PV interneurons rely exclusively on P/Q-type channels at their output synapses (Rossignol, Kruglikov, van den Maagdenberg, Rudy, & Fishell, 2013; Zaitsev, Povysheva, Lewis, & Krimer, 2007). These channels have the fastest gating among all Ca^{2+} channel subtypes (Li et al., 2007), thus contributing to the shortening of the synaptic delay and the increase in temporal precision of neurotransmitter release. The tight “nanodomain” coupling between Ca^{2+} channels and release sensors of exocytosis increases the efficacy of release, shortens the synaptic delay, and increases the temporal precision of release (Bucurenciu, Kulik, Schwaller, Frotscher, & Jonas, 2008; Eggermann, Bucurenciu, Goswami, & Jonas, 2012). Further, PV

interneurons express only a small number of Ca^{2+} channels, thereby helping to avoid the broadening of presynaptic APs or the generation of Ca^{2+} spikes in presynaptic terminals, contributing to fast and temporally precise neurotransmitter release (Bucurenciu, Bischofberger, & Jonas, 2010). Finally, a subset of PV cells employs synaptotagmin 2 as a release sensor for synaptic transmission, which is one of 15 members of the synaptotagmin family and a reliable marker for PV inhibitory boutons in the mouse visual cortex (Sommeijer & Levelt, 2012). Synaptotagmin 2 has the fastest Ca^{2+}-binding kinetics throughout the synaptotagmin family (Xu, Mashimo, & Südhof, 2007), thus also contributing to the rapid signaling. Importantly, even the expression of PV itself affects GABA release. PV has EF-hand domains, which bind both Ca^{2+} and Mg^{2+} ions. Considering that the Ca^{2+} concentrations are low inside the cell, it is generally thought that Mg^{2+} is bound and must leave before Ca^{2+} can bind (Schwaller, Meyer, & Schiffmann, 2002) and is therefore considered to be a slow Ca^{2+} buffer. However, even though the fraction of "free" PV is relatively low, the absolute concentration of free buffer becomes substantial if PV concentrations are upregulated during behavior (e.g. during contextual fear conditioning), as observed in hippocampal PV interneurons (Donato, Rompani, & Caroni, 2013). Hence, PV may modulate transmitter release by acting as an antifacilitation factor (Eggermann & Jonas, 2012).

5.5. PV cell plasticity

Recent research has shown another very special feature about PV cells. PV cells themselves are of plastic nature and their plasticity is developmentally regulated (Donato et al., 2013). The CA3 subregion of the hippocampus is responsible for rapid generation and contextualization of episodic memories, which can be affected by experience. Environmental enrichment enhances hippocampal learning and memory, meaning that these mice can more readily discriminate between novel and familiar objects. On the other hand, Pavlovian fear conditioning restricted to a specific training context impairs novel object recognition and is associated with memory consolidation. Both conditions induce changes in the state of PV interneurons during adulthood; while environmental enrichment induces a low PV expression state, fear conditioning induces a shift towards high PV content. This switch is correlated with the expression of GAD67, the synthetic enzyme for GABA. Low PV configurations are paralleled by an increase of GABAergic synaptic inputs and high PV configurations by an increase of excitatory synaptic inputs onto PV cells, indicating that a low PV configuration state results in decreased inhibitory output of PV, while a high PV configuration results in increased inhibition provided by PV. The activation of PV cells alone promotes a high PV state and reduces hippocampal plasticity. The PV network is biased towards a low PV state during learning phases and shifts to high PV contents when the memory becomes consolidated. A low PV configuration state, therefore, seems to be of plastic nature, as throughout development, the PV configuration state shifts from primarily low PV-expressing to primarily high PV-expressing networks (Donato et al., 2013), which is associated with a shift from a plastic immature state to a consolidated mature state.

5.6. PV-mediated inhibition

PV interneurons are involved in both feedforward and feedback inhibition (Buzsàki & Eidelberg, 1981;Pouille & Scanziani, 2001). In feedforward inhibition, afferent glutamatergic axons activate pyramidal cells and interneurons in parallel. This narrows the window for temporal summation of

EPSPs and APs in pyramidal cells (Pouille & Scanziani, 2001) and expands the dynamic range of activity in large pyramidal neuronal ensembles (Pouille, Marin-Burgin, Adesnik, Atallah, & Scanziani, 2009). Since PV-mediated inhibition has to be fast enough to ensure a substantial inhibitory conductance before an AP is initiated in pyramidal cells, the fast-spiking properties of PV are critically important. In feedback inhibition, afferent glutamatergic axons activate pyramidal cells, which then activate interneurons in series. While early inhibition is primarily mediated by perisomatic inhibition, late inhibition during trains is primarily mediated by dendritic interneurons. Feedback inhibition works according to the "winner takes all" mechanism (Almeida, Idiart, & Lisman, 2009), meaning that the pyramidal cells with the strongest input fire, while the AP initiation in the remaining cells is inhibited. Since the percentage of the maximum excitation is determined by the ratio of delay of disynaptic inhibition, the fast signaling properties of PV, which define the delay of disynaptic inhibition, are also here critically important (Almeida et al., 2009).

5.7. Role of TrkB/BDNF in regulation of PV

Although research is limited, some evidence points towards a role of the BDNF/TrkB pathway in the development of PV interneurons. In the rat visual cortex, TrkB is strongly expressed in the cell body of PV interneurons, and while PV cells express TrkB mRNA, BDNF mRNA expression is absent in PV, suggesting that BDNF is primarily synthesized and released by pyramidal neurons (Cellerino, Maffei, & Domenici, 1996; Gorba & Wahle, 1999). In organotypic cultures of the visual cortex, PV expression is dependent on activity and TrkB ligands through PI_3K signaling (Patz, Grabert, Gorba, Wirth, & Wahle, 2004).

In the prefrontal cortex, mice with a genetic mutation in promoter IV of the BDNF gene, resulting in disruption of promoter IV-mediated Bdnf expression, exhibit significant deficits in GABAergic interneurons and particularly the PV subtype (Sakata et al., 2014). These deficits include impaired inhibitory synaptic transmission and aberrant appearance of spike timing-dependent synaptic potentiation.

Mice lacking TrkB expression in PV interneurons exhibit a strong aberrant phenotype, including vestibular dysfunction and extreme hyperactivity primarily in females. Heterozygous PV-specific TrkB knockout mice, in contrast, do not exhibit any aberrant phenotype, but have impaired extinction consolidation in the fear conditioning paradigm (Lucas et al., 2014). In another study, PV-specific TrkB knockout mice have reduced gamma oscillations along with increased firing of excitatory neurons. Further, knockout mice had reduced numbers of PV interneurons and the inhibitory synaptic connections between basket and pyramidal cells was decreased (Xenos et al., 2017). Therefore, TrkB expression in PV interneurons seems to have significant effects on their properties.

6. PERINEURONAL NETS (PNNs)

6.1. Introduction

In 1882, Camillo Golgi described Perineuronal nets (PNNs) as reticular structures that surround the cell body of many nerve cells, extending along their dendrites. During the early works the function of PNNs was divers and included it as part of the terminal arborizations of axis-cylinders around the perikarya of nerve cells as well as an artifact derived from the coagulation of pericellular fluid (Celio, Spreafico, De Biasi, & Vitellaro-Zuccarello, 1998). With advances in experimental techniques,

immunohistochemical studies enabled insights into the structural components of PNNs and elucidation of their functions. Nowadays, PNNs are identified as specialized extracellular matrix (ECM) surrounding neuronal cell bodies and proximal dendrites in mesh-like structures with holes at the sites of synaptic contacts (Celio & Blumcke, 1994; Marco R Celio et al., 1998; S Hockfield & McKay, 1983; Zaremba, Guimaraes, Kalb, & Hockfield, 1989). PNNs can be detected when the maturation is almost complete and the nervous system stabilized. The function of PNNs is still a matter of debate, but they have been implicated in neuroprotection, synaptic stabilization, ionic buffering, and neuronal development and plasticity (Slaker, Blacktop, & Sorg, 2016).

6.2. *Structure and formation of PNNs*

PNN structure is similar to that of cartilage and composed of ECM molecules, most of which are widely expressed in the brain. The main components are hyaluronan (HA), link proteins, CSPGs, and tenascin-R (Carulli et al., 2010, 2006; Carulli, Rhodes, & Fawcett, 2007; Deepa et al., 2006; Köppe, Bruckner, Hartig, Delpech, & Bigl, 1997) (Fig. 6A). Within the extracellular space, CSPGs interact with HA polymer chains on the cell surface and the linking proteins stabilize their interaction. The C-terminal domain of CSPG core proteins then bind to tenascin-R to form a matrix that manifests as a coating on the neuronal surface.

Interestingly, the components of PNNs, including CSPGs, HA, and tenascins, can already be detected in neonatal animals, long before the onset of PNN formation (Bignami, Hosley, & Dahl, 1993; Delpech, Delpech, Brückner, Girard, & Maingonnat, 1989; Oohira, Matsui, Watanabe, Kushima, & Maeda, 1994; Steindler, Cooper, Faissner, & Schachner, 1989). Studies have shown that the formation of PNNs coincides with an increased expression of the link protein Crtl1, and experimental evidence suggests the importance of Crtl1 in triggering PNN formation (Carulli et al., 2010, 2006, 2007). While dark rearing results in a prolonged visual critical period, it also prevents PNN formation and reduces the levels of Crtl1 expression and other PNN components (Carulli et al., 2010). Hence, manipulating neuronal activity during early postnatal development appears to modify the deposition and establishment of PNNs.

6.3. *Role of PNNs in visual cortex plasticity*

As already mentioned, the formation of PNNs in the visual system coincides with the stabilization of synaptic connections and the closure of critical periods and are therefore considered as molecular brakes (Guimarães et al., 1990; Hensch, 2005; Lander, Kind, Maleski, & Hockfield, 1997; Pizzorusso et al., 2002). Alongside the PNN formation, changes in ECM include general upregulation of several CSPG core proteins as well as changes in GAG sulfation with the disappearance of 6-sulfated CS and an increase in 4-sulfated CS (Carulli et al., 2010). Decreasing the visual input by dark rearing prolongs critical periods and the deposition of aggrecan and PNNs (Hockfield & Sur, 1990; Lander et al., 1997; Pizzorusso et al., 2002). However, activity-dependent changes in PNNs can also be induced during adulthood. For example, animals housed in an enriched environment respond to monocular deprivation and shift their ocular dominance during adulthood. This shift is accompanied by a reduction in the number of PNNs, decreased cortical inhibition, and increased BDNF levels (Sale et al., 2007). Further, Crtl1-deficient mice retain their ocular dominance plasticity into adulthood and their visual acuity remains sensitive to deprivation, suggesting that specifically CSPGs within the PNNs restrict plasticity (Carulli et al., 2010; Kwok, Carulli, & Fawcett, 2010).

6.4. *PNNs and PV interneurons*

During critical periods PNNs preferentially enwrap PV interneurons, triggering their maturation and subsequently promoting the closure of critical periods. Increasing evidence suggests a role for the homeoprotein Otx2 in regulating the binding of PNNs specifically to PV interneurons. Homeoprotein Otx2 is a transcription factor that plays a major role during embryonic development and is transferred from the retina and choroid plexus to the visual cortex during postnatal development. This process is necessary and sufficient for the onset and closure of the visual critical period (Sugiyama et al., 2008). As the name implies, homeoprotein transcription factors share a highly conserved DNA-binding domain called the homeodomain, but many homeoproteins share activities beyond their classical transcriptional role, as they are paracrine signaling factors that transfer between cells (Derossit, Joliott, Chassaingl, & Prochiantztn, 1994; Joliot et al., 1998). Otx2 is preferentially internalized by PV interneurons and the time course of Otx2 accumulation parallels that of PV interneuron maturation, suggesting an Otx2 binding site on PV interneurons. In fact, Otx2 conditional heterozygous knockout mice display a delayed onset of the visual critical period, indicating that a pure reduction of this homeoprotein is sufficient to alter the maturation of PV interneurons (Sugiyama et al., 2008). It is thought that PV interneurons are maintained by a positive feedback loop by interactions of PNN components enabling persistent uptake of Otx2, which in turn promotes PNN formation (Beurdeley et al., 2012). Hence, the critical period is triggered as Otx2 is captured by PV interneurons and then closes as maturing PNNs condense in response to Otx2 accumulation by PV interneurons (Spatazza et al., 2013).

6.5. *Possible functions of PNN*

Even though the relationship between PNNs, PV interneurons, and plasticity has been well established, the molecular mechanism and processes by which PNNs could restrict plasticity are still matters of debate. First, PNNs could exert their function as a physical barrier, thereby restricting the formation of new neuronal contacts (Fig. 6B a). This can be achieved by the ability of CSPGs to inhibit neurite outgrowth (Oohira, Matsui, & Katoh-Semba, 1991), or by receptors of PNN components such contactin-1 (Mikami, Yasunaga, & Kitagawa, 2009), RPTPσ (Shen et al., 2009) and leukocyte common antigen-related phosphatase (LAR) (Fisher et al., 2011). Second, PNNs could restrict plasticity by scaffold binding to molecules affecting plasticity such as repulsive guidance molecule semaphorin 3A (De Wit, De Winter, Klooster, & Verhaagen, 2005; Williams, De Wit, & Ghosh, 2010) (Fig. 6B b). Third, PNNs could act as an ionic buffer around PV interneurons. PNNs enwrap PV interneurons, which express Kv3 potassium channels and are commonly associated with intracortical inhibition, and could serve as a rapid local buffer of excess cation changes (Härtig et al., 1999, 2001). Moreover, it has been shown that PNNs protect PV interneurons against oxidative stress, thereby preserving their fast rhythmic synchrony and serving a neuroprotective role (Cabungcal et al., 2013). Further, using cultured hippocampal neurons, PNNs have been shown to restrict the motility of surface AMPA receptors, which could change the efficiency of receptor exchange (Frischknecht et al., 2009) (Fig. 6B c). Enzymatic breakdown of the extracellular matrix increased the surface mobility of AMPA receptors and increased the area exploited by them (Fig. 6B).

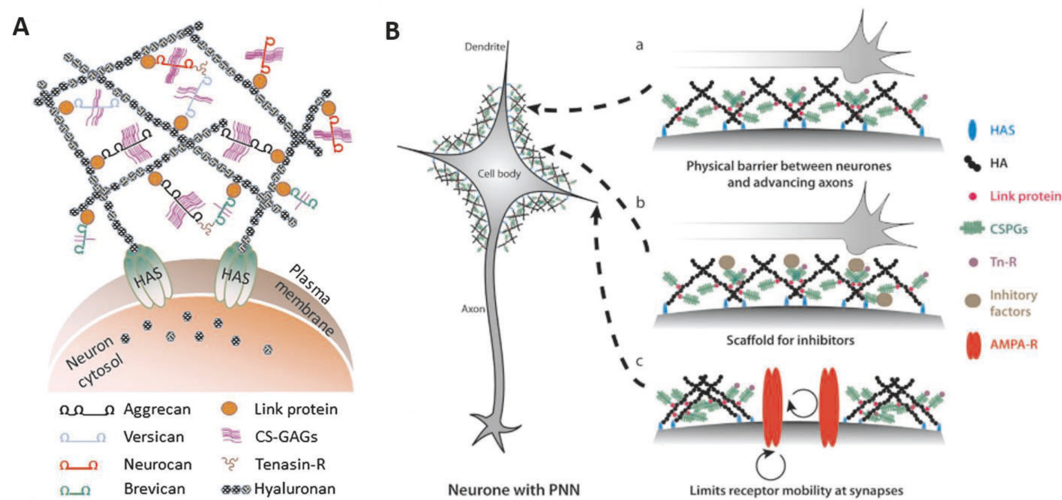

Fig. 6. Structure and proposed functions of PNNs. (A) PNNs are composed of ECM molecules with the main components being hyaluronan (HA), link proteins, CSPGs, and tenascin-R. (B) (a) PNNs could act as a physical barrier, preventing the formation of new synaptic contacts. (b) PNNs could act as a scaffold for the binding of molecules that could inhibit synapse formation. (c) PNNs may limit the receptor mobility at synapses. Modified from Tsien (2013) and Wang (2012).

7. iPLASTICITY AND INTERVENTIONS

As mentioned earlier, a stable neuronal circuitry enables the consolidation and retrieval of important memories, however, networks maladapted during early life require major restructuring, which can only take place if the brain is in a plastic state. Research has therefore explored ways to reinstate a critical period-like plasticity or iPlasticity (induced plasticity) that, in combination with training and rehabilitation, could adjust the acquired maladaptation. Increasing research has identified different interventions, including drug treatment and environmental enrichment that seem to result in iPlasticity.

7.1. Antidepressants

Introduction

The monoamine oxidase (MAO) inhibitor iproniazid was accidentally discovered when it was first tested for the treatment of tuberculosis, but it became clear that iproniazid could improve the mood of depressed patients. Soon after, the first tricyclic antidepressant imipramine followed and given the recognition that both drugs increase the brain levels of monoamines, the monoamine hypothesis of depression was established, describing depression as being caused by a deficiency in monoaminergic neuromodulators (Castrén, 2013; Schildkraut, 1965). This led to the development of more selective drugs focusing on serotonin levels and brought the selective serotonin reuptake inhibitors (SSRIs) on the market.

Even though the monoamine hypothesis of depression has dominated the thinking about mood disorders, it could not explain the weeks of delayed onset of their therapeutic effects, as the drug-

induced elevations of monoamine levels are rapid. Research of the last decade has readdressed this question and the focus has shifted to neuronal plasticity, with speculation that antidepressants could mediate their effects by regulating the expression of genes related to adaptation and structural and functional reorganization (Castrén, 2013).

Activation of TrkB by antidepressants

More recently, it has been found that TrkB receptors are not entirely exclusive for the binding of BDNF, but can also be activated by antidepressant treatment (Saarelainen et al., 2003). The initial idea that the BDNF/TrkB pathway could be involved in the antidepressant drug response occurred with the postulation that depression is related to lower levels of BDNF and a lack of neurotrophin signaling. These effects would impair the survival and connectivity of neurons, resulting in brain atrophy and thereby impaired information processing in brain areas related to the regulation of mood (Duman, Heninger, & Nestler, 1997). Indeed, chronic treatment with antidepressant drugs increases the expression of BDNF and TrkB mRNA (Nibuya, Morinobu, & Duman, 1995), observed in the brain and serum of depressed patients after antidepressant treatment (Chen, Dowlatshahi, MacQueen, Wang, & Young, 2001).

Also, BDNF itself has been shown to induce antidepressant-like effects. For example, BDNF infusion into the midbrain for 6-7 days results in an antidepressant-like behavior in behavioral paradigms that have long been used to assess depression-like behavior, such as the forced swim test, suggesting that BDNF action itself is sufficient to induce antidepressant-like behaviors (Siuciak, Lewis, Wiegand, & Lindsay, 1997). BDNF administration into the dentate gyrus or CA3 area of the hippocampus also results in antidepressant-like behavior in the learned helplessness and forced swim test (Hoshaw, Malberg, & Lucki, 2005; Shirayama, Chen, Nakagawa, Russell, & Duman, 2002).

These antidepressant-like effects of BDNF are likely to be mediated via its receptor TrkB. In fact, overexpression of TrkB induces effects similar to BDNF and antidepressant treatment in the forced swim test (Koponen et al., 2005). Intact BDNF/TrkB signaling seems to be required for the behavioral effects induced by antidepressant treatment, as BDNF heterozygous knockout mice, BDNF conditional knockout mice, and mice overexpressing the truncated isoform of the TrkB receptors lack the response to antidepressant drugs (Monteggia et al., 2004; Saarelainen et al., 2003). Acute or chronic antidepressant treatment results in autophosphorylation and activation of TrkB receptors and its downstream signaling in several regions of the mouse brain (Rantamäki et al., 2007; Saarelainen et al., 2003).

Considering that the effects of antidepressant treatment occurs with a delay of several weeks to months in mice and humans, the hypothesis that the relief of depressive-like behaviors is related to structural changes in the brain seems supported (Castrén, 2013; Castrén & Hen, 2013). The plasticity processes involved in these structural changes include the generation of new neuronal connections and cells, indicating adult neurogenesis, and the strengthening or weakening of synapses (Castrén & Hen, 2013). Antidepressant treatment increases the turnover of hippocampal neurons and requires intact BDNF signaling for the long-term survival of newborn neurons, as both heterozygous BDNF knockout mice and mice overexpressing the truncated isoform of TrkB lose the survival of newborn neurons (Sairanen, Lucas, Ernfors, Castrén, & Castrén, 2005).

Antidepressant-induced plasticity

Intensive studies using different models of plasticity have proven the potential of antidepressants to regulate the restructuring of the adult neuronal network (Fig. 7).

In the visual cortex, Maya-Vetencourt et al. (2008) provided direct evidence that antidepressants can restore plasticity in adulthood. The authors showed that chronic treatment with the SSRI fluoxetine successfully reinstates ocular dominance plasticity (Maya-Vetencourt et al., 2008) (Fig. 7). Importantly, the shift was not due to enhanced responses of the open eye, which has been shown during ocular dominance plasticity in adult animals (Frenkel & Bear, 2004; Sawtell et al., 2003), but to a decrease in responses of the deprived eye, typically observed during the critical period. Moreover, chronic fluoxetine treatment also recovered visual functions in adult amblyopic rats. However, for this, the opposite eye had to be deprived, providing evidence that antidepressant-induced plasticity requires sensory manipulations and guidance. In the same study, the shift in ocular dominance induced by fluoxetine treatment was accompanied by increased levels of BDNF and decreased GABA levels. Interestingly, direct administration of BDNF via minipumps during monocular deprivation similarly induced a shift in ocular dominance, suggesting that activation of the BDNF/TrkB pathway alone is sufficient to mediate the structural rewiring required for visual cortex plasticity. In contrast, intracortical infusion of the $GABA_A$ receptor agonist diazepam prevented the fluoxetine-induced shift in ocular dominance, indicating that fluoxetine specifically acts through the GABAergic network (Maya-Vetencourt et al., 2008).

In humans, however, chronic fluoxetine treatment did not enhance the effect of game-based perceptual training on visual functions (Huttunen et al., 2018); reasons for this include: (i) the relatively small dose of fluoxetine (20 mg) used; (ii) the treatment period of 10 weeks may be too short; or (iii) the training paradigm was so effective that the impact of fluoxetine could no longer be detected since the control group also showed improved visual outcomes. Hence, the computer game could act as a sort of environmental enrichment, and the combination of environmental enrichment and fluoxetine can occlude each other.

In the fear circuitry of infants, fear memories can readily be erased, however, fear acquired after the closure of the critical period is difficult to extinguish, a condition that can result in post-traumatic stress disorder (PTSD). However, chronic fluoxetine treatment results in the erasure of previously acquired fear memory during adulthood when combined with extinction training (Karpova et al., 2011). Notably, fluoxetine treatment had no effect without extinction training, providing additional evidence that guidance is necessary for plasticity induced by antidepressants. Fluoxetine treatment was also accompanied by increased LTP after tetanus stimulation and a reduction of PNNs surrounding PV cells in the amygdala, a brain area associated with emotions and emotional memory (Karpova et al., 2011).

Finally, fluoxetine treatment also induces plasticity during social behavior. Combining social rehabilitation with chronic fluoxetine treatment results in enhanced social learning, limiting aggression induced by post-weaning social isolation, and recovered mBDNF expression (Mikics et al., 2018).

7.2. *ChABC*

Enzymatic degradation of PNNs using chondroitinase ABC (ChABC) was among the first experimental manipulations to actively target determinants of critical period closure (Hensch & Bilimoria, 2012) (Fig. 7). Disruption of PNNs using enzymatic digestion by ChABC, which breaks down the GAG chains of CSPGs, is sufficient to reopen critical periods during adulthood when combined with monocular deprivation (Pizzorusso et al., 2002). In another set of experiments, rats in which ocular dominance was shifted during the critical period (a model of human amblyopia) completely recovered their ocular dominance, visual acuity, and dendritic spine density when injected with ChABC and simultaneously deprived of the stronger eye (Pizzorusso et al., 2006). Further, PNN digestion in the adult visual cortex not only reactivates ocular dominance plasticity, but also decreases the endogenous Otx2 concentration in PV cells (Sugiyama et al., 2008). These findings demonstrate that CSPGs are important in restricting visual cortex plasticity once the critical periods are closed.

Further, degradation of PNNs by ChABC injection into the amygdala during adulthood results in erasure of previously acquired fear memory, indicating that intact PNNs mediate the formation of erasure-resistant fear memories (Gogolla, Caroni, Lüthi, & Herry, 2009). Nevertheless, it should be noted that the use of ChABC is still far from clinical applications.

7.3. *HDAC inhibitors*

Another biochemical way to reopen plasticity during adulthood is the use of a histone deacetylase (HDAC) inhibitor, such as valproate, a commonly used anticonvulsant and mood stabilizer, that modulates the epigenome to promote neuroplasticity (Gervain et al., 2013; Machado-Vieira, Ibrahim, Zarate, & Zarate, 2011) (Fig. 7). In humans, the administration of valproate resulted in better learning to identify pitch, meaning the ability to identify or produce the pitch of a sound without a reference point, compared with placebo-treated controls, indicating that valproate facilitates critical period learning during adulthood (Gervain et al., 2013).

7.4. *Other factors*

Besides pharmacological and biochemical interventions, environmental factors have been shown to have a large impact on plasticity processes in the adult brain.

Environmental enrichment, a condition in which animals are housed in an environment with toys, tunnels, and running wheels, promotes recovery from amblyopia through reduction in inhibition (Sale, 2007), similar to fluoxetine treatment, extends visual plasticity into adulthood, and protects against stroke-induced impairments in plasticity (Greifzu, Kalogeraki, & Löwel, 2016; Greifzu et al., 2014) (Fig. 7). Interestingly, voluntary exercise alone, as part of an enriched environment, promotes visual cortex plasticity during adulthood (Kalogeraki, Greifzu, Haack, & Löwel, 2014). Exercise can also replicate the benefits of antidepressant treatment in humans suffering from major depressive disorder (Blumenthal et al., 2007) and results in increased levels of BDNF, thereby promoting brain plasticity processes (Cotman & Berchtold, 2002; Gomez-Pinilla, Zhuang, Feng, Ying, & Fan, 2011; Voss, Erickson, et al., 2013; Voss, Vivar, Kramer, & van Praag, 2013).

Finally, caloric restriction reopens the critical period for ocular dominance and reduces intracortical inhibition. In contrast, the restoration of plasticity is prevented by benzodiazepam treatment, while

low dose corticosterone administration mimics the effects of food restriction on visual cortex plasticity (Spolidoro et al., 2011).

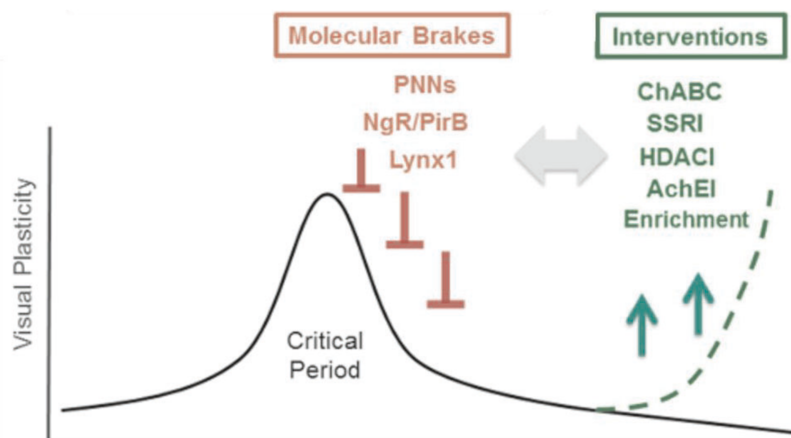

Fig. 7. Interventions during adulthood that can reinstate a critical period-like plasticity (iPlasticity). ChABC, chronic antidepressant treatment, HDAC inhibitors, AchE inhibitors, and environmental enrichment can reinstate plasticity in the adult visual cortex by acting on the molecular brakes that promote the closure of critical periods. Modified from Nabel (2013).

7.5. MeHg

Besides interventions that can induce and promote neuronal plasticity, attention should also be paid to factors that can impair and harm plasticity processes. Given the high sensitivity of the brain during early development, adverse interference, such as alterations in environmental conditions, can result in long-lasting pathological conditions. These conditions can include sensory stimuli, as discussed earlier, maternal care, and stress, but also drug treatment and toxic compounds (McEwen, 1999; Meaney, 2001; Mendola, Selevan, Gutter, & Rice, 2002; Onishchenko et al., 2007).

Methylmercury (MeHg) is one of the neurotoxic compounds known to contaminate certain seafoods, accumulating especially in larger fish species, and is the main source for human exposure (Björnberg, Vahter, Grawé, & Berglund, 2005; Mahaffey, 2005). MeHg is the methylated form of mercury, a periodic table element. Since mercury cannot be destroyed, the total amount on the planet will always be the same and widely distributed (Mahaffey, 2005). Mercury cycles in the environment due to natural phenomena, including release through volcanos, industrial processes, and combustion of mercury-containing wastes (Pirrone & Mahaffey, 2005) (Fig. 8). As a result, mercury is released into the air as mercury vapor or inorganic mercury, where it is finally redeposited in the earth waterways with precipitation, incorporated into sludge or sediments, and methylated (Mahaffey, 2005) (Fig. 8). The plants and sedimentary materials are then consumed by smaller fishes, which in turn are consumed by progressively larger fishes, resulting in bioaccumulation of MeHg (Fig. 8). Humans are exposed to MeHg because they consume fish and shellfish in which MeHg has accumulated. The fishes at the top of the aquatic food chain generally have higher MeHg concentrations than those lower in the food chain. Hence, such fishes as sharks,

tuna, swordfish, and salmon contain 10-20 times higher MeHg concentrations than such fishes as herring, cod, shrimp, and scallops (Mahaffey, 2004). Dietary MeHg is almost completely absorbed in the gastrointestinal tract (Clarkson, 1972), quickly entering the bloodstream and distributing throughout the body, including the brain, where approximately 10% of the ingested MeHg is deposited (Clarkson, 2002). MeHg can also cross the placenta, resulting in higher concentrations in fetal cord blood than in maternal blood (Vahter et al., 2000). Infants are believed to have a lower capacity to excrete MeHg and are therefore particularly vulnerable considering their sensitive nervous system (Nordenhäll, Dock, & Vahter, 1995).

In the 1950-70s, the health consequences of MeHg exposure, mainly damage to the nervous system, became apparent, and neurodevelopmental effects were observed in infants of mothers with no or little signs of toxicity (Johansson et al., 2007).

Developmental exposure to low levels of MeHg has been associated with depression-like behavior in young and adult mice (Onishchenko et al., 2007), and these long-lasting behavioral changes are associated with decreases in BDNF mRNA and a repressive state of the chromatin structure of the BDNF promoter region (Onishchenko, Karpova, Sabri, Castrén, & Ceccatelli, 2008). Interestingly, MeHg-induced depression-like behavior could be reversed by chronic fluoxetine treatment. Chronic fluoxetine treatment also restored BDNF mRNA levels and improved the epigenetic changes at the BDNF promoter region (Onishchenko et al., 2008). Moreover, TrkB overexpression prevents the development of depression-like behavior and memory deficits in mice exposed to MeHg. This effect was paralleled by increased transcription of BDNF, suggesting a substantial role of the BDNF/TrkB pathway in buffering against MeHg-induced effects (Karpova et al., 2014a). The effects of MeHg exposure on the BDNF/TrkB pathway have also been demonstrated in humans. For example, girls born to mothers exposed to MeHg during pregnancy had lower serum BDNF concentrations (Spulber et al., 2010).

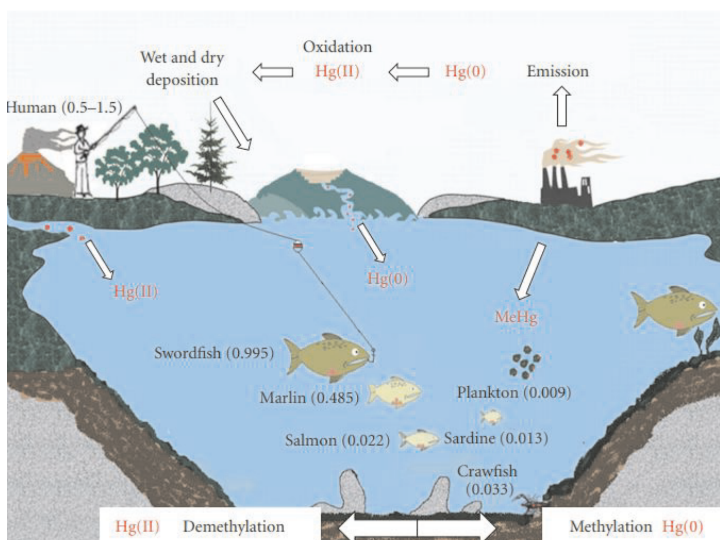

Fig. 8. MeHg cycle and its bioaccumulation in plankton and fish. The values of MeHG are indicated as ppm (parts per million). Modified from Roos (2012).

AIMS OF THE STUDY

TrkB receptors are powerful regulators of synaptic plasticity and increasing research indicates a role for TrkB actions in iPlasticity. Considering the heterogeneous population of neurons that express TrkB receptors, the question to be answered is through which neuronal subpopulation in the visual cortex and fear circuitry are these effects mediated. We therefore aimed to understand whether TrkB receptors expressed and activated in PV interneurons regulate visual cortex plasticity. In addition, we aimed to uncover the role of TrkB activation specifically in pyramidal neurons of the ventral hippocampus in the induction of LTP. Finally, we aimed to contribute new knowledge of the effects of fluoxetine and MeHg during pregnancy on the time course of critical periods.

The specific aims were as follows:

I. To identify the role of TrkB receptors expressed and activated in PV interneurons on visual cortex plasticity
II. To examine the effects of optoTrkB activation in pyramidal neurons of the CA1 region of the ventral hippocampus on LTP induction
III. To examine the effects of perinatal fluoxetine and methylmercury exposure on PV and PNN expression as markers for critical periods

MATERIALS & METHODS

1. Animals (I, II, III)

All animal experiments in this thesis were performed according to the guidelines of the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the experimental Animal Ethical Committee of Southern Finland. The experiments were done under the external license ESAVI/10300/04.10.07/2016.

For the experiments, either wild-type mice, mice expressing cre-recombinase in PV cells, or heterozygous mice with TrkB deletion specifically in PV+ interneurons (hPV-TrkB CKO mice; $PV^{pvr/wt}$, $TrkB^{flx/wt}$) were used.

To assure complete closure of the critical periods, all mice were older than 100 days at the start of the experiments.

2. Virus construction and injection (I, II)

Juzoh Umemori modified and optimized optoTrkB constructs described elsewhere (Chang et al., 2014). To obtain optoTrkB, TrkB was conjugated to a photolyase homology region (PHR) domain, which, upon blue LED light (470 nm) stimulation, promotes the dimerization and autophosphorylation of TrkB. Juzoh Umemori developed the following two versions in a lentivirus backbone:

A. CaMKII-optoTrkB

   For electrophysiological recordings in the hippocampus, optoTrkB was expressed under the calmodulin kinase II (CaMKII) promoter to allow optoTrkB expression in principal neurons of the ventral hippocampus.

B. DIO-optoTrkB

   For experiments in the visual cortex, optoTrkB was expressed in a double-inverted open reading frame structure (DIO), which has two incompatible lox-P sites flanking the optoTrkB sequence, allowing cre-dependent expression. For electrophysiological experiments, DIO-optoTrkB constructs were co-expressed with Td-Tomato to identify virus-infected cells.

During stereotaxic surgery under isoflurane anesthesia (2-2.5%) CaMKII-optoTrkB was injected into the ventral hippocampus (at 3.1 mm caudally and +/- 2.0 mm laterally from the Bregma with a depth of 3.9 mm and an angle of 18°) of WT mice. For the fear conditioning paradigm, the optic fiber cannulas were implanted 3 weeks after the virus infection and allowed to recover for one week before starting the behavioral paradigm.

DIO-optoTrkB was injected into the contralateral visual cortex of PV-cre mice. For this, the functional part of the binocular area of the visual cortex was identified by obtaining the blood vessel and signal maps after IOS I imaging. For electrophysiological, immunohistochemical, and Western blot experiments, multiple injections (2/hemisphere) into the visual cortex were performed to allow a wider expression of optoTrkB.

To avoid light exposure through the transparent skull, a thin layer of black nail polish was applied, which was removed during monocular deprivation to stimulate optoTrkB with blue LED light (488 nm) through the transparent skull twice per day for 30 sec (at 8-10 am and 4-6 pm).

3. Drug treatment (I, III)

Fluoxetine (0.08 mg/ml) was administered via drinking water and the treatment started after the surgical procedures (I) and continued for 21 days. Perinatal fluoxetine (0.08 mg/ml) and

methylmercury (0.59 mg/kg/day) were administered via drinking water and the treatment started at gestational day 6 and was performed by Nina Karpova (II).

4. Shift in ocular dominance (I)

Transparent skulls were prepared as previously described (Steinzeig, Molotkov, & Castrén, 2017) to allow chronic imaging of intrinsic signals in the shift in ocular dominance paradigm. The intrinsic optical signals (IOS) were measured before (IOS I and IOS III) and after (IOS II and IOS IV) 7 days of monocular deprivation. The ocular dominance index (ODI) was calculated from the vessel maps obtained from the binocular visual cortex based on the formula (C-I)/(C+I), where "C" refers to the response magnitude of the contralateral eye and "I" to that of the ipsilateral eye. For each animal, several ODIs were collected and averaged. Positive ODI values represent contralateral eye dominance, negative ODI values represent ipsilateral eye dominance, and ODI values of 0 correspond to equally strong contralateral and ipsilateral eyes.

To deprive the animals, the eyelashes were trimmed and the eyelid margins were closed with three mattress sutures.

5. Fear extinction with optical stimulation (II)

The fear conditioning paradigm was conducted by Juzoh Umemori and Giuliano Didio. Briefly, the mice were put into Context A, where they received an electric foot shock (0.6 mA) after a 30-sec sound cue (beep sounds 80 dB) that was repeated four times with a 30- to 60-sec interval. Two days later, the mice were placed in Context B for extinction training and received only the sound cue immediately followed by optical stimulation for 5 sec, which was repeated 12 times with different intervals (25-60 sec) for 2 days. One week later, the mice were tested in Context B (spontaneous recovery), followed by exposure to Context A (fear renewal). Spontaneous recovery and fear renewal were tested again 3 weeks later as an estimate of remote memory. The durations of freezing were measured as an index of conditioned fear.

6. Electrophysiology in acute slices (I, II)

To measure changes in physiological properties after fluoxetine treatment in WT and hPV-TrkB CKO mice and after optoTrkB stimulation, extracellular field potentials (fEPSPs) in acute slices in layer II/III of the visual cortex were recorded. The animals were deeply anesthetized with isoflurane, the brains were dissected and subsequently immersed in ice-cold dissection solution containing (in mM): 124 NaCl, 3 KCl, 1.25 NaH_2PO_4, 1 $MgSO_4$, 26 $NaHCO_3$, 15 D-glucose, 9 $MgSO_4$, and 0.5 $CaCl_2$ bubbled with CO_2/95% O_2. The cerebellum and anterior part of the brain were removed and horizontal 350-µm-thick slices of the visual cortex were cut on a vibratome (Leica Biosystems, Buffalo Grove, IL, USA). The slices were incubated for 30 min at 31-32°C in artificial cerebrospinal fluid (ACSF) containing (in mM): 124 NaCl, 3 KCl, 1.25 NaH_2PO_4, 1 $MgSO_4$, 26 $NaHCO_3$, 15 D-glucose, and 2 $CaCl_2 \cdot 4H_2O$ and bubbled with 5% CO_2/95% O_2 before starting the recordings.

Field excitatory postsynaptic currents (EPSPs) were recorded in an interface chamber at 35°C. The recording electrode was positioned within layer II/III of the visual cortex and a concentric bipolar stimulation electrode (100 µsec duration) was placed at the border of the white matter (WM) and layer VI. fEPSPs were recorded using an Axonpatch 200B amplifier (Molecular Devices, San Jose, CA, USA). Baseline synaptic responses were evoked every 20 sec with a stimulation intensity that yielded a half-maximum response and after obtaining a 15 min stable baseline θ burst stimulation (TBS) (4 sweeps at 0.1 Hz, 10 trains at 5 Hz, 4 pulses at 100 Hz) was delivered and fEPSCs were

recorded for 45 min. For the data acquisition, the WinLTP (0.95b or 0.96, www.winltp.com) program was used. Slices infected with optoTrkB were stimulated for 30 sec with LED light 60 min before TBS stimulation.

For hippocampal recordings of fEPSCs, slices were prepared from CaMKII-optoTrkB infected mice as described above. ACSF-filled glass microelectrodes (2-4 MΩ) were placed into the stratum radiatum of the CA1 region in the hippocampus, and the stimulating electrode (100 µsec duration) was positioned at the Schaffer collateral. After obtaining a 15 min stable baseline, the slices were stimulated with light 3x5 sec every minute, and subsequently tetanus stimulation (200 ms pulse interval; 100 pulses; 0.1 ms pulse duration), subthreshold tetanus stimulation (20 Hz), or subthreshold TBS stimulation (1 sweep at 0.1 Hz, 2 trains at 5 Hz, 4 pulses at 100 Hz) were delivered and field potentials recorded for 45 min.

To measure intrinsic excitability, the brains were dissected as described above, but cut in a protective NMDG ACSF, as previously described (Ting, Daigle, Chen, & Feng, 2014) containing (in mM): 92 NMDG, 2.5 KCl, 1.25 NaH_2PO_4, 30 $NaHCO_3$, 20 HEPES, 25 glucose, 2 thiourea, 5 Na-ascorbate, 3 Na-pyruvate, 0.5 $CaCl_2 \cdot 4H_2O$, and 10 $MgSO_4 \cdot 7H_2O$ and the pH was titrated to 7.3–7.4 with concentrated hydrochloric acid. The slices were then transferred for 10 min to 32°C in the same solution before keeping them in HEPES with ACSF containing (in mM): 92 NaCl, 2.5 KCl, 1.25 NaH_2PO_4, 30 $NaHCO_3$, 20 HEPES, 25 glucose, 2 thiourea, 5 Na-ascorbate, 3 Na-pyruvate, 2 $CaCl_2 \cdot 4H_2O$, and 2 $MgSO_4 \cdot 7H_2O$ bubbled with CO_2/95% O_2, where they were kept throughout the recordings.

Whole-cell patch-clamp recordings from PV cells were obtained with glass microelectrodes (3-5 MΩ) filled with a low Cl^--filling solution containing (in mM): 135 K-gluconate, 10 HEPES, 2 KCl, 2, $Ca(OH)_2$, 5 EGTA, 4 Mg-ATP, 0.5 Na-GTP and recorded with a Multiclamp 700A amplifier (Molecular devices, San Jose, CA, USA).

Intrinsic excitability of PV cells was recorded by injecting current steps ranging from -50 to 600 pA for 600 ms in 50 pA steps in current clamp mode. The recordings were analyzed in Clampfit (Molecular Devices, San Jose, CA, USA).

7. Immunohistochemistry (I, II, III)

For immunohistochemical analysis, the mice were perfused with chilled 4% paraformaldehyde (PFA) in PBS, the brains were removed and left for fixation in 4% PFA overnight at 4°C. Next, the brains were transferred to PBS solution containing 0.04% sodium azide (NaN_3) until cutting. For cutting, the brains were embedded in 3% agar and 40-µm coronal sections of the visual cortex were cut on a vibratome (Leica Biosystems). The sections were washed with PBST (1x PBS and 0.2% TritonX100), incubated in 10% donkey serum (Vector Laboratories, UK) and 3% Bovine Serum Albumin (BSA) (Sigma-Aldrich) in PBST for 30 min at room temperature and incubated with the following primary antibodies: 1) guinea pig anti-parvalbumin (1:1000; Synaptic Systems, Göttingen, Germany), 2) biotinylated lectin from Wisteria floribunda (WFA; 1:200; Sigma-Aldrich, Helsinki, Finland), 3) rabbit anti-delta FosB (1:200; H-75; Santa Cruz Biotechnology, TX, USA), 4) mouse anti-c-myc (1:15; DSHB, IA, USA) overnight at 4°C. The sections were washed and further incubated in the following secondary antibodies: 1) goat anti-guinea pig secondary antibody conjugated with Alexa Fluor647/546 (1:1000; Abcam, Cambridge, UK/Life Technologies, Carlsbad, CA, USA), 2) streptavidin conjugated with Alexa Fluor488 (1:1000; Thermo Fisher Scientific, Waltham, MA, USA), 3) Goat anti-rabbit conjugated with Alexa Fluor 647 (1:1000; Life Technologies), and 4) donkey anti-mouse conjugated with Alexa Fluor488 (1:1000; Life Technologies) for 1 h at room temperature in light-protected tubes. Finally, the sections were washed again, transferred to PB with gelatin, mounted

on glass slides, and covered with DAKO mounting medium (Sigma Aldrich, Helsinki, Finland).

Immunohistochemical analyses for CaMKII-optoTrkB expressed in the ventral hippocampus were performed by Juzoh Umemori and Giuliano Didio. Briefly, the ventral hippocampus was exposed to blue LED light using the same protocol as during the extinction training (12 times for 5 sec after a 30-sec sound with different intervals (25-60 sec)), and 24 h later the mice were perfused. The brains were processed as described above and the following primary antibodies were used: mouse anti-CaMKII (1:500; Abcam, Cambridge, UK), chicken anti-GFP (1:1000; Abcam), and rabbit anti-FosB (1:500; H-75; Santa Cruz Biotechnology, TX, USA). For secondary antibody reaction, the following Alexa-conjugated antibodies were used: goat anti-mouse 546 (1:400; Life Technologies), donkey anti-rabbit 546 (1:500; Thermo Fisher Scientific, Waltham, MA, USA), and donkey anti-chicken 488 (1:500; Jackson, Cambridge, UK).

To test the perinatal influence of either methylmercury or fluoxetine treatment, immunohistochemical analysis on perfused brains from WT mice at postnatal days 17 and 24 (P17, P24) was performed. The dams were treated and the brains collected by Nina Karpova.

The brains were cryoprotected in 30% sucrose, embedded in O.C.T. compound (Tissue-Tek, Sakura, the Netherlands) and stored at -80°C until sectioning. Coronal sections of 40-μm thickness were obtained with a Leica CM3050 S cryostat (Leica Microsystems, Wetzlar, Germany), and the slices were stored in cryoprotective solutions (30% glycerol, 30% ethylene glycol in PBS) at -20°C until staining.

Immunohistochemistry was performed on free-floating brain sections. After washing with PBS, the sections were incubated in the blocking reagents streptavidin/biotin blocking solutions (Vector Laboratories, Burlingame, CA, USA) for 15 min each and mouse-on-mouse (MOM) blocking reagent (Vector Laboratories, Burlingame, CA, USA) for 1 h and in blocking buffer containing 10% goat serum (Vector Laboratories, UK) and 3% bovine serum albumin (Sigma-Aldrich, Helsinki, Finland) in PBST (1x PBS and 0.4% TritonX100). The sections were then incubated with anti-parvalbumin primary antibodies (1:5000; Swant, Bellinzona, Switzerland) and biotinylated lectin from Wisteria floribunda (WFA; 1:200; Sigma-Aldrich, Helsinki, Finland) at 4°C overnight. After washing with PBST, the sections were incubated in goat anti-mouse secondary antibody conjugated with Alexa Fluor568 (1:1000; Molecular Probes, Invitrogen, Espoo, Finland) and streptavidin conjugated with Alexa Fluor488 (1:1000; Molecular Probes, Invitrogen, Espoo, Finland) for 2 h at room temperature. Finally, the sections were washed in PBS, mounted on glass slides, and covered with Prolong®Gold antifade reagent (Invitrogen, Espoo, Finland). The negative controls were stained without the primary antibody and WFA.

8. Image acquisition and analysis (I, II, III)

To allow blinded quantitative analysis of the immunostainings, the samples were coded until the analyses were finished. Images were taken from the primary visual cortex, determined according to the mouse brain atlas, of fluoxetine-treated hPV-TrkB CKO and WT samples and of LED-stimulated/non-stimulated optoTrkB samples. Juzoh Umemori obtained images of the dentate gyrus (DG) and CA1 of the hippocampus and basolateral amygdala complex, including the basolateral (BLA) and lateral (LA) amygdala, of P17 and P24 samples after methylmercury and fluoxetine treatment.

Laser scanning confocal microscopy was used to detect PV positive (PV+), PNN positive (PNN+), double positive (PV+PNN+), FosB positive (FosB+), TdT positive (TdT+), and c-myc positive (c-myc+)

cells. Using the confocal microscope LSM 700 (Carl Zeiss) equipped with a 10× objective lens (10x Plan-Apochromat 10x/0.45, Carl Zeiss) and imaging software ZEN 2012 lite (Zeiss, Vantaa, Finland), z-stacks containing at least 10 consecutive images were obtained from each section. A minimum number of three sections per animal using the same microscope and the same camera settings for all samples were used. Image processing was done with the ImageJ software version 1 (National Institutes of Health), and all images in each z-stack were analyzed and the number of cells was averaged per z-stack.
For the PV intensity analysis, non-stimulated optoTrkB or water-treated WT mice served as the reference group. The PV populations were defined as follows: low PV (0-8000 a.u.), intermediate-low PV (int-low PV, 8000-16000 a.u.), intermediate-high PV (int-high, 16000-24000 a.u.), and high PV (24000-36000 a.u.) expressing cells, and the thresholds were applied to the other groups.

FosB expression in CaMKII-optoTrkB neurons in the CA1 region of the ventral hippocampus was analyzed by Juzoh Umemori by measuring the mean gray value of FosB of that area using Image J software.

9. Sample collection (I)
Western blot and qPCR samples were collected from optoTrkB-infected mice under dark conditions. The animals were deeply anesthetized with isoflurane, and the brains were dissected and immersed in ice-cold dissection solution containing (in mM): 124 NaCl, 3 KCl, 1.25 NaH_2PO_4, 1 $MgSO_4$, 26 $NaHCO_3$, 15 D-glucose, 9 $MgSO_4$, and 0.5 $CaCl_2$. The visual cortex was dissected and incubated at 31-32°C in ACSF containing (in mM): 124 NaCl, 3 KCl, 1.25 NaH_2PO_4, 1 $MgSO_4$, 26 $NaHCO_3$, 15 D-glucose, and 2 $CaCl_2$ and bubbled with 5% CO_2/95% O_2. The tissue samples were either immediately collected (control) or stimulated with blue light for 30 sec and collected after 15 min, 30 min, or 60 min. The tissue samples were homogenized in NP lysis buffer and further processed.

10. Cortical neuronal cultures (II) performed by Juzoh Umemori and Juliana Harkki

Rat primary cortical cultured neurons at the age of E17, were spread onto 12 multi-well plates or on covers slips in a 24 multi-well plate in Neurobasal Medium+ (1% L-Glutamine, 1% Penicillin/Streptomycin and 2% B27) at 37°C. The cells were infected with CKII-optoTrkB lentivirus at day in vitro 3 (DIV3) for immunoblotting and cells at DIV9 for morphological analyses. The plates were kept in darkness after the infections. The cells were exposed to blue light at 10 DIV and 17 DIV for immunoblotting and immunocytology, respectively. The cells were stimulated 12 times for 5 sec with a 1-min interval. The cells were collected immediately after stimulation for immunoblotting and 24 h later for immunocytology. For immunoblotting, the cells were lysed and stored in darkness at -80°C. The samples for immunocytology were fixed with 4% PFA and stored in PBS containing 0.02% NaN_3 at 4°C.

11. Immunocytology and image analysis (II)

The antibodies used for immunocytology performed by Juzoh Umemori and Juliana Harkki were mouse anti-GFP (1:625, 1:667; Memorial Sloankettering, NY, USA) and chicken anti-MAP2 (1:5000; Abcam, Cambridge, UK), followed by Alexa-conjugated goat anti-mouse 546 (1:400; Life Technologies, Carlsbad, CA, USA) and goat anti-chicken 647 (1:400; Life Technologies). The stained cells (Ctr, n = 63; Ctr BDNF, n = 51; optoTrkB, n = 61; optoTrkB light, n = 48) were imaged with a Leica TCS SP8 X with a magnification of 40x for analysis of primary neurites and spines. The primary

branches sprouting from the soma were counted blindly and manually. Spines on the second branches were randomly and blindly selected. The number and type of spines were analyzed manually.

12. Western blot (I, II)

For the preparation of the samples collected for Western blot, the tissue samples were centrifuged (16000 g, 15 min at 4°C) and the supernatant was used to measure the protein concentrations with the Lowry method (Biorad DC protein assay; Lowry et al., 1951). Then, the samples were separated in a SDS-PAGE (2-4% gradient gel, NuPage™; Invitrogen, CA, USA) and blotted to a PVDF membrane (300 mA, 1 h, 41°C). The membranes were washed in Tris buffer solution with 0.001% Tween ®20 (TBST), blocked in TBST with 3% BSA for 1 h and incubated in primary antibody solutions (in TBST with 3% BSA) directed against phosphorylated and non-phosphorylated forms of TrkB (Y816, Y705/6, 515), CREB, and Erk at 4°C overnight. After washing in TBST, the membranes were further incubated in secondary antibody solutions (TBST with 5% non-fat dry skinned milk and horseradish peroxidase conjugated secondary antibodies Goat Anti-Rabbit/Mouse, 1:10000) for 2 h. After washing with TBST and rinsing with PBS, secondary antibodies were visualized by an electrochemiluminescence kit (ECL plus, Thermo Scientific®, CA, USA) according to the manufacturer's instructions and detected using a FUJIFILM LAS-3000 dark box. The same antibodies were used for the lysate of the cultured cortical neurons infected with CaMKII-optoTrkB by Giuliano Didio.

13. qPCR (I)

The RNA was purified from the lysate samples following the manufacturer's protocol using a combined protocol of QIAzol® (Qiagen) and NucleoSpin® (Macherey-Nagel). Briefly, the organic layer was extracted using Qiazol and chloroform. Next, the RNA was washed in 100% ethanol and the DNA was digested in spin columns. Finally, the purified RNA was reverse-transcribed to cDNA using Maxima First Strand cDNA Synthesis Kit (Thermo Scientific), and the amount of cDNA synthesized from the target mRNA was quantified by real-time PCR (qPCR). The following primers were used to amplify cDNA regions of the transcripts of interest:

Kv3.1 (5'-AGAGATTGGCACTCAGTGACT-3' and 5'-TTGTTCACGATGGGGTTGAAG-3'), Kv3.2 (5'-AGGCTATGGGGATATGTACCC-3' and 5'-TGCAAAATGTAGGCGAGCTTG-3'), PV (5'-TGTCGATGACAGACGTGCTC-3' and 5'-TTCTTCAACCCCAATCTTGC-3'), and FosB (5'-AGTTTGTCCTGGTGGCCC-3' and 5'-GGATGTTGACCCTGGCAAAT-3').

14. Statistics (I, II, III)

All statistical graphs were generated using Graphpad Prism v. 6.07. Unpaired t-test was used in the analysis of PV and PNN abundance after optoTrkB activation, one-way ANOVA was used for the analysis of qPCR data, and two-way ANOVA was used in all other experiments, followed by Tukeys, Bonferroni, or Fisher LSD post hoc tests. The confidence level was set to 0.05 (P value), and all results are presented as means ± s.e.m.

RESULTS

1. TrkB activation in PV interneurons orchestrates plasticity modes in cortical networks (I)

1.1. OptoTrkB activation in PV interneurons is sufficient to induce ocular dominance plasticity

The shift in ocular dominance paradigm is a classical model to study plasticity of the visual cortex. During the visual critical period the maturation of the PV inhibitory network promoted by BDNF results in closure of critical periods (Fagiolini & Hensch, 2000; Huang et al., 1999). To identify actions of TrkB in PV interneurons on adult cortical plasticity, we used an optically activatable form of TrkB, where a plant-derived photolyase homology region (PHR) domain added to the C-terminus of full-length TrkB regulates light-activated dimerization of TrkB monomers (Chang et al., 2014; Fenno, Mattis, Ramakrishnan, & Hyun, 2014). Injecting DIO-optoTrkB lentivirus into the binocular region of the visual cortex of PV-cre mice enabled us to specifically express optoTrkB in PV interneurons.
We measured the intrinsic optical signals before (IOS I) and after (IOS II) 7 days of monocular deprivation, and during monocular deprivation half of the mice were stimulated with blue LED light through the exposed skull (Steinzeig et al., 2017) for 30 sec twice daily. Control mice were infected, but not exposed to light. Non-stimulated mice failed to shift their ocular dominance towards the non-deprived eye, demonstrating that optoTrkB expression itself does not have any effect on plasticity. Light stimulation, however, successfully reinstated plasticity and shifted the ocular dominance towards the non-deprived/ipsilateral eye after monocular deprivation (IOS II).
Next, we wondered whether the shift remains when the sensory input is balanced (by not depriving the mice). When comparing IOS II with IOS III, we observed no change in the ODIs of the mice within the light-stimulated and non-stimulated groups and concluded that the shift is preserved.
Finally, we tested whether we can repeatedly induce plastic states. Therefore, we deprived the mice of the ipsilateral eye for 7 days combined with either light stimulation of 30 sec twice daily or without. As expected, non-stimulated mice had no changes in their ODI. Strikingly, mice that have been stimulated with light, however, shifted their ODI back towards contralateral eye dominance. These results demonstrate that the combination of optoTrkB activation in PV cells and monocular deprivation is sufficient to switch the visual cortex into high plasticity states.

1.2. TrkB expression in PV interneurons is necessary for ocular dominance plasticity

Finding that TrkB activation in PV interneurons is sufficient to reinstate visual cortex plasticity, we wondered whether it is also necessary. To test the hypothesis, we used heterozygous PV-specific conditional TrkB knockout mice (hPV-TrkB cKO) and pharmacologically induced plasticity with chronic (21 days) fluoxetine treatment (Maya-Vetencourt et al., 2008). These mice do not show an overt phenotype compared with homozygous knockout mice, which exhibit hyperlocomotion, vestibular dysfunction (Lucas et al., 2014), and disruptions in network activity, including reduced gamma oscillations and increased firing of excitatory neurons (Xenos et al., 2017).
We again measured the ODI before (IOS I) and after (IOS II) 7 days of monocular deprivation. After 7 days of monocular deprivation, fluoxetine treatment successfully reinstated ocular dominance plasticity in WT mice by shifting their ocular dominance from the contralateral to the ipsilateral eye as previously observed (Maya-Vetencourt et al., 2008; Steinzeig et al., 2017). In hPV-TrkB cKO mice, however, fluoxetine treatment failed to induce a shift in ocular dominance. These results indicate that TrkB activation in PV cells is both necessary and sufficient for the reinstatement of ocular dominance plasticity.

1.3. TrkB activation in PV interneurons induces a rapid shift in network plasticity

A shift in ocular dominance requires structural remodeling and takes place over several days. Therefore, we wondered how rapidly activation of TrkB in PV cells promotes network plasticity. In the primary visual cortex, the induction of LTP has been used as an in vitro analog to test visual cortex plasticity and is likewise restricted to critical periods (Kirkwood et al., 1996). However, chronic fluoxetine treatment can reactivate the induction of LTP in the adult visual cortex (Maya-Vetencourt et al., 2008). Hence, we used LTP as an assay to test whether an acute single activation of optoTrkB is already sufficient to permit LTP in the visual cortex. We injected DIO-optoTrkB lentiviruses into the visual cortex of PV-cre mice and 4 weeks later cut acute cortical slices from the infected area. Slices kept in dark showed no LTP in layer II/III of the visual cortex after TBS stimulation. Strikingly, a single 30-sec light exposure of optoTrkB-infected slices 60 min prior the induction of LTP by TBS stimulation induced LTP in layer II/III.

Chronic fluoxetine treatment delivered via drinking water for 21 days prior to the experiment resulted in the induction of LTP after TBS stimulation in the same way as the activation of optoTrkB did. However, deleting TrkB from PV cells abolished the ability of fluoxetine treatment to permit LTP in layer II/III of the visual cortex.

These results demonstrate that TrkB activation and expression in PV interneurons are sufficient and necessary to permit LTP and disinhibit pyramidal cells.

1.4. TrkB activation in PV interneurons triggers intrinsic changes

Activation of TrkB in pyramidal neurons promotes LTP in the hippocampus (Figurov et al., 1996; Kang & Schuman, 1994). Unexpectedly, we find that activation of TrkB in PV interneurons that provides inhibitory control of pyramidal cells also permits the induction of LTP. To identify the mechanisms underlying this surprising rapid regulation of plasticity, we performed patch clamp recordings from optoTrkB-positive PV neurons, which co-express the fluorescent reporter Td-tomato. We tested the intrinsic excitability of PV cells by injecting currents ranging from -50 to 600 pA in current clamp mode. We found a significant decrease in the intrinsic excitability of infected PV cells 30-60 min after optoTrkB activation, which was accompanied by trends towards increased AP half width.

Next, we confirmed that chronic fluoxetine treatment exerts similar effects by activating TrkB expressed in PV interneurons and performed electrophysiological recordings from acute slices obtained from WT and hPV-TrkB cKO mice, which co-express Td-tomato in PV cells, and treated the mice with fluoxetine or tap water. In WT mice, chronic fluoxetine treatment resulted in a reduction in their intrinsic excitability similarly as optoTrkB did. This effect was accompanied by an increase in AP half width. The deletion of TrkB from PV cells, however, abolished the ability of fluoxetine treatment to decrease the intrinsic excitability and had no effect on the AP half width.

A decrease in the intrinsic excitability of PV cells is likely to be mediated by changes in potassium currents, and it is known that particularly Kv3 channels, which are highly expressed in cortical PV cells, regulate the fast-spiking phenotype. We therefore extracted mRNA under dark conditions from optoTrkB-infected mice. The samples either were not stimulated or were collected 15 min, 30 min, or 60 min after light stimulation, and then the relative amount of Kv3.1 and Kv3.2 mRNA was

measured by qPCR. We found a reduction in Kv3.1 mRNA 60 min after light stimulation. Strikingly, Kv3.2 mRNA was already reduced 15 min after light stimulation with a more pronounced reduction 30-60 min after stimulation. Kv3.1 and Kv3.2 channels are known to regulate the repolarization of AP, and blocking these channels results in widening of the AP width similar to what we observed after optoTrkB activation (Erisir, Lau, Rudy, & Leonard, 1999). To exclude the possibility that optoTrkB activation could inactivate PV interneurons, we also measured the relative amount of FosB mRNA. In line with our results, we found a twofold increase of FosB expression 30 min after light stimulation and a fourfold increase 60 min after stimulation.

These results demonstrate that activating TrkB receptors in PV interneurons rapidly triggers intrinsic changes by downregulating the expression of Kv3.1 and Kv3.2 channels, resulting in disinhibition of the cortical network. In addition, chronic fluoxetine treatment induces very similar effects to those obtained with acute optoTrkB activation and the fluoxetine-induced effects are dependent on TrkB expression in PV interneurons. This indicates that most, if not all, plasticity-related effects elicited by fluoxetine are likely to be mediated by TrkB activation in PV interneurons.

1.5. OptoTrkB activation induces downstream signaling in PV interneurons

To test whether optoTrkB activation also results in the induction of downstream signaling in PV interneurons, we examined FosB expression, an immediate early gene. We collected the brains 2 h after the imaging sessions of the ocular dominance paradigm and immunohistochemically examined the expression of FosB, PV, and c-myc tagged to optoTrkB. We found that c-myc was only expressed in PV, indicating reliable and specific infection of PV cells. The infected cells were also positive for FosB. Activation of optoTrkB by light increased FosB intensity of the infected PV, indicating that stimulation of optoTrkB activated PV interneurons and gene expression.

TrkB receptors have three tyrosine kinase domains, Y816, Y706, and Y515, which upon phosphorylation, regulate downstream signaling and induce gene expression. To test whether and when optoTrkB stimulation by light induces autophosphorylation of optoTrkB (200kDa) and subsequent downstream signaling, we collected tissue samples from optoTrkB-infected visual cortices at different time points (control, 15 min, 30 min, 60 min) after light stimulation.

We found an increase in the phosphorylation of Y816 and Y515 60 min after light stimulation, but no significant increase in the phosphorylation of Y706. Then, we tested whether phosphorylation of Y816, which activates the PLCγ pathway, induces phosphorylation of CREB. Indeed, 60 min after light stimulation CREB phosphorylation was strongly increased. Usually, phosphorylation of the Y515 domain recruits Shc and subsequently activates the MAPK/ERK pathway. However, even 60 min after optoTrkB stimulation, the phosphorylation levels of MAPK/ERK remained unchanged.

These results demonstrate that activation of optoTrkB expressed in PV interneurons indeed results in downstream signaling 60 min after light stimulation.

1.6. TrkB activation resets the PV and PNN network into a plastic configuration state

After identifying a novel mechanism by which TrkB activation in PV rapidly orchestrates the cortical network, we analyzed PV and PNN expression profiles, two markers known to regulate critical periods by promoting the maturation of the inhibitory network. Enzymatic removal of PNNs during adulthood reinstates a juvenile-like plasticity and reduces intracortical inhibition (Lensjø, Lepperød,

Dick, Hafting, & Fyhn, 2017; Pizzorusso et al., 2002). Moreover, Donato et al. (2013) demonstrated that PV expression in the hippocampus itself is dynamic and regulated by experience. A high PV expressing configuration state is associated with a consolidated network and a low PV configuration state is associated with a plastic network. Throughout development, the neuronal network shifts from primarily low PV expression to primarily high PV expression in adulthood.

To test whether TrkB activation could mediate PV and PNN states, we used immunohistochemistry to examine the expression and expression intensities of PV and PNNs after activation of optoTrkB by repetitive stimulation with light (twice daily for 7 days, consistent with the ocular dominance paradigm). First, we quantified the absolute numbers of PV positive (PV+), PNN positive (PNN+), and PV/PNN double positive (PV+PNN+) cells, then we calculated the percentage of PV+PNN+ within the total PV+ and PNN+ population as previously reported (Karpova et al., 2011). After light stimulation, the numbers of PNN+ and PV+PNN+ cells and particularly PV+PNN+ cells within the PV population were decreased.

Next, we examined the distribution pattern of PV intensities within the whole PV cell population in samples obtained from non-stimulated optoTrkB-infected mice and used these as reference values. The PV intensities were then categorized into four groups (Donato et al., 2013): low PV, intermediate-low PV (int-low PV), intermediate-high PV (int-high PV), and high PV expressing cells, and we compared the effects of light stimulation within these groups. Stimulation of optoTrkB resulted in a reduction in PV intensities specifically in the high PV expressing cells. When measuring the corresponding PNN intensity of each PV cell, we found a strong reduction in the PNN intensities specifically in the high PV expressing cells after optoTrkB activation. Moreover, the PNN intensities correlated with PV intensities and were higher in high-PV group, however, light stimulation reduced PNN intensities to lower levels throughout all PV configuration groups. Interestingly, using the mRNA samples obtained after acute stimulation of optoTrkB (control, 15 min, 30 min, and 60 min after light stimulation), we found that PV mRNA expression is rapidly regulated already 30 min after light stimulation, with a more than twofold decrease 60 min after light stimulation.

Finally, we tested whether chronic fluoxetine treatment exerts similar effects as optoTrkB and alters the PV and PNN network configurations, and whether the deletion of TrkB from PV interneurons would abolishes the effects in hPV-TrkB cKO mice. Chronic fluoxetine treatment induced a trend towards a reduction of PNN+ cells in WT mice but this effect was absent in hPV-TrkB cKO mice. As observed after optoTrkB activation, fluoxetine treatment reduced the abundance of PNN+ within the PV population in WT mice but the deletion of TrkB from PV abolished this effect.
We then analyzed the PV expression intensities throughout the four PV populations (low PV, int-low PV, int-high PV and high PV). Similar to optoTrkB, chronic fluoxetine treatment decreased the PV intensities specifically in high PV-expressing cells. In hPV-TrkB cKO mice, however, the fluoxetine effect was abolished. When measuring the corresponding PNN intensities we found that fluoxetine treatment decreased PNN intensities in int-high and high PV expressing cells in WT mice but this effect was absent in hPV-TrkB cKO mice.
These results show that activation of TrkB in PV interneurons is sufficient and necessary to switch the PV and PNN network into a plastic and immature network state by removing PNNs and shifting the PV configuration towards a low PV network (Donato et al., 2013).

2. **Optical activation of TrkB attenuates fear memory combined with fear extinction training (II)**

2.1. Optical stimulation of optoTrkB activates TrkB signals and neural plasticity in vitro

Juzoh Umemori and Giuliano Didio performed immunoblotting for phosphorylated TrkB (pY706, pY515 and pY816), non-phosporylated TrkB, and phosphorylated and non-phosphorylated ERK. After light stimulation phosphorylation of optoTrkB at pY706, pY515 and pY816 were increased, however, endogenous TrkB was only increased after BDNF treatment. Next, they verified the phosphorylation of downstream signals of the BDNF/TrkB pathway and observed increased phosphorylation of CREB and pERK after light stimulation. Interestingly, BDNF failed to further increase pCREB and pERK responses induced by light, indicating that optoTrkB activation occludes the effects of each other.

In addition, light stimulation of cultured cortical cells showed an increase in the number of primary dendrites extending from the cell 24 hours after light stimulation but not after BDNF treatment. Furthermore, the number of spines in light-stimulated CaMKII-optoTrkB infected cells was increased compared to non-stimulated cells.

2.2. Activation of optoTrkB and downstream signals in the ventral hippocampus

To confirm the activation of optoTrkB after light stimulation, optoTrkB lentivirus-infected mice were perfused 24 h after 2 days of optic stimulation (12 x 5 sec exposure; comparable to the protocol used during extinction training). Immunohistochemistry showed an increase of delta FosB expression in regions close to the infection sites in the CA1 of the vHP, strongly suggesting that optoTrkB activates the pyramidal cells in the ventral hippocampus in vivo.

2.3. Optical activation of TrkB during extinction training modifies remote fear memory

Briefly, Juzoh Umemori and Giuliano Didio found that the activation of optoTrkB during extinction training resulted in faster extinction of the acquired fear memory. When testing spontaneous recovery and fear renewal one week later, optoTrkB activation by light did not alter the freezing behavior. Three weeks later, remote memory was tested and mice stimulated with light during extinction training showed significant decreases in freezing during remote spontaneous recovery and fear renewal. These results indicate that optoTrkB activation during extinction training modifies the remote fear memory.

2.4. Optical activation of TrkB in pyramidal cells results in increased LTP

To investigate the underlying mechanism of the attenuated contextual fear memory after CKII-optoTrkB activation during extinction training, we performed fEPSP recordings at the CA3/CA1 synapse. We stimulated CKII-optoTrkB just before the delivery of a brief TBS protocol to induce LTP. Our results demonstrate that a brief TBS stimulation in combination with CKII-optoTrkB activation is sufficient to result in increased LTP 45 min after induction. Notably, using stronger stimulation protocols, such as tetanus or 4 sweeps of TBS, resulted in indistinguishable LTP between light-stimulated and non-stimulated recordings, indicating that the overexpression of (CKII-opto)TrkB results in saturation of LTP.

3. Distinct effects of perinatal exposure to MeHg and Flx on PV and PNN expression (III)

3.1. Effects of perinatal exposure to fluoxetine on PV and PNN expression

In the basolateral amygdala complex, the number of PV+ and PNN+ but not PV+PNN+ cells was increased from P17 to P24. Fluoxetine exposure had no effect on the number of PV+ cells without PNNs but reduced the numbers of PNN+ cells within and without the PV population as compared to control. The decrease in PNN+ cells was particularly pronounced for PV+PNN+ cells at P17 and for PNN+ cells without PV expression at P24. The PV intensity increased in both groups from P17 to P24, however, fluoxetine exposure slightly increased PV intensity at P17 but in turn reduced the intensity at P24.

Similarly, in the DG and CA1 of the hippocampus, the number of PV+ and PNN+ cells increased with age, except PNN+ cells without PV. The perinatal exposure to fluoxetine decreased the abundance of PNN+ expressing neurons, with pronounced effects PNN cells without PV expression at P24 in the DG. The PV cell intensity increased in both groups from P17 to P24 and fluoxetine exposure did not result in differences to control mice.

To summarize, perinatal exposure to fluoxetine treatment reduces the numbers of PNN-surrounded neurons, indicating a delayed closure of critical periods.

3.2. Effects of perinatal exposure to MeHg on PV and PNN expression

In the amygdala complex, the number of PV+ and PNN+ cells increased from P17 to P24, while not affecting the number of PV+PNN+ cells. Though not significant, MeHg exposure resulted in a 2-3 fold reduction in the number of PV+ cells with and without PNNs at P17. At P24, the number of PV+ cells with and without PNN was recovered to the level of control mice. Moreover, the number of PNN cells with and without PV were not affected at P17 but increased above the levels of controls at P24.

Similarly, in the DG and CA1 of the hippocampus, the numbers of PV+ and PNN+ cells but not PNN+ cells without PV expression increased with age. MeHg exposure reduced the number of all PV+ neurons and PV+ cells without PNNs at P17 but increased the numbers at P24.

Together, perinatal exposure to MeHg does not affect the formation of PNNs but affects the expression of PV cells by inhibiting the development of PV neurons, an indicator for delayed onset of critical periods.

DISCUSSION

The main work of this thesis has focused on the effects of TrkB activation in PV interneurons on visual cortex plasticity during adulthood. To our surprise, TrkB activation in PV interneurons is sufficient and necessary to rapidly orchestrate cortical networks and induce a high plasticity state usually observed during critical periods. The ability to increase neuronal plasticity during adulthood is of particular interest for the treatment of neuropsychiatric diseases, such as depression, PTSD and addiction but also neurodegenerative diseases, including Alzheimer's and Parkinson could benefit from it. Hence, TrkB receptors are an interesting therapeutic target.

Our lab has focused on TrkB receptors and has shown that a class of widely prescribed antidepressant drugs, SSRIs and specifically fluoxetine, are able to activate TrkB receptors. This led researchers to re-question the hypothesis underlying depression and shifted the focus towards deficits in brain plasticity. In fact, this was a moment emphasizing the importance of brain plasticity in maladapted networks, a revolution for the field of neurotrophins and their receptors, and the necessity to understand the underlying mechanisms and their possible implications. It also demonstrates, however, that antidepressants are not as specific in their actions as we thought they would be. Having identified TrkB as a target of antidepressants, it is also possible that antidepressants can bind to other proteins.

Considering that the brain is composed of a very heterogeneous population of cells and essentially all are expressing TrkB receptors, it is a natural question to ask which neuronal population might be leading the effects observed after chronic fluoxetine treatment. A large extent of research has investigated TrkB actions on pyramidal cells in the hippocampus mainly due to the limitation that bath application of BDNF activates all TrkB receptors with the majority being pyramidal cells, and the hippocampus being a well understood brain region.

Using optoTrkB we were able to circumvent this problem and could identify TrkB actions in a specific cell population, the PV interneurons, which in fact comprise only about 2.6% of the total neuron population. We complemented this approach by using genetically modified animals with a reduced expression of TrkB receptors in PV interneurons and used chronic fluoxetine treatment to pharmacologically induce plasticity.

TrkB activation in PV interneurons induces visual cortex plasticity

Visual cortex plasticity is a well understood model for the study of critical period plasticity. In contrast to other networks, such as the fear or social behavior circuitry, it is a fairly simple network, which does not intermingle and interact with many inputs from other brain regions. Hence, it is a reliable way to study basic cellular mechanisms. We have shown previously that chronic fluoxetine treatment can reinstate ocular dominance plasticity during adulthood if combined with monocular deprivation (Maya-Vetencourt, 2008). This effect was accompanied by decreased GABA and increased BDNF levels, as well as the induction of LTP after TBS stimulation, an in vitro analogue of visual cortex plasticity. These results indicate the involvement of the inhibitory network, which upon maturation promotes the closure of critical periods and restricts visual cortex plasticity (Huang et al., 1999; Maya-Vetencourt et al., 2008). Although PV interneurons cover only a small percentage of the total neuron population, they are the predominant inhibitory cells regulating the maturation and plasticity of the visual cortex. As BDNF promotes the maturation of those cells during critical

periods, we hypothesized that TrkB activation in PV could also affect plasticity processes during adulthood.

Interestingly, activating optoTrkB in PV interneurons twice daily during 7 days of monocular deprivation now induced visual cortex plasticity. Animals that expressed optoTrkB but were not exposed to light stimulation did not show alterations in their ocular dominance, indicating that over-expression of optoTrkB itself has no effects. Importantly, however, the induction of visual cortex plasticity requires a combination of optoTrkB activation and sensory deprivation. This implies that TrkB activation makes the brain more responsive to external guidance and cues, and is further supported by our finding that the ocular dominance shift can be reversed if optoTrkB activation is combined with monocular deprivation of the ipsilateral eye. This finding demonstrates that the plasticity machinery in the adult brain is well intact beyond the closure of critical periods but needs the right tools to be reactivated. The same is true for plasticity induced by fluoxetine treatment, which has important clinical implications. If antidepressant treatment requires cues and guidance to be successful, it means that antidepressant treatment should be combined with psychotherapy or other sorts of training to exert its effects (Amin, Ban, Pecknold, & Klingner, 1977; Brent et al., 2008; Chollet et al., 2011; Müller et al., 2007; Pampallona, Bollini, & Tibaldi, 2015).

TrkB activation in PV increases excitatory transmission

It is widely accepted that visual cortex plasticity requires a reduction in inhibitory transmission. How could TrkB activation in PV interneurons lead to this effect? To address this question, we used electrophysiology to record the activity of living cells intra- and extracellularly. These experiments were particularly challenging for the following reasons: (i) intracellular recordings by patch clamping become increasingly difficult with age, hence, the success rate of patch clamping a cell can be frustratingly low. (ii) virus-modified or genetically-modified animals alter the cell properties and can therefore also affect the vulnerability and health of the cells. (iii) OptoTrkB is a light-sensitive construct, hence, all procedures had to be performed in darkness.

Despite the challenges, our results quickly revealed that a single 30 sec light stimulation of optoTrkB 60 min prior TBS stimulation is sufficient to permit LTP in layer II/III of the visual cortex. In contrast, TBS stimulation without prior optoTrkB stimulation could not evoke LTP, which is in line with evidence that LTP induction in the visual cortex is restricted to critical periods (Kirkwood et al., 1995). Extensive research has shown that TrkB generally increases excitability and activity of pyramidal neurons and therefore, increases the excitability and excitatory transmission of the neuronal network (Figurov et al., 1996; Levine, Dreyfus, Black, & Plummer, 1995, 1996). We also show that optoTrkB activation in pyramidal neurons of the ventral hippocampus increases LTP expression after subthreshold TBS stimulation, supporting the hypothesis that TrkB activation specifically in pyramidal neurons increases the transmission of the excitatory network (III). This seems to be in conflict with our findings showing that also TrkB activation in PV interneurons increases excitatory transmission, which is driven by a decrease (rather than an increase) in PV cell excitability even though we see activation of PV interneurons and downstream signaling as shown by rapid increases of FosB mRNA and intensity, and phosphorylation of CREB. Therefore, the induction of downstream signaling in PV does not increase their activity and firing as it does in pyramidal cells. These results suggest that TrkB actions are not universal but differ among cell types. Importantly, however, the network effect remains the same as it results in increased excitation.

TrkB activation in PV rapidly regulates potassium channels

Fast-spiking interneurons, such as PV, express significantly larger potassium currents compared to pyramidal cells and a larger potassium channel density contributes to the differences in firing properties of these cells (Hamill, Huguenard, and Prince 1991). Certain potassium channels, such as Kv3 channels, have unique phenotypes, as they rapidly activate and deactivate to facilitate sustained high frequency firing of neurons (Erisir et al., 1999; Hu et al., 2014). Indeed, Kv3 (Kv3.1 and Kv3.2) channel expression is high in PV interneurons and particularly the expression of the Kv3.1 subtype has nearly 100% overlap with the expression of superficial cortical PV interneurons (Chow et al., 1999). Throughout development and maturation, PV cells display a substantial upregulation of potassium channels, which is accompanied by increases in their excitability and firing rates (Okaty, Miller, Sugino, Hempel, & Nelson, 2009). PV interneurons exhibit their mature phenotype by the closure of critical periods and the upregulation of Kv3.1 and Kv3.2 channels could therefore contribute to the closure of visual critical periods.

In fact, activation of TrkB reduces PV intrinsic excitability within 30 min by rapid downregulation of the expression of Kv3.1 and Kv3.2 mRNA. In addition, Kv3.1 and Kv3.2a/b channels are inhibited by PKC. PKC signaling is induced downstream upon Y816 phosphorylation, which we see increased after optoTrkB stimulation and hence, can directly inhibit Kv3.1 and Kv3.2 activation. Further, it is known that blocking these channels results in a widening of the AP width that is associated with a decrease in the cell excitability (Erisir et al., 1999). Kv3.2-deficient mice have impaired fast spiking activity, suppressed cortical inhibition and increased susceptibility to seizures, which could also be seen as an excessive state of plasticity (Lau et al., 2000). The decreased firing frequency of PV cells thus enhances excitatory transmission to such an extent that it allows visual cortex plasticity.

There is additional evidence that TrkB actions can also mediate changes in other potassium channels, thereby regulating the resting membrane potential, AP initiation and decay as has been shown by BDNF bath applications (Nieto-Gonzalez & Jensen, 2013). BDNF exposure efficiently reduced the intrinsic excitability of PV cells by activating an M-like current and possibly blocking Kv1 potassium channels (Nieto-Gonzalez & Jensen, 2013). However, the use of BDNF bath application in electrophysiological experiments has major restrictions, as BDNF acts on all cell types expressing TrkB and feedback mechanisms regulated by pyramidal cells are unavoidable.

PV and PNN configurations are reset to an immature state after TrkB activation in PV

The maturation of the PV inhibitory network promotes the closure of critical periods and ensures the stabilization of the neuronal network (Huang et al. 1999; Fagiolini and Hensch 2000). This maturation is driven by different factors, a key regulator being the formation of PNNs (Pizzorusso et al., 2002; Sugiyama et al., 2008). Substantial research investigated the putative role of these extracellular matrix assemblies, some of which proposing a protection of PV cells against oxidative stress (Cabungcal et al., 2013; Morawski, Brückner, Riederer, Brückner, & Arendt, 2004) or an active role in activity-dependent gating of PV cell function (Favuzzi et al., 2017). In addition, lifting this regulator can restore plasticity in adulthood and is associated with a decrease in inhibitory activity (Lensjø et al., 2017). We demonstrated that activation of TrkB reduces PNN expression and the molecular mechanisms underlying this phenomenon are now under investigation in our lab Since the removal of PNNs requires structural changes, it is more likely that the intrinsic changes of PV cells, such as changes in excitability, occur first and the removal of PNNs could reinforce the compromised fast-spiking activity of PV cells. Recent research by Devienne et al. elegantly showed

that transient chemogenetic silencing of PV interneurons induces the regression of PNNs, indicating that PNNs might act as sensors of the local microcircuit and provide PV cells with an activity-dependent mechanism to control network dynamics (published on BioRxiv, https://www.biorxiv.org/content/biorxiv/early/2019/06/17/671719.full.pdf). Considering the unique fast-spiking properties of these cells, it is likely that there might be a protective correlation between PV cell function and PNN assembly to preserve their properties. Hence, TrkB receptors could regulate PV intrinsic excitability to increase excitatory transmission of the cortical network, subsequently promoting PNN regression.

We also observed a decrease in PNN intensity in high PV expressing cells. The expression intensity of PNNs was stable throughout all PV configuration states (low PV, int-low PV, int-high PV and high PV) after optoTrkB activation, while PNN intensity progressively increased from low to high PV configurations if not activated. This decrease in PNN intensity in high PV expressing cells could resemble the removal of PNNs.

The PV network itself is dynamic and a decrease in PV cell intensity is associated with a plastic network configuration as has been shown in the hippocampus (Donato et al., 2013). While contextual fear conditioning promoted a high PV configuration state, environmental enrichment shifted the network towards a low PV expressing state. Throughout development, the PV cell intensity progressively increases reaching a high PV configuration state upon the closure of critical periods. A low PV configuration observed after environmental enrichment therefore resembles a critical period, immature-like state (Donato et al., 2013). Here, we show that TrkB activation in PV robustly decreases PV cell intensity and PV mRNA is reduced already 30 min after optoTrkB activation. Interestingly, studies from the hippocampus show that the PV cell intensity is generally higher when enwrapped by PNNs and PV cells with weak staining intensity are likely to lack PNNs (Yamada, Ohgomori, & Jinno, 2014). Enzymatic removal of PNN by ChABC does not affect the abundance of PV cells but reduces PV cell fluorescence one week after the injection, which is accompanied by a decrease in PV mRNA expression levels (Yamada et al., 2014), indicating a direct correlation between PNNs and PV expression and intensity.

Hence, TrkB activation in PV could downregulate the expression of PV and their excitability, promoting the removal of PNNs, thereby shifting the network into a plastic, immature state. However, to identify the underlying targets of TrkB that could mediate these effects remain a subject for further studies.

PV and PNN configurations are altered upon perinatal exposure to fluoxetine and MeHg

Our findings indicate that exposure to either fluoxetine or MeHg during pregnancy has distinct effects on PV and PNN expression during critical period of the offspring. While perinatal exposure to fluoxetine decreased the formation of PNNs, MeHg exposure inhibited the development of PV interneurons, suggesting a delayed closure and onset of critical periods, respectively.This has important clinical relevance as MeHg is highly enriched in fish and it is recommended to consume fish several times per week, even for pregnant and breastfeeding women (FDA, https://www.fda.gov/food/consumers/advice-about-eating-fish). While it is advised to choose fish that is low in mercury, it is impossible to avoid mercury completely. In our study, we administered a low-dose of MeHg that is comparable with that found in sea food and has been shown to also result in cognitive deficits in humans, who have prenatally been exposed to this concentration of MeHg (Debes, Weihe, & Grandjean, 2016). Generally, MeHg is distributed to all tissues and about

10% can be found in the brain within 30h. Although MeHg is the predominant form of mercury and is slowly metabolized to inorganic mercury (at a rate of about 1% of the body burden per day) by mechanisms that are still largely unknown, inorganic mercury slowly accumulates and resides for long periods in the central nervous system (Clarkson, 2002). The half-times vary among tissues from about 45-70 days. Most of MeHg is eliminated from the body by demethylation and excretion of the inorganic form in the feces (Clarkson, 2002). The mechanisms underlying the adverse effects of MeHg on the brain are still poorly understood. However, our data suggest that MeHg has substantial effects on early brain development. A briefer critical period narrows the time window of plasticity and therefore, the child has less time to develop properly and might be the reason for increased risks for brain disorders. Karpova et al. (2014) showed that TrkB overexpression can buffer at least against some of the adverse effects caused by MeHg (Karpova et al., 2014b). However, the molecular mechanisms still need further investigation.

Conversely, perinatal exposure to fluoxetine delayed the closure of critical periods, thereby prolonging the time window of plasticity. This is an interesting finding as the use of antidepressants during pregnancy is still a matter of debate proposing risks of malformations (Bérard, Zhao, & Sheehy, 2017) or autism spectrum disorders (Croen, Grether, Yoshida, Odouli, & Hendrick, 2011). However, the consequences of a prolonged critical period on the actual brain development needs further research and depends also on the environment a child is exposed to.

Implications of TrkB actions in antidepressant treatment

Antidepressants are a widely used class of drugs with nearly 13% of the US population taking antidepressant medication over age 12. There was a 64% increase in the percentage of people using these drugs between 1999 and 2014. The use of antidepressants increases with age and 19.1% of adults over age 60 (every fourth person) consume these drugs (American Psychological Association). Also in Finland the consumption of antidepressants has greatly increased and nearly doubled from about 2.8% to 5% between 1994 and 2001 (Korkeila, Salminen, Hiekkanen, & Salokangas, 2007). Those are significant numbers considering that 50-60% of people using antidepressants are treatment-resistant (Fava, 2003). Hence, the understanding of how antidepressants work or do not work is of fundamental interest. The finding that at least part of the effects are mediated by plasticity induced by TrkB receptors offers a new target for the development of more specific and efficient treatments. While antidepressant-induced plasticity requires chronic treatment of several weeks, we now show that the TrkB-mediated effects are rapid and immediately orchestrate the neuronal network. This discrepancy reopens the question why the effects of antidepressant treatment occur with a delay when TrkB actions are actually fast. The growing field of rapid-acting antidepressants suggests that it is not the plasticity processes that require time to take place, as Ketamine and Isofluorane rapidly induce antidepressant-like effects likely by activating the TrkB pathway (Antila et al., 2017; Duman, Li, Liu, Duric, & Aghajanian, 2012).

Remarks and Future Prospects

This thesis work is based on mouse models and both the shift in ocular dominance and fear conditioning model have been validated to reliably represent amblyopia and PTSD in humans, respectively. In fact, findings from both mouse models led to clinical trials and have at least partially been successful and resulted in treatment advances. However, still not all findings found in mouse

models have been replicated in humans and there are a number of possible reasons: (i) the human brain remains more complex than a mouse brain and certain networks might not work exactly the same. (ii) In animal research, the experimental conditions are standardized as much as possible to minimize individual variation, however, humans represent a highly heterogeneous population with very complex environmental influences, including different mental, physical and social stressors that are known to influence neuroplasticity processes. (iii) It is very difficult to transfer certain experimental conditions, such as drug doses and treatment protocols that are working successfully in a mouse to human. Hence, while the findings of this thesis work are promising and provide new understandings of molecular mechanisms underlying TrkB induced plasticity, they also open new questions and challenges. Nevertheless, using mouse models we are able to look at molecular and functional properties of individual cells and how these regulate behavior. This thesis work has looked at plasticity processes at all levels and therefore, provides a strong body of evidence on how these processes are regulated.

It should further be noted that TrkB activation is not always beneficial. As mentioned in the literature review, the BDNF/TrkB pathway is not restricted to neuronal cells but is also expressed and active in non-neuronal cells. Initially, TrkB was described as an oncogene, hence, promoting tumorgenesis by stimulating tumor cell survival and angiogenesis providing a promising target for the treatment of cancer (Thiele, Li, & McKee, 2009). In addition, TrkB activation has been associated with temporal lobe epilepsy caused by status epilepticus and transient TrkB inhibition after status epilepticus prevented recurrent seizures (Liu et al., 2013). As epilepsy can be seen as an exaggerated form of plasticity, an over-activation of TrkB can therefore have adverse effects. Maybe TrkB acts in an inverted "U" shape: too little TrkB activation results in a consolidated network, where inhibition is strong, and too much TrkB activation produces exaggerated excitability leading to seizures.

Answering one research question usually creates 10 more questions. Similarly, this thesis work leaves questions for future studies: how does TrkB activation in PV affect other inhibitory neurons in the visual cortex, such as somatostatin and VIP (vasoactive intestinal peptide) neurons? How does PV activity regulate PNN assembly and disruption and how is PV expression itself regulating PV activity? Finally, what are TrkB actions in other cell types, such as glial, serotonergic and dopaminergic cells, and other cell circuitries?

The biggest challenge, however, will be the translation and application to humans. The advantage of using mouse models is that it allows us to perform genetic manipulations in order to target specific proteins in certain cell types. In humans, we will have to find alternative ways. As mentioned above, simply increasing TrkB activity by for example pharmacological means causes off target TrkB activation and could promote tumorgenesis or seizures. In addition, one might want to manipulate TrkB activity only in the brain region involved in the pathology. To achieve this the CRISPR technology could offer help but it still seems like an ambitious goal.

Nevertheless, I hope this thesis work will encourage other researchers to investigate the potential of neuronal plasticity in adjusting maladapted networks underlying neuropsychiatric pathologies.

CONCLUSION

In the present thesis, we aimed to understand the actions of TrkB specifically in PV interneurons on adult visual cortex plasticity. TrkB activation in PV interneurons rapidly reduces PV excitability by downregulation of Kv3.1 and Kv3.2 channels, thereby enhancing excitatory transmission (Fig. 9). Moreover, TrkB activation results in increased FosB expression and intensity, and CREB phosphorylation, indicating that PV interneurons are not silenced but their intrinsic properties altered (Fig. 9). Further, PV and PNN intensities are reduced as well as PNN abundance, suggesting a plastic, immature network configuration (Fig. 9). Chronic fluoxetine treatment induced very similar effects to those obtained with optoTrkB activation, suggesting that at least part, if not all, effects are mediated via TrkB receptors expressed in PV interneurons. When deleting TrkB from PV interneurons, however, the fluoxetine-induced plasticity effects were prevented, supporting the idea that TrkB activation is sufficient and necessary for visual cortex plasticity. While the effects induced by fluoxetine require chronic treatment, the effects of optoTrkB activation were rapid demonstrating that TrkB activation immediately orchestrates network plasticity.

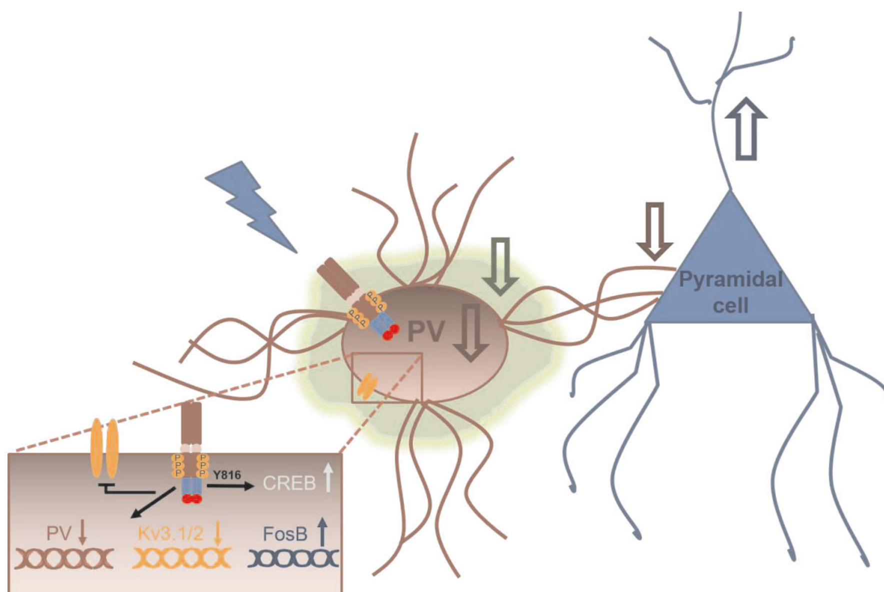

Fig. 9. Proposed model how optoTrkB orchestrates cortical network plasticity. Activation of optoTrkB rapidly downregulates the expression of Kv3.1 and Kv3.2 and might directly inhibit these channels through PKC signaling. This results in a rapid decrease of PV intrinsic excitability and subsequent enhanced excitatory transmission to allow cortical plasticity. At the same time, FosB expression and CREB phosphorylation are increased, supporting the hypothesis that optoTrkB activation induces intracellular signaling. Finally, optoTrkB activation rapidly decreases PV mRNA expression and PNN regression to reset their configuration state into a plastic, immature state.

Conversely, optoTrkB activation in pyramidal neurons of the ventral hippocampus also increases excitatory transmission, suggesting that TrkB employs different mechanisms in PV and pyramidal neurons, however, in both cases resulting in enhanced excitatory drive, a hallmark of plasticity.

Finally, the perinatal exposure of fluoxetine and MeHg had distinct effects on PV and PNN expression during critical periods. While fluoxetine treatment decreased the formation of PNN, thereby prolonging critical periods, MeHg exposure inhibited the formation of PV, suggesting delayed onset of critical periods (Fig. 10).

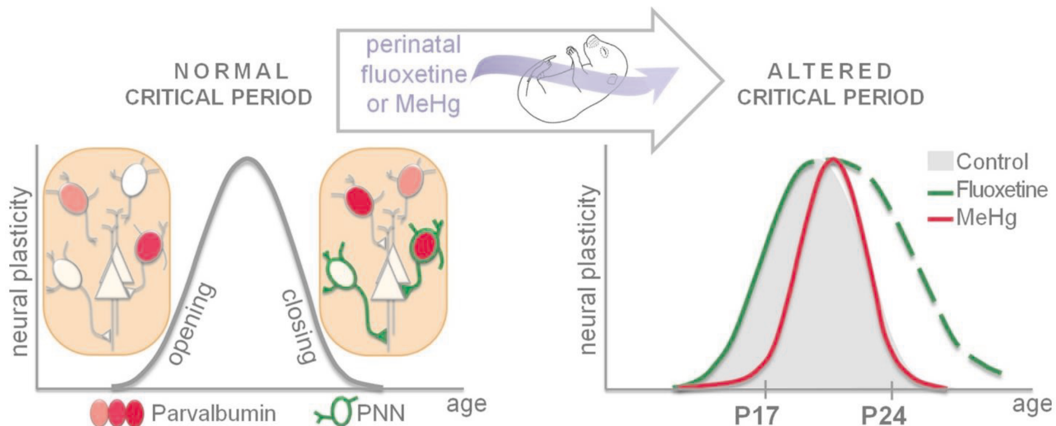

Fig. 10. Distinct effects of perinatal exposure to fluoxetine and MeHg. The onset and closure of critical periods are driven by the maturation of the inhibitory PV interneuron network. In the normal critical period, the increase in PV abundance and intensity promotes the onset of critical period, while the expression of PNNs promotes the closure. Perinatal exposure to fluoxetine delays the expression of PNN, indicating a delayed closure of critical periods. Conversely, perinatal exposure to MeHg delays the expression of PV interneurons, suggesting that the onset of critical periods is delayed. Modified from Umemori et al. 2015

The main conclusions are:

I. TrkB activation in PV interneurons rapidly orchestrates cortical network plasticity
II. The effects of fluoxetine treatment on visual cortex plasticity are at least in part, if not completely, driven by TrkB receptors expressed in PV interneurons
III. TrkB receptors in PV interneurons are sufficient and necessary for visual cortex plasticity
IV. TrkB actions differ between PV and pyramidal neurons
V. Perinatal exposure to fluoxetine and MeHg have distinct effects on the development of critical periods

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