Regulation of critical period plasticity in normal development and in Neurofibromatosis type 1

van Lier, M.

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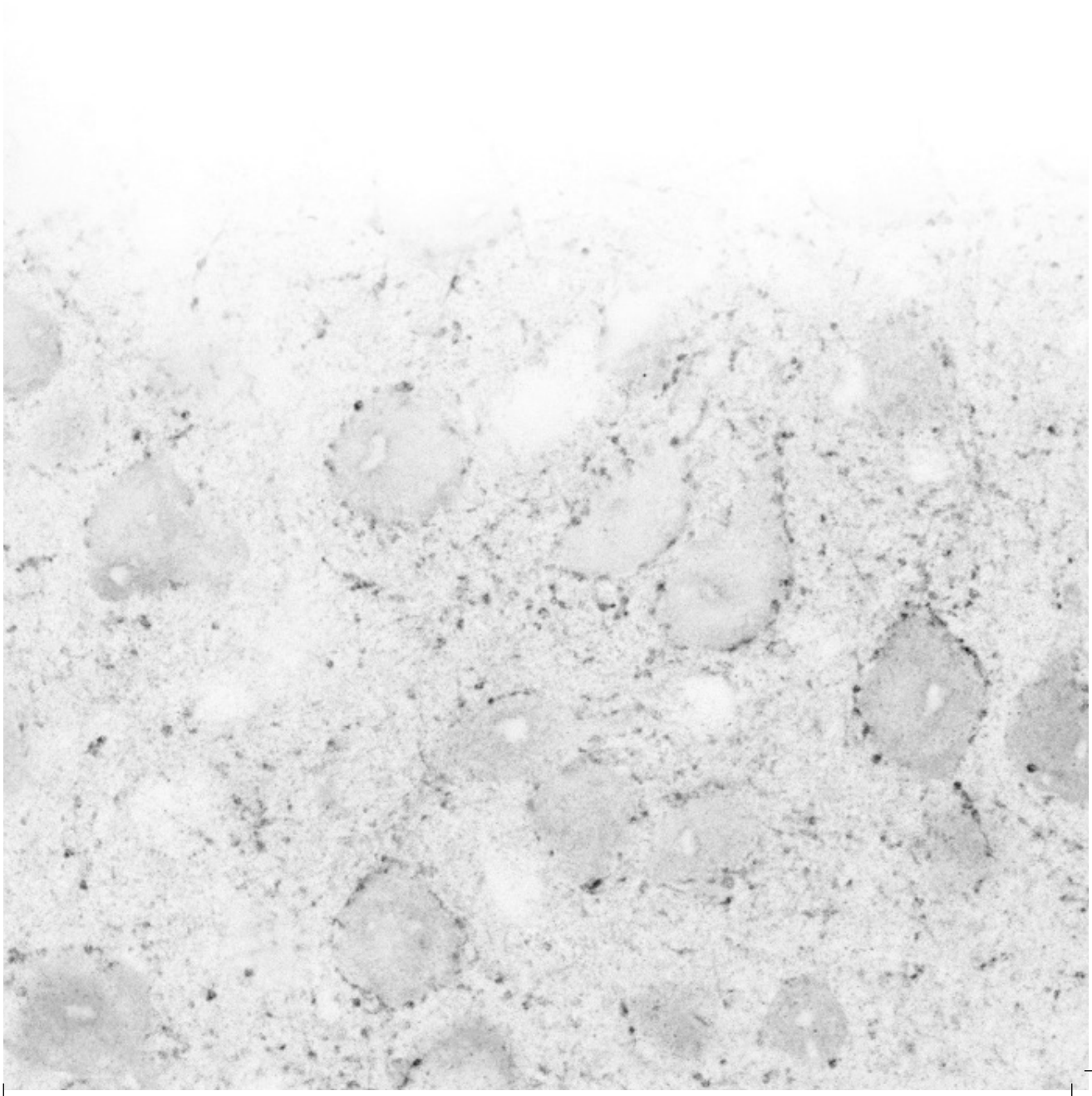
Chapter 5

General Discussion



During critical periods of development, brain regions show heightened levels of plasticity during which they can arrange their connectivity in order to adjust their function based on experience. A hallmark of critical period plasticity, is that extensive rearrangement of axonal projections can take place. During OD plasticity for example, thalamocortical projections from the deprived eye retract, while those from the non-deprived eye become more elaborate (Antonini & Stryker 1996; Antonini et al. 1999; Hübener 2003). But also intracortical projections can undergo extensive rearrangement during the critical period, for example when binocular vision is interfered with by the misalignment of the eyes (Trachtenberg & Stryker 2001). Once critical periods are closed, axonal rearrangements are much more limited and plasticity is thought to be mediated mostly by local connectivity changes mediated by synapse turnover.

How the temporary increase in structural and functional plasticity during critical periods is regulated has been extensively studied over the past two decades. Considering the strong reduction of structural plasticity after critical period closure, one mechanism that closes the critical period may be the stabilization of axons and synapses. Evidence supporting this idea is the observation that a receptor which inhibits axonal outgrowth, the Nogo-66 receptor, is important for critical period closure (Beurdeley et al. 2012; McGee AW et al. 2005). In the absence of the Nogo-66 receptor, animals show continued plasticity in the visual cortex into adulthood (McGee AW et al. 2005). Moreover, the paired immunoglobulin-like receptor B (PirB) is also important for critical period closure in the visual cortex by negatively regulating spine density and limiting the formation of new functional synapses (Bochner et al. 2014; Djurisic et al. 2013; Syken et al. 2006). Furthermore, maturation of silent synapses is important for critical period closure (Huang et al. 2015). These synapses lack AMPA receptors are therefore functionally dormant but can be activated by insertion of AMPA receptors through experience.

Another theory is that GABAergic inhibition has crucial roles in the regulation of critical periods. Mice with reduced levels of GABAergic inhibition due to the deletion of the gad65 gene encoding an enzyme involved in GABA synthesis have deficient OD plasticity (Fagiolini & Hensch 2000; Hensch 2004). Increasing GABAergic inhibition in these mice using positive allosteric modulators of GABA activate the critical period. In addition, mice producing too much brain-derived neural growth factor (BDNF) develop inhibitory synapses prematurely and also show a precocious critical period onset and closure.

These two mechanisms are not necessarily mutually exclusive. Both mechanisms may contribute to plasticity. They may even interact directly through changes of excitatory input onto the main subtype of inhibitory neurons that regulates the critical period: PV-expressing (PV+) basket cells. During the critical period PV+ interneurons become enwrapped by perineuronal nets (PNNs), which are

specialized extracellular matrix structures responsible for synaptic stabilization in the adult brain. Interestingly, the destruction PNNs in adult primary visual cortex (V1) reactivates ocular dominance (OD) plasticity and restores visual acuity (Pizzorusso et al. 2002, 2006). Moreover, closure of the critical period for OD plasticity can be achieved by deleting the Nogo-66 receptor specifically in PV+ interneurons (Stephany et al. 2016). PNNs may stabilize excitatory inputs onto PV+ interneurons. Because a temporary decrease of inhibition is required for OD plasticity to take place (Kuhlman et al. 2013; van Versendaal et al. 2012), it is possible that PNNs interfere with such temporary disinhibition, thus reducing plasticity levels.

In this thesis we find evidence for both processes to be involved in the regulation of critical periods. In chapter 2 we show that genes known for regulating Wallerian degeneration also control experience-dependent plasticity during development. Wallerian degeneration is a naturally occurring process for retraction of axons, which occurs after damage. In chapters 3 and 4 we show that increased inhibition in *nf1*$^{+/-}$ mice results in early closure of the critical period for OD plasticity. This might partially explain cognitive- and behavioral symptoms in Neurofibromatosis type 1.

In chapter 2 we demonstrate that the signaling pathway that regulates Wallerian degeneration also controls experience-dependent plasticity during development. This pathway is interfered with in Wld^{S} mice, which carry a spontaneous mutation causing the production of an UBE4b-NMNAT1 fusion protein. This fusion protein is known to slow down Wallerian degeneration by increasing NMNAT activity in the cytoplasm (Chang et al. 2010). We demonstrate that in Wld^{S} mice, OD plasticity declines prematurely and visual acuity increases at an early age. We also demonstrate that OD plasticity was reduced in a transgenic mouse line overexpressing NMNAT3, which localizes to mitochondria and also reduces Wallerian degeneration (Avery et al. 2009; Yahata et al. 2009). In a transgenic mouse line overexpressing nuclear NMNAT1, which does not interfere with Wallerian degeneration, OD plasticity in unaffected. Therefore, our experiments confirm that increased cytoplasmic NMNAT levels interfere with OD plasticity. This means that OD plasticity and critical period plasticity are regulated by a signaling cascade that is also involved in Wallerian degeneration. Although intrinsic optical imaging is an indirect method to quantify neuronal activity, and therefore has its limitations, this method is sufficient for the purpose of this research question. It might be interesting for future studies to investigate which different neuronal subpopulations are involved. More direct approaches such as single unit recordings might then be used.

Whether NMNAT proteins may also play a role in critical period regulation is humans is not known. So far, the only known monogenetic disease associated with NMNAT proteins is Leber congenital amaurosis (Brazill et al. 2017). This form of inherited blindness is caused by a mutation in NMNAT1, resulting in retinal degeneration. However, patients have normal physical and mental health, suggesting that

NMNAT1 is selectively required for maintenance of neuronal tissue in the retina and not in the brain. However, because we found that also in mice, nuclear NMNAT1 does not seem to be involved in the regulation of critical periods, the fact that NMNAT1 mutations in human do not cause neurodevelopmental issues does not mean that the Wallerian signaling pathway is not involved in human brain plasticity.

Interestingly, we did not find any signs of Wallerian degeneration during OD plasticity. There are several possible explanations for this observation. Possibly, axon degeneration during OD plasticity may not occur as synchronously or extensively as after nerve damage. This would make it much more difficult to detect using the methods we employed. Alternatively, considering the discovery that the thalamus also undergoes OD plasticity (Rose & Bonhoeffer 2018; Sommeijer et al. 2017), Wallerian degeneration might occur in other parts of the visual pathway, such as axons from the retina to the thalamus. While we have performed analysis of Wallerian degeneration in the thalamus upon monocular deprivation, it is possible that we have not investigated this at the correct timepoint or using a sufficiently sensitive method. It would thus be interesting to investigate the possible involvement of thalamic OD plasticity in the phenotype observed in Wld^S mice. For example, one could test whether OD plasticity in the dLGN is also reduced by making use of electrophysiological recordings in dLGN in monocularly deprived mice and control litter mates (Sommeijer et al. 2017). Alternatively, chronic two-photon calcium imaging of thalamocortical input to the binocular visual cortex could be performed before and after MD, to determine the involvement of the thalamus on OD plasticity (Jaepel et al. 2017).

Of course, it is also possible that Wallerian degeneration as such does indeed not take place during OD plasticity, but that the signaling pathways regulating axon retraction observed in OD plasticity and Wallerian degeneration share various components, including NMNAT proteins. Exactly how cytoplasmic NMNATs regulate OD plasticity, whether this is through preventing SARM1-dependent NAD^+ depletion, as shown to occur during Wallerian degeneration (Sasaki et al. 2016) or through different signaling cascades such as through chaperone activity (Brazill et al. 2017; Lavado-Roldán & Fernández-Chacón 2016), remains to be tested. It is also not clear which of the NMNAT proteins would be involved in regulating the critical period during development. In Wld^S mice, NMNAT1 is overexpressed as a fusion protein with Ube3a, causing it to be localized in the cytoplasm. However, our data do not support a role for NMNAT1 in critical period regulation when it is localized in the nucleus, where it is expressed in its unmutated form. We do find evidence for NMNAT3 overexpression to alter critical period regulation, but this does not necessarily mean that it also has a role in OD plasticity under normal conditions. While NMNAT3 overexpression slows down Wallerian degeneration, inactivating its gene does not result in increased axon degeneration. Neither is NMNAT3 expression

downregulated during Wallerian degeneration. In contrast, NMNAT2 expression rapidly declines after axonal injury, promoting axon degeneration (Araki et al., 2004; Sasaki et al., 2006; Babetto et al., 2013). NMNAT2 is therefore thought to be the member of the NMNAT family that is responsible for regulating Wallerian degeneration. Whether this is also true for OD plasticity remains unknown. We did not find a change in NMNAT2 expression during OD plasticity, but this could be due to technical issues, such as the precise timepoint at which this would occur.

The signaling pathway that is shared between the cellular signaling events that regulate Wallerian degeneration and OD plasticity may affect axon retraction at different sites. It may involve thalamocortical or corticocortical connections between excitatory neurons within V1. As mentioned above, this could involve connections in the thalamus, originating in the retina or in cortex. Another interesting idea is that excitatory inputs to inhibitory neurons in V1 are affected. During the critical period for OD plasticity, a brief period of disinhibition takes place involving reduced excitatory input to PV+ basket cells (Kuhlman et al. 2013). It is thus possible that NMNAT overexpression interferes with retraction of axons innervating PV+ interneurons. This can be tested by chronic two-photon calcium imaging of PV+ interneurons or by patch clamp recordings of PV+ interneurons in slices of V1 in Wld^S and wild-type mice that were monocularly deprived or reared normally.

Our observation that plasticity was reduced at the end of the critical period while acuity increased at an earlier age may imply that V1 matures too rapidly in Wld^S mice. If so, one would expect that the critical period would also start prematurely, as is also observed in mice overexpressing BDNF. This could be directly tested by determining the youngest age at which an OD shift could be induced, as we also did in Chapter 4 of this thesis in a mouse model of Neurofibromatosis type 1. Such analysis could differentiate between a precocious critical period or an isolated early closure of the critical period. Alternatively, it is possible that Wld^S differentially regulates plasticity in the early and late stages of the critical period. However, no evidence currently suggests that OD plasticity involves different signaling pathways at different ages.

Another question that remains is whether the same signaling pathway is also involved in plasticity in other brain regions, or in adulthood. There are some studies that show that Wld^S mice have a delay in working memory- and spatial learning impairments after damage (Fox & Faden 1998; Yin et al. 2016). However, whether these delays in cognitive impairments are exclusively due to delayed axon degeneration or through other mechanisms remains to be tested.

Overall, our findings extend our knowledge of the mechanisms involved in critical period closure during cortical development and might advance the discovery of novel drug targets for enhancing brain plasticity for therapeutic purposes. Enhanced brain

plasticity might benefit patients to regain brain function after a stroke or trauma and might slow down progression of dementia or neurodegenerative diseases (Conforti et al. 2014; Ehninger et al. 2008; Hensch & Bilimoria 2012). Being able to influence critical period opening or closure may also be relevant for the treatment of neurodevelopmental disorders, as shown in chapters 3 and 4 of this thesis.

In chapters 3 and 4 we investigated the idea that critical period plasticity could be affected in neurofibromatosis type 1 (NF1). This disorder is characterized by café-au-lait spots, neurofibromas and Lisch nodules and also cognitive symptoms such as learning disabilities, motor delays and social problems (Champion et al. 2014; Cnossen et al. 1998; Ferner et al. 2007; Hyman et al. 2005; Williams et al. 2009).

So far, studies in mice lacking one nf1 allele (*nf1*$^{+/-}$ mice, a mouse model of the neurodevelopmental deficits of NF1) have shown that GABAergic inhibition is increased in adult hippocampus (Costa et al. 2002; Cui et al. 2008; Gonçalves et al. 2017; Shilyansky et al. 2010). This is caused by increased GABA release due to increased vesicle release and hyperexcitability of inhibitory neurons. While increased vesicle release is caused by reduced Ras-MAPK signaling, the hyperexcitability is caused by reduced activity of hyperpolarization-activated cation channel 1 (HCN1) predominantly in inhibitory neurons. Previous studies had shown that normalizing hippocampal inhibition in adult *nf1*$^{+/-}$ mice using drugs that acted on the affected signaling pathways also restored hippocampus-dependent learning deficits. Unfortunately, clinical trials using these approaches have so far been unsuccessful (Krab et al. 2008; Payne et al. 2016; Stivaros et al. 2018; van der Vaart et al. 2013). A possible explanation for the lack of success may be that in human subjects suffering from NF1, cortical deficits are the main cause of cognitive deficits. While the hippocampus remains highly plastic throughout life, cortical plasticity strongly reduces due to critical period closure. Because critical period closure is regulated by GABAergic inhibition we tested the possibility that NF1 was associated with dysregulation of cortical critical periods of development.

We first assessed whether inhibitory and excitatory innervation was altered in developing *nf1*$^{+/-}$ mice and whether this had consequences for further cortical development. These *nf1*$^{+/-}$ mice, in which one allele of the *nf1* gene is deleted, show spatial learning and attention deficits similar to NF1 patients (Silva et al. 1997). We found that in V1 of *nf1*$^{+/-}$ mice, inhibitory inputs were strongly increased throughout development, while changes in the activity of excitatory neurons were less pronounced and occurred predominantly during early cortical development. Just after eye opening at P12, the frequency of spontaneous excitatory currents increased significantly in both WT and *nf1*$^{+/-}$ mice, while the excitability of pyramidal neurons only decreased in WT mice and remained higher in *nf1*$^{+/-}$ mice. Additionally, after eye opening, the frequency of spontaneous inhibitory currents increased significantly in *nf1*$^{+/-}$ mice. Because at early stages of postnatal development,

spontaneous activity of inhibitory and excitatory neurons refine neuronal connections before eye opening (Ackman et al. 2012; Bonifazi et al. 2009; Xu et al. 2011), we assessed the development of spontaneous calcium activity in *nf1*$^{+/-}$ mice before and just after eye opening. Despite of the changes in excitability and inhibitory inputs, there were no changes in retinal- or cortical derived events and thus no signs of early developmental deficits. Interestingly, at a later stage, developmental increases in the inhibitory/excitatory ratio regulate the onset and closure of critical periods (Fagiolini & Hensch 2000; Hensch 2005; Hensch et al. 1998). However, also critical period plasticity onset was unaltered in *nf1*$^{+/-}$ mice (chapter 4).

How is it possible that early cortical development and critical period onset are unaffected, while both excitation and inhibition are increased in *nf1*$^{+/-}$ mice? One possibility is that the increase in excitation actually compensates for the increased inhibition during early cortical development. It is also possible that a homeostatic process ensures that excitatory responses compensate for the enhanced activity of inhibitory neurons, thus resulting in a similar frequency of spontaneous excitatory currents in wild-type and *nf1*$^{+/-}$ mice (Saiepour et al. 2014; Turrigiano & Nelson 2004).

In chapter 4 we investigated whether critical period closure was altered in *nf1*$^{+/-}$ mice and found that it closed prematurely. As the onset of the critical period was not altered, this means that the time during which cortical wiring could be fine-tuned was reduced. Again, we assessed inhibitory and excitatory inputs in the visual cortex of these mice, now during the critical period. At this age, we found that the frequency of inhibitory currents was still increased in *nf1*$^{+/-}$ mice but that the excitability of pyramidal neurons was now the same in *nf1*$^{+/-}$ mice and control littermates. These observations are thus compatible with the idea that an increase in the inhibition/excitation ratio closes the critical period.

In adult hippocampus, it was found that PV+ interneurons are hyperexcitable in *nf1*$^{+/-}$ mice (Omrani et al. 2015). Therefore, we also assume that the increased inhibitory currents observed in the developing cortex of *nf1*$^{+/-}$ mice is caused by the same mechanism. We did not find any changes in the frequency or amplitudes of miniature inhibitory currents in the visual cortex of *nf1*$^{+/-}$ mice, indicating that no changes in vesicle release, synapse number, or synaptic efficacy took place. This was corroborated by our immunohistochemical assessment of the sizes and densities of inhibitory synapses formed by PV+ basket cells. However, it would be interesting for future experiments to determine the excitability of PV+ interneurons and other interneuron subsets in *nf1*$^{+/-}$ mice and the amount of input they receive just after eye opening and during the critical period.

While we were investigating the contribution of altered cortical inhibition on critical period plasticity *nf1*$^{+/-}$ mice, it was discovered in our laboratory that thalamic inhibitory circuits also play a central role in the regulation of the critical period (Sommeijer et

al. 2017). It is thus possible that thalamic inhibition is also increased in *nf1*$^{+/-}$ mice and may affect cortical plasticity. We have measured the amplitude and frequency of spontaneous inhibitory currents and excitability in relay neurons within the dLGN in slices from *nf1*$^{+/-}$ and wild-type mice, but found no evidence for thalamic differences (data not shown). Therefore, it seems unlikely that local interneurons in dLGN are in the plasticity phenotype observed. At this point, we cannot rule out that inhibitory inputs from the thalamic reticular nucleus (TRN) are increased in *nf1*$^{+/-}$ mice. Connections from TRN neurons to dLGN were likely cut in our coronal slice preparations. Therefore, we were not able to measure consequences of possible TRN hyperexcitability in the dLGN. It would be interesting to test this in the future by cutting slices for electrophysiological recordings at a specific angle in which TRN-dLGN connections remain intact, or to simply measure the excitability of TRN inhibitory neurons. If TRN interneurons are indeed more active in *nf1*$^{+/-}$ mice, there are possibly additional cognitive problems such as deficits with selective visual attention or sleep (Fernandez et al. 2018; John et al. 2018).

Because our findings and previous studies all indicate that the cognitive deficits in NF1 are caused predominantly by increased inhibition (Costa et al. 2002; Cui et al. 2008; Omrani et al. 2015; Shilyansky et al. 2010), reducing GABAergic transmission seems like a sensible therapeutic approach. It may however be highly challenging to correct critical period deficits using a pharmacological approach, considering that different brain regions may require reduced inhibition at different ages. Possibly, the approach taken by Elgersma, in which HCN1 function is directly affected, may be better (Omrani et al. 2015). However, considering that critical period plasticity is affected due to the *nf1* mutation, it is likely that clinical trials should start at an earlier age than 8 years as currently done, as most cortical critical periods are then already closed.

A promising alternative, at least in mice, is to use environmental enrichment (Baroncelli et al., 2010; Begenisic et al., 2011; Greifzu et al., 2014; Sale et al., 2007). We found that when rearing mice in an enriched environment, there were no differences in frequency or amplitude of spontaneous inhibitory currents between *nf1*$^{+/-}$ and WT mice. Moreover, the critical period for OD plasticity closed normally in *nf1*$^{+/-}$ mice, showing that this approach can indeed overcome developmental deficits. Training approaches in children with NF1, such as intensive phonics training and remedial teaching using multisensory instruction, might therefore be very beneficial (Arnold et al., 2016; Barquero et al., 2015).

Critical periods are important for normal development of primary and higher cortical areas. Altered timing of critical periods or aberrant pathophysiology during critical periods has been shown in some other neurodevelopmental and psychiatric disorders such as Fragile X syndrome, Rett syndrome and schizophrenia. Therefore, we propose that cognitive- and behavioral symptoms in NF1 are partially caused by

dysregulation of critical periods of development caused by increased levels of cortical inhibition. These findings illustrate how cellular mechanisms that are important for adult physiology, or thought to act exclusively during neurodegeneration, are also used for regulating development of the brain. This is an important warning that drugs for one purpose may have very unexpected side effects during development. Also, this illustrates that understanding developmental plasticity mechanisms may have important value for treating brain disease. Current clinical trials for learning disabilities or attention deficits in NF1 start at 8 years old (Krab et al. 2008; Payne et al. 2016; van der Vaart et al. 2013). We believe that the absence of effective treatments is not always a lack of understanding of their neurobiological substrates. However, benefits of treatment might only be seen if started in early childhood. Possibly, approaches to increase axonal dynamics may also help critical periods to remain open longer, by keeping PV plasticity mechanism active (Stephany et al. 2016). Especially if signaling pathways can be identified that regulates axons that innervate PV+ interneurons selectively.

Taken together, the precise timing of critical periods during development is very important. An altered onset or closure of critical periods can result in neurodevelopmental disorders and developmental problems, such as cognitive, behavioral and motor deficits. In this thesis we elucidated both the structural aspect of critical period closure, where axonal rearrangements diminish after the critical period, and a role of inhibition in critical period closure. We found that cytoplasmic NMNATs are involved in OD plasticity, possibly by acting on rearrangements of axonal projections or synaptic stability. Additionally, we found that increased GABAergic inhibition results in early critical period closure in NF1 and that this can be rescued by environmental enrichment. These findings extend our knowledge of the mechanisms involved in regulating the closure of critical periods. This gives more insight in the mechanisms involved in the regulation of critical periods and might advance the discovery of new targets for therapeutic approaches.

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