Summary

The role of TrkB/BDNF-signaling in the developing and immature brain is multifaceted. However, it has been difficult to study the effects of BDNF in the intact adult brain, without influencing the development of the brain. It is not clear if discrete regions of the brain and specific cell types have different sensitivities to TrkB signaling in the mature brain. This thesis aims at elucidating the role of TrkB signaling in adult cortical plasticity to answer some of the following questions.

What are the structural and functional effects of inhibiting TrkB signaling in the adult cortex? Are these effects different in a similar cell type from another brain area? Can the pre- and post-synaptic effects of TrkB signaling be discerned? Does TrkB signaling act as a competitive substrate for cortical plasticity? What are the mechanisms that bring about these effects?

Due to the lack of appropriate tools to address these long-standing questions, a new approach had to be developed to counteract the problems. **Chapter 2** deals with the development of transgenic mice that express a membrane targeted enhanced green fluorescent protein (EGFP-F). The transgene expression starts at 6 weeks in individual excitatory neurons of the neocortex and hippocampus in a Golgi-staining like fashion. The EGFP-F expression levels are strong enough to perform acute and chronic in vivo imaging of layer II/III pyramidal neurons of the adult visual cortex from two different transgenic lines. Multiple transgenes can be expressed in the same individual neurons to facilitate morphological and functional analyses on the effects of different proteins**.**

In **Chapter 3,** viral-mediated Cre expression is used to increase the flexibility of this Cre-lox recombination approach to regulate gene expression in a temporal and spatial fashion. We use two different viral

systems, Adeno-associated virus (AAV) and Lentiviruses to deliver Cre stereotactically and drive the expression of β-galactosidase in R26R Cre-reporter mice. The recombination occurs in the first week of transduction and the expression pattern is similar in both viruses. There is stable transduction without any observable toxic effects.

We take this a step forward in **Chapter 4** by driving mosaic expression of a Cre-dependent functional protein, the dominant negative form of the TrkB receptor, TrkB.T1, fused to EGFP (TrkB.T1-EGFP). This allows us to visualize the individual neurons in which TrkB signaling is inhibited. TrkB.T1-EGFP expressing neurons from layer II/III of the primary visual cortex (V1) show fewer mature spines but have more of immature spine forms and filopodia when compared to EGFP-F expressing neurons. The amplitude and frequency of miniature excitatory postsynaptic currents (mEPSCs) are also reduced in these neurons. The reduction in the head size of the mature spines indicates that postsynaptic TrkB signaling is essential for spine maintenance in the adult V1. However, such morphological and electrophysiological changes are not observed in the adult hippocampal CA1. This suggests that different mechanisms govern synaptic maintenance in distinct brain areas.

In **Chapter 5,** we express TrkB.T1-EGFP in all pyramidal neurons of V1 by using a broad expressing Cre mouse. In comparison to the broad expression EGFP-F mouse, TrkB.T1-EGFP expressing neurons do not show a difference in the spine density and spine type. There is no change in the amplitude and frequency of mEPSCs. The spine head size is also similar, suggesting that inhibition of TrkB signaling in a large population of pyramidal neurons does not affect spine maintenance and other excitatory

properties. However, the inhibitory input to these neurons is reduced, as characterized by fewer Parvalbumin expressing puncta. The size and intensity of these puncta and the frequency of miniature inhibitory postsynaptic currents (mIPSCs) are also lower.

We hypothesize that synaptic maintenance by postsynaptic TrkB signaling is a competitive process that could possibly be controlled by the inhibitory system. The population activity seems to be a crucial determinant to trigger inhibition. If TrkB signaling is reduced in a single neuron, excitation is diminished in only this cell and does not affect the network activity. On the other hand, when TrkB signaling is disrupted in a majority of neurons in V1, the population activity also reduces to initiate a negative feedback of the inhibitory input.

In conclusion -

- The generated transgenic mice can drive mosaic expression of transgenes in the adult forebrain without affecting the development or the environment of these neurons.
- Multiple Cre-dependent transgenes can be expressed in the same individual neurons of the adult cortex to facilitate gene interaction studies.
- Postsynaptic TrkB signaling regulates synaptic maintenance in a bidirectional manner in the adult visual cortex, but not in the hippocampal CA1.
- Synaptic maintenance by TrkB signaling is a competitive process regulated by the inhibitory input which, in turn, is triggered by population activity.

Identifying the role of pre and postsynaptic effects of TrkB in the thalamocortical synapses and studying dynamic changes during synapse formation and maintenance by in vivo imaging would be useful complementary studies.

Samenvatting

Regulatie van de instandhouding van spines in de adulte visuele cortex van de muis door TrkB signalering

De rol van TrkB/BDNF-signalering in de ontwikkelende en onvolwassen hersenen is veelzijdig. Het is echter moeilijk gebleken de effecten van BDNF te bestuderen in de intacte volwassen hersenen, zonder de ontwikkeling van de hersenen te beinvloeden. Het is onduidelijk of afzonderlijke hersengebieden in verschillende mate gevoelig zijn voor TrkB-signalering in het volwassen brein. Dit proefschrift heeft als doel de rol van TrkB-signalering in volwassen corticale plasticiteit te verhelderen en de volgende vragen te beantwoorden.

Wat zijn de structurele en functionele gevolgen van het inhiberen van TrkB-signalering in de adulte cortex? Zijn deze effecten anders in een vergelijkbaar celtype in een ander hersengebied? Kunnen de pre- en postsynaptische effecten van TrkB-signalering van elkaar worden onderscheiden? Fungeert TrkB-signalering als competitief substraat voor corticale plasticiteit? Wat zijn de mechanismes die deze effecten tot stand brengen?

Vanwege het gebrek aan geschikte methodes om deze vragen te beantwoorden moest een nieuwe benadering worden ontwikkeld om deze problemen te omzeilen. **Hoofdstuk 2** behandelt de productie en analyse van een nieuw transgeen muizenmodel waarin membraan-gebonden groen fluorescent eiwit (enhanced green fluorescent protein; EGFP-F) tot expressie wordt gebracht in individuele hersencellen. De transgenexpressie begint op een leeftijd van 6 weken in individuele excitatoire neuronen in de

neocortex en hippocampus, volgens een patroon dat lijkt op een Golgi-kleuring. De EGFP-F expressieniveaus zijn hoog genoeg om acute en chronische *in vivo* imaging uit te voeren van laag II/III pyramidaalcellen van de adulte visuele cortex. In dit muismodel kunnen verschillende transgenen tot expressie worden gebracht in dezelfde individuele neuronen wat de morfologische en functionele analyse van de effecten van verschillende eiwitten mogelijk zal maken**.**

In **Hoofdstuk 3** is virus-gemedieerde expressie van Cre gebruikt om de flexibiliteit te vergroten van deze Cre-lox recombinatie benadering, zodat genexpressie temporeel en spatieel gereguleerd kan worden. We hebben van twee verschillende virus-systemen gebruik gemaakt om Cre stereotactisch toe te dienen en expressie van β-galactosidase in R26R Cre-reporter muizen tot stand te brengen: adeno-geassocieerd virus (AAV) en lentivirus. Cre-recombinatie was detecteerbaar in de eerste week na de transductie, en het expressiepatroon is vergelijkbaar met beide virussen. De virale transductie was stabiel en zonder waarneembare toxische effecten.

In **Hoofdstuk 4** hebben we dit een vervolg gegeven door mozaieke expressie van een Cre-afhankelijk functioneel eiwit, de dominant negatieve vorm van de TrkB receptor, TrkB.T1, gefuseerd met EGFP (TrkB.T1-EGFP). Dit maakt het mogelijk de individuele neuronen waarin TrkB-signalering was geinhibeerd te visualiseren. Neuronen in laag II/III van de primaire visuele cortex (V1), die TrkB.T1-EGFP tot expressie brengen, hebben minder mature spines maar een toename van het aantal immature spines en filopodia vergeleken met neuronen die alleen EGFP-F tot expressie brengen. Amplitude en frequentie van miniature excitatory postsynaptic currents (mEPSCs) zijn ook gereduceerd in deze neuronen. De

afname van de grootte van de kop van mature spines geeft aan dat postsynaptische TrkB-signalering essentieel is voor het in stand houden van spines in de adulte primaire visuele cortex. Zulke morfologische en electrofysiologische veranderingen worden echter niet waargenomen in het adulte hippocampale gebied CA1. Dit suggereert dat in verschillende hersengebieden verschillende mechanismes verantwoordelijk zijn voor het in stand houden van synapsen.

In **Hoofdstuk 5** hebben we TrkB.T1-EGFP tot expressie gebracht in alle pyramidaal neuronen in V1 door gebruik te maken van een muis die Cre breed to expressie brengt. In vergelijking met de muis waarin alleen EGFP-F breed tot expressie komt, laten neuronen die TrkB.T1-EGFP tot expressie brengen geen verschillen zien in spinedichtheden of spinetype. Er is geen verandering in de amplitude en frequentie van de mEPSCs. De gemiddelde omvang van de spine kop is ook vergelijkbaar, wat erop wijst dat het gelijktijd remmen van TrkB-signalering in een groot deel van de pyramidaalcellen geen effect heeft op het in stand houden van de morfologie van spines of de efficientie van excitatoire synaptische verbindingen. Echter, inhibitoire input naar deze neuronen is verminderd, wat wordt gekenmerkt door een vermindering van het aantal parvalbumine-positieve puncta rondom het cellichaam van pyramidaalcellen. De grootte en intensiteit van deze puncta, en de frequentie van inhibitory postsynaptic currents (mIPSCs) zijn ook beide verminderd.

Onze hypothese is dat de instandhouding van synapsen door postsynaptische TrkB-signalering een competitief proces is, gecontroleerd door het inhibitoire systeem. Populatieactiviteit lijkt een cruciale determinant voor de totale hoeveelheid inhibitie die de excitatoire cellen krijgen. Als TrkB-

signalering in een enkel neuron verminderd is, dan is excitatie alleen in deze cel verminderd en heeft het geen effect op netwerkactiviteit en zodoende ook niet op de totale inhibitie. Echter, wanneer TrkB-signalering wordt verminderd in een groot deel van de neuronen in V1, dan vermindert de populatieactiviteit ook, waardoor een negatieve feedback van de inhibitoire input wordt veroorzaakt. Hierdoor wordt verlies van excitatoire synaptische contacten vermeden.

Concluderend -

- De gegenereerde transgene muizen kunnen mozaieke expressie van transgenen tot stand brengen in de adulte voorhersenen, zonder de ontwikkeling of omgeving van de neuronen te beinvloeden.
- Meerdere Cre-afhankelijke transgenen kunnen tot expressie worden gebracht in hetzelfde individuele neuron van de adulte cortex, om gen-interactie studies mogelijk te maken.
- Postsynaptische TrkB-signalering reguleert de instandhouding van synapsen in beide richtingen in de adulte visuele cortex, maar niet in het hippocampale gebied CA1.
- Instandhouding van synapsen door TrkB-signalering is een competitief proces gereguleerd door inhibitoire input, die op zijn beurt getriggerd wordt door populatieactiviteit.

Het bepalen van de rol van pre- en postsynaptische effecten van TrkB in thalamocorticale synapsen, en het bestuderen van dynamische veranderingen tijdens synapsformatie en -instandhouding door middel van *in vivo* imaging zouden nuttige toegevoegde studies zijn.

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Curriculum Vitae

Sridhara Chakravarthy was born on 20th November 1976 in Bangalore, India. He obtained his Bachelor of Science degree in Microbiology from Bangalore University in 1997. He received a summer intern scholarship for four months at Astra Zeneca, Bangalore in June 1997 to work with Dr. Meenakshi Balganesh on the molecular mechanisms that regulate *Eschelrichia coli* and *Staphylococcus aureus* to develop multiple drug resistance. In October 1997, he was awarded a research scholarship to pursue a Master's by Research degree in Molecular Neuroscience from National Centre for Biological Sciences (Tata Institute of Fundamental Research), Bangalore. During the four year research programme in Prof. Mitradas Panicker's lab, he set up an in vitro system to probe mammalian gene regulation, with special interest in the transcriptional regulation of Serotonin (5-HT) receptors. In October 2001, he joined the group of Dr. Christiaan Levelt as a PhD student at Netherlands Institute for Neuroscience, Amsterdam. He studied the role of TrkB signaling in the regulation of synaptic plasticity in the adult visual cortex of transgenic mice. The work conducted during this period is part of this doctoral thesis. In December 2008, he started his postdoctoral research in the group of Dr. Susana Cohen-Cory, Department of Neurobiology and Behavior at University of California, Irvine.