Studying synapses

In the quest to improve our understanding of brain function, **Dr Corette J Wierenga**'s research focuses on the role of synapses, with a view to developing treatments for neurodevelopmental disorders such as autism

Can you outline your previous experience and explain what most interests you about the study of synapses?

After initially studying physics, I realised I had satisfied my curiosity in this field and that my true fascination was with the brain. I still find it absolutely amazing how the human brain works and develops in a strongly self-organised fashion. Throughout our lives, we have the same set of nerve cells in our brain. By changing the properties of the connections between these nerve cells, our brains learn to deal with ever-changing circumstances and develop a personal history. I would like to understand how this is regulated.

Why is it important for neuroscience researchers to understand chemical synapses?

Every time we learn something new or undergo a new experience, our brain changes a little bit. Our personal history is, to a large extent, incorporated in the changes in the synaptic connections of our nerve cells. We have a good general understanding of how synapses can undergo changes and it becomes increasingly clear that there are many diverse ways to change synaptic connections. Different synaptic connections display specific plasticity mechanisms and these often change during development. Even though a newborn brain is strongly determined by its genetic makeup, it is subsequently moulded and shaped by its environment. To understand these processes, it will be essential to unravel the many mysteries of the synapse.

What are some of the methods that you use to conduct your research?

In my lab, we use brain slices from mice as a model to study synaptic plasticity. In general, we use two techniques to examine changes at synaptic connections. We can record the small electrical signals produced by communicating nerve cells and can thereby determine if (and how) connections are changed. We also use two-photon laser scanning microscopy to visualise synaptic connections. For this, specific nerve cells are coloured red and/or green and synapses between coloured cells can be followed when they are formed or changed in live brain slices. We combine this with, for instance, molecular biology techniques to study the role of specific molecules in these processes, or with behavioural studies to examine the effect of specific experiences on synaptic connections in the brain.

Can you provide a brief summary of your research proposal to investigate the effects of early social experience on the brain's development? What do you hope to gain from this study?

We have recently initiated an exciting new project in collaboration with Professor Louk Vanderschuren from the Faculty of Veterinary Medicine at Utrecht University in the Netherlands. We will study the links between social development in rats and changes in excitatory and inhibitory synapses in their brains. The prefrontal cortex is a brain region involved in higher cognitive behaviour, such as social interactions, planning and decision making. This brain area is one of the last to mature, as it reaches its 'adult state' only during adolescence or early adulthood. We will test how social interactions during adolescence shape the synaptic connections in the prefrontal cortex and how this affects social behaviour and cognitive performance.

How is your research contributing to a better understanding of mental health disorders?

Many mental health disorders are thought to have a basis in synaptic dysfunction or maladaptive synaptic plasticity. It is important that the role of inhibitory synapses is also taken into account, as in many disorders the balance between excitation and inhibition is distorted. Understanding how inhibitory synapses respond to changes in excitation and vice versa will be of fundamental importance for understanding how such disorders may occur during development or how the brain can respond to specific experiences or insults. Another potential contribution is that studying inhibitory synapses could help in finding new drug targets.

Balancing the brain

Scientists at **Utrecht University** in the Netherlands are studying the interactions between excitatory and inhibitory synapses in the brain. Their research has uncovered fundamental differences between the mechanisms of formation

THE HUMAN BRAIN consists of billions of neurons that are interconnected by chemical synapses. As well as being crucial for information processing, synapses give the brain its capacity to adapt to the environment, through their highly plastic nature. Understanding synapses and how they are formed is therefore fundamentally important in neuroscience.

Wierenga's work is solving outstanding questions about how the brain functions, and enhancing understanding of the processes that regulate the homeostasis of excitatory and inhibitory synapses

Broadly, there are two types of synapses. Approximately 80 to 90 per cent are excitatory, which have a small positive effect on the receiving nerve cell and use glutamate as a neurotransmitter. The other major type uses the inhibitory transmitter gamma aminobutyric acid (GABA) and usually generates a small negative signal. So far, most studies have focused on the formation of excitatory synapses, but in recent years, the indispensable role of inhibitory synapses for proper functioning of the brain has become clearer. Inhibitory plasticity has been shown to be crucial during brain development and for a variety of behaviours. Furthermore, experimental evidence has demonstrated that disorders such as autism and schizophrenia are strongly associated with imbalances between excitatory and inhibitory synaptic transmission.

STUDYING INHIBITORY SYNAPSES

Improving knowledge about the similarities and differences between the two types of synapses and how they interact is necessary in order to further understand how the brain functions. Based at Utrecht University in the Netherlands, Dr Corette J Wierenga is devoting her current research to discovering how synapses are changed as a function of previous experience. Information is processed in networks of nerve cells and the synaptic connections within these are continuously changed by the neuronal activity of involved nerve cells. Wierenga suspects that coordination takes place between different plasticity mechanisms at different synapses, and is especially interested in elucidating how this works. "Synaptic changes have to be coordinated because, despite the continuous changes that are taking place, our brain is able to function and interpret the world around us while producing relevant behaviour," she explains.

Wierenga's team is using high-resolution two-photon imaging to examine the formation of inhibitory synapses in living brain slices taken from mice. Studying inhibitory synapse formation is especially challenging because basic information on the molecular composition is not complete, and there seems to be an enormous diversity within inhibitory synapses.

NEW TREATMENTS FOR NEURODEVELOPMENTAL DISORDERS

To date, the group has made some remarkable discoveries; most significantly, that inhibitory synapses are formed in a fundamentally different manner to excitatory synapses. Their time-lapse two-photon imaging of inhibitory axons further showed that inhibitory synaptic boutons – the area that contains neurotransmitters – are highly dynamic structures that can appear, disappear, re-appear or change shape or size over the course of a few minutes or hours. "This discovery changed our view of how inhibitory synapses can respond to changes in their local environment," Wierenga enthuses. The researchers also recently showed that these dynamics are affected by the activity of nearby neurons and are currently examining which molecular factors play a role in this inhibitory plasticity.

Wierenga's work is solving outstanding questions about how the brain functions, and enhancing understanding of the processes that regulate the homeostasis of excitatory and inhibitory synapses. Elucidating how normal brain development is regulated will lead to important new insights into the aetiology of neurodevelopmental disorders such as autism, as well as to a better understanding of the mechanisms behind disturbed adult brain functioning, for instance, in addiction or anxiety disorders. "I am convinced that a detailed knowledge of synaptic plasticity and network interactions is necessary to open up new possibilities for interventions or therapeutics for many brain diseases," she concludes.

BALANCING THE BRAIN: LOCAL INTERACTIONS BETWEEN EXCITATORY AND INHIBITORY SYNAPSES

OBJECTIVES

- To test how activity of excitatory synapses affects the plasticity of nearby inhibitory boutons
- To examine to what extent an inhibitory synapse can affect signalling and plasticity of nearby excitatory synapses
- To examine how correlated plasticity events are involved in brain development in health and disease

KEY COLLABORATORS

Professor Tobias Bonhoeffer; **Fiona Müllner**, Max Planck Institute of Neurobiology, Germany • **Professor Louk Vanderschuren**, Utrecht University, Netherlands • **Dr Suzanne Paradis**, Brandeis University, USA • **Professor Martin Korte**; **Dr Marta Zagrebelsky**, Technical University Braunschweig, Germany • **Dr Andreas Vlachos**, Goethe University Frankfurt, Germany

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CONTACT

Dr Corette J Wierenga

Cell Biology, Room N511
Faculty of Science
Utrecht University
Padualaan 8
3584CH Utrecht
The Netherlands

T +31 6 1397 8993
E c.j.wierenga@uu.nl

http://bit.ly/CoretteWierenga

http://linkd.in/1I9amUj

CORETTE J WIERENGA studied Physics at the VU University Amsterdam, followed by a PhD in Neurobiology (2002) at the University of Amsterdam under the supervision of Professor Wytse Wadman. Subsequently, Wierenga worked as a postdoctoral researcher in the lab of Professor Gina Turrigiano at Brandeis University (2002-05), and at the Max Planck Institute of Neurobiology in the group of Professor Tobias Bonhoeffer (2005-11). In October 2011, Wierenga returned to the Netherlands and is now an assistant professor at the Cell Biology Division at Utrecht University.

Utrecht University