

On Neuroimmunology and Brain Function: Experimental and Clinical Studies

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentlig försvaras i hörsal Ivan Östholm, Medicinargatan 13, Göteborg, torsdagen den 13 juni 2019, klockan 9:00

av

Nina Strenn

Fakultetsopponent:

Daniel Lindqvist, leg läk, med dr

Lunds Universitet, Sverige

Avhandlingen baseras på följande delarbeten

- I. **Nina Strenn**, Petra Suchankova, Staffan Nilsson, Christina Fischer, Gregers Wegener, Aleksander A. Mathé, Agneta Ekman. 2015. Expression of inflammatory markers in a genetic rodent model of depression. *Behavioural Brain Research* 281:348-357
- II. **Nina Strenn**, Gregers Wegener, Christina Fischer, Staffan Nilsson, Agneta Ekman. Effects of chronic escitalopram treatment on the expression of inflammatory markers in the Flinders rat model of depression. *Manuscript*.
- III. **Nina Strenn**, Daniel Hovey, Lina Jonsson, Henrik Anckarsäter, Sebastian Lundström, Paul Lichtenstein, and Agneta Ekman. Associations between autistic-like traits and polymorphisms in *NFKBIL1*. *Acta Neuropsychiatrica* 2019. *Manuscript in press*.
<https://doi.org/10.1017/neu.2019.18>
- IV. **Nina Strenn**, Erik Pålsson, Benny Liberg, Mikael Landén, Agneta Ekman. Influence of variations in *IL1B* on brain region volumes in bipolar patients and controls. *Manuscript*.

**SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH
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ABSTRACT

The immune system has been implicated in the mechanisms underlying many psychiatric disorders. Immune mediators are expressed in the central nervous system (CNS) not only in response to harmful stimuli, but also in a constitutive manner, and serve as important plasticity factors during development. There is complex bidirectional communication between the immune system and the CNS throughout life which is based on interactions between neurotransmitters, neuroendocrine hormones, cytokines, and their respective receptors. Exploring the interplay between brain, behaviour and immunity is central to our understanding of the pathology of psychiatric morbidity.

The aim of this thesis is to investigate the role of some aspects of the immune system in several psychiatric conditions, both in experimental and clinical contexts. We used the Flinders sensitive line (FSL), a genetic animal model of depression, to study central gene expression of markers related to immune response and neurotransmission following immune stimulation and antidepressant treatment. Several genes were found to be expressed differently in rats displaying depressive-like behaviour compared to their controls (Paper I), a finding that we replicated in Paper II. Additionally, we showed that antidepressant treatment with escitalopram altered expression of several genes, notably the astrocyte-derived protein S100B, and the serotonin receptor 5-HT_{2A}, in the amygdala and hypothalamus (Paper II), two brain regions that have been shown to be of relevance for the effect of antidepressant treatment. Our results support the use of the FSL model for studying the role of these immune-related markers in depression and antidepressant treatment.

In the clinical studies included in this thesis, we found that genetic variants in immune-related genes were associated with neuropsychiatric traits and the volume of certain brain regions. The gene encoding the NF- κ B inhibitor-like protein 1 (*NFKBIL1*) was found to be associated with autistic-like traits, as well as with language impairment in a cohort from the general population (Paper III). We further investigated the effect of genetic variation in the gene coding for interleukin-1beta (*IL1B*) on the volume of several brain regions in a case-control population of patients diagnosed with bipolar disorder (Paper IV). Genotype distribution did not differ between patients and controls, suggesting that variants in *IL1B* may not be associated with bipolar disorder. However, we found associations between *IL1B* polymorphisms and the volume of the putamen in the left hemisphere in patients and controls, suggesting that genetic variation in *IL1B* may influence neurodevelopment.

In conclusion, this thesis demonstrates associations between immune mediators and mental functions, as well as altered brain development in humans. Also, insight is gained into the use of the FSL animal model for investigating the impact of the immune system for depression. Taken together, our findings confirm the importance of the immune system for the development of psychiatric disorders.

Keywords: immune system, mental disorders, polymorphisms, depression, autism, bipolar disorder, SSRI, S100B, 5-HTR2A, Flinders sensitive line