

## **The role of microglia in the pathogenesis of schizophrenia**

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### Research question and background

Schizophrenia (SCZ) and bipolar disorder (BPD) are severe chronic psychiatric disorders. Despite intensive research their pathogenesis is still unclear. It is known that both genetic and environmental factors contribute to these diseases. Furthermore, it is accepted that neurodevelopmental processes and neuronal functioning are affected, including neurogenesis, synaptic pruning and neurotransmission. Increasing evidence supports a role for immune processes in the pathogenesis of both disorders. Evidence for a causal relationship between the immune system and these disorders comes from their genetic association with immune genes and pathways. Furthermore, autoimmune and atopic disorders have a higher prevalence in patients with these diseases and their families. How altered immune processes lead to aberrant neuronal functioning in BPD and SCZ is still unclarified. Neuropathological studies showed that both are not clear-cut neuroinflammatory or autoimmune diseases, since lymphocyte infiltrates are absent. Recent studies proved that immune pathways in the central nervous system are involved in neuroinflammation, neurodevelopment and neuronal functioning (e.g. MHC class-I is shown to be expressed on neurons and crucial to neurogenesis). Furthermore, it is shown that the neuron-glia interaction is important for neurotransmission, neurogenesis and synaptic development and is mediated by various molecules known for their role in the immune system, such as fractalkine, TNF- $\alpha$ , TGF- $\beta$  and the complement system. We therefore hypothesize that immune processes are affected in BPD and SCZ by genetic or environmental factors, leading to dysfunction of microglia and their interaction with neurons. Previous studies have investigated microglia in SCZ and BPD and found indications of microglia activation and increased densities in SCZ patients. Both suggest altered microglia in SCZ and BPD, but how their function is altered is not yet clear. In this project we further investigate how the function of microglia in BPD and SCZ is altered, with special attention to neuron-glia interacting molecules.

### Methods and tissue used

Phenotype and function of microglia are studied *in situ* and *ex vivo*. *Ex vivo*, microglia are isolated from fresh post mortem tissue<sup>1</sup> and phenotyped by qPCR and flow cytometry for a panel of markers indicative of several important microglia functions. In addition, microglia response to pro- and anti-inflammatory cytokines and phagocytic properties will be measured. *In situ*, gene and protein expression are studied on frozen tissue of patients and controls with qPCR and flow cytometry. Microglia are studied in several anatomical structures selected based on symptomatology and pathological evidence from structural, functional and histopathological studies: medial frontal gyrus, superior temporal gyrus, hippocampus, subventricular zone and thalamic region.

### Results and conclusion

The isolation and characterization of microglia was set up and further optimized in our lab. We are in the progress of collecting and characterizing microglia from healthy controls, SCZ and BPD patients. Increased RNA expression of translocator protein (TSPO), a microglia marker used in PET imaging, was found in temporal, but not frontal, cortex of SCZ patients and coincides with our recent PET study<sup>2</sup>. In addition, we found a trend for higher MHC-related gene expression in both GFM and GTS of SCZ patients compared to controls, assuming altered function of microglia and/or neurons.

### References

1. Melief, J. *et al.* Microglia in normal appearing white matter of multiple sclerosis are alerted but immunosuppressed. *Glia* **61**, 1848–1861 (2013).
2. Doef, T. van der *et al.* *In vivo* and post-mortem evidence for altered immune function in the temporal cortex of patients with schizophrenia. in submission (2015).