

## S15. Gene expression in schizophrenia

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### S15.1

Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia

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To identify molecular substrates associated with schizophrenia, DNA microarray analysis was used to assay gene expression levels in post-mortem dorso-lateral prefrontal cortex from patients with schizophrenia and controls. Genes determined to have altered expression levels in schizophrenics relative to controls are involved in a number of biological processes, including synaptic plasticity, neuronal development, neurotransmission and signal transduction. Most notable was the differential expression of myelination-related genes suggesting a disruption in oligodendrocyte function in schizophrenia. Follow-up studies to this initial series of experiments as well as the advantages/disadvantages of various data analysis paradigms will be presented.

### S15.2

The use of the microarray-technology in schizophrenia

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Changes in gene expression have been observed in schizophrenia and other neuropsychiatric disorders. In particular, alterations in gene products related to neurotransmission (e.g. Schramm et al. 1998) or second messenger systems have been observed. However, each of these studies have focused on only one or a few gene products at a time, without the ability to investigate the simultaneous expression of large number of genes. Microarray technology provides an opportunity for application of gene expression analysis to complex clinical diseases and these approaches have been successful in addressing fundamental biological questions in human cancer. However, due to the inherent complexity of nervous tissue and the need to utilize postmortem material, few microarray studies of the human central nervous system in schizophrenia have been conducted so far (e.g. Mirmics et al. 2000). Published studies and own data are presented and inherent problems are discussed. They are e.g. the moderate extent of change (often not exceeding a 2-fold change), the clinical heterogeneity in psychiatric disorders and the interpretation of the findings.

Schramm et al. (1999) *J Neural Transm* 106,329–35.  
Mirmics et al. (2000) *Neuron* 28: 53–67.

### S15.3

Serotonin receptor gene expression in the pathology of schizophrenia

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There is considerable evidence for the involvement of serotonin (5-HT) receptors in the pathophysiology of schizophrenia. We have investigated 5-HT1A, 5-HT2A, 5-HT2C, 5-HT6 and 5-HT7 receptor mRNA abundance, and binding site densities in various neocortical and hippocampal regions of schizophrenic and control subjects. Age, agonal state (brain pH) and post mortem interval were included where necessary as covariates in our analyses. In schizophrenics, 5-HT1A receptor binding site densities, but not mRNA, were significantly increased (+23%) in the dorsolateral prefrontal cortex. 5-HT2A receptor binding sites were decreased in the dorsolateral prefrontal cortex (-27%) and parahippocampal gyrus (-38%) in schizophrenia, whereas 5-HT2A receptor mRNA abundance was reduced in the frontal, temporal and striate cortices only. Finally, a reduction in the abundance of 5-HT2C and 5-HT6 receptor mRNAs was observed in the hippocampus in schizophrenia, but not the dorsolateral prefrontal cortex. 5-HT7 receptor mRNA abundance was decreased in the dorsolateral prefrontal cortex but not hippocampus. The molecular and regional specific alteration of 5-HT receptor genes in schizophrenia will be considered in terms of the local pathology and aberrant connectivity proposed in this disorder.

### S15.4

Glutamate system gene expression in schizophrenia

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**Objective:** do gene expression studies suggest glutamate function is abnormal in schizophrenia? Are there differential changes in frontal vs temporal structures as we have previously suggested?

**Method:** review of gene expression studies in the context of earlier data and new data from our group.

**Results:** 1) glutamate AMPA receptor expression is not altered in prefrontal cortex and decreased in the hippocampus. 2) Glutamate uptake site binding is decreased in left polar temporal cortex and increased in the orbitofrontal region of the prefrontal cortex, however, mRNA studies report reductions in both prefrontal cortex and hippocampus. 3) We found gene expression for the obligatory NMDA receptor subunit NR1, decreased in left-sided regions of the hippocampus, but in dorsolateral prefrontal cortex single studies have reported an increase, no change and a decrease. In orbitofrontal cortex increased NMDA receptor binding and mRNA for a metabotropic glutamate receptor have been reported but we now report no change in NR1 expression in orbitofrontal cortex in the Stanley Consortium brains.

**Conclusion:** No generalised changes in glutamate function from gene expression studies. Losses mainly in the hippocampus & more on the left.

### S15.5

Neuropeptide gene expression in psychiatric subjects

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Dysfunction of endogenous neuropeptides has been proposed in the pathophysiology of psychiatric disorders. We have been interested