# Determinants of psychosis vulnerability; focus on MEF2- and glucocorticoid signaling

Speksnijder, N.

# Determinants of Psychosis Vulnerability

## Focus on MEF2- and Glucocorticoid Signaling

**Niels Speksnijder**

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# Preface

**PREFACE**

Schizophrenia is often inherited, but even in monozygotic twins one sibling can be more susceptible to schizophrenia than the other. This raises the question what the cause of this difference in susceptibility in genetically identical individuals might be. The objective of this thesis research was to identify novel susceptibility genes and pathways for psychosis in a psychostimulant mouse model which is considered a model for psychosis.

Using genome-wide micro-array analysis of transcripts expressed in discrete laser-dissected brain regions of mouse brain we found a large number of genes differentially expressed particularly in the hippocampal CA1, a region known to drive mesocortical dopaminergic activity which has a prominent role in the pathogenesis of schizophrenia. Profound differences were found in expression of target genes of Myocyte Enhancer Factor 2 (MEF2) and the Glucocorticoid Receptor (GR), suggesting that this gene network is involved in sensitivity to amphetamine. In primary hippocampal neuronal cultures knockdown of MEF2 not only reduced the expression of its target gene c-Jun, but also abolished its regulation by GR. Moreover, activation of MEF2 by depolarization of these neurons was found to be attenuated by glucocorticoids suggesting a complex mutual feedback regulation of the two transcription factors. Finally, *in vivo* in the mouse MEF2 and GR appeared to be active in the induction rather than in the expression phase of amphetamine sensitization.

Taking our data together, the findings suggest that in the hippocampus the effect of stress, via glucocorticoid activation of GR, can modulate the role of MEF2 target genes in induction of behavioral sensitization. This finding points to the hippocampus as an exciting target for further studies on the role of MEF2 and GR in the precipitation of psychosis susceptibility.