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# Determinants of Psychosis Vulnerability

Focus on MEF2- and Glucocorticoid Signaling

**Niels Speksnijder**

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

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# Determinants of Psychosis Vulnerability

Focus on MEF2- and Glucocorticoid Signaling

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## Table of contents

	Preface	7
<b>Chapter 1  </b>	General Introduction	9
<b>Chapter 2  </b>	Hippocampal CA1 region shows differential regulation of gene expression in mice displaying extremes in behavioral sensitization to amphetamine: relevance for psychosis susceptibility?	39
<b>Chapter 3  </b>	Glucocorticoid Receptor and Myocyte Enhancer Factor 2 cooperate to regulate the expression of c-JUN in a neuronal context	69
<b>Chapter 4  </b>	Depolarization-induced binding of MEF2 to the promoter region of NR4A1 is prevented by GR activation	93
<b>Chapter 5  </b>	Hippocampal MEF2 phosphorylation is enhanced during induction of sensitization	111
<b>Chapter 6  </b>	General Discussion	127
<b>Addendum  </b>	Summary	145
	Samenvatting	149
	Dankwoord	153
	Curriculum Vitae	157
	List of publications	159





# 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.