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

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Chapter 1 | General Introduction

Contents of Introduction

1.1 Schizophrenia and Psychosis

Schizophrenia has a prevalence of approximately 1% and is one the most life-debilitating psychiatric disorders. It is also a very costly disorder since the onset of the disease is typically during young adulthood, leaving the patients with a reduced ability to contribute to society, while life expectancy is high (McEvoy 2007, Wu *et al.* 2005, Mangalore & Knapp 2007).

Schizophrenia is characterized by a combination of positive, negative and cognitive symptoms. Positive symptoms, such as hallucinations, delusions, disordered thought and speech, are not normally experienced by most individuals, but are present in schizophrenics as manifestations of psychosis. Negative symptoms are deficits in emotional and cognitive processes and become manifest as depressed mood, blunted affect and lack of motivation. Cognitive impairment can already be observed at young age and may serve as a prodromal factor to monitor children with a high risk of developing schizophrenia in later life.

The diagnosis of schizophrenia is set in most cases when the patient is suffering from overt psychosis. A psychotic episode is defined, according to DSM-IV, as a state of two or more of the following symptoms: delusions, hallucinations, disorganized speech, disorganized behavior and negative symptoms for at least 1-6 months, with significant negative pressure on social life (e.g. work) (American Psychiatric Association. & American Psychiatric Association. Task Force on DSM-IV. 1994).

Psychoses can be triggered by several factors such as exposure to a severe stressor or psychostimulant drugs. The moment of the first psychotic episode is generally considered to be preceded by several neurodevelopmental deficits that can be divided in several factors that will be described below (Velakoulis *et al.* 2000, Brown 2011)

1.2 Development of schizophrenia

Over the years numerous causes and correlates for schizophrenia have emerged, ranging from paternal age, prenatal events like bacterial and viral infections, obstetric complications to postnatal experiences, and even the season of birth and urbanicity have been suggested as risk factors. All these possible contributors have been extensively studied and reviewed elsewhere (Brown 2011, Velakoulis et al. 2000, Rapoport *et al.* 2005, Fatemi & Folsom 2009). More generally, the developmental cascade precipitating full-blown schizophrenia can be divided in 3 steps: 1. genetic vulnerability; 2. adverse environmental factors; and 3. a trigger (Cannon *et al.* 2003). This is also called the two- or three-hit model of schizophrenia depending on whether a distinction is made between genetic vulnerability and adverse environmental factors (Maynard *et al.* 2001) (Fig. 1).

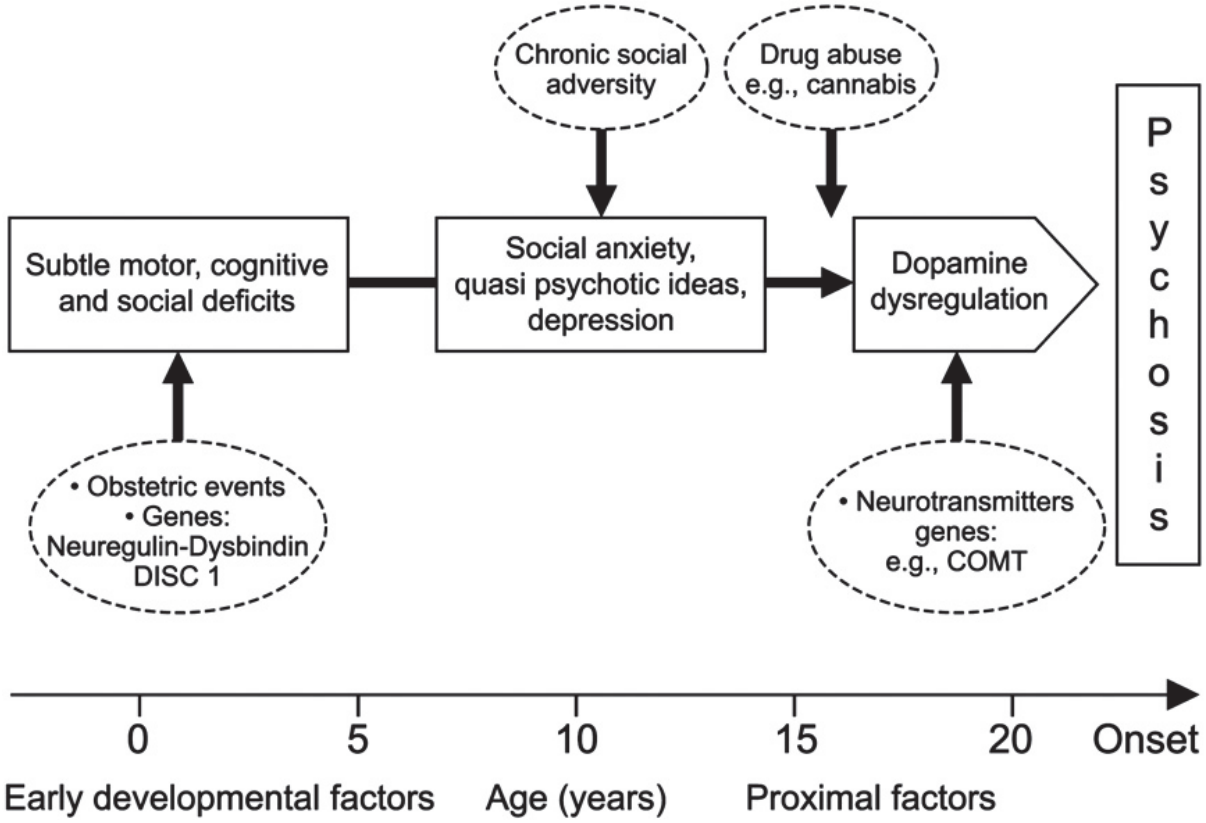

Figure 1| Developmental cascade of schizophrenia. Genetic predisposition for schizophrenia may lead to prodromal symptoms such as cognitive deficits. Combined with chronic social adversity this predisposition may give rise to an altered neuronal development giving rise to quasi psychotic ideas that at this point are difficult to distinguish from normal childhood fantasies. Drug abuse or another stressor during adolescence might then trigger a full-blown psychotic event, the first stage of schizophrenia (Murray *et al.* 2008). Reprinted with permission.

1.3 Genetics of schizophrenia

Twin studies are invaluable for studying the relative contribution of genetic predisposition to polygenic disorders. Especially the comparison of dizygotic and monozygotic twins, who share ~50% and 100% of their genetic makeup respectively, provides information on the extent of the genetic contribution to a disorder (Rahmioglu & Ahmadi 2010). For schizophrenia the concordance rate is 50% in monozygotic twins, while as genetic homogeneity with the schizophrenic individual decreases the risk of developing schizophrenia is concomitantly reduced, reaching approximately 1% in the general population (Cardno & Gottesman 2000). Hence it is clear that genetic make-up plays a major role in susceptibility to schizophrenia. Many different genetic studies have been conducted in order to gain more insight into which genes or chromosomal loci contribute to schizophrenia susceptibility, including linkage studies, genome-wide association studies (GWAS), copy number variation studies (CNV) and candidate gene approaches. These different approaches will be briefly described below, including their best validated susceptibility genes/loci.

1.3.1 Genetic linkage studies

Genetic linkage studies are designed to find susceptibility genes within pedigrees of families with a higher than average disease prevalence. With regard to schizophrenia, linkage studies were the first genetic studies designed to understand schizophrenia vulnerability. The basis of this type of studies is to find the common denominators of genetic make-up within a family where several members might suffer from schizophrenia while others do not. Together with other linkage studies, several chromosomal loci have been found and replicated that are connected to schizophrenia such as 1q42, 6p22-24, 1q21-22 and 13q32-34 (Brzustowicz *et al.* 2000, Straub *et al.* 2002, Blouin *et al.* 1998, Riley & Kendler 2006, Lewis *et al.* 2003, Millar *et al.* 2001, Ng *et al.* 2009).These chromosomal regions harbor many genes that were the first likely candidates to study in schizophrenia development such as Disrupted in Schizophrenia 1 (DISC1), Regulator of G-protein Signaling 4 (RGS4), Dystrobrevin DTNBP1, D-Amino Acid Oxidase (DAAO/G72).

1.3.2 Genome-wide association studies

Genome-wide association studies (GWAS) compare occurrence of single nucleotide polymorphisms (SNPs) between unrelated groups of patients and (matched) controls. SNPs are heritable genetic changes that occur frequently (>1%) in the general population and might result in altered expression or functionality of the protein. GWAS studies are relatively new for schizophrenia, with the first study published only 7 years ago (Mah *et al.* 2006). Within this short timespan the studies have evolved enormously, both in design and number of subjects. For example, the previously mentioned study by Mah et al compared over 300 patients with matched controls, while one of the more recent studies

by Lee et al included almost 9,000 patients and 12,000 controls (Mah et al. 2006, Lee *et al.* 2012). The number of SNPs screened increased as well from ~26,000 to almost 1 million. Among the replicated results are the MHC region (Major Histocompatibility Complex), DTNBP1 and TCF4 (Transcription Factor 4) (Bergen & Petryshen 2012). The MHC region is the region most strongly linked to schizophrenia in all genetic studies and harbors genes that play an important role in the immune system, of which the role in schizophrenia is largely unknown (de Jong *et al.* 2012, Girard *et al.* 2012). DTNBP1 plays a role in glutamate release from synaptic vesicles and is reportedly downregulated in the hippocampus and prefrontal cortex of schizophrenia patients (Coyle 2006) and enhanced expression of TCF4 has been found in brains of schizophrenia patients as well as in the brains of psychostimulant-treated animals (Kurian *et al.* 2011, Mudge *et al.* 2008)..

1.3.3 Copy-number variations

Copy-number variations (CNVs) are large deletions or multiplications of DNA sequences and give rise to enhanced or repressed expression of certain genes or splice variants. Well known examples are Down syndrome, where subjects have an additional copy of chromosome 21, and velocardiofacial syndrome (VCFS) were patients have a deletion of a part of chromosome 22.

CNVs are more frequently apparent in schizophrenia patients compared to healthy controls (Walsh *et al.* 2008), although it is estimated that only 2-4% of the genetics of schizophrenia can be linked to CNVs (St Clair 2009). CNV studies in schizophrenia patients found changes at loci such as 22q11.2, the locus where the DISC1 gene is located (Xu *et al.* 2008) and which is also part of the deletion found in VCFS. Approximately 1% of the schizophrenic population has the deletion of this locus but up to 25% of the people carrying the deletion have schizophrenia (Bassett *et al.* 2005). It is therefore considered one of the major genetic vulnerability factors linked to schizophrenia. Although it is difficult to link the CNV to certain genes, because CNVs often span multiple genes, recent advances in CNV studies implicate a role specifically for postsynaptic glutamate signaling underlying neural plasticity (Kirov *et al.* 2012, Walsh et al. 2008).

Table I | Chromosomal locations identified in schizophrenia genetic studies.

Chromosome	Region/genes	Study Type[a]	Cases/controls[b]	P/OR/LOD[c]	Reference
1q21-q22	Regulator of G-protein signaling 4 (RGS4)	Linkage	22 /304	6.5 (LOD)	(Brzustowicz et al. 2000)
1q21.1	Regional deletions	CNV	Original: 1433/33250 Follow-up: 3285/7951	14.83 (OR) $P = 2.9*10^{-5}$	(Stefansson et al. 2008)
1q21.1		CNV	11372/47311	9.5 (OR) $P = 8.5*10^{-6}$	(Levinson *et al.* 2011)
1q42	Disrupted in Schizophrenia 1 (DISC1)	Linkage	1 /87	3.6 (LOD)	(Blackwood *et al.* 2001)
2q32.1	Zinc Finger Protein 804A (ZNF804A)	GWAS	Original: 479/2937 Follow-up: 6829/9897	1.12 (OR) $P = 1.61*10^{-7}$	(O'Donovan *et al.* 2008)
6p21.32	Major Histocompatibility (MHC) Region	GWAS	3322/3587	0.82 (OR) $P = 4.79*10^{-8}$	(Purcell *et al.* 2009)
		GWAS	Original: 2663/13498 Follow-up: 4999/15555	1.21 (OR) $P = 2.1*10^{-8}$	(Stefansson et al. 2009)
6p21.3-p22.1	Major Histocompatibility (MHC) Region	GWAS meta-analysis	2681/2653	0.88 (OR) $P = 9.54*10^{-9}$	(Shi *et al.* 2009)
		GWAS	Original: 9394/12462 Follow-up: 8442/21397	1.15 (OR) $P = 2.18*10^{-12}$	(Ripke et al. 2011)
6p22.3	Dystrobrevin binding protein 1 (DTNBP1)	Linkage	270 /1425	2.2 (LOD)	(Straub et al. 2002)
8p22-p21	Neuregulin 1 (NRG1)	Linkage	54 /363	3.6 (LOD)	(Blouin et al. 1998)
		Linkage	33 /110	2.5 (LOD)	(Stefansson *et al.* 2002)
13q22-34	D-Amino Acid Oxidase (DAAO/ G72)	Linkage	54 /363	4.2 (LOD)	(Blouin et al. 1998)
		Linkage	Original: 213/241 Follow-up: 183/183	P = <0.05 P = <0.05	(Chumakov *et al.* 2002)
15q13.3	Regional deletion	GWAS	Original: 1433/33250 Follow-up: 3285/7951	11.54 (OR) $P = 5.3*10^{-4}$	(Stefansson et al. 2008)
	Regional deletion	CNV	Meta-analysis: 10866/45913	12.1 (OR) $P = 6.9*10^{-7}$	(Levinson *et al.* 2011)
16p11.2	Regional duplications	CNV	9859/29589	9.5 (OR) $P = 2.6*10^{-8}$	(Levinson et al. 2011)
		CNV	Original: 1906/3971 Follow-up: 2645/2420	14.5 (OR) $P = 4.8*10^{-7}$	(McCarthy *et al.* 2009)
18q21.2	TCF4	CNV	Original: 2663/13498 Follow-up: 4999/15555	1.23 (OR) $P = 4.1*10^{-6}$	(Stefansson et al. 2009)
		GWAS	Original: 9394/12462 Follow-up: 8442/21397	1.23 (OR) $P = 1.05*10^{-6}$	(Ripke et al. 2011)
22q11.2	Regional deletions	CNV	Meta-analysis: 11365/45361	20.3 (OR) $P = 7.3*10^{-13}$	(Levinson et al. 2011)
		CNV	695 patients	unknown	(Karayiorgou *et al.* 1995)

Chromosomal locations and allocated genes found to be associated with the diagnosis of schizophrenia. Note that some studies included a two-stage approach, where the original findings where followed up by an additional set of cases and controls. In that case, odds ratios are combinations of both the original and the follow-up study.

[a] Study type: CNV: Copy-number variation; GWAS: Genome-wide association study

[b] Linkage studies often don't include controls. The numbers given in that case refer to the number of pedigrees or child-parents trios vs total members included in the study.

[c] Differences are calculated based on study type. LOD scores are defined as the Logarithm of ODds; for example: a LOD of 2 means 100 to 1 odds that the observed linkage did not occur by chance. OR is Odds Ratio and is defined as the fold difference in risk of a schizophrenia patient of carrying a specific CNV or SNP vs healthy controls. P-values are given when provided in the study and define the strength of the give OR.

1.3.4 Gene expression studies

In gene expression studies an underlying hypothesis or genes and pathways that emerged from genetic studies or from mRNA expression analysis are the central focus. For example, by studying

gene expression in post-mortem brain material of schizophrenic patients and controls, DISC1 was identified as a candidate gene that correlated with a high degree of schizophrenia, as well as DTNBP1, NRG1, Calcineurin (CaN) and members of the CaN pathway (Yamada *et al.* 2007, Norton *et al.* 2006, Stefansson et al. 2002) and many others. However, post mortem studies generally consist of small sample sizes and confounders such as cause of death, medication history and postmortem delay. This has significant effects on gene expression, making it hard to draw conclusions on causality. Nevertheless, candidate gene studies, performed almost exclusively in animals and cell culture, have provided enormous insight in the pathways of candidate genes and the underlying mechanisms (for references to all known target genes see Heimer 2012, Carter 2012).

Overall, genetic studies have provided insight on possible genes and pathways that are involved in schizophrenia. New methods are still being developed to integrate results from different genetic studies to find common genes and pathways that are linked in the development of schizophrenia (Ayalew *et al.* 2012). However, it remains challenging to determine the causality of the observed changes in relation to the development of the disorder. Research is still very much needed to pinpoint which genes contribute to the disorder and also in which phase of the development. Nonetheless, the development of schizophrenia can only partly be explained by genetics, and understanding the environmental factors that contribute to disease onset is equally important.

1.4 Environmental effects

Throughout the years, a growing number of environmental effects have been pinpointed as possible contributors to schizophrenia development. Some examples are in utero infections, famine, in utero vitamin D deficiency, obstetrical complications (Cannon *et al.* 2002, St Clair *et al.* 2005, Buka *et al.* 2008, McGrath *et al.* 2010), urbanicity, migrant status, social isolation, cannabis use and early-life stress (van Os *et al.* 2010, van Os *et al.* 2003, Scheller-Gilkey *et al.* 2004, Myin-Germeys & van Os 2007, Morgan & Fisher 2007, McGrath et al. 2004, Allardyce *et al.* 2005). However, many controversies exist in these studies and the need for prospective studies is becoming increasingly important (Oh & Petronis 2008). In the next sections of this thesis the focus will be on the stress system and the effect of early-life adverse events.

1.4.1 Adverse Life Events and the role of the stress system

Stressful life events during childhood, like physical or sexual abuse, potentiate the susceptibility to a wide variety of physical and mental disorders, including psychotic disorders (Shevlin *et al.* 2008, Agid *et al.* 1999). There are large individual differences in the impact of stressors, but generally the most stressful experience is uncertainty, lack of information and the inability to predict and control situations perceived as fearful (Dickerson & Kemeny 2004, Jones & Fernyhough 2007). Interestingly, several studies failed to show differences in the severity of adverse life events to which schizophrenia patients and healthy controls are exposed (Devylder *et al.* 2012, Rabkin 1980), but rather suggested that schizophrenic patients may perceive events as being more stressful and fearful than healthy controls. It has therefore been suggested that stressful life events in themselves are not enough to evoke schizophrenia but may contribute to the onset of schizophrenia in combination with an enhanced stress vulnerability. This is called the "*diathesis-stress model*" or "*stress-vulnerability hypothesis of schizophrenia*" (Zubin & Spring 1977). Adverse life events have been linked to relapse (Hirsch *et al.* 1996, Bebbington *et al.* 1996, Norman & Malla 1993) and predict worse outcome in schizophrenia patients (Rosenberg *et al.* 2007, Gil *et al.* 2009).

Besides the psychological reaction, the body also rapidly responds to a stressor by activation of the sympathetic nervous system, which triggers the release of adrenaline from the adrenal medulla. Adrenaline activates the fight-or-flight response and directs the blood flow, and hence the energy expenditure, away from systems that are not needed, such as the gastro-intestinal and reproductive systems, to organs such as the brain and the muscles. This response happens within seconds and is normalized after several minutes. At this time the hypothalamic-pituitary-adrenal (HPA)-axis is activated (Figure 2). The activity of the HPA axis is initiated by signals of limbic brain regions such as the amygdala, hippocampus and prefrontal cortex and by pathways ascending from the brain stem

that regulate the release of corticotrophin releasing hormone (CRH) and vasopressin from the paraventricular nucleus (PVN) of the hypothalamus. CRFand vasopressin trigger the synthesis of pro-opiomelanocortin (POMC) and the release of one of its cleavage products, adrenocorticotropic hormone (ACTH) by the anterior pituitary corticotrophs. ACTH is released in the bloodstream and subsequently triggers the release of the glucocorticoids (GCs) cortisol (man) and corticosterone (rodents) by the adrenal cortex. GCs are agonists of the mineralocorticoid and glucocorticoid receptors (MR and GR) (Reul & de Kloet 1985). GCs feedback via GR on the HPA-axis at the level of the pituitary and the hypothalamus to inhibit the system (De Kloet et al. 1998, Sarabdjitsingh et al. 2010). In addition trans-synaptic inputs to the PVN from higher brain regions in the limbic system, e.g. hippocampus, amygdala and prefrontal cortex, that are themselves under control of MR and GR mediated actions, can modulate HPA axis activity. In a healthy individual this negative feedback loop will result in a rapid normalization of the stress response and corticosterone will reach pre-stress levels within a few hours, depending on the initial height of the corticosterone response (de Kloet *et al.* 2005).

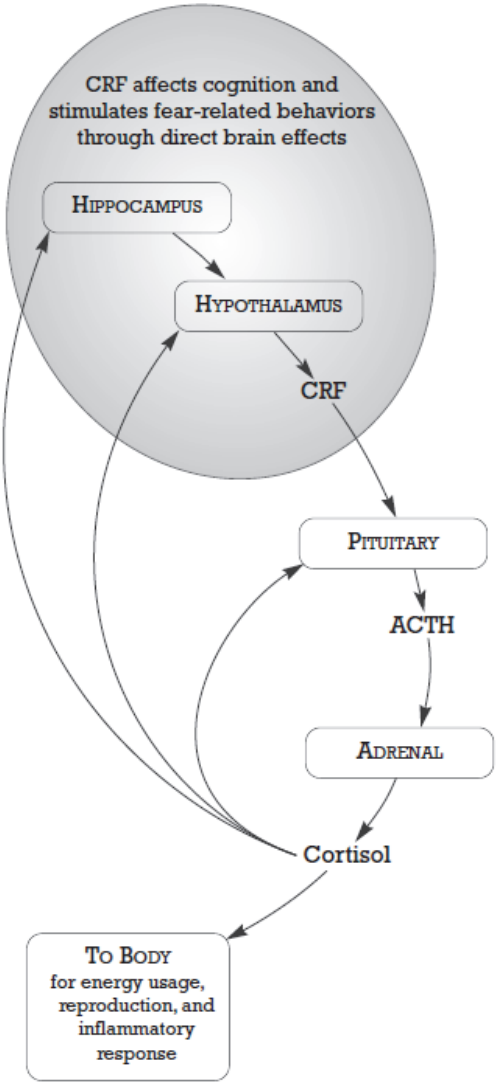

Figure 2 | Graphical representation of the HPA-axis and how cortisol feeds back on the pituitary, hypothalamus and hippocampus (Corcoran *et al.* 2001). Reprinted with persmission.

1.4.2 Glucocorticoid Receptor

The GR is ubiquitously expressed throughout the brain, but occurs most abundantly in the hippocampus, hypothalamus and anterior pituitary corticotrophs (De Kloet *et al.* 1998). The GR belongs to the group of nuclear receptors. Under basal conditions it resides in the cytoplasm, associated with chaperone proteins. Upon binding of GCs, GR dissociates from the chaperones and translocates to the nucleus where it binds to the DNA and initiates transcription of target genes (Datson *et al.* 2001).

Upon binding of the ligand to GR, several other proteins bind to GR such as cyclin-dependent kinase 5 (CDK5). CDK5 phosphorylates GR at serine 211 (220 in mice and 232 in rat (Beck *et al.* 2009)) and thereby attenuates its transcriptional potential (Kino *et al.* 2007, Wang *et al.* 2002). The amount of phosphorylation is correlated to the transcriptional activity induced by the ligand, with the synthetic glucocorticoid dexamethasone (DEX), inducing the strongest effects (Wang et al. 2002). In absence of CDK5 or in the case that GR is mutated, replacing serine 211 with an alanine group, the transcriptional activity of GR is significantly enhanced (Kino et al. 2007). In vivo in rats both acute and chronic stress enhance phosphorylation at the corresponding serine, suggesting that increased CDK5 activity is responsible for the increase in phosphorylation of GR (Adzic *et al.* 2009).

Within several minutes after treatment with a GR agonist, GR proteins dimerize and translocate to the nucleus where the dimers bind to the DNA. GR homodimer bind either directly to the DNA to so-called GR response elements or GREs or are tethered indirectly to the DNA by binding as monomers to other transcription factors such as NFkB or AP1 (Wei *et al.* 1998, King *et al.* 2009), thereby modulating the expression of other sets of genes (Morsink *et al.* 2006). Binding to GREs is generally considered to promote gene transcription, while binding via other transcription factors will indirectly lead to transrepression of genes. Much more information exists regarding factors that can influence GR-regulated gene transcription such as different GR isoforms, GR phosphorylation, the type of agonist binding to the GR and even the exact DNA sequence to which GR binds (Lu & Cidlowski 2005, Meijsing *et al.* 2009, Kino et al. 2007).

1.4.3 HPA-axis, glucocorticoids and psychotic symptoms

In untreated schizophrenic patients baseline HPA-axis activity is enhanced, resulting in elevated cortisol levelscompared to healthy controls (Ryan *et al.* 2004), although some inconsistencies have been observed (Yeap & Thakore 2005). Immediately preceding a psychotic episode, cortisol levels can rise up to 250% on top of the already elevated baseline levels (Sachar *et al.* 1973). In agreement with these results, post mortem studies in schizophrenic patients revealed reduced GR mRNA and protein levels in several brain regions like CA1, CA3 and DG of the hippocampus (Suchecki *et al.* 1995, Webster *et al.* 2002) as well as a decreased volume of the total hippocampus (Wright *et al.* 2000). GR downregulation is hypothesized to be a compensatory mechanism to protect against chronic hypercortisolism. As a consequence of GR downregulation , the HPA-axis becomes less responsive to negative feedback, resulting in prolonged cortisol secretion after exposure to a stressor. Approximately 25% of schizophrenia patients vs 5% of controls show this decreased negative feedback, which also can be demonstrated by a reduced ability of the synthetic glucocorticoid DEX to block the secretion of endogenous cortisol release (Duval *et al.* 2000, Yeragani 1990, Sharma *et al.* 1988).

In line with these findings in schizophrenia, GR blockade with the antagonist mifepristone has been reported to have beneficial effects in the treatment of psychotic depression, in particular in relation to the positive symptoms (Blasey *et al.* 2009, DeBattista *et al.* 2006). Furthermore mifepristone was found to enhance spatial working memory in bipolar patients (Watson *et al.* 2012).

1.5 Glucocorticoids and Dopamine

The stress system is hyperactive in schizophrenia. This has consequences for many neurotransmitter systems in the brain including the dopamine system which is the neurotransmitter system first implicated in the etiology of schizophrenia. How the dopamine system is involved in schizophrenia and how the interaction between dopamine and GCs proceeds will be described below.

1.5.1 Dopamine dysregulation in schizophrenia

Dopamine (DA) is released from dopaminergic neurons residing mainly in two locations, the Substantia Nigra (SN), or A9 and the Ventral Tegmental Area (VTA), or A10. DAergic efferents from the SN project to the striatum in the nigrostriatal pathway. DAergic neurons originating in the VTA project to the Prefrontal Cortex (PFC) via the mesocortical pathway, while VTA neurons projecting to the Nucleus Accumbens (NAc) constitute the mesolimbic pathway (Figure 3). In addition DA is released from a number of other cell groups among which the arcuate/periventricular A12 and A14 DA tubero-infundibular pathway controling pituitary prolactin release is the most prominent.

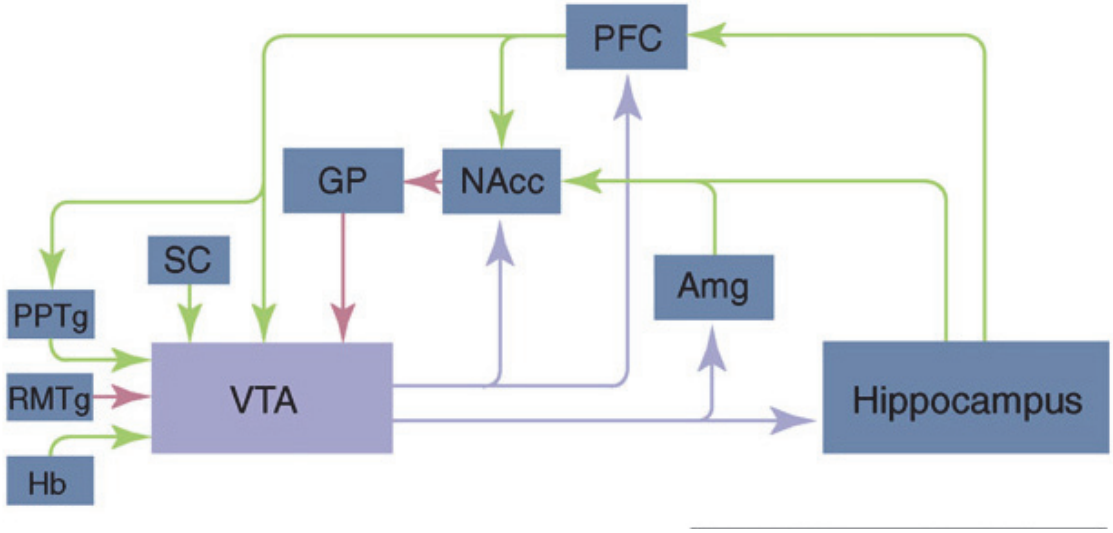

Figure 3 | Schematic representation of neuronal connections to and from the ventral tegmental area (VTA). Purple lines indicate dopaminergic connections to the nucleus accumbens (NAcc), prefrontal cortex (PFC), amygdala and hippocampus. Green represents excitatory glutamatergic connections and red inhibitory GABAergic connections (Shohamy & Adcock 2010). Reprinted with permission.

The first antipsychotic, chlorpromazine, as well as the other classical antipsychotics, were all found to target the Dopamine D_2 receptor (Stone *et al.* 2007). Moreover, clinical efficacy was found to correlate with the ability of antipsychotics to bind to the D_2 receptor (Seeman *et al.* 1975). This observation gave rise to the "*dopamine theory of schizophrenia*". Key components of this theory are that the mesolimbic dopamine pathway is hyperactive while the mesocortical dopamine pathway is hypoactive. The positive and negative symptoms of schizophrenia are attributed to these respective

changes in activity. In agreement with this, *invivo* imaging studies in humans revealed that pre-synaptic dopamine synthesis was significantly enhanced especially in acutely psychotic patients (Hietala *et al.* 1995) showing a marked correlation between positive symptoms and dopamine levels (Hietala *et al.* 1999). Moreover, post-mortem studies showed that D_2-receptors in schizophrenic individuals were significantly more sensitive to dopamine compared to non-schizophrenic persons (Seeman *et al.* 2006).

1.5.2 Interaction between glucocorticoids and dopamine signaling

Since stress and GCs are likely involved in the development of schizophrenia and preceding a psychotic episode GC levels rise, the question can be raised: do GCs influence the DA system?

As a first indication that GCs have an effect on the DA system, in rodents corticosterone was shown to enhance extracellular DA levels in the NAc, resulting in enhanced locomotor activity (LA), which is considered to be a reliable readout to measure dopaminergic effects. Subsequently dividing the animals in high responders (HR) and low responders (LR) to novelty based on their LA response, revealed that only the HR showed enhanced LA upon a corticosterone injection (Piazza *et al.* 1996). This suggests that corticosterone is able to enhance DA output in the HR. Furthermore, HR to novelty showed higher endogenous corticosterone levels, indicating that a hyperactive DA system is correlated with enhanced HPA-axis activity. Moreover, blocking GR with mifepristone (RU486) in amphetamine-sensitized animals (the process of repeated stimulations with amphetamine resulting in an enhanced response to the drug), prior to an amphetamine challenge, completely prevented the behavioral effect, showing that the GR plays an important role in the expression of sensitization (De Vries *et al.* 1996, Deroche *et al.* 1992, Piazza et al. 1991). Finally, both acute and chronic treatment with DEX significantly attenuated amphetamine-induced LA (Wrobel *et al.* 2005). Since DEX poorly enters the brain and is given preceding the amphetamine injection, it likely shuts down the HPA-axis at the level of the pituitary. This results in lower levels of corticosterone that are insufficient to enhance the amphetamine-induced LA, further reinforcing the notion that GCs are required for an enhanced dopaminergic function in the brain.

Many of the above-mentioned studies make use of a well-known animal model of schizophrenia, also known as the "*amphetamine sensitization model*". In the next chapter this model is discussed in more detail.

1.6 Modeling Vulnerability

In an attempt to model the changes in schizophrenia and search for neurobiological underpinnings and treatments, many different animal models have emerged. These models can roughly be divided in 4 different groups; 1. Genetic models, 2. Lesion-induced models, 3. Pharmacological models and 4. Neurodevelopmental models (Jones *et al.* 2011). Despite the wealth of information and new drug targets that have emerged from these models a general weakness of schizophrenia animal models is that features like delusions, hallucinations and poverty of speech cannot be modeled. Therefore most models fitting one of the four above-mentioned categories focus only on some of the symptoms of schizophrenia or on so-called endophenotypes, hereditary changes that underlie the overt symptomatology and are brought about after stimulation of the animal with e.g. a stressor or psychostimulant and/or specific testing (Feifel & Shilling 2010). To model the positive symptoms of schizophrenia the amphetamine model is often used since repeated amphetamine administration inducesdopaminergic changes and behaviors comparable to psychosis (Peleg-Raibstein *et al.* 2008, Featherstone *et al.* 2007, Shilling *et al.* 2006, Tueting *et al.* 2006). This includes enhanced LA and decreased sensorimotor gating, defined as the reduced ability of an individual to filter out irrelevant stimuli (Tenn *et al.* 2003). These endophenotypes are easier to model since their underlying pathophysiology is more comparable to humans.

1.6.1 Amphetamine Sensitization

The most accepted theory for the working mechanism of amphetamine is called the "*weak base"* or "*vesicle depletion model*". This model implies that amphetamine inhibits the dopamine transporter and the vesicular monoamine transporter, thereby increasing the dopamine concentration in the synaptic cleft (Figure 4). Increased dopamine release is found in the shell of the NAc (Gambarana *et al.* 1999) and seems to be the result of so-called dopamine supersensitivitiy (Seeman *et al.* 2005). Enhanced sensitivity to amphetamine is mediated by enhanced expression of a more sensitive isoform of the D2 receptor, also known as the D_2L isoform, in the dorsal striatum. The upregulation of the D_2L isoform was found to be significantly correlated with enhanced sensitivity towards amphetamine (Giordano *et al.* 2006).

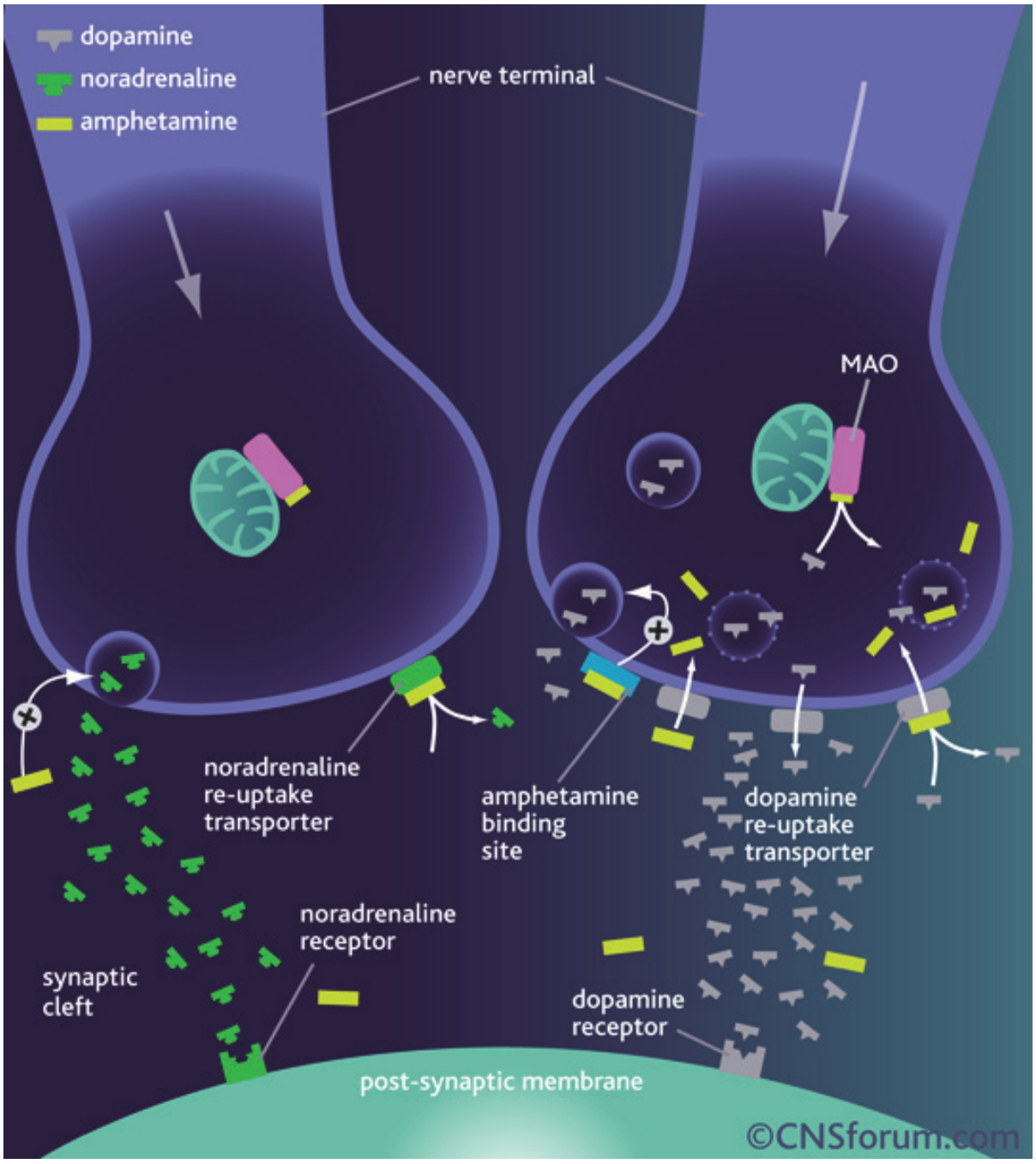

Figure 4 | Working mechanism of amphetamine. For explanation, see chapter 1.6.1. First, amphetamine releases newly synthesized dopamine into the synaptic cleft. Second, it enhances vesicle fusion at the membrane, Third, it blocks reuptake of dopamine and fourth it blocks MAO-mediated breakdown of dopamine. Reprinted with permission.

For an animal to become sensitive to a psychostimulant it has to be treated repeatedly with the drug. Several theories exist on how sensitivity arises, but this goes beyond the scope of this thesis. Generally a sensitization paradigm consists of three stages (Figure 5) (Peleg-Raibstein et al. 2008, Robinson & Becker 1986). First the animal is injected for several days with the psychostimulant, ranging from three times daily to three times a week across a variable time period. This period is called the initiation of sensitization. Despite the fact that different time periods, dosages and times in

between injections are common, they cannot be considered equal. It was shown that a short-term escalating dose regimen of amphetamine resulted in diminished latent inhibition, defined as the ability of a subject to filter out irrelevant information. Long-term, intermittent injections of amphetamine however also resulted in disrupted PPI, the ability of an organism to attenuate a startle response to a stimulus by sensing a (weaker) prestimulus (Peleg-Raibstein et al. 2008, Tenn et al. 2003, Peleg-Raibstein *et al.* 2006). Disrupted PPI is a hallmark of the inability to filter out irrelevant stimuli and is often found in schizophrenic patients as well.

The second stage is the actual sensitization or withdrawal period (Pierce & Kalivas 1997). It has been shown that up to a year or longer after the last psychostimulant injection the sensitivity remains, both in rodents and humans (Vanderschuren *et al.* 1999, Sato *et al.* 1983). The third stage, often several days or weeks after the last injection at the first stage, is called the expression of sensitization and is brought about by a single low dose injection of the psychostimulant. The extent to which the animal reacts to this injection is a measure of its sensitivity to the drug.

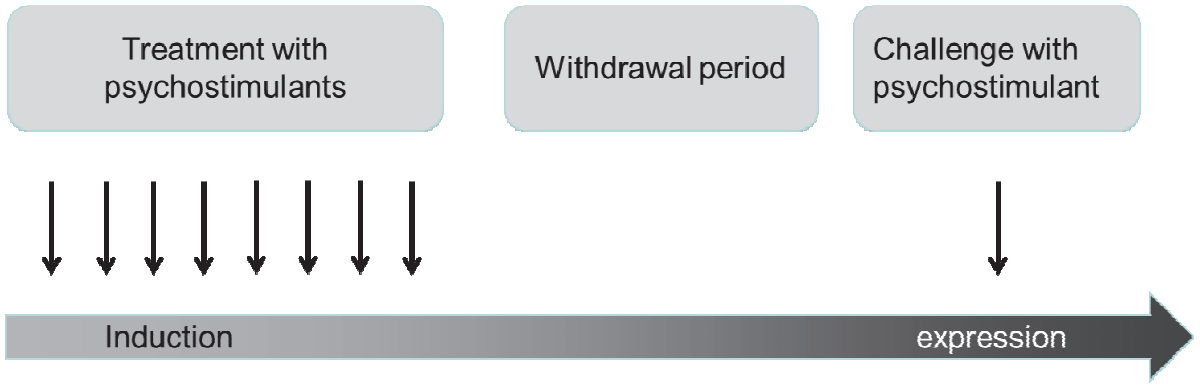

Figure 5| Graphical representation of the sensitization paradigm. In short, an animal is repeatedly injected with a psychostimulant, the induction period. The animal is then withdrawn from psychostimulant treatment during which the animal is building up sensitivity towards the psychostimulant, the withdrawal period. Upon challenging the animal again with the psychostimulant, often with a lower dose compared to the induction period, the animal shows sensitized behavior, the expression of sensitization.

1.6.2 Glucocorticoids and Amphetamine Sensitization

Since stress and GCs can exacerbate dopamine signaling and psychotic symptoms, do they also influence amphetamine sensitivity? As a first indication that GCs are implicated in the sensitization process it was shown that a strong stressor, applied 20 minutes before a cocaine injection, enhanced cocaine-induced locomotor activity as well as the dopamine release in the ventral striatum (Sorg & Kalivas 1991). The effect of cocaine on locomotor activity was attenuated by adrenalectomy (ADX),

which depletes the animals of endogenous GCs. Subsequent replacement with corticosterone pellets reinstated the cocaine-induced locomotor response in a dose-dependent fashion (Marinelli *et al.* 1997), pointing to a key role for GCs in the response to cocaine. Interestingly, in DBA/2J mice it was found that corticosterone alone is not enough to reinstate sensitization since both adrenalin (also released from the adrenals) together with corticosterone were necessary for the locomotor response to cocaine (de Jong *et al.* 2009). This study also revealed an important genetic component in psychostimulant sensitivity since C57Bl/6 mice do not show the same magnitude of sensitization, whether adrenalectomized or not (de Jong *et al.* 2007).

Conversely, it was also observed that amphetamine treatment changes GR mRNA expression in the hippocampus. Acute amphetamine treatment upregulates GR expression while chronic amphetamine downregulates GR expression (Shilling et al. 1996). Another study pinpointed GR mRNA downregulation, after chronic methamphetamine treatment, specifically in the CA1 region of the hippocampus (Kabbaj *et al.* 2003). It was also observed that blocking the GR in the hippocampus flattens the dose-dependent sensitization to cocaine, indicating that the loss of GR expression by chronic amphetamine is a compensatory mechanism for the psychostimulant sensitization (Deroche-Gamonet *et al.* 2003).

Other studies in HR and LR to novelty found higher expression of the GR in the hippocampus of LR rats (Kabbaj *et al.* 2000). Novelty-seeking behavior of the LR rats becomes similar to that of the HR animals when they are treated with a GR antagonist. Conversely, when HR rats are exposed to isolation stress, which is considered more stressful than novelty exposure, they are not different anymore from LR rats. Whether the response to amphetamine also becomes similar in LR and HR was not studied.

1.7 Molecular Basis of Vulnerability

Vulnerability to psychostimulants such as amphetamine has been the subject of many studies and, as explained in chapter 1.5, also has consequences for disorders of the dopaminergic neurotransmitter system. In order to study the molecular basis of vulnerability, animal models have been developed where animals are subjected to regimes of psychostimulant injections. This section briefly describes the most common molecular pathways derived from these studies.

Psychostimulant treatment first leads to cyclic AMP-regulated induction of CREB, a pathway that is also implicated in long-term memory formation (Impey *et al.* 1998). CREB is an activity-regulated transcription factor and binds to cAMP/calcium response element (CRE) sites which in turn lead to the expression of multiple genes. One of the most well-known molecular targets of CREB is delta-FosB (Conversi *et al.* 2008, Levine *et al.* 2005, McClung & Nestler 2003, McClung *et al.* 2004). Delta-FosB poorly responds to a single psychostimulant injection but slowly builds up in concentration after repeated psychostimulant injections as well as after exposure to chronic stress (Perrotti *et al.* 2004). This build-up is partly due to its slow degradation as opposed to other Fos genes such as c-FOS (Ulery *et al.* 2006).

Delta-FosB acts both as a transcriptional repressor by recruiting histone deacetylase 1 (HDAC1) as well as a transcriptional enhancer (Kumar et al. 2005, Renthal et al. 2008). Two important genes that are regulated by delta-FosB are cyclin dependent kinase 5 (CDK5) and p35 (Kumar et al. 2005). CDK5 is a kinase that plays an important role in psychostimulant sensitization since blockade of CDK5 by the inhibitor roscovitine potentiates the behavioral effect of the psychostimulant cocaine (Bibb *et al.* 2001). P35 is known as the activator of CDK5 and the expression of p35 is transiently enhanced by amphetamine (Mlewski *et al.* 2008). CDK5 can phosphorylate GR and myocyte enhancer factor 2 (MEF2), both known to play major roles in psychostimulant sensitization (Pulipparacharuvil *et al.* 2008, Adzic *et al.* 2009, Gregoire *et al.* 2006)

1.8 Myocyte Enhancer Factor 2

MEF2 was first found to enhance transcription of muscle-specific genes and was hence designated as myocyte-specific enhancer factor 2 (Gossett *et al.* 1989). However, subsequent studies revealed that the expression of MEF2 is not specific for muscle tissue, but is also expressed in other cells that are subject to differentiation such as endothelial cells, T-cells and neurons (Potthoff & Olson 2007). Several years after MEF2 was identified, MEF2C was the first of the four MEF2 proteins found to bind to MEF2 specific sites within the cerebral cortex (Leifer *et al.* 1993) and thus the name was changed to myocyte enhancer factor 2. Apart from MEF2B the other three proteins are highly expressed throughout the brain. However, the expression patterns of the different proteins are quite distinct and change throughout development. MEF2D is ubiquitously expressed, as is MEF2A, albeit to a lesser extent than MEF2D. MEF2C is mainly expressed within the amygdala and MEF2B in cerebral cortex. MEF2A, C and D expression is high in hippocampus (Lin *et al.* 1996), while both MEF2A and –D are highly expressed in the striatum (Neely *et al.* 2009).

MEF2 functions as a transcription factor that is preferentially regulated by posttranslational modification. The most studied modification is phosphorylation of serine 408 in MEF2A, which is structurally similar to serine 444 in MEF2D. This serine resides in the transactivation domain and it is therefore not surprising that phosphorylation of this site mainly revolves around its transcriptional activity. Multiple studies showed that MEF2 is inactivated when it is phosphorylated at this site, but that phosphorylated MEF2 is still capable of binding to the DNA (Gregoire *et al.* 2006). It is therefore suggested that MEF2 represses transcription in an active way, by recruiting transcriptional repressors such as HDACs 4, 5, 7 and 9 (Chawla *et al.* 2003, Nebbioso *et al.* 2009).

Functioning of MEF2 has been implicated in neuronal plasticity, formation of dendrites and spines, neuronal survival and behavioral sensitization (Flavell *et al.* 2006, Flavell *et al.* 2008, Pulipparacharuvil *et al.* 2008, Shalizi *et al.* 2006, Tian *et al.* 2010, Gong *et al.* 2003). *In vitro* studies in primary neurons showed that KCl-induced neuronal depolarization significantly enhances the transcriptional activity of MEF2 (Flavell et al. 2006), in correlation with an increase in dendrite formation (Fiore *et al.* 2009). Knockdown of both MEF2A and –D results in a concomitant decrease of dendrites, clearly showing the effect of MEF2 on neuronal plasticity. On top of this, MEF2A and –D knockdown enhances cocaine-induced spine formation in the NAc (Pulipparacharuvil et al. 2008), thereby resulting in a strengthening of existing synapses.

Surprisingly, at a behavioral level MEF2 overexpression in the NAc, which blocks the cocaine-induced increase in dendritic spine density, resulted in an accelerated sensitization to cocaine, while

knockdown had the opposite effect. Although animals reached the same level of behavioral sensitization compared to scrambled shRNA transfected animals, they did so in a significantly slower way (Pulipparacharuvil et al. 2008). This indicates that expression and activity of MEF2 contributes to the process of sensitization and a change in the activity of the protein may lead therefore to differences in psychostimulant vulnerability.

1.9 Scope and outline of the thesis

The pathogenesis of schizophrenia is extremely complex and involves an intricate combination of genetic vulnerability and adverse environmental events. Each gene and event contributes only to a small extent to the overt symptomatology of schizophrenia. The aim of this thesis was to determine the individual vulnerability of inbred DBA/2 mice to amphetamine sensitization, which is considered to be a model for psychosis. For this purpose HR and LR to an amphetamine sensitization paradigm were selected. These extremes in amphetamine sensitization were then used to generate transcriptional profiles in several key brain areas removed by laser dissection technology. Next susceptibility pathways for amphetamine sensitization were identified and examined for interaction with GR. The study was concluded with validation of the novel targets *in vivo* in the amphetamine sensitization paradigm.

1.9.1 Objective

The objective of this thesis was to identify genes and pathways involved in psychosis susceptibility

1.9.2 Specific aims

- To generate transcriptional profiles in several dopaminergic brain areas of genes that are differentially expressed between HR and LR in an amphetamine sensitization paradigm
- To study the effect of GCs mediated by GR on MEF2 function *in vitro* in neuronally differentiated PC-12 cells
- To study the context-dependent effect of the GR on MEF2 function *in vitro* in a model of depolarized neurons.
- To manipulate the activity of MEF2 *in vivo* and to study its effects in the amphetamine sensitization paradigm

1.9.3 Outline

In **chapter 2** transcriptional profiles are presented that were generated in three dopaminergic brain areas from animals that were selected for either a low or high locomotor response to amphetamine. We show that the largest differences in gene expression between HR and LR can be found in the CA1 area of the hippocampus and that target genes of the
transcription factors GR and MEF2 are overrepresented among the differentially expressed genes.
In **chapter 3** we demonstrate that GR and MEF2 signaling pathways converge at multiple levels in the control of their shared target gene c-JUN.
In **chapter4** the cooperation is reported of GR and MEF2 signaling pathways under depolarizing conditions, using the MEF2 target gene NR4A1 as a proof-of-principle.

In **chapter 5** studies are described aimed at measuring the effect in vivo of manipulating MEF2 and GR activity using roscovitine, a potent inhibitor of CDK5, on the behavioral reaction to amphetamine. In **chapter 6** the results are discussed and a model is presented of MEF2 and GR regulation by GCs to explain vulnerability to psychostimulants.

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