THE PREFRONTAL CORTEX AND INFORMATION PROCESSING:

NITRIC OXIDE SIGNALING STUDIED IN AN ANIMAL MODEL OF SCHIZOPHRENIA

Kim Fejgin

2008

UNIVERSITY OF GOTHENBURG

Department of Pharmacology

Institute of Neuroscience and Physiology

The Sahlgrenska Academy at University of Gothenburg

Sweden

Printed by Chalmers Reproservice, Göteborg, Sweden

Cover illustration by Joel Nordenskjöld

ISBN 978-91-628-7658-6

Till min Malin

Contents

ABSTRACT

The prefrontal cortex has been extensively linked to several cognitive domains that are severely compromised in schizophrenia. It has therefore become a key region for studies on the disabling cognitive dysfunction commonly observed in patients with schizophrenia. The absence of effective treatment options for cognitive deficits makes the identification of novel drug targets urgent, and this search is largely dependent on validated animal models. Administration of the NMDA receptor antagonist phencyclidine (PCP) has proven effective in mimicking several features of schizophrenia, including disrupted information processing and aberrant prefrontal cortex function. Previous studies show that a range of cognition-related behavioral deficits induced by PCP in experimental animals, including impaired pre-attentive information processing as measured by prepulse inhibition (PPI), can be blocked by inhibiting the production of nitric oxide (NO). The aim of the present thesis was to study the role of prefrontal NO signaling in the effects of PCP on information processing. Measurements of NO and its main effector, cGMP, were performed using *in vivo* voltammetry and microdialysis. This was combined with PPI and locomotor activity studies following pharmacological modulation of NO and GABA signaling. Systemic administration of PCP to mice disrupted PPI, which was blocked in a dose-dependent manner by inhibiting substrate availability for NO synthase using L-lysine, and by microinjections of an inhibitor of cGMP synthesis into the mouse medial prefrontal cortex. Furthermore, PCP caused an increase in prefrontal cGMP levels that was blocked by the NO synthase inhibitor, L-NAME. Similarly, prefrontal NO release, as measured by a novel microelectrochemical sensor, was increased by PCP, and this increase was blocked by pretreatment with L-NAME in the rat. Finally, systemic pretreatment with a combination of sub-threshold doses of the $GABA_B$ agonist baclofen, and L-NAME, increased PPI *per se*, and prevented the effects of PCP on PPI. On a regional level, prefrontal microinjections with baclofen fully blocked the effects of PCP on PPI in mice, and NO levels in the rat prefrontal cortex were decreased following systemic baclofen administration. In conclusion, the present thesis presents biochemical and behavioral support for the involvement of a prefrontal NO/cGMP signaling pathway in the effects of PCP. Furthermore, this mechanism may partly be explained by a decrease in inhibitory power of GABAergic interneurons, followed by increased NO signaling in the prefrontal cortex. Thus, studies of GABA/NO interactions in the prefrontal cortex may prove valuable when searching for novel treatment targets for cognitive dysfunction in schizophrenia.

Keywords: schizophrenia, nitric oxide, prepulse inhibition, phencyclidine, prefrontal cortex, cGMP, baclofen, cognition

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals;

I. Pålsson E, **Fejgin K**, Wass C, Engel JA, Svensson L, Klamer D (2007). The amino acid L-lysine blocks the disruptive effect of phencyclidine on prepulse inhibition in mice. *Psychopharmacology (Berl) 192(1): 9-15.*

II. **Fejgin K**, Pålsson E, Wass C, Svensson L, Klamer D (2008). Nitric oxide signaling in the medial prefrontal cortex is involved in the biochemical and behavioral effects of phencyclidine. *Neuropsychopharmacology 33(8): 1874-1883.*

III. Pålsson E*, Finnerty N*, **Fejgin K*,** Klamer D, Wass C, Svensson L, Lowry J. Increased cortical nitric oxide release after phencyclidine administration. *Under revision*

IV. **Fejgin K*,** Pålsson E*, Wass C, Finnerty N, Lowry J, Klamer D. Prefrontal $GABA_B$ receptor activation attenuates phencyclidine-induced impairments of prepulse inhibition: Involvement of nitric oxide. *Under revision*

LIST OF ABBREVIATIONS

AMPA	∝- amino-3-hydroxy-5-methyl-4-isoaxole propoionic acid
APO	apomorphine
ASR	acoustic startle response
cAMP	cyclic adenosine monophosphate
CAT	cationic amino acid transporter
cGMP	cyclic guanosine monophosphate
CSF	cerebrospinal fluid
d-AMP	dextro-amphetamine
EDRF	endothelium-derived relaxing factor
EEG	electroencephalogram
eNOS	endothelial nitric oxide synthase
EPS	extrapyramidal symptoms
EPSC	excitatory post-synaptic current
ERP	event-related potential
GABA	γ-Aminobutyric acid
GAD	GABA decarboxylase
GAT	GABA tranposrter
GTP	guanosine triphosphate
i.p.	intraperitoneally
iNOS	inducible nitric oxide synthase
ITA	intertrial activity
L-NAME	NG -nitro-l-arginine methyl ester
mGluR	metabotropic glutamate receptor
mRNA	messenger RNA
nAcc	nucleus accumbens
NMDA	N-methyl-D-aspartic acid
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
ODQ	(1,2,4)oxadiazolo(4,3-a)quinoxalin-1-one
PANSS	positive and negative syndrome scale
PCP	phencyclidine
PFC	prefrontal cortex
PKG	protein kinase G
PnC	pontine reticular nucleus
PPI	prepulse inhibition
PPTg	pedunculopontine nucleus
s.c.	subcutaneously
sGC	soluble guanylyl cyclase
vGlut	vesicular glutamate transporter
WCST	Wisconsin card sorting test

PREFACE

"Men ought to know that from the brain, and from the brain alone, arise our pleasures, joys, laughter and jests, as well as our sorrows, pain, grief, and tears, … "

Hippocrates, 5th century BC

Although the underpinnings of consciousness and personality probably have been a debated topic since the beginning of our civilization, little doubt now exists that the brain is the organ that executes all functions that we consider as human and unique. The urge for separating the body and the soul as different entities is for some people a necessary means to be able to look at the world without a feeling of emptiness and fatality. Nevertheless, to me it is not a problem that my personality is the product of an amazingly complex interaction between different signaling networks that is constantly modulated by my genes, my environment and the present situation I am in. On the contrary, I feel that this is a fascinating situation, where a combination of biological, psychological and epidemiological studies of the brain may lead to novel insights into what really defines an individual.

Not being a clinician, I have limited personal insight into the lives of patients with brain diseases such as schizophrenia, but it is clear that these persons face many challenges. A major obstacle probably lies in coping with the constant bombardment of difficulties arising from their condition, such as problems with hallucinations, delusions, anhedonia and cognitive deficits, all pushing them toward a social and functional isolation in society. Antipsychotic treatment, and to some extent behavioral therapy, have in one way revolutionized the everyday life for many patients, although many also suffer from side effects and/or the treatment resistance commonly observed for negative and cognitive aspects of the disease. Unfortunately, it is obvious that not much progress has been made in the field since the introduction of chlorpromazine, about half a century ago. Although advances in tolerability and safety of antipsychotic drugs have been substantial, the fact that the etiology of schizophrenia is not known, has complicated the search for novel treatment options in both medicine and psychology. However, I am convinced that this lack of knowledge should be viewed as an absence of evidence rather than the evidence of an absence.

Many would consider the phenomenological nature of the diagnosis a core problem, but no one would deny that we have to make progress regardless of this limitation. Schizophrenia has to be studied at different levels, using different approaches, in different disciplines. The challenge that lies ahead is to integrate this research, come to new conclusions, and find common grounds for advances. Although the present thesis is based on purely preclinical work in animal models, the past 4 years have been very enjoyable much due to the mix of disciplines involved in schizophrenia research. It has allowed me to be a reductionist in one situation, and almost philosophical at other times. For this I am very grateful.

Göteborg, November 2008

INTRODUCTION

Schizophrenia

Background

Schizophrenia is a disabling brain disorder (or cluster of disorders) that debutes in early adulthood and severely affects the lives of the affected individuals. It was first called *dementia praecox* ("early dementia") by Emil Kraepelin, who defined it as a disease of the brain that was separated from affective disorders (Kraepelin, 1907). About a decade later, Eugen Bleuler coined the term schizophrenia (originating from the Greek words *schizein* "to split" and *phren* "mind"), giving special emphasis to the alteration of thinking and the relation to the external world (Ban, 2004).

The prognosis of schizophrenia is generally poor, with approximately two thirds of the affected individuals suffering throughout their lifetime (Saha *et al*, 2005). This chronic and relapsing disease has a similar incidence across continents (Saha *et al*, 2006; Sartorius *et al*, 1986) but a slightly higher incidence has been associated with urban living (Kirkbride *et al*, 2006; Lewis *et al*, 1992), migration (Fearon *et al*, 2006), and lower social-economic class. Currently, the lifetime risk of developing schizophrenia is estimated to 0.7% (McGrath *et al*, 2008). Interestingly, schizophrenia is more common in males (Aleman *et al*, 2003; McGrath *et al*, 2008), who tend to have both an earlier age of onset (Seeman, 1982) and a slightly poorer outcome (Loebel *et al*, 1992).

The concordance of schizophrenia in monozygotic twins has been estimated to roughly 50% in comparison to 20% in dizygotic twins. This translates into a strong heritability of schizophrenia, reaching a value of approximately 80% (Sullivan *et al*, 2003; Tsuang, 2000). Although this points to an important genetic predisposition, no strong candidate gene for schizophrenia has been identified, but rather a number of genes that all contribute to a smaller extent (for review see Harrison and Weinberger, 2005). This indicates that schizophrenia has a complex polygenetic background in which environmental factors also play an important role.

Symptomatology

Schizophrenia is diagnosed in a phenomenological manner, using either the "Diagnostic and Statistical Manual, Fourth Edition" (DSM-IV) (APA, 1994) or the "Tenth Revision of the International Classification of Diseases (ICD-10) (WHO, 1992). These diagnostic manuals have high inter-reliability (Peralta and Cuesta, 2003), and use a similar approach to sub-divide schizophrenia symptomatology, with the major difference that DSM-IV requires a duration of illness of 6 months (vs. 1 month for ICD-10) and social or occupational dysfunction (not required in ICD-10).

Three broad classes of symptoms characterize schizophrenia; positive symptoms, negative symptoms and cognitive dysfunction (Andreasen, 1995). *Positive (psychotic) symptoms* relate to aberrant behavior that is additional to normal function such as hallucinations, paranoid delusions, and disorganized behavior. These symptoms are commonly the cause for the patient's first encounter with psychiatric care, and typically vary in intensity throughout the duration of the illness. Positive symptoms are very disabling, but are often satisfactorily

alleviated by antipsychotic treatment. *Negative symptoms* are characterized by loss of function such as social withdrawal, anhedonia (lack of pleasure), flattened affect (lack of emotional responses) and alogia (lack of words). These symptoms are pervasive and do not fluctuate over time as much as positive symptoms. *Cognitive dysfunction*, sometimes viewed as a sub-category of negative symptoms, is strongly associated with functional impairment (Green *et al*, 2000) and was already considered a core symptom of schizophrenia by Kraepelin. Cognitive dysfunction is relatively common in schizophrenia (90% of patients show deficits in at least one cognitive domain) and is normally manifested as problems with information processing such as learning and memory, attention, concentration, executive function, and cognitive flexibility (for review see Green, 2007). The cognitive performance of patients with schizophrenia appears to be in the range of 1.5 standard deviations lower than controls (Bilder *et al*, 2000; Saykin *et al*, 1994) and subtle cognitive deficits can be detected already in childhood (Maccabe, 2008). Additionally, improvement in these deficits has been shown to be a better predictor of social and functional outcome than improvement in psychotic symptomatology (Green, 2007). Compared to premorbid functioning, a cognitive decline can be observed at the onset of the disease, but then remains relatively stable over time (Saykin *et al*, 1994). How these deficits are linked to functional outcome is not known, but a putative intermediate link may be an impaired social cognition including deficits in social perception, emotion processing and theory of mind (Brekke *et al*, 2005; Green *et al*, 2005; Penn *et al*, 1997; Sergi *et al*, 2006). Since cognitive dysfunction predicts functional outcome and is only modestly improved (or sometimes compromised) by currently available antipsychotic treatment (Woodward *et al*, 2005), the search for novel treatment targets has become a task of highest priority in schizophrenia research.

A person with schizophrenia can suffer from symptoms belonging to each of the three classes mentioned above simultaneously. This may reflect that these symptoms relate to pathological changes within schizophrenia, rather than distinct sub-classes of the disease (Liddle, 1987). However, the validity of the schizophrenia "construct" is often debated, given the striking heterogeneity in pathophysiological findings, and the amount of interindividual difference that is allowed for in the diagnosis.

Pathophysiology

Despite almost a hundred years of research since Bleuler's introduction of the term schizophrenia, its underlying pathophysiology remains to a large extent unknown. A wide array of possible mechanisms has been suggested throughout this period, including both environmental and genetic factors. Although the formation of a credible "unified theory of schizophrenia" appears very distant at the moment, the findings described below are rather consistent and comprise some of the key pathophysiological findings in schizophrenia research to this date.

Morphological findings

In addition to a general decrease in brain volume and enlarged third and lateral ventricles (Johnstone *et al*, 1976; Nesvag *et al*, 2008; Van Horn and McManus, 1992), a reduction in grey matter volume of subjects with schizophrenia has been demonstrated. These regions include the hippocampus, the thalamus and the prefrontal cortex (Davidson and Heinrichs, 2003; Galderisi *et al*, 2008; Shenton *et al*, 2001; Weiss *et al*, 2005; Wright *et al*, 2000). These findings indicate widespread but subtle morphological changes that are present at

the onset of disease, and may be either causative or a reflection of an aberrant function in certain signaling networks. Schizophrenia is not generally considered to be a degenerative disease, although some evidence from clinical studies suggests that both symptoms and morphological characteristics of the disease worsen over time. For example, aberrant brain morphology appears to be more frequent and of greater magnitude in chronic multi-episode patients than in first-episode patients. It remains to be shown whether such differences occur because chronic patients are more severly affected from the beginning, or if it is a long-term consequence of having the illness. Nevertheless, the limitations of current methodology suggest that it may be premature to conclude that a neurodegenerative process does not contribute to the pathophysiology of schizophrenia (Lieberman, 1999).

Affected Signaling systems in schizophrenia

Several neurotransmitters have been proposed to be involved in the pathophysiology of schizophrenia including the dopaminergic, glutamatergic, GABAergic, nitrinergic, cholinergic and serotonergic signaling systems (for review see Abi-Dargham, 2007; Bernstein *et al*, 2005; Laruelle *et al*, 2003; Lewis and Moghaddam, 2006; Raedler *et al*, 2007). Out of these systems, the first three have been studied most extensively and are generally considered to be involved, at least to some extent, in the pathophysiology of schizophrenia.

Dopamine

The discovery of the first useful pharmacological treatment for schizophrenia, chlorpromazine (Delay *et al*, 1952), revolutionized psychiatry half a century ago. About a decade later the characterization of dopamine in the brain and the role of monoamines (Carlsson, 1959; Carlsson and Lindqvist, 1963; Carlsson *et al*, 1957; Carlsson *et al*, 1958) lay the foundation for the dopamine hypothesis of schizophrenia, which stated hyperactivity of the dopamine system as playing a key role (van Rossum, 1966). This theory gained further support by the finding that there was a strong correlation between the clinically effective dose of any given antipsychotic and its ability to bind to dopamine D_2 receptors (Creese *et al*, 1976; Seeman and Lee, 1975).

The dopamine system

Apart from its fundamental role in motor control and endocrine signaling, dopamine plays an important role for many behavioral functions, including reward and drug abuse, attention, motivation, and different aspects of cognition (Ahlenius *et al*, 1975; Arias-Carrion and Poppel, 2007; Castner and Williams, 2007; Larsson and Engel, 2004). Dopaminergic neurons are distributed in four discrete dopamine systems in the brain named after their origin and terminal region; the mesolimbic, the mesocortical, the nigrostriatal, and the tuberoinfundibular dopamine system. Five sub-classes of G protein-coupled dopamine receptors are currently known and each subtype belongs either to the D_1 family or the D_2 family. The D_1 family (D_1 and the D_5 receptors) activates G_s, thus stimulating the production of cyclic adenosine monophosphate (cAMP) by adenylyl cyclase, whereas the D_2 family (D_2, D_3 and D_4), which activates G_i, inhibits cAMP production (for review see Girault and Greengard, 2004). All of these receptors can be found post-synaptically, although the D_2 and D_3 receptors also are situated pre-synaptically, where they act as autoreceptors and inhibit transmitter release.

Dopamine and schizophrenia

The classical dopamine hypothesis of schizophrenia has undergone several modifications since it was first postulated and currently states that (1) a hyperactive, subcortical dopamine

system (mainly involving D_2 receptors) is primarily responsible for positive symptoms of schizophrenia, whereas (2) the negative symptoms and cognitive dysfunction to a large extent originate from a hypodopaminergic state (resulting in decreased stimulation of D_1 receptors) in cognition-related regions such as the prefrontal cortex (for review see Goldman-Rakic *et al*, 2004; Toda and Abi-Dargham, 2007).

Imaging studies performed in patients with schizophrenia have consistently shown a hyperactive D_2 system in subcortical regions both at rest (Farde *et al*, 1990; Laruelle, 1998; Lindstrom *et al*, 1999; McGowan *et al*, 2004; Meyer-Lindenberg *et al*, 2002; Zakzanis and Hansen, 1998) and following amphetamine administration (Breier *et al*, 1997; Laruelle and Abi-Dargham, 1999), which is well in line with the earlier mentioned findings of the importance of D_2 receptor occupancy for antipsychotic effect. Furthermore, a correlation has been found between the increase in psychotic symptoms and dopamine release following treatment with the indirect dopamine agonist amphetamine in patients with schizophrenia (Abi-Dargham *et al*, 1998). In non-schizophrenic subjects, amphetamine can induce both paranoid psychosis and a sensitization to psychotomimetics in analogy to what has been observed in patients with schizophrenia (Angrist and Gershon, 1970; Yui *et al*, 1999). In addition, a large number of post-mortem studies show an increased density of striatal D_2 receptors (for review see Laruelle, 1998), further emphasizing that this receptor may play a particularly important role in the positive symptoms of schizophrenia.

At the functional level, the role of prefrontal dopamine (acting on D_1 receptors) for cognitive function has been extensively documented in preclinical studies (for review see Goldman-Rakic *et al*, 2004). Indirect evidence for a hypodopaminergic state in the PFC of patients with schizophrenia comes from studies showing a beneficial effect of dopamine agonists on prefrontal activation (Daniel *et al*, 1991; Dolan *et al*, 1995), and the correlation of low CSF levels of the dopamine metabolite homovanillic acid with poor performance on cognitive tasks (Kahn *et al*, 1994; Weinberger *et al*, 1988). Interestingly, a schizophrenia-associated allele (val/val) of the gene coding for the dopamine-degrading enzyme, cathecol-O-methyl-transferase (COMT), appears to predict both performance on PFC-dependent tasks and D_1 receptor occupation. This occurs in both healthy subjects and patients with schizophrenia (Bilder *et al*, 2002; Diaz-Asper *et al*, 2008; Goldberg and Weinberger, 2004; Slifstein *et al*, 2008; Tan *et al*, 2007). Although the evidence for altered D_1 receptor occupancy in schizophrenia is inconclusive (Abi-Dargham *et al*, 2002; Karlsson *et al*, 2002; Okubo *et al*, 1997), these findings suggest that a hypoactive prefrontal dopamine system may have negative effects on cognitive function in patients with schizophrenia.

Glutamate

In the 1950s, phencyclidine (PCP) was developed as a dissociative anesthetic. Interestingly, it was soon found that this non-competitive NMDA receptor antagonist could induce a state in humans that closely resembled schizophrenia, including positive symptoms, negative symptoms and cognitive dysfunction (Javitt and Zukin, 1991; Luby *et al*, 1959; Yesavage and Freman, 1978). PCP possesses abuse liability and has frequently been used as a recreational drug (*e.g.* under the name of "Angel Dust" or "Horse"). Chronic PCP abusers could initially be misdiagnosed with schizophrenia (Morris *et al*, 2005), and schizophrenia patients using PCP experienced an exacerbation of their symptoms (Itil *et al*, 1967). These striking effects of a single compound, acting primarily on the glutamate system, spurred investigations of the role of this transmitter in the pathophysiology of schizophrenia.

The glutamate system

Glutamate is an amino acid that acts as the main excitatory transmitter in the mammalian brain, and is primarily released by pyramidal neurons and astrocytes. The glutamatergic synapse consists of a presynaptic terminal, a postsynaptic spine, and the astrocyte end-foot; all closely connected to form a tightly regulated unit (Araque *et al*, 1999; Coyle *et al*, 2002). Glutamate is synthesized from glutamine that is supplied to the neuron by the astrocytes, and released glutamate can act at both pre- and post-synaptic targets. *Post-synaptic* effects are mediated by three families of ionotropic receptors that allow Na^+ and Ca^{2+} to enter, and K^+ to exit the intracellular compartment: (1) widely distributed AMPA receptors that play a primary role in generating fast excitatory post-synaptic currents (EPSCs); (2) selectively distributed kainate receptors that to a large extent resemble AMPA receptors; (3) widely distributed NMDA receptors that contribute to slow EPSCs and are essential for synaptic plasticity such as long-term potentiation (LTP) but also have been shown to be involved in excitotoxicity (Liu *et al*, 2007). *Pre-synaptic* effects of glutamate are mediated through a class of G protein-coupled receptors called metabotropic glutamate receptors (mGluRs).

The NMDA receptor is a tetramer consisting of two different subunits, NR1 and NR2. NR1 is essential for channel function, contains a glutamate/NMDA recognition site, and has high permeability for Ca^{2+}, Na^+ and K^+, whereas NR2 (A-D) affects pharmacological and biophysical properties of the receptor (Lynch and Guttmann, 2001). A prerequisite for activation of the receptor is a depolarization of the membrane, which removes the Mg^{2+} that blocks the channel at resting potential. This has to co-occur both with the simultaneous binding of glutamate at its recognition site, and glycine / D-Serine at the glycine modulatory site. The NMDA receptor is expressed in all brain regions, but can be found in particularly high densities in the nucleus accumbens, the hippocampus, and the frontal cortex (Monaghan and Cotman, 1985).

The mGluRs are actually situated both pre- and post-synaptically. Eight receptors have been identified in this family, one example being the pre-synaptic mGluR3 receptor that inhibits glutamate release (Xi *et al*, 2002), and the postsynaptic mGluR5, which is coupled to the inositol triphosphate transduction system and modulates NMDA receptors (Nakanishi *et al*, 1998).

Glutamate and schizophrenia

The interest in a dysregulated glutamate signaling as an underlying factor for schizophrenia stems from several observations in patients and healthy volunteers. An initial finding demonstrated decreased levels of glutamate in the CSF of schizophrenic patients (Kim *et al*, 1980), but this could not be replicated in later studies. Later, a PCP-related dissociative anesthetic and non-competitive NMDA receptor antagonist, ketamine, was shown to produce PCP-like behavioral alterations in normal volunteers, particularly negative symptoms and cognitive impairments (Adler *et al*, 1999; Honey *et al*, 2003; Krystal *et al*, 1994; Newcomer *et al*, 1999). In addition to these findings, subjects with schizophrenia appear especially susceptible to ketamine. Thus, challenge with this compound may act on neurocircuitry relevant for schizophrenia and mimic negative symptoms and cognitive dysfunction (Lahti *et al*, 2001).

Further evidence for the involvement of glutamate in the pathophysiology of schizophrenia can be derived from studies on kynurenic acid, an endogenous non-competitive NMDA receptor antagonist at the glycine modulatory site (Kessler *et al*, 1989). Kynurenic acid has

been shown to be elevated both in the CSF (Erhardt *et al*, 2001; Nilsson *et al*, 2005) and in the prefrontal cortex of subjects with schizophrenia (Schwarcz *et al*, 2001). Furthermore, glutamate carboxypeptidase II, the enzyme that converts the endogenous NMDA receptor antagonist N-acetylaspartylglutamate into N-acetylaspartate and glutamate, has been shown to be reduced in the temporal cortex, the prefrontal cortex and the hippocampus of subjects with schizophrenia (Tkachev *et al*, 2007; Tsai *et al*, 1995). A deficit in glutamate metabolism, as evidenced by an increase in glutamine/glutamate ratio, has also been recently demonstrated in patients with schizophrenia (Hashimoto *et al*, 2005).

On the synaptic level, alterations in the expression of glutamate transporters and interacting proteins have been demonstrated in the prefrontal cortex and thalamus of patients with schizophrenia (Bauer *et al*, 2008; Huerta *et al*, 2006). A recent smaller scale tracer study provides the first *in vivo* evidence for reduced NMDA receptor binding in medication-free patients (Pilowsky *et al*, 2006). In addition, several studies point to a relationship between changes in gene and protein expression of glutamate-related genes in various brain regions of patients with schizophrenia, including the subunits of NMDA, AMPA and kainate receptors, D-serine and glycine transporters, PSD-95, neuregulin 1 and the vesicular glutamate transporter 1 (Harrison *et al*, 2003; Harrison *et al*, 2005; Ohnuma *et al*, 2008).

Importantly, recent clinical evidence implicates a key role for the glutamate system in schizophrenia, as glycine agonists and partial agonists have been shown to improve negative symptoms (for review see Javitt, 2008). In addition, the mGluR2/3 agonist LY2140023 has shown comparable efficacy to olanzapine in ameliorating positive and negative symptoms of schizophrenia (Patil *et al*, 2007).

γ-Aminobutyric acid (GABA)

GABAergic interneurons maintain the complex functional balance of the cerebral cortex by regulating synaptic integration, temporal precision and network oscillations. Given the prevalent findings of aberrations in the GABA system in clinical and post-mortem studies of patients with schizophrenia (see below), altered GABA signaling has received much interest as a potential contributing factor in the pathophysiology of this disease.

The GABA system

GABA is the major inhibitory neurotransmitter in the CNS and is released from several types of interneurons displaying different morphological and functional characteristics. It is widely distributed, much like glutamate, and participates in both afferent and efferent pathways in virtually all brain regions. However, GABA is most abundant in telencephalic regions such as the cerebral cortex (Jones, 1987). In the neocortex, these interneurons constitute up to 30% of all neocortical neurons (for review see Markram *et al*, 2004). GABA is synthesized from glutamate (derived from astrocytic glutamine) by glutamate decarboxylase (GAD), and mediates a biphasic response in analogy to many other neurotransmitters. The early (fast) components of this response are mediated by the ionotropic $GABA_A$ and $GABA_C$ receptors (Macdonald and Olsen, 1994), which depolarize the cell membrane due to the inward passage of chloride ions. The later (slower) component of GABA-induced inhibition is dependent on signaling through the G protein-coupled $GABA_B$ receptor. This receptor mediates hyperpolarization of the post-synaptic membrane and also inhibits neurotransmitter release from presynaptic terminals as an auto- or heteroreceptor. In addition to their obvious role in inhibiting other cell types, GABAergic interneurons are involved in several important functions including the regulation of synaptic integration,

the timing and probability of action potential generation, and plasticity in neuronal networks (Huang *et al*, 2005).

GABA and schizophrenia

One of the most consistent findings in post-mortem studies of patients with schizophrenia is the reduction of the 67kD form of the GABA-generating enzyme GAD (GAD_{67}), especially in the dorsolateral PFC and hippocampus (for review see Lewis *et al*, 2005). Additional post-mortem studies have also revealed reductions in cortical GABA levels and in the mRNA expression of the GABA membrane transporter (GAT) in the prefrontal cortex (Volk *et al*, 2001). The majority of the observed changes lie in the concentration of GABA-related proteins such as GAD, GAT, and the calcium-binding protein parvalbumin, although there is a modest reduction in the number of interneurons (Lewis *et al*, 2006). Approximately 25% of all GABAergic interneurons express parvalbumin and can be distinguished from other interneurons by their fast-spiking firing pattern and morphological features (Hashimoto *et al*, 2003; Lewis *et al*, 2005). The consistency and abundance of these findings have been interpreted as a compromised inhibitory function in schizophrenia, which has also been demonstrated using transcranial magnetic stimulation (Daskalakis *et al*, 2002). A possible reflection of this inhibitory deficit can be observed in the axon initial segments of the parvalbumin positive chandelier neurons in the DLPFC of patients with schizophrenia. In this region, $GABA_A$ receptors are upregulated, perhaps in response to deficient GABA release (Lewis *et al*, 2005). Further support for the pathophysiological mechanisms described above comes from a recent study that shows beneficial effects of a novel benzodiazepine-like drug acting on $GABA_A$ receptors. This drug improves behavioral and electrophysiological measures of prefrontal function in patients with schizophrenia (Lewis *et al*, 2008).

Nitric oxide (NO)

The NO system

Early observations suggested the existence of an NMDA-related signaling molecule that could be substituted by exogenous NO and was important for cell-cell communication (Garthwaite, 1985; Garthwaite and Garthwaite, 1987). In parallel, the endothelium-derived relaxing factor (EDRF) that was present in blood vessels was identified as NO (Furchgott, 1999; Ignarro *et al*, 1987; Palmer *et al*, 1987). Since these initial findings, NO has been implicated in a number of physiological functions both peripherally and in the CNS, including learning and memory formation, feeding behavior, sleep, reproduction, smooth muscle relaxation, and sensory function (for review see Garthwaite, 2008).

The intercellular messenger NO is synthesized (Fig 1) from L-arginine by nitric oxide synthase (NOS), following a Calcium/Calmodulin – dependent activation of the enzyme. One route for this activation is the influx of Ca^{2+} following NMDA receptor stimulation by glutamate, but also other co-factors such as molecular oxygen and tetrahydrobiopterin have to be present for NO production. Three isoforms of NOS are currently known; neuronal NOS (NOS I/nNOS), endothelial NOS (NOS II/eNOS), and inducible NOS (NOS III/iNOS) where the two first isoforms are constitutive. *nNOS* is the predominant isoform in the brain showing a wide but uneven distribution much like classical neurotransmitters (Bredt *et al*, 1991; Vincent and Kimura, 1992). *eNOS* is expressed in endothelial cells both peripherally and in the brain. Apart from its dilating effect on blood vessels, eNOS-derived NO also appears to have a signaling function in the brain, since eNOS can be found in microcapillaries where no smooth musculature is present (Garthwaite, 2008). Finally, *iNOS* has been associated

with pathological inflammatory processes and is predominantly found in macrophages such as microglia (Brown, 2007).

NO is an unconventional signaling molecule in the sense that it can be synthesized both pre- and post-synaptically (and also mediate simultaneous signals between these two elements), diffuses freely from its site of production, and has a half-life in the range of seconds. The main receptor of NO signaling is soluble guanylyl cyclase (sGC) (Karatinos *et al*, 1995), which generates cyclic guanosine monophosphate (cGMP) by cleaving guanosine triphosphate (GTP). The effects of NO may also be mediated through other routes such as cAMP formation and protein nitrosylation. The second messenger, cGMP, then mediates the downstream effects of NO primarily by activating protein kinase G (PKG) and downstream phosphorylation/dephosphorylation cascades (Garthwaite, 2008). Although some differences in NOS distribution can be observed between species, the expression of sGC is complementary to that of nNOS (Gotti *et al*, 2005; Southam and Garthwaite, 1993), and the NO/sGC system appears to be comparable between rodents and primates (Pifarre *et al*, 2007).

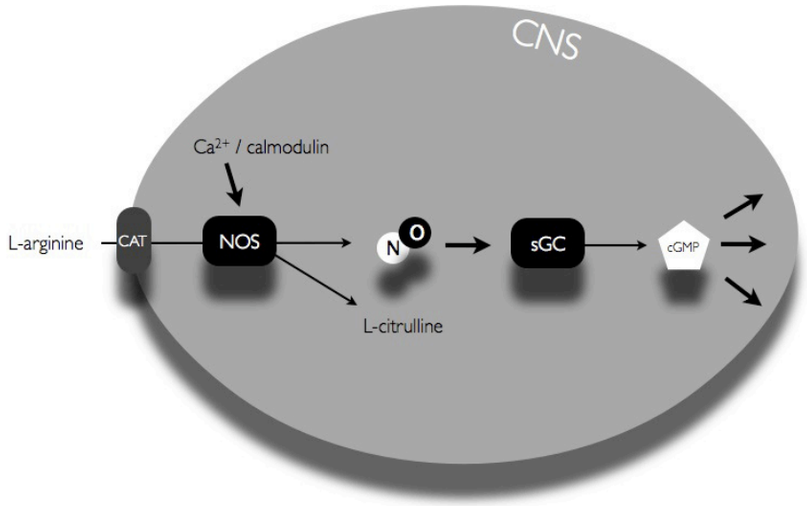

Figure 1. Overview of NO metabolism in the brain. CAT=cationic aminoacid transporter, cGMP=cyclic guanosine monophosphate, NO=nitric oxide, sGC=soluble guanylyl cyclase.

NO has been demonstrated to have effects on storage, uptake and/or release of most neurotransmitters including glutamate, GABA, dopamine and serotonin. Thus, it is well positioned to play an integrative role in brain function and pathology (Bernstein *et al*, 2005; Garthwaite, 2008; Prast and Philippu, 2001).

NO and schizophrenia

Apart from its above-mentioned ability to affect transmitters implicated in the pathophysiology of schizophrenia, metabolites of NO have been shown to be increased and sometimes also decreased in the blood (Das *et al*, 1996; Das *et al*, 1995; Herken *et al*, 2001; Srivastava *et al*, 2001; Suzuki *et al*, 2003; Taneli *et al*, 2004; Yanik *et al*, 2003; Yilmaz *et al*, 2007; Zoroglu *et al*, 2002), and CSF (Lee and Kim, 2008; Ramirez *et al*, 2004; Yao *et al*, 2004) of patients with schizophrenia. Interestingly, polymorphisms in the nNOS gene have been associated with both schizophrenia and PFC dysfunction in schizophrenic patients (Reif *et al*, 2006; Shinkai *et al*, 2002). The influence of aberrant NO signaling for cognitive dysfunction is further advocated by the findings of (1) abnormal distribution of nitrinergic neurons in the frontal and temporal cortex (Akbarian *et al*, 1993a; Akbarian *et al*, 1993b), (2) an increase in

prefrontal nNOS mRNA (Baba *et al*, 2004) and (3) a decrease in prefrontal nNOS activity (Xing *et al*, 2002) in patients with schizophrenia. In line with these findings, single nucleotide polymorphisms in the gene for the nNOS related protein CAPON have been associated with schizophrenia and performance on PFC-dependent cognitive tasks (Brzustowicz *et al*, 2004; Zheng *et al*, 2005).

The above listed clinical findings propose a complex role for NO in schizophrenia, such that both a hyper- and a hypoactive NO system may be of importance, potentially dependent upon brain region, time-course, severity of the disease and antipsychotic treatment. Thus, it remains to be shown whether interference with this signaling system may prove beneficial in the treatment of schizophrenia.

System interactions

Dopamine and glutamate interactions

As dopamine- and glutamate-containing neurons communicate extensively in the brain, it is likely that the above-mentioned deficits in these two transmitter systems (and likely others) are interrelated. A highly influential theory was suggested by Carlsson and colleagues, in which glutamatergic projections from the PFC and/or other areas modulate midbrain dopamine neurons through a direct activating (glutamate) pathway, and an indirect inhibitory (glutamate-GABA) pathway (Carlsson and Carlsson, 1990). A hyperdopaminergic condition is proposed to result from prefrontal NMDA receptor hypofunction, with reduced inhibition of midbrain dopamine neuron firing as a consequence, and may thus precipitate positive symptoms (Kegeles *et al*, 2000). On the other hand, excessive stimulation of D_2 receptors can inhibit the glutamate-mediated information flow at the level of the striatum, thus inducing deficits in an already compromised NMDA signaling system (Laruelle *et al*, 2005). Interestingly, the D_1 receptors, which are the dominant dopamine receptor subtype in the PFC, instead facilitate NMDA transmission (Levine *et al*, 1996). These findings suggest the presence of a complex interaction between dopamine and glutamate signaling.

GABA-glutamate interactions – the concept of disinhibition

The earlier mentioned evidence for dysregulation of both GABA and glutamate signaling in schizophrenia also points to some potentially important interactions between these two signaling systems. An important link may be that NMDA receptors are more important for the excitation of GABAergic interneurons than for the excitation of pyramidal cells, which are known to rely more on AMPA receptors for the generation of excitatory postsynaptic potentials (Grunze *et al*, 1996; Jones and Buhl, 1993; Lei and McBain, 2002). In fact, interneurons are about 10 times more sensitive to NMDA receptor antagonism than pyramidal cells, and inhibition of these cells in turn reduce their inhibitory output (Greene *et al*, 2001; Grunze *et al*, 1996; Olney and Farber, 1995).

In addition to the earlier mentioned compromised function of fast-spiking interneurons in schizophrenia, recent studies show that the NMDA receptor subunit NR2A, which is known to regulate parvalbumin and GAD expression, is decreased in prefrontal interneurons of these patients (Woo *et al*, 2008; Woo *et al*, 2004). Such a profound decrease of inhibitory power should increase pyramidal cell firing, thus creating a *disinhibition*. This theory is supported by both clinical and animal studies showing an increase in cortical activity following NMDA antagonist administration (Breier *et al*, 1997; Gozzi *et al*, 2007; Jackson *et al*, 2004; Lahti *et al*, 1995; Moghaddam *et al*, 1997). In line with this, a recent study shows that NMDA receptor antagonism decreases the activity of fast-spiking interneurons in the PFC,

causing a subsequent disinhibition of pyramidal cells (Homayoun and Moghaddam, 2007). In addition, several preclinical studies demonstrate disruptive effects of NMDA receptor antagonists on cortical interneurons (Abekawa *et al*, 2007; Behrens *et al*, 2007; Cochran *et al*, 2002; Cochran *et al*, 2003; Cunningham *et al*, 2006; Keilhoff *et al*, 2004).

The proposed activation of pyramidal cells may in turn be excitotoxic. Olney and Farber reported swelling and signs of cellular stress following PCP administration (Olney *et al*, 1995; Olney *et al*, 1989), which may be a consequence of disinhibited glutamate signaling. Interestingly, several studies have shown a regional metabolic hyperactivation in the brains of schizophrenic patients (Friston *et al*, 1992; Heckers *et al*, 1998; Malaspina *et al*, 2004) or healthy volunteers receiving NMDA antagonists (Breier *et al*, 1997), possibly reflecting such a disinhibition (see also "the concept of hypofrontality in schizophrenia"). These findings point to a possible interaction whereby glutamate output is increased, possibly to excitotoxic levels, due to a disrupted inhibitory output in the brains of patients with schizophrenia (Lisman *et al*, 2008).

Neurophysiological deficits in schizophrenia

Pre-attentive information processing

Prepulse inhibition

Early clinical observations showed that patients with schizophrenia are unable to filter irrelevant sensory stimuli in an optimal manner (Bleuler, 1911/1950; Kraepelin and Robertson, 1919; Venables, 1964), leading to the theory that these patients suffer from "gating deficits." The prepulse inhibition (PPI) model was developed as a paired-pulse paradigm, assessing pre-attentive information processing (Braff *et al*, 1978). PPI is defined as the phenomenon by which a weak prepulse attenuates the response to a subsequent (30–500 ms later) startling stimulus (Fig 2). The startling stimulus commonly used is acoustic, and the acoustic startle response (ASR) can then be measured. To induce the gating process, acoustic, tactile, and visual (light) prepulse stimuli can be used (Swerdlow *et al*, 2008). PPI was first shown to be reduced in schizophrenic subjects in 1978 (Braff *et al*, 1978), and this finding has then been replicated in a number of studies involving both medicated and drug naive patients (for review see Braff *et al*, 2001; Swerdlow *et al*, 2008).

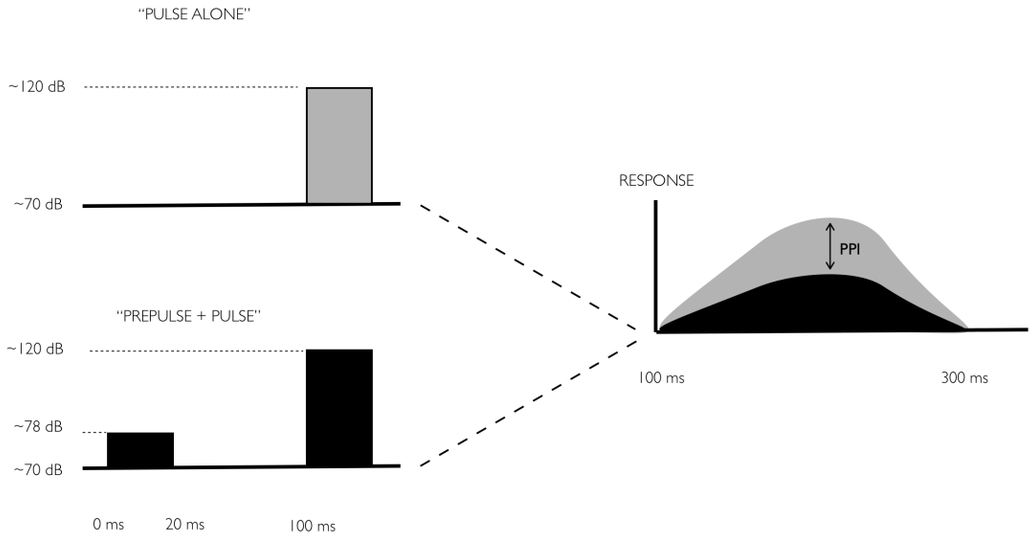

Figure 2. Schematic drawing showing the generation of a normal PPI response in a paradigm for assessing PPI in human subjects, defined as the reduction of reflex response to a strong stimulus ("pulse alone") when preceded by a weaker prestimulus ("prepulse+pulse"). Patients with schizophrenia typically show a larger response to the prepulse+pulse condition (black area) compared to controls, thereby generating a lower PPI.

PPI deficits are not unique to schizophrenia, as they can also be observed in other brain disorders, such as obsessive-compulsive disorder (Swerdlow *et al*, 1993b), Tourette's syndrome, attention deficit hyperactivity disorder (Castellanos *et al*, 1996), and Huntington's disease (Swerdlow *et al*, 1995). This suggests that PPI is a neurophysiological tool for assessing filter mechanisms rather than useful for the diagnosis of schizophrenia. Although longitudinal studies of PPI in schizophrenia are scarce, some correlations between PPI levels and aspects of cognitive function and global functioning have been observed in this patient group (Karper *et al*, 1996; Perry and Braff, 1994; Swerdlow *et al*, 2006a). It was recently demonstrated that PPI levels correlate with the degree of grey matter volume loss in the frontal cortex of patients with schizophrenia (Kumari *et al*, 2008). However, correlations between PPI and positive or negative symptom scores have been harder to obtain. In healthy individuals, positive correlations between PPI and cognitive function, such as working memory, have been demonstrated (Bitsios *et al*, 2006; Csomor *et al*, 2008).

Antipsychotic treatment, particularly with atypical antipsychotics such as olanzapine, has been reported to increase PPI both in schizophrenic subjects and healthy but "low gating" controls (Swerdlow *et al*, 2006b; Vollenweider *et al*, 2006; Wynn *et al*, 2007). However, a recent study on drug-naïve patients with schizophrenia did not show an improvement in PPI after appropriate antipsychotic treatment, suggesting that PPI rather may constitute a stable vulnerability indicator (Mackeprang *et al*, 2002).

The prevalence of PPI deficits in many brain disorders, and the fact that unaffected siblings of patients with schizophrenia display decreased PPI (Kumari *et al*, 2005), suggests that PPI deficits represent a "trait" rather than a "state" marker of a disrupted gating mechanism. Nevertheless, given the high test-retest reliability in both healthy volunteers and subjects with schizophrenia (Abel *et al*, 1998; Geyer *et al*, 2001), as well as the presence of this reflex in all mammals, PPI measurements constitute a robust, translational experimental tool for investigating genetic and biological factors underlying information processing deficits in schizophrenia.

The PPI circuit

The primary ASR response (Fig 3) is present in all mammals and some additional species. It has a relatively short latency of approximately 10 ms (from tone onset to muscular contraction), indicating that the underlying circuit consists of a limited number of synaptic connections (Ison *et al*, 1973; Koch, 1999). As revealed by a combination of anatomical and functional studies, the auditory input from the cochlear nerve reaches the cochlear nucleus complex (Coch), which is forwarded to the caudal pontine reticular nucleus (PnC), and relayed to spinal interneurons and lower motor neurons (Davis *et al*, 1982; Koch, 1999; Lingenhohl and Friauf, 1994). The response is proportional both to stimulus intensity and interval, and can be modified in both a positive and negative direction by these and other factors (Koch, 1999).

Two important processes emerging from the modulation of the ASR response are habituation, which is defined as a decreased response due to repeated stimulus presentation (Pilz and Schnitzler, 1996), and PPI. The latter process potently inhibits the primary startle circuit by output from the pedunculopontine nucleus (PPTg) that mediates PPI through its impact on the PnC. This *mediatory* PPI circuit can then be *modulated* by signals from the cortico-striato-pallido-thalamic system (Fig 3) (Koch, 1999; Swerdlow *et al*, 2001). The fact that PPI remains intact following decerebration in the rat, demonstrates that PPI is mediated at the level of the pons or lower, and thus does not include any part of the forebrain (Davis *et al*, 1982; Fox, 1979).

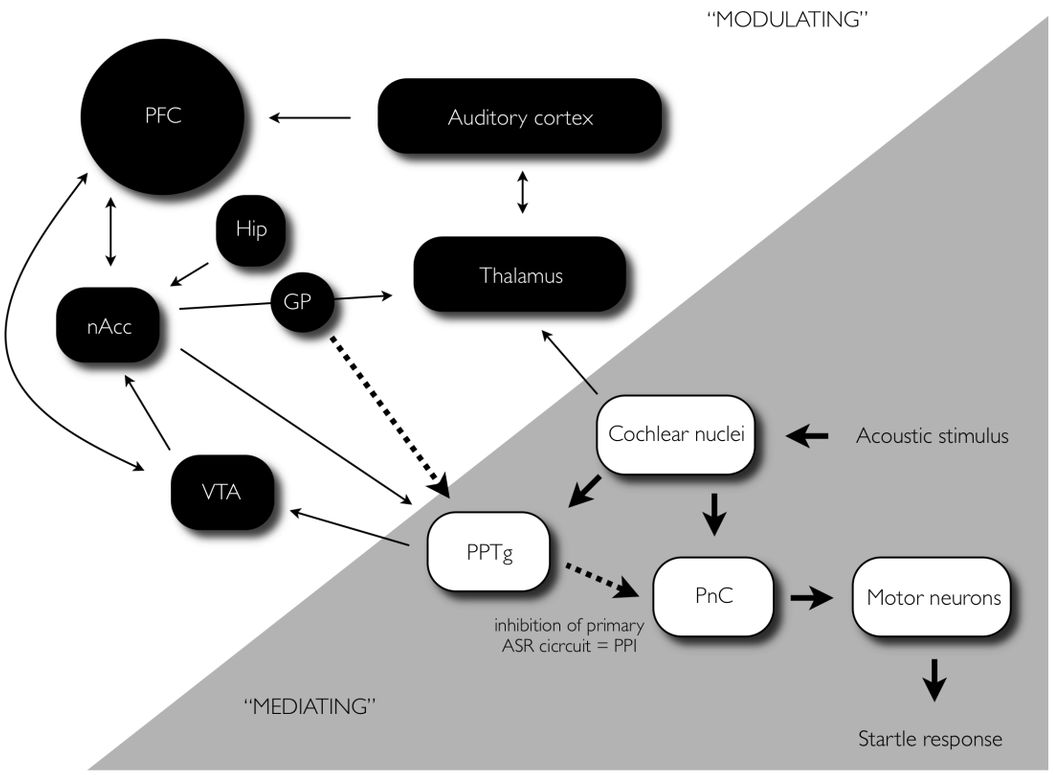

Figure 3. Schematic and simplified overview of the pathways that mediate or modulate PPI of the acoustic startle response. Hip=hippocampus, nAcc=nucleus accumbens, GP=globus pallidus, PFC=prefrontal cortex, PPTg=pedunculopontine nucleus VTA=ventral tegmental area, PnC=caudal pontine reticular nucleus. Bold arrows represent projections responsible for ASR, dashed arrows represent inhibitory projections that are important for, or proximal to the generation of PPI. For the sake of simplicity, additional arrows may indicate both excitatory and inhibitory projections and do not always represent a single synaptic connection (Based on Koch, 1999; Swerdlow *et al*, 2001; Zhang *et al*, 1999).

Modulation of the PPI response

The high test-retest consistency for PPI observed in both healthy volunteers and patients with schizophrenia indicates that PPI does not involve learning processes that change the PPI response after repeated testing. Apart from the potentially beneficial effects of antipsychotics on PPI in schizophrenic subjects (see above), many preclinical studies show beneficial effects of these compounds on disrupted PPI in animal models of schizophrenia. PPI disruption following pharmacological (*e.g.* PCP or d-amphetamine administration), developmental (*e.g.* ventral hippocampus lesions), and genetic (*e.g.* NR1 knock-down) challenge in rodents and primates, can all be blocked or attenuated by pretreatment with clinically used antipsychotics (Bakshi and Geyer, 1995; Fejgin *et al*, 2007; Linn *et al*, 2003; Swerdlow *et al*, 2004). In general, classical antipsychotics only block deficits induced by modulation of the dopaminergic systems, whereas newer antipsychotics are effective against PPI disruptions induced both by dopaminergic and glutamatergic modulation, although several studies challenge this view (Fejgin *et al*, 2007; Geyer *et al*, 2001; Johansson *et al*, 1995; Swerdlow *et al*, 2008).

An extensive body of evidence shows that PPI can be modulated by several brain regions that do not participate in the mediation *per se*, including the nucleus accumbens (nAcc), hippocampus (particularly the ventral portion), the amygdala, and the medial PFC (for review see Swerdlow *et al*, 2008). The latter region has received much attention given its involvement in the cognitive deficits in schizophrenia. The PFC is likely three or four synapses away from the primary startle circuit (Fig 3). It can still potently modulate the PPI response since lesions or dopaminergic blockade of this region decrease basal PPI (Afonso *et al*, 2007; Day-Wilson *et al*, 2006; Shoemaker *et al*, 2005). However, such manipulations are more likely to alter the sensitivity to pharmacologically induced PPI-disruption (de Jong and van den Buuse, 2006; Schneider and Koch, 2005; Schwabe and Koch, 2004).

The similarity of the PPI reflex and the parameters used to assess it across species (Swerdlow and Geyer, 1998) provides an excellent framework for the development and evaluation of hypotheses for compromised information processing in certain brain disorders.

Other measures relating to sensory information processing

A seemingly similar method of estimating the processing of sensory information in schizophrenia uses the suppression of the P50 event related potential (ERP, EEG response 50 ms after stimulus delivery) in response to a click stimulus following the introduction of a click 500 ms earlier (Brenner *et al*, 2004) This filter mechanism is lower or absent in subjects with schizophrenia (Judd *et al*, 1992) and is not consistently modulated by antipsychotic treatment (Adler *et al*, 2004; Arango *et al*, 2003). Despite the apparent similarity to PPI, these two measures do not appear to be correlated when estimated in the same patient population (Brenner *et al*, 2004; Light and Braff, 2001; Schwarzkopf *et al*, 1993), with the exception of one study (Oranje *et al*, 1999). Thus these two paradigms appear to assess separate neural mechanisms, possibly relating to different aspects or stages of information processing (Brenner *et al*, 2004).

Additional neurophysiological deficits

In addition to the altered PPI and P50 gating in schizophrenia, a number of stable neurophysiological deficits have been observed. Although a detailed description of these deficits is not within the scope of the present thesis, a brief overview of the measures frequently used in schizophrenia research may be of value. Abnormalities in *smooth pursuit eye*

movements have consistently been reported in patients with schizophrenia and their relatives (Calkins and Iacono, 2000; Holzman, 2000; Levy *et al*, 1994), and appear to be correlated to primarily negative symptoms. *Mismatch negativity*, a negative ERP (using scalp EEG) that follows introduction of a "deviant" stimulus after series of similar stimuli, is also impaired in schizophrenia (for review see Michie, 2001). This measure is thought to reflect error signaling, and deficits in mismatch negativity correlate to both negative symptoms and social independence (Catts *et al*, 1995; Light and Braff, 2005). Recently, deficits in the communication between local and distributed neural circuits through *gamma-band EEG oscillations* have been shown to be disturbed in schizophrenia (Brenner *et al*, 2003; Gallinat *et al*, 2004; Light *et al*, 2006). These oscillations may play a role in the cognitive dysfunction of schizophrenia as they appear to be of importance for information selection (Salinas and Sejnowski, 2000), selective attention (Fries *et al*, 2001), and working memory (Howard *et al*, 2003). In summary, these measures all appear to be independent physiological deficits that may form valuable endophenotypes when searching for pathophysiological pathways in schizophrenia.

Pharmacological treatment options for schizophrenia

Based on the timing of introduction to the market and pharmacological profiles, antipsychotics are commonly divided into three main categories: first generation, second generation, and third generation. Despite this subdivision, all currently effective antipsychotics inhibit signaling through the dopamine D_2 receptor to varying degrees.

First generation antipsychotics

First generation antipsychotics, also referred to as "typical" include early-developed substances with a strong dopamine D_2 receptor antagonism. Drugs of this class, such as haloperidol or chlorpromazine are effective at reducing positive symptoms in most, but not all patients. D_2 receptor occupancy above 70% in the striatum is usually required for an antipsychotic effect of these substances, but at 80% occupancy, the risk for side effects such as extrapyramidal symptoms (EPS) starts to emerge (Kapur *et al*, 1996; Sedvall *et al*, 1988; Zipursky *et al*, 2005).

Second/Third generation antipsychotics

Clozapine is the prototype drug for the "atypical" or second-generation antipsychotics with some unique properties. It has a higher efficacy than first-generation antipsychotics in treatment-resistant schizophrenia (Kane *et al*, 1988). Furthermore, clozapine is thought to be able to mediate its antipsychotic effect at a D_2 receptor occupancy of only 50% (Farde *et al*, 1994), although this matter is under debate (Seeman and Tallerico, 1998). Clozapine is considered superior to the first generation antipsychotics in that it has some beneficial effects on both negative symptoms and cognitive dysfunction, as well as a low incidence of EPS (Claghorn *et al*, 1987; Galletly *et al*, 2005; Kane *et al*, 1988; McGurk, 1999). In addition to its effects on all types of dopamine receptors, clozapine has high affinity to other receptors such as noradrenergic receptors (α_1 and α_2), serotonergic receptors ($5HT_1$, $5HT_2$, $5HT_7$) and histaminergic receptors (H_1) (Hertel *et al*, 1999; Meltzer and Gudelsky, 1992).

Because of the ability of clozapine to induce the lethal condition of agranulocytosis in some patients, it is prescribed with caution. This side effect has led to the search for safer "clozapine-like" compounds with similar receptor profiles (*e.g.* olanzapine, sertrindole, risperidone, quetiapine). In general, these drugs are well tolerated and do not induce EPS, but may instead cause other side effects such as weight gain, insulin resistance, and sedation.

Recently, a third generation of antipsychotics has emerged, the "dopamine stabilizers," aiming at normalizing dopamine transmission by stabilizing both the hyper- and hypo-dopaminergic state that may be present in schizophrenia. A representative of this class that has reached the market is aripiprazole, a partial D_2 receptor agonist with high affinity and low intrinsic activity underlying its dopamine-stabilizing properties (Burris *et al*, 2002; Tamminga and Carlsson, 2002). In addition, aripiprazole has affinity for serotonergic, adrenergic and histaminergic receptors (Keck and McElroy, 2003). Aripirazole has now been evaluated in a number of controlled trials, and appears to improve positive and some negative symptoms in patients, while avoiding prolactin secretion or EPS to the same extent as first generation antipsychotics (Kane *et al*, 2002). Many dopamine stabilizers, both partial agonists and partial antagonists, are under development, but it remains to be seen whether any of these compounds alleviate negative symptoms and/or cognitive deficits to any larger extent. At the moment, the main asset of dopamine stabilizers appears to be their lower propensity to cause EPS, agranulocytosis, or other severe side effects.

Current limitations

Treatment with atypical antipsychotics has been documented to improve cognitive deficits in schizophrenia to a greater extent than typical antipsychotics in both clinical studies and meta-analyses (Keefe *et al*, 2007a; Keefe *et al*, 2007b). However, the proposed effect of these compounds on cognition is currently debated due to (1) the common lack of control groups which makes it impossible to account for practice effects in cognitive tests; (2) the potential bias of patients switching from cognition-impairing treatment to the test drug; (3) industry sponsorship (Goldberg *et al*, 2007). The notion of practice effects as an important confounder in treatment-studies of cognition in schizophrenia has recently gained support by the CATIE study (Clinical Antipsychotic Trials in Intervention Effectiveness), where no difference in cognitive performance could be observed between first and second generation antipsychotics after 2 months of treatment (Keefe *et al*, 2007a). A similar picture has been observed in a smaller randomized study of atypical compounds (Keefe *et al*, 2007b). Two recent studies (one clinical study and one meta-study) using healthy controls show that neurocognitive improvement in patients with schizophrenia is nearly identical to what is observed in controls (Goldberg *et al*, 2007; Szoke *et al*, 2008). Thus it is very clear that practice-related bias has to be taken into account, both in the evaluation of currently available treatment options and in the development of novel compounds targeting cognitive deficits in schizophrenia.

The prefrontal cortex (PFC)

In the cerebral cortex, the prefrontal regions are considered to organize behavior in relation to time. Thus, this brain region has to integrate sensory and motor information in a way that permits the individual to initiate a behavioral sequence that promotes survival (Uylings *et al*, 2003). Briefly, such a temporal organization is based on initial detection of a reaction-

requiring situation, followed by attention to the specifics of that situation, while recalling past experiences to then plan and execute an appropriate behavioral sequence (Fig 4) (Moghaddam and Homayoun, 2008; Uylings *et al*, 2003). Accordingly, the PFC has been implicated in cognitive functions such as attention, working memory, and executive function (planning and monitoring of behaviors), all demanding a dynamic interaction between several brain regions (Elvevag and Goldberg, 2000; Fuster, 1997; Sawaguchi and Goldman-Rakic, 1994). The PFC is extensively interconnected to the rest of the brain including nearly all cortical and sub-cortical areas. It receives its main input from the basal ganglia, which reaches the PFC through reciprocal connections with thalamic nuclei, particularly the mediodorsal thalamic nucleus (Leonard, 1969; Uylings *et al*, 2003; Uylings and van Eden, 1990). In primates, a common sub-division can be made of the PFC into a dorsolateral, medial (anterior cingulate), and orbital region that are associated with different cognitive functions (Barbas and Blatt, 1995). Interestingly, a similar division has emerged from studies of the rodent PFC, where the major functionally and anatomically defined regions are the medial PFC (similar to primate dorsolateral), the anterior cingulate region, and the orbital frontal cortex (OFC, similar to primate orbital subdivision) (Uylings *et al*, 2003).

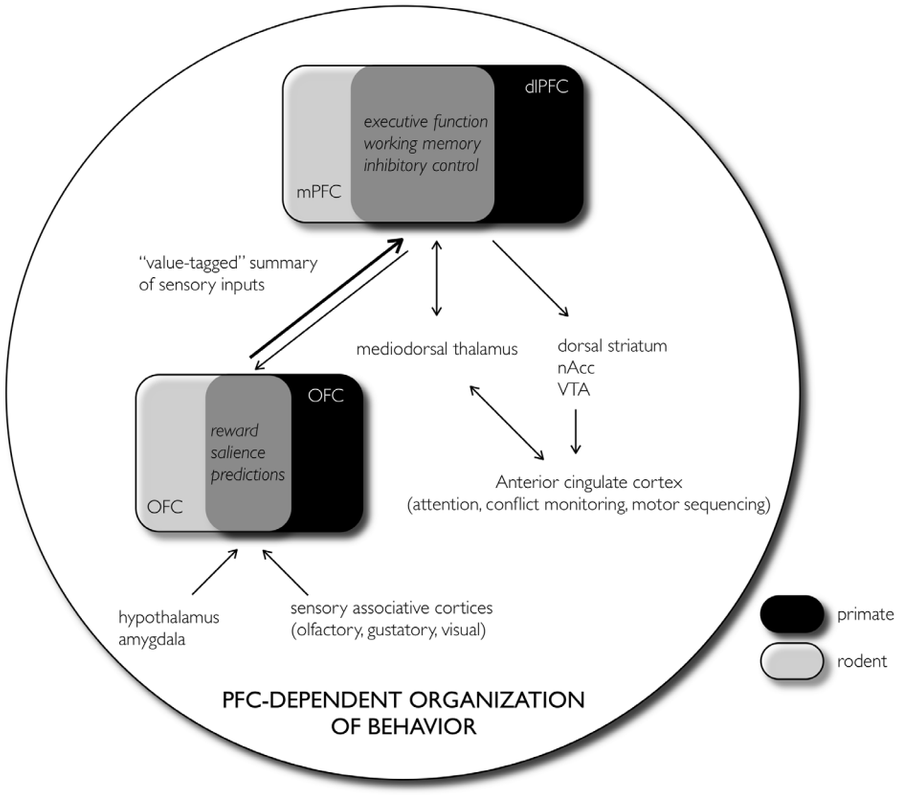

Figure 4. Overview of the PFC and its general sub-divisions and their corresponding function in primates and rodents. dlPFC=dorsolateral PFC, mPFC=medial PFC, nAcc=nucleus accumbens, OFC=orbitofrontal cortex, VTA=ventral tegmental area.

The concept of "hypofrontality" in schizophrenia

Working memory deficits have consistently been demonstrated in patients with schizophrenia (Barch *et al*, 2001; Park and Holzman, 1992) and are relatively resistant to treatment with currently available antipsychotics (Goldberg and Weinberger, 1996). The dorsolateral

PFC (dlPFC) is known to be highly involved in working memory in non-human primates, and has therefore become the focus when studying this cognitive domain in healthy volunteers and schizophrenic patients (Cohen *et al*, 1996; Manoach, 2003). Neuroimaging studies have showed a *hypoactive* dlPFC both under resting conditions (Ingvar and Franzen, 1974; Weinberger *et al*, 1986) and during working memory tasks (Andreasen *et al*, 1992; Barch *et al*, 2001; Menon *et al*, 2001; Weinberger *et al*, 1988). These findings led to the theory of hypofrontality as a characteristic trait of schizophrenia.

Interestingly, recent findings have demonstrated either an equal (Curtis *et al*, 1999; Honey *et al*, 2002; Volz *et al*, 1999) or a *hyperactive* dlPFC during working memory tasks in patients with schizophrenia (Callicott *et al*, 2000; Manoach *et al*, 2000; Manoach *et al*, 1999; Ramsey *et al*, 2002). This apparent paradox can likely be attributed to differences in group averaging, choice of working memory tasks, motivation differences between patients and controls, and medication status (Manoach, 2003). In addition, recent studies suggest that patients with schizophrenia are more heterogeneous than controls in their activation of dlPFC (Manoach *et al*, 2000). Given that the human dlPFC does not have any precise boundaries, differences in anatomical definitions between studies may affect the outcome when averaging the activation during task performance. Furthermore, patients and controls do not appear to differ in dlPFC activation under conditions of matched performance, suggesting that hypofrontality is the likely outcome only when working memory load does exceed the capacity of patients but not controls (Callicott *et al*, 2000; Honey *et al*, 2002; Manoach, 2003; Perlstein *et al*, 2001). At low cognitive load, schizophrenia patients instead need to activate their dlPFC to a greater extent than controls, which can be interpreted as a compromised efficiency (Callicott *et al*, 2003). This "inverted U"-shaped response (Fig 5) may help to explain how both hypo- and hyperactivity can be seen as related rather than discrepant reflections of PFC dysfunction in schizophrenia.

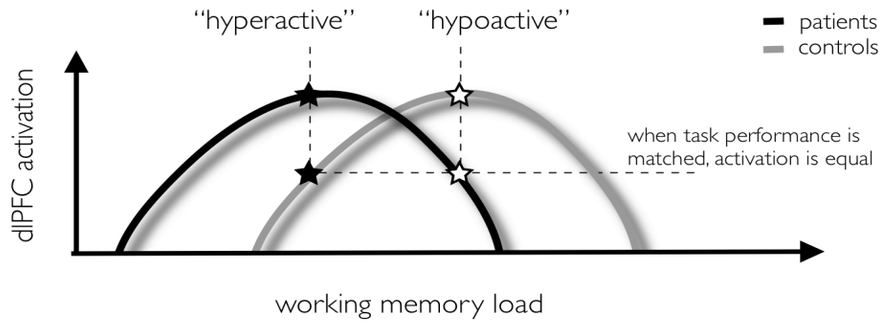

Figure 5. Hypothetical, inverted-U-shaped, relationship showing dlPFC activation in controls and patients with schizophrenia during increasing working memory load. At lower working memory load, patients may show a hyper activation or "ineffiency" whereas a high load (that exceeds the patient's capacity) may render a hypoactivity (Modified from Manoach *et al* 2003 and Callicott *et al* 2003).

Structural and developmental aspects of PFC dysfunction

PFC sub-regions have a later maturation and synaptic pruning period compared to other parts of the brain, which is similar in temporal aspects to the disease development of schizophrenia (Rakic, 2002; Weinberger, 1987). As mentioned earlier, the PFC is also one of the brain regions where grey matter volume is reduced in schizophrenia (see "morphological findings") and several studies map aberrant glutamate, dopamine and GABA signaling to this area (see "affected signaling systems in schizophrenia").

Together, the above-mentioned findings suggest that PFC function is severely compromised in many, but not all, patients with schizophrenia. Studies of this cortical network may elucidate key pathways that may be of interest when aiming to understand the cognitive deficits in this disorder and to find suitable treatment targets.

Animal models of schizophrenia

In the search for pathophysiological mechanisms and new treatment strategies, schizophrenia research relies heavily on animal models to generate novel ideas, form hypotheses and then test them. A major limitation of these studies is of course that schizophrenia is uniquely human, and affects many higher cognitive functions that may not be present in rodents or even non-human primates. It is thus important to clarify that any animal model used in schizophrenia research, can at best mimic one or a few aspects of the disease. Given these obvious shortcomings, it is quite striking how successful the use of animal models in neuropsychiatric research has proven. The development of currently existing antipsychotics, which originated in the seminal discovery of dopamine as a transmitter (Carlsson, 1959), has been heavily based on animal studies.

The relevance of models for schizophrenia is constantly debated, and caution is needed when evaluating their relative validity for this disorder. Willner proposed a classification system of animal models for neuropsychiatric conditions based on different concepts of validity (Willner, 1984). This system states that a given animal model can be mapped on to each of the following dimensions:

1) *Construct validity*; how well the model mimics the underlying neurophysiological basis of the disease.

2) *Face validity*; how similar the measurement endpoints are between the clinical situation and the experimental model.

3) *Predictive validity*; how the sensitivity to pharmacological modulation of the model compares to clinical studies.

By nature, developmental models such as neonatal lesions may have relatively high construct validity, whereas acute pharmacological models have high scores on predictive, and sometimes face validity. Logically, a model cannot rely only upon a pharmacological or developmental insult, but is also dependent on the use of an output measure with some relevance for the disease. Some of the most frequently used animal models of schizophrenia are described below, with a special emphasis on PCP administration combined with PPI studies, as this has been the focus of the present thesis.

Developmental models

Schizophrenia is hypothesized to be the consequence of aberrant neurodevelopment in both cortical and subcortical systems. A number of approaches have been used to induce such deficits with some success, including adult or neonatal lesions (Lipska, 2004; O'Donnell *et al*, 2002; Schwabe *et al*, 2004; Tseng *et al*, 2007), virus inoculation (Engel *et al*, 2000; Pletnikov *et al*, 2002; Shi *et al*, 2003), and social isolation (Geyer *et al*, 1993; Jones *et al*, 1990).

In addition, the search for genetic factors underlying schizophrenia has highlighted many potential genes of interest that have been targeted by developing knock-out or knock-down mice. Several of these genetic models mimic important aspects of schizophrenia, such as reduction in grey matter volume, decreased PPI, deficits in long-term and spatial memory and disturbed social interaction (for review see Carpenter and Koenig 2008). Interestingly, many of these genes are closely linked to the glutamate system, including Neuregulin 1/erB, DISC 1, NR1/NR2 and dysbindin (Boucher *et al*, 2007; Clapcote *et al*, 2007; Kamiya *et al*, 2005; Li and He, 2007; Mohn *et al*, 1999; Murotani *et al*, 2007; Roy *et al*, 2007). In addition, knock-out mice targeting the dopamine transporter (Trinh *et al*, 2003) and the $GABA_A$ receptor (Yee *et al*, 2005) display schizophrenia-like phenotypes.

The recent development of methodologies for creating conditional knock-out mice will probably expand this field further, and allow specific questions to be asked about critical time windows and brain regions involved in the development of schizophrenia (Bannerman *et al*, 2008; Miyakawa *et al*, 2003; Wallén-Mackenzie *et al*, 2008, manuscript).

Pharmacological models

Dopaminergic models

Based on the earlier mentioned connection between disrupted dopamine signaling and preferentially positive symptoms of schizophrenia, direct or indirect dopamine agonists such as apomorphine (APO) and d-amphetamine (d-AMP) have been used to model aspects of schizophrenia. When administered acutely or in a sensitizing regime, these compounds typically induce hyperlocomotion, deficits in PPI (Johansson *et al*, 1995; Mansbach *et al*, 1998; Swerdlow *et al*, 2001), habituation (Davis *et al*, 1975; Klamer *et al*, 2004c), latent inhibition (Ellenbroek *et al*, 1997; Weiner *et al*, 1984), social withdrawal (Sams-Dodd, 1995) and also attentional set-shifting (Featherstone *et al*, 2008). These effects have been used to evaluate novel dopamine-targeting compounds with antipsychotic potential, particularly in PPI studies (for review see Geyer *et al*, 2001; Swerdlow *et al*, 2008). A striking example of the predictive validity of this model is that the ED_{50} of typical and atypical antipsychotics for reversing APO-induced PPI disruption in the rat, correlate with their clinical potency (Swerdlow *et al*, 2008).

Despite the proven disruption of the dopamine system (such as increased sensitivity to d-AMP administration) following neurodevelopmental insults (for review see Lipska, 2004), models based on dopamine disruption do not, in general, mimic the cognitive dysfunction observed in schizophrenia to the same extent as glutamate-based models (for review see Javitt, 2007; Jentsch and Roth, 1999). In addition, dopamine alterations have been suggested to result as a consequence of upstream pathophysiological events, such as alterations in GABA or glutamate signaling. Nevertheless, systemic administration of D_2 receptor agonists, and systemic and prefrontal administration of D_1 receptor antagonists to rats disrupts PPI (Ellenbroek *et al*, 1996; Swerdlow *et al*, 2001; Swerdlow *et al*, 2005), suggesting that dopamine signaling is involved in the regulation of pre-attentive information processing. In addition, prefrontal depletion of dopamine levels decreases PPI, further emphasizing the role of PFC in the modulation of this filter mechanism (Bubser and Koch, 1994). A potential drawback of dopaminergic models is that they tend to be susceptible to false positives (Pouzet *et al*, 2004). They are also very sensitive to dopamine antagonism, thus promoting the development of drugs similar to currently available antipsychotics, which do not alleviate the negative and cognitive aspects of the disease to any greater extent.

Thus, in order to discover novel targets suitable for the treatment of cognitive dysfunction in schizophrenia, additional models are needed.

The PCP model

The schizophrenia-like behavioral effects of PCP in humans, which mimic both positive and negative symptoms as well as the cognitive dysfunction in schizophrenia (see "glutamate and schizophrenia"), have made administration of PCP to research animals widely used to model these aspects of the disease (for review see Jentsch *et al*, 1999; Morris *et al*, 2005).

Pharmacology of PCP

PCP acts primarily as a channel blocker on the NMDA receptor (Anis *et al*, 1983) and has an affinity for this receptor in concentrations consistent with the plasma levels of PCP in chronic abusers (Bailey, 1979; Morris *et al*, 2005). It also inhibits other ion channels including voltage-dependent sodium and potassium channels (ffrench-Mullen and Rogawski, 1989; Vincent *et al*, 1983). In addition, PCP acts as an agonist at serotonergic ($5HT_2$) and dopaminergic (D_2) receptors, and also inhibits both the dopamine and the noradrenaline transporter (Garey and Heath, 1976; Kapur and Seeman, 2002; Pubill *et al*, 1998; Rothman *et al*, 1989; Seeman and Lasaga, 2005). Despite this rich pharmacology, PCP primarily acts on NMDA receptors, as the effects on other receptor systems appear to be less potent (Morris *et al*, 2005).

Relevance to schizophrenia

PCP and other non-competitive NMDA receptor antagonists such as dizocilpine (MK-801) and ketamine, have been shown to induce both behavioral, morphological and biochemical alterations that resemble schizophrenia:

1) Acute, systemic administration of PCP, and its analogues, dose-dependently disrupts PPI in both rodents (Fejgin *et al*, 2007; Klamer *et al*, 2001; Mansbach and Geyer, 1989) and non-human primates (Linn and Javitt, 2001; Linn *et al*, 2003). These deficits are not alleviated to any greater extent by antipsychotic pretreatment, particularly not by typical antipsychotics (Bubenikova *et al*, 2005; Cilia *et al*, 2007; Fejgin *et al*, 2007; Linn *et al*, 2003). This suggests that the PCP model may be used to distinguish between different types of antipsychotic effects, and thus possibly has a potential to detect principally novel treatment targets. In addition to the effects on pre-attentive information processing, acute PCP treatment induces hyperlocomotion and cognitive deficits that affect long-term memory, working memory, social function, non-associative learning (habituation) and selective attention (latent inhibition) (Adams and Moghaddam, 1998; Corbett *et al*, 1995; Klamer *et al*, 2004c; Palsson *et al*, 2005; Sams-Dodd, 1995; Wass *et al*, 2006a; Wass *et al*, 2006b).

2) Repeated administration of PCP (in subchronic or chronic dosing regimes) to rodents and primates does not typically disrupt PPI or affect locomotion but instead targets cognitive functions that rely heavily on PFC integrity such as attentional set-shifting and working memory (Egerton *et al*, 2008; Jentsch *et al*, 1997a; Jentsch *et al*, 1997b; Pratt *et al*, 2008; Rodefer *et al*, 2008). Furthermore, repeated PCP administration causes reduced activity in specific brain regions such as the PFC and hippocampus suggesting that this treatment regime affects neurocircuitry in a different way than acute administration (Cochran *et al*, 2003).

Both of the above mentioned treatment regimes appear to affect the prefrontal cortex in particular, as evidenced by studies based on electrophysiology, immunocytochemistry, microdialysis, and gene/protein expression analyses (Abdul-Monim *et al*, 2007; Adams *et al*, 1998; Anastasio and Johnson, 2008; Cochran *et al*, 2003; Egerton *et al*, 2005; Molteni *et al*, 2008). Interestingly, acute administration of NMDA antagonists to both humans and animals may cause both an increase (Breier *et al*, 1997; Gozzi *et al*, 2007; Jackson *et al*, 2004; Lahti *et al*, 1995; Moghaddam *et al*, 1997) and a decrease (Cochran *et al*, 2003) in cortical activity depending on treatment regime. In general, hyperactivation is seen after acute administration and hypoactivation after repeated treatment, in analogy to the conflicting findings when studying cortical activity of patients with schizophrenia (see "the concept of hypofrontality in schizophrenia"). As mentioned earlier, NMDA antagonists also have profound effects on interneuron integrity and function; thereby further supporting the validity of the PCP model as a useful tool in schizophrenia research (see "GABA-glutamate interactions – the concept of disinhibition"). In summary, the PCP model is able to mimic several aspects of schizophrenia depending on experiment design. Further, this model has recently been shown to have predictive validity for detecting principally novel mechanisms as evidenced by a recent clinical study with the first antipsychotic drug that exclusively targets the glutamate system by agonist activity at the mGluR2/3 (Moghaddam, 2004; Patil *et al*, 2007).

Nitric oxide and PCP

Several studies have shown that the ability of PCP to induce schizophrenia-like behaviors in rodents can be blocked by administering the non-selective NOS inhibitor, NG-nitro-l-arginine methyl ester (L-NAME), or nNOS selective inhibitors. This has been shown for PCP-induced deficits in PPI and hyperlocomotion (Johansson *et al*, 1999; Johansson *et al*, 1997; Klamer *et al*, 2001, 2004b; Klamer *et al*, 2005b; Wiley, 1998), habituation (Klamer *et al*, 2004c) and latent inhibition (Klamer *et al*, 2005c; Palsson *et al*, 2005). Furthermore, PCP-induced deficits in several aspects of spatial memory (as assessed by the Morris watermaze) are also blocked by NOS inhibition. These include learning and memory (Wass *et al*, 2006b), working and reference memory (Wass *et al*, 2006a) and cognitive flexibility (Wass *et al*, 2008b). Interestingly, NOS inhibition does not appear to attenuate deficits induced by d-AMP to the same extent as it ameliorates the effects of PCP (Johansson *et al*, 1998; Klamer *et al*, 2004c). This suggests that the NO system is involved in a broad range of behavioral effects of PCP and that it may constitute a novel treatment target for particularly the cognitive deficits in schizophrenia.

The mechanism by which L-NAME interferes with the effects of PCP remains to be elucidated. However, it is not likely caused by direct interference with the PCP site of the NMDA receptor as evidenced by a recent binding study (Klamer *et al*, 2005d). Further support for the aforementioned role of nNOS in PCP-induced deficits stems from several studies on knockout mice lacking the nNOS gene. These mice are not sensitive to the stimulatory effects of PCP on locomotion or PPI (Bird *et al*, 2001; Klamer *et al*, 2005a; Wiley *et al*, 1999). Other means of interfering with the NO system have also been investigated. Methylene blue, a NOS and guanylyl cyclase inhibitor blocks the effects of PCP on PPI in mice (Klamer *et al*, 2004a) and has a beneficial effect when given as an adjuvant to patients with schizophrenia (Deutsch *et al*, 1997). Tentatively, this adds translational potential to the concept of interference with the NO system as a novel target for treatment of schizophrenia.

In combination with the clinical evidence for NO dysregulation (see "nitric oxide and schizophrenia"), the above listed findings appear very promising. However, they do not reveal much about: (1) how effects downstream or upstream of NO release relate to the effects of PCP; (2) the regionality of these effects, *i.e.* where in the brain these NO-dependent mechanisms are situated; (3) the temporal and qualitative dynamics of NO signaling in different brain regions; (4) if NO signaling interacts with other major transmitter deficits in schizophrenia apart from glutamate. To further understand the putative role of the NO system in schizophrenia, these are key questions that need to be addressed from a preclinical perspective. Obviously, clinical studies using subtle modulation of the NO system would be an indispensable tool to test these hypotheses.

Aim of thesis

The general aim of this thesis was to use the PCP model to investigate the role of prefrontal NO signaling for biochemistry and information processing in schizophrenia.

Specific aims

1. To outline the principal NO-related components participating in the effects of PCP by selectively interfering with the NO pathway, both upstream and downstream of the enzymatic step where NO is generated by NOS.

2. To study the role of prefrontal NO signaling for the behavioral effects of PCP and characterize the temporal and qualitative dynamics of NO release in this brain region in real-time.

3. To investigate the relation between prefrontal NO and GABA signaling in the PCP model.

MATERIALS AND METHODS

Animals

NMRI mice (Charles River, Germany, paper I and II, or B&K Universal, Sweden, paper I, II and IV, 28–40g), Male Wistar rats (UCD, Ireland, paper III, 280–400g), and Sprague-Dawley rats (Taconic, Denmark, paper III and IV, 280–400g) were used in the present thesis. These strains are commonly used in behavioral pharmacology mainly because they are outbred and therefore display a greater interindividual variance, thus being somewhat more representative of a population, than inbred strains. The initial body weights correspond to an age when the animals have passed puberty according to breeders.

Animals were allowed to acclimatize for at least one week prior to surgery or behavioral testing and were housed nine mice per cage or four rats per cage, in a colony room under constant temperature (20±1°C) and humidity (50±5%). After surgery, animals were housed individually in standard plastic cages until the experiments were terminated. The daylight cycle was maintained artificially (lights on from 0600 to 1800 hours) and behavioral experiments and biochemical measurements were conducted during the light phase. Food and water were available ad libitum. All experimental procedures used in the present studies were approved by the National University of Ireland Maynooth Ethics Committee for Animal Experimentation (Paper III) and the Ethics Committee for Animal Experiments, Göteborg, Sweden (Paper I, II, III, IV).

Drugs

All drugs for systemic injections were dissolved in saline (sal, 0.9% NaCl) and administered either intraperitoneally (i.p., in mice) or subcutaneously (s.c., in rats). Mice were always injected a volume of 10 ml/kg and rats 2 ml/kg. For local injections, R-baclofen was dissolved in Ringer's solution and ODQ was dissolved in 100% DMSO and then stored in batches at –20°C and diluted in Ringer's solution on the day of testing, reaching a final DMSO content of 1%. All local injections were bilateral reaching a final volume 0.5 (paper II) or 1.0 µL (paper IV) per side.

Drug	Vendor
Phencyclidine hydrochloride (1-(1-phenylcyclohexyl)piperidine HCl)	Sigma Chemicals, St Louis, MO, USA
L-NAME (NG -nitro-L-arginine methyl ester)	RBI, Natick, USA or Sigma-Aldrich, Germany
L-lysine	Sigma-Aldrich, Germany
ODQ (1H-(1,2,4)oxadiazolo(4,3-a)quinoxalin-1-one)	Sigma-Aldrich, Stockholm, Sweden
R-Baclofen	Sigma-Aldrich, Germany
Isoflurane	Isofluran Baxter, Apoteket AB, Sweden
Carprofen	Rimadyl vet, Apoteket AB, Sweden
Ketoprofen	Romefen, Apoteket AB, Sweden

Table 1. Overview of drugs used in the present thesis.

Surgical procedures

In vivo microdialysis (paper II)

The mice were anesthetized with isoflurane (Isofluran Baxter; Apoteket AB, Sweden), placed in a Kopf stereotaxic instrument (David Kopf Instruments, Tujunga, CA, USA), and kept on a heating pad to prevent hypothermia. The skull was exposed and two holes, one for the dialysis probe (either right or left hemisphere) and one for the anchor screw were drilled. The dura was removed using a sharp needle, and the guide cannulas and the anchor screw were secured with dental cement (Dentalon plus, AgnTho's AB, Lidingö, Sweden). The coordinates used for the medial PFC region relative to the bregma were as follows: anterior +1.8 mm, lateral to midline ±0.8 mm, and ventral –1.6 mm from the brain surface (Franklin and Paxinos, 1996). After surgery, the mice were administered 1.0 ml of saline, s.c., to avoid post-operative dehydration. 10 mg/kg/ml of ketoprofen was administered s.c as a prophylactic analgesic. The mice were then allowed to recover for 2 days before the experiment. They were housed individually in standard plastic cages (Macrolon III; 400 x 250 x 150 mm).

Microinjections (paper II and IV)

As for *in vivo* microdialysis, but two holes for the guide cannulas (stainless steel, length 10 mm, with an o.d./i.d. of 0.6/0.45 mm), and one hole for an anchor screw were drilled. The coordinates used for the medial PFC region relative to the bregma were instead: anterior +1.8 mm, lateral to midline ±0.8 mm, and ventral –1.0 mm from the brain surface (cannula was inserted the additional 0.6mm at the test day). Mice were allowed to recover for 3–4 days prior to behavioral testing.

In vivo voltammetry (paper III and IV)

The rats were anesthetized with isoflurane, placed in a Kopf stereotaxic instrument and kept on a heating pad to prevent hypothermia. An incision was placed down the midline of the skull and the bone was exposed. Four holes for the anchor screws, two holes for the reference (8T Ag wire, 200-µm bare diameter; Advent Research Materials, UK) and auxiliary (8T Ag wire) electrodes and one hole for the sensor electrode was drilled. Electrodes were then implanted following a previously described procedure (Lowry et al, 1997). The coordinates used for the medial PFC relative to bregma were as follows: anterior +3.2 mm, lateral to midline ±0.8 mm, and ventral –4.2 mm (experiment 2, paper III; paper IV) or –5.2 mm (experiment 1, paper III) from the brain surface. The electrode was inserted into the brain and connected to a pedestal that was secured to the anchor screws with dental cement. Sensor placement was balanced between the left and right hemispheres throughout the experiment. During surgery, the rats were administered 2.0 ml of saline (s.c.), to reduce postoperative dehydration and an analgesic (carprofen or buprenorphine) to reduce post-operative pain. The animals were allowed to recover for 2–4 days before commencing experiments. They were housed individually in standard plastic cages.

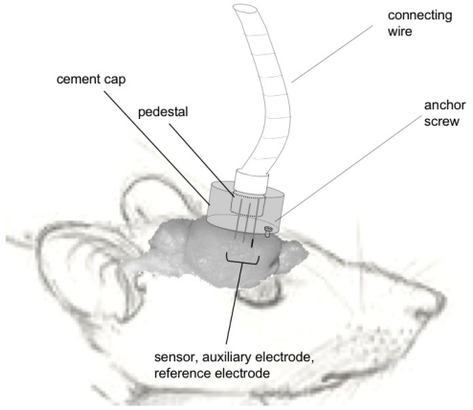

Figure 6. Schematic view of surgical preparation for electrochemical measurements of NO levels by in vivo voltammetry.

Probe and sensor placements

After termination of the local injection and voltammetry experiments the mice and rats were decapitated. The brains were removed and either frozen at –80°C or fixated (Accustain, Sigma-Aldrich, Stockholm, Sweden). Injection or sensor placement (Fig 7) was verified by sectioning the brains using a cryostat or vibratome and an atlas of the mouse or rat brain for reference (Franklin *et al*, 1996; Paxinos and Watson, 2005). Animals with erroneous cannula or sensor placement were excluded from the experiments.

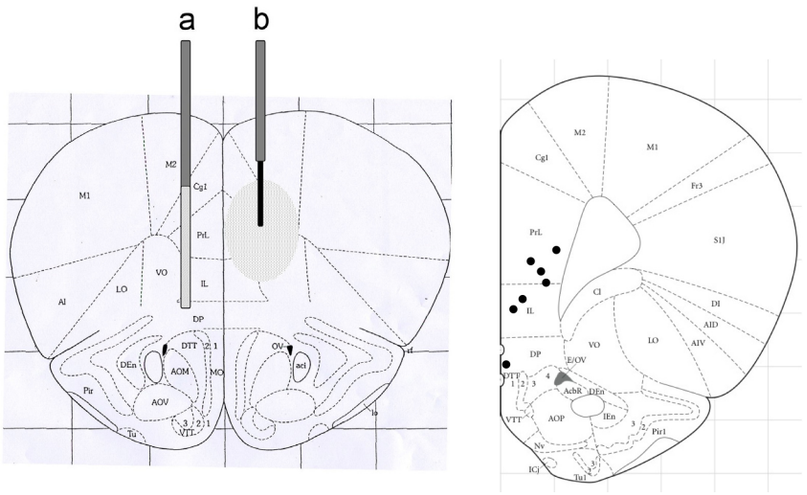

Figure 7. Overview of probe, cannula and sensor placements in the present thesis. Left frame: Approximate location of (a) microdialysis probe and (b)cannula placements in the mouse mPFC (Paper II). Right frame: Actual sensor placements in the rat mPFC in Paper IV (also representative of sensor placements in Paper III).

Prepulse inhibition of the acoustic startle

Apparatus

Paper I and II

Acoustic startle was recorded by a MOPS 2b startle response recording system (Metod och Produkt, Svenska AB, Göteborg, Sweden). The animals were placed in small wire-mesh cages (10 x 5.5 x 5.5 cm) made of stainless steel, which were suspended at one point at the top to a piston in such a way that they could move freely under the piston (Fig 8). A sudden movement of the animal inside the cage caused a displacement of the piston, the acceleration of which was converted to an analogue signal by a moving coil transducer. This signal was sampled and digitized with a 12 bit analogue-to-digital (A/D) resolution by a microcomputer, which also served to control the delivery of acoustic stimuli. Startle amplitude was defined as the maximum signal amplitude (A/D units) that occurred during the first 40 ms after delivery of the startle-eliciting stimulus. Three cages were used simultaneously and each cage was housed in a separate, dimly lit and sound-attenuated cabinet (52 x 42 x 38 cm). The cages were calibrated for equal sensitivity before testing and a mouse tested in one cage was always tested in the same cage at subsequent tests. The acoustic signal consisted of white noise delivered to the animal by two high-frequency loudspeakers built into the ceiling of the cabinet. Each test lasted approximately 24 minutes.

Paper IV

As described for Paper I and II, with the following exceptions: Acoustic startle was recorded using a newly developed MOPS 3 startle response recording system (Metod och Produkt Svenska AB, Sweden). The animals were placed in small plexi-glass cages (10 x 5.5 x 6 cm), the acceleration was registered by a piezo-electric accelerometer and startle amplitude was defined as the maximum signal amplitude occurring 8–30 ms after the startle-eliciting stimulus. Four cages were used simultaneously and each cage was housed in a dimly lit and sound-attenuated cabinet (52 x 42 x 38 cm).

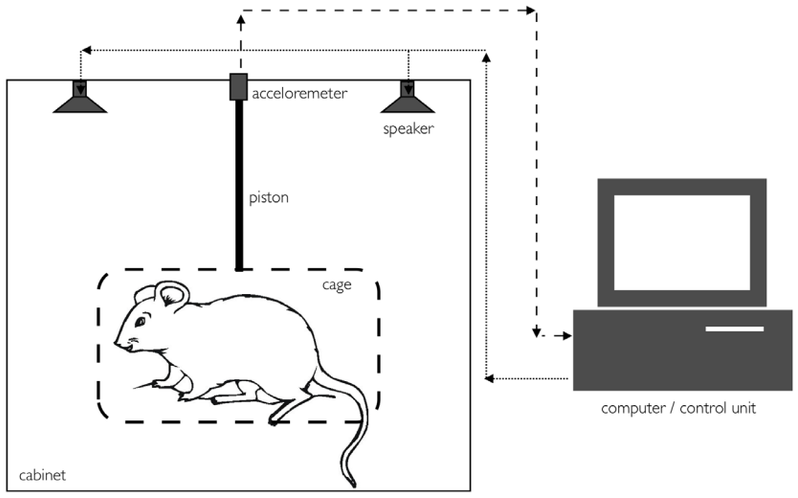

Figure 8. Schematic drawing showing the technical setup for prepulse inhibition experiments.

PPI paradigms

Paper I and II

Each test session started with a 10-min adaptation period containing only white background noise 62 dB(A). The background noise was interrupted at stimulus presentations by a burst of white noise with a rise/decay time of less than 1 ms. Startle pulse intensity was set to 105 dB(A) and prepulse intensity to 70 dB(A). Startle pulse duration was set to 20 ms and prepulse duration to 60 ms. The prepulse was presented immediately before the startle pulse. After the 10-min adaptation period, the animals were presented with a series of five startle pulse-alone trials followed by a series of five prepulse-alone trials. The pulse-alone trials served only to accommodate the animals to the sudden change in stimulus conditions and were omitted from the data analysis and the prepulse-alone trials were analyzed only to ensure that these stimuli did not evoke any startle responses on their own. Thereafter the animals were presented, three times repeatedly, with a series of five prepulse-pulse trials followed by a series of five pulse-alone trials, *i.e.*, a total of 30 trials. The time between trials was always 10 s and the time between any series of trials was 70 s.

Paper IV

Each test session started with an 8-min adaptation period containing only white background noise at 62 dB(A). Startle pulse was set to 105 dB(A) and prepulse intensities to 9, 12 and 15 dB(A) above background. Duration of acoustic stimuli was set to 20 ms for both prepulses and startle pulses and interstimulus interval (ISI) was set to 40 ms. After the adaptation period the animals were subjected to a series of 5 startle pulse-alone trials that were omitted from the analysis since they only served to accommodate the animals to the sudden stimulus onset. The animals were then subjected to a pseudo-randomized combination of 3 prepulse-alone trials for each prepulse intensity, 45 pulse-alone trials and 15 prepulse+pulse trials for each prepulse intensity. Trials were separated by 5–15 s intervals and all these intervals included a measurment of intertrial activity (ITA). This served as a general marker of basal animal activity (not stimulus-evoked) throughout the experiment. The full PPI test lasted approximately 24 min including the adaptation period.

Startle recording system	MOPS 2b	MOPS 3
Startle detection	moving coil transducer	piezo-electric sensor
Adaptation period (min)	10	8
Prepulse type	continous	separated
Prepulse duration (ms)	60	20
Interstimulus interval (ms)	-	40
Prepulse intensity (dB above background)	8	9,12, 15
Program type	block-based	pseudo-randomized
No. of cabinets	3	4
Cage type	wire mesh	plexi-glass

Table 2. Overview of the main differences in startle recording procedures between paper I + II (MOPS 2b) and paper IV (MOPS 3).

Locomotor activity

Apparatus

Locomotor activity of the mice (defined as accumulated number of crossed photocell beams) was recorded using eight box-shaped Plexiglas devices with a floor area of 42 x 42 cm. The activity boxes were housed in dimly lit and sound-attenuated cabinets (420 x 420 x 45 cm). A computer-based system determined the horizontal location of the animal at all times using five times five rows of photocell beams.

Experimental layout

Biochemical measurements

In vivo microdialysis – cGMP immunoassay

The animals were divided into 4 treatment groups: sal+sal; sal+PCP; L-NAME+sal; L-NAME+PCP. They were connected to the microdialysis apparatus via a liquid swivel (FEB-tubing, CMA/Microdialysis AB, Stockholm, Sweden) and were able to move freely during the experiment. The dialysis probes were perfused with Ringer solution, at a constant rate of 1.5 µl/min, for a 60 min habituation period to establish a stable baseline. Thereafter, dialysate samples (135 µl) were collected over two 90 min periods (Vial Plastic 300 ml, CMA/Microdialysis AB, Stockholm, Sweden. Saline (10 ml/kg) or L-NAME (40 mg/kg/10 ml) was administered 80 min after the start of the first of these sampling periods, followed by saline (10 ml/kg) or PCP (5 mg/kg/10 ml) 10 min later. The dialysate samples were stored at –35°C until assayed for cGMP using an enzyme immunoassay.

The cGMP amount was assessed using a commercial enzyme immunoassay kit (CG-201 cGMP Enzyme Immunoassay Kit, Sigma-Aldrich). The acetylated version of the protocol of the manufacturer was followed with a single modification. The standard range was shifted from 100–0.16 pmol, to 20–0.032 pmol. The assay is based on the competition between sample cGMP and a fixed quantity of cGMP, with an alkaline phosphatase molecule covalently bound to it, for a limited number of binding sites on a cGMP-specific antibody. A fixed amount of substrate is then added and after a short incubation period the enzyme reaction is terminated and the intensity of the resulting yellow color is read on a microplate reader at 405 nm. The intensity of the bound color is inversely proportional to the amount of cGMP in either standards or samples. All standards and samples were analyzed in duplicates and the mean readings were used to calculate cGMP content.

Electrochemical measurements of nitric oxide

Prefrontal cortex NO levels were determined using a NO selective amperometric microsensor. The microsensor is a Nafion®-modified Pt disk electrode (patent no. S2007/00774). The sensor design has been validated for *in vitro* and *in vivo* NO sensitivity (Brown *et al*, 2005; Finnerty, 2008) and *in vitro* selectivity against ascorbic acid, uric acid and dopamine (Brown and Lowry, 2003). The NO oxidation current (electrode potential of +0.90 V against a Ag reference electrode) was detected using a low-noise potentiostat (Biostat II, Electrochemical and Medical Systems, UK) and converted using an A/D converter (PowerLab, ADInstruments, United Kingdom). The digital signal was then recorded using Chart software (v5, ADInstruments) running on a PC. Each animal was connected to the *in vivo* voltammetry equipment on the day before an experiment to allow the NO oxidation current to reach a stable baseline. All experiments were carried out with the animal in its home cage.

The current over time (sampling rate 4/s) recorded in Chart was used as data. The mean of an approximately 5 min long sampling period just before drug treatment was used as baseline. The mean current change from baseline was calculated for a 5 min sampling period surrounding the time points of 30, 60 and 90 min after injection.

Behavioral testing

Prepulse inhibition

In most PPI experiments involving systemically administered compounds only (paper II and IV), a balanced cross-over design was used, where each animal received all treatment combinations (veh+sal, pretreatment+sal, veh+PCP and pretreatment+PCP). Each test was separated by a 3–4 day long wash-out period to minimize any potential carry-over effects. PCP was always administered at a dose of 5 mg/kg (i.p.), 15 min prior the onset of the first startle stimulus in the PPI test.

As an exception to the above procedure, animals in paper I (both acute and subchronic experiments) were matched into four homogenous groups according to PPI and startle amplitudes. For the acute experiments each group received one of four possible treatment combinations (veh+sal, L-lysine+sal, veh+PCP and L-lysine+PCP). In the subchronic experiments the mice received an injection with the assigned pretreatment once daily, for four consecutive days. In the morning of the fifth day, all animals were injected with saline and tested for PPI for the first time. Three hours later all groups were administered PCP (5 mg/kg) and tested a second time. The reason for the alternative experimental layout in the acute experiments of paper I was that this specific design removed the potential confound of long-term effects of L-lysine and facilitated comparisons with the subchronic experiment.

In experiments using prefrontal microinjections the animals were matched into four treatment groups with comparable basal PPI and startle reactivity (based on pre-test): veh+sal, pretreatment+sal, veh+PCP and pretreatment+PCP. At the day of the experiment a dummy cannula was inserted and retracted from the cannula guides to reduce the risk of spreading depression. After this, the animals were allowed to rest for 60 min before a first PPI test. The mice then received a bilateral injection of either 0.5 µl ODQ (paper II), 1 µl baclofen (paper IV) or vehicle (Ringer's solution): The local injection lasted 1 min and the cannula was left in place for another 45 s to allow diffusion of the drug. Immediately after the local injection the animals were administered PCP (5 mg/kg) or saline systemically, and 15 min later the second PPI test commenced.

Locomotor activity

The animals (n=30) were divided into 4 treatment groups: veh + sal (n=6); veh + PCP (n=8); ODQ 0.1 mM + sal (n=8); ODQ 0.1 mM + PCP (n=8). After the insertion of a dummy cannula (as described above) to control for spreading depression, the mice were placed in the activity boxes and allowed to habituate for 60 min before injection. The animals were then administered either ODQ (0.1mM) or vehicle in analogy with the PPI experiments and placed in the activity boxes for 10 min before an i.p. injection with either PCP (5 mg/kg) or saline. After this, the mice were placed in the activity boxes and their locomotion, defined as the accumulated number of crossed photocell beams, was recorded for 60 min. The first 30 min of this recording period were excluded from the analysis, to reduce the influence of injection-induced hypermotility and to allow PCP to exert its effect. Verification of cannula placement was performed as described above for the PPI experiments.

Statistical analysis

Statistical analysis was performed using different variants of ANOVA with Bonferroni's post-hoc comparisons where appropriate (see Table 3). Detailed descriptions of statistical procedures can bee viewed in each corresponding paper (see appendix).

Biochemical measurements

In vivo microdialysis – cGMP immunoassay

The consecutive cGMP contents of the dialysis samples were used as data. The cGMP content of the second sample (90–180 min) was divided by the content of the first sample (0–90 min) and multiplied by 100 to obtain the change in cGMP level relative to the baseline.

Electrochemical measurements of nitric oxide

The current over time (sampling rate 4/s) recorded in Chart was used as data. The mean of an approximately 5 min long sampling period just before drug treatment was used as baseline. The mean current change of the sampling period from 15–45 min after each treatment, compared to baseline was calculated from the Chart data (paper III)- Alternatively, the mean current change from baseline was calculated for a 5 min sampling period surrounding the time points of 30, 60 and 90 min after injection (paper IV).

Behavioral testing

Prepulse inhibition

The mean response amplitude for pulse-alone trials (P) was calculated for each mouse and test. This measure was used in the statistical analysis to assess drug-induced changes

in acoustic startle response. The mean response amplitude for prepulse-pulse trials (PP) was also calculated and used to express the percent prepulse inhibition according to the following formula:

Prepulse inhibition (%) = 100 – [(PP/P) * 100]

Using this formula, a 0% value denotes no difference between pulse-alone and prepulse-pulse response amplitudes and consequently no PPI.

Locomotor activity

Locomotor activity was defined as the accumulated number of crossed photocell beams during 60 min. The fist 30 min were omitted from analysis to avoid the potential confound of injection-induced stress and to allow the effects of PCP to fully appear.

Paper	Experiment	ANOVA	Within subjects factor(s)	Between subjects factor(s)	Post-hoc analysis
I	PPI- acute pretreatment	1- WAY	-	treatment	Bonferroni's test
I	PPI- subchronic pretreatment	2-WAY MM	treatment	pretreatment	Bonferroni's test
II	in vivo microdialysis	2-WAY	-	pretreatment treatment	Bonferroni's test
II	PPI - local pretreament	2-WAY	-	pretreatment treatment	Bonferroni's test
II	LMA - local pretreatment	2-WAY RM	-	pretreatment treatment	Bonferroni's test
III	in vivo voltammetry	2-WAY RM	pretreatment treatment	-	Bonferroni's test
IV	in vivo voltammetry	2-WAY RM	treatment time point	-	Bonferroni's test
IV	PPI - systemic pretreatment	3-WAY RM	pretreatment treatment prepulse identity	-	Bonferroni's test
IV	PPI - local pretreatment	3-WAY MM	prepulse intensity	pretreatment treatment	Bonferroni's test

Table 3. Overview of methods used and differences and similarities in statistical approach in paper I – IV. MM=mixed model, RM=repeated measures, LMA=locomotor activity, PPI=prepulse inhibition.

RESULTS AND DISCUSSION

Overview

The present thesis is based on four papers, investigating different parts of the NO pathway in relation to the biochemical and behavioral effects of PCP (Fig 9). Previous studies have investigated the role of NO in the effects of PCP using systemic administration of NOS inhibitors and mice with a genetic deletion of nNOS. In brief, these findings were expanded by: (1) interfering with NO synthesis by reducing substrate availability for NOS; (2) investigating the role of cGMP signaling downstream of NO; (3) real-time measurements of NO release in the medial PFC in response to PCP and the NOS inhibitor, L-NAME; (4) studying the role of $GABA_B$ receptor signaling in NO release and the behavioral effects of PCP.

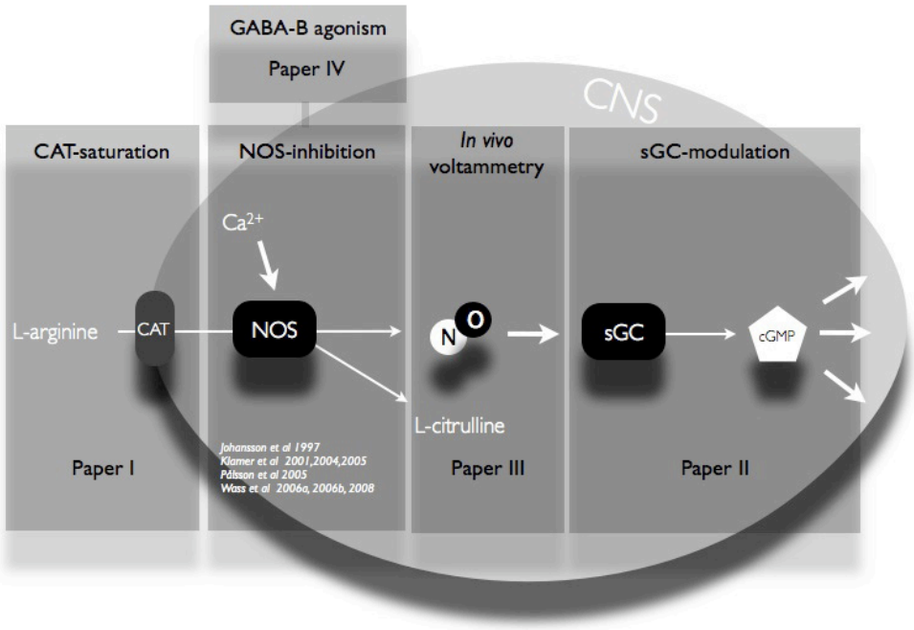

Figure 9. Overview of the NO pathway, indicating the different approaches used to investigate NO signaling in the present thesis. CAT=cationic aminoacid transporter, cGMP=cyclic guanosine monophosphate, NO=nitric oxide, sGC=soluble guanylyl cyclase.

Paper I. The amino acid, L-Lysine, reduces the disruptive effect of phencyclidine on prepulse inhibition in mice.

The substrate for NO production, the semi-essential amino acid L-arginine, is predominantly localized in glial cells and thus needs to be transferred to the neurons to refill neuronal L-arginine pools (Grima *et al*, 1997). Furthermore, L-arginine is not synthesized *de novo* in the brain (Wiesinger, 2001), suggesting that transport across the blood-brain barrier may be a limiting factor for NO synthesis. The transport of L-arginine across membranes is governed by the cationic amino acid transporter (CAT) (White *et al*, 1982), which also is responsible for its passage over the blood-brain barrier (O'Kane *et al*, 2006). The CAT system is used in a parallel and competitive manner by two other cationic amino acids, L-lysine and L-ornithine (White *et al*, 1982). In line with this, L-lysine has been shown to deplete intracellular L-arginine stores (Closs *et al*, 1997) and may thus serve as an indirect regulator of NO synthesis by competing with L-arginine for CAT.

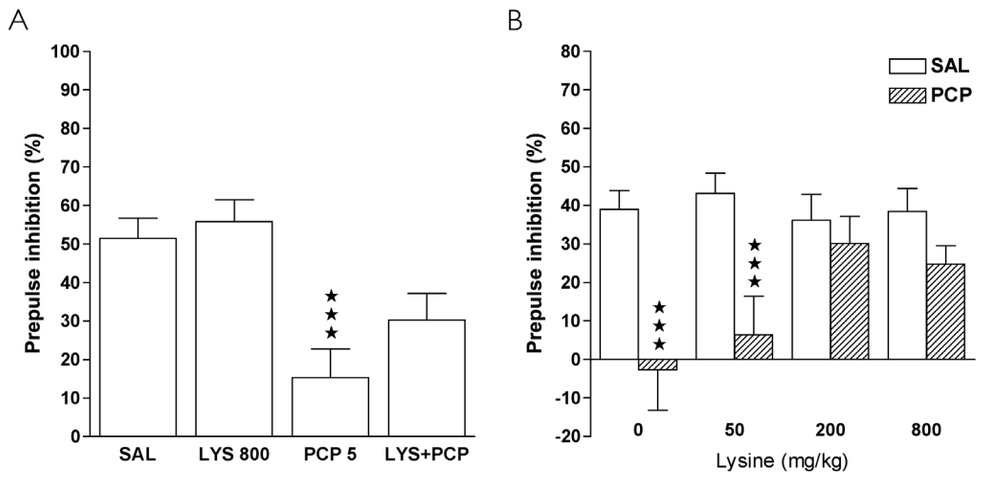

Figure 10. (A) Effects of acute pretreatment with L-lysine (800 mg/kg, i.p.) on PCP-induced (5 mg/kg, i.p.) PPI deficits in mice. (B) Effects of subchronic L-lysine treatment on PCP (5 mg/kg, i.p.) induced PPI deficits in mice. For details see Paper I.

The main finding of Paper I was that systemic pretreatment with the amino acid, L-lysine, blocked the effects of PCP on PPI in a dose-dependent manner. Acute pretreatment with L-lysine partly attenuated the effects of PCP (Fig 10A), whereas subchronic L-lysine blocked the PCP-induced PPI disruption at the two highest doses used (Fig 10B). Given that the depletion of L-arginine is not likely to be a fast process, it is feasible that the subchronic treatment regime was more effective than acute administration of L-lysine in ameliorating the effects of PCP due to more profound depletion of L-arginine. However, the above-mentioned effects could, at least partly, be explained by some other effects of L-lysine than inhibition of the L-arginine-NO pathway. L-arginine is known to play a role in several metabolic pathways coupled to neuromodulation, including the formation of the NMDA receptor antagonist and NOS inhibitor agmatine (Reis and Regunathan, 2000), which recently has been shown to attenuate the effects of PCP on PPI (Palsson *et al*, 2008). Nevertheless, L-lysine has been shown to inhibit both NO release from rat synaptosomes (Lopes *et al*, 1994) and to reduce the NMDA-induced cGMP response in rat brain slices

(Grima *et al*, 1998), lending further support to its dampening effect on NO synthesis. In addition, preliminary data indicates that acute systemic L-lysine administration decreases NO levels in the medial PFC (Fig 11), whereas the opposite can be observed after L-arginine administration (Finnerty, 2008).

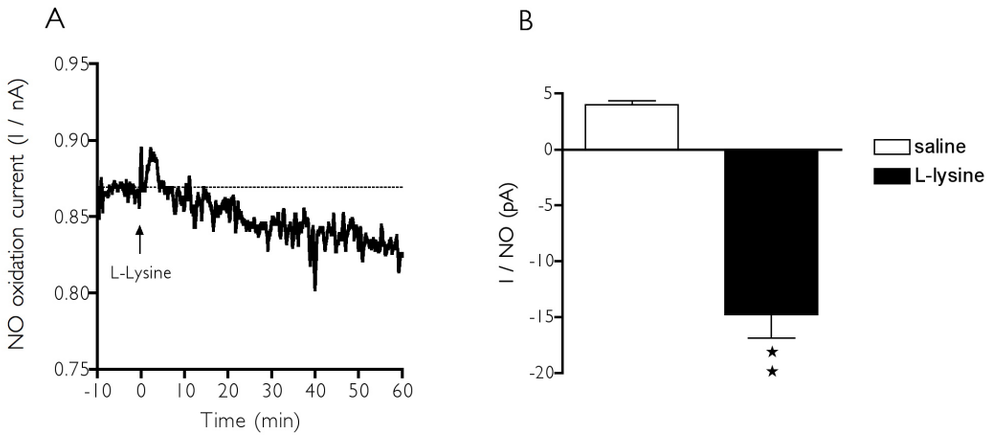

Figure 11. Preliminary data showing the effects of L-lysine on NO levels in the rat medial PFC. (A) Representative voltammogram of NO oxidation current after acute systemic administration of L-lysine (400 mg/kg, i.p.). (B) Average change in NO oxidation current after saline (2 ml/kg, i.p., n=5) and L-lysine (400 mg/kg, i.p., n=3) treatment. Data represented as mean current +/− SEM, ★★= p<0.01, Students t-test (adapted from Finnerty 2008).

Given the involvement of NO in many physiological processes other than neuromodulation, such as regulation of blood-flow and inflammation (for review see Beckman and Koppenol, 1996), direct targeting of NOS involves risks for adverse side effects. Depletion of the substrate for NO synthesis using L-lysine may thus offer a novel strategy for stabilization of NO signaling in the brain. Based on our preclinical findings, we have recently performed a small placebo-controlled pilot study with L-lysine as an add-on treatment to ten patients with schizophrenia. L-lysine, at a dose of 6 g per day for four weeks, was tolerated well and caused a decrease in symptom severity as measured by the Positive and Negative Syndrome Scale (PANSS). Furthermore, L-lysine increased the capacity for problem solving and cognitive flexibility as measured by the Wisconsin Card Sorting Test (WCST), suggesting potential beneficial effects of L-lysine on cognitive dysfunction in patients with schizophrenia (Wass *et al*, 2008a, manuscript). Although these effects may be related to the observed increase in L-lysine plasma levels, they have to be confirmed in a larger, double-blinded study. Nevertheless, this preliminary study points to the translational value of the PCP model in generating novel putative targets for treating cognitive dysfunction in schizophrenia.

Paper II. Nitric oxide signaling in the medial prefrontal cortex is involved in the biochemical and behavioral effects of phencyclidine.

The downstream effects of NO release are primarily mediated by formation of the second messenger, cGMP, catalyzed by sGC. This has been demonstrated in several studies, and is supported by the absence of NO-mediated vascular relaxation following genetic deletion of sGC in mice (Friebe and Koesling, 2003). These "NO receptors" are readily activated by NO without observable delay, suggesting a very efficient and sensitive transduction mechanism. sGC appears to be distributed throughout the CNS of both rodents and humans in a complementary way to nNOS, suggesting a close relationship between these two proteins (Gotti *et al*, 2005; Southam *et al*, 1993). In Paper II, the importance of prefrontal cGMP signaling for the effects of PCP was investigated using the sGC inhibitor, ODQ, by a combination of microdialysis and behavioral experiments.

Prefrontal cGMP release was increased following systemic PCP administration and this increase could be blocked by pretreatment with the NOS inhibitor, L-NAME. Furthermore, prefrontal microinjections with ODQ completely blocked the effects of systemic PCP on PPI (Fig 12), but not the PCP-induced hyperlocomotion. These results indicate that a NO/sGC/cGMP signaling mechanism is present in the medial PFC, which plays an important role in the effects of PCP on cognition-related behavior such as PPI, rather than on behavior more related to mesolimbic dopamine transmission.

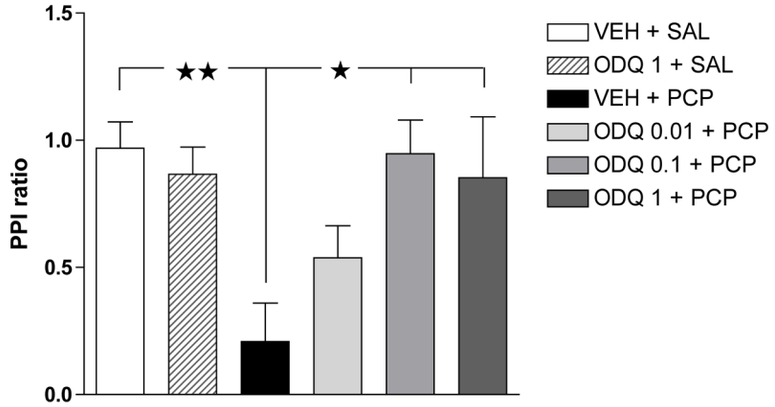

Figure 12. Local pretreatment with ODQ (0.01, 0.1, 1 mM) in the medial PFC of mice blocks PCP-induced disruption of PPI in a dose-dependent manner. PPI ratio = drug treatment PPI / baseline PPI. See Paper II for details.

One of the major limitations of microdialysis experiments, apart from the rather low temporal resolution, is the fact that only molecules present in the extracellular environment can be detected by this technique. Since the second messenger, cGMP, is both produced and has its main targets (*e.g.* PKG) situated intracellularly, it is reasonable to ask what the cGMP levels measured in Paper II reflect. Several studies have demonstrated that intracellular cGMP can be extruded in the extracellular milieu through ATP-dependent efflux pumps, which is thought to serve as a means of terminating intracellular cGMP signaling in addition to the effects of phosphodiesterases (Adachi *et al*, 2002; Jedlitschky *et al*, 2000; Tjornhammar *et al*, 1986). Thus, the extracellular level of cGMP corresponds to intracellular changes and may serve as a measure of endogenous NO formation that can be assessed by microdialysis

(Pepicelli *et al*, 2004; Vincent *et al*, 1998). However, cGMP efflux may also serve an additional signaling role, since extracellularly applied cGMP has been shown to affect ion channels such as the Na^+/H^+ exchanger and the kainate receptor (Poulopoulou and Nowak, 1998; Touyz *et al*, 1997).

The normalization of prefrontal cGMP levels caused by L-NAME, while not affecting basal cGMP levels, is at variance with previous findings. Laitinen and colleagues (1997) could demonstrate a decrease in cGMP levels in the rat frontal cortex following L-NAME administration. This discrepancy is likely explained by the highly efficient degradation of cGMP by phosphodiesterases in this brain region (Pepicelli *et al*, 2004). Actually, to observe effects of L-NAME on cGMP, Laitinen and colleagues had to increase the basal levels of cGMP by the use of the non-specific phospshodiesterase inhibitor, isobutylmethyl xantine (IBMX) (Laitinen *et al*, 1997). An earlier study, that did not use IBMX, could not detect any decrease in frontal cGMP levels (Laitinen *et al*, 1994). Thus, the relatively long sampling period used in Paper II (90 min) was necessary to assess basal cGMP levels in the presence of a high phosphodiesterase activity in the prefrontal cortex.

The strong effect of prefrontal sGC inhibition on the PPI-disruptive effects of PCP can be interpreted as if cGMP plays a major role in mediating the effects of PCP-induced NO release. However, the effects downstream of cGMP are less clear as this second messenger may transduce its effects through several mechanisms in addition to PKG activation (Garthwaite, 2008). For example, cGMP can block the hydrolysis of cyclic adenosine monophosphate (cAMP), thereby increasing the concentration of this second messenger. In line with this, a potential role for cAMP signaling in the effects of PCP was demonstrated in an earlier study, where PCP caused an L-NAME-sensitive increase in hippocampal cAMP levels that was temporally associated to the disruption of PPI (Klamer *et al*, 2005b). Possibly, some of the effects observed in Paper II were mediated through the indirect modulation of cAMP release by cGMP, although this was not investigated specifically.

In summary, the ability of prefrontal sGC inhibition to ameliorate deficits in cognition-related measures, such as PPI, indicates that the NO/sGC/cGMP pathway plays an important role in preserving PFC function after PCP treatment. The similarities between the sGC distribution in rodents and primates indicate that the role of the NO system is translatable across species (Pifarre *et al*, 2007) and thus that the present findings may be applicable to humans.

Paper III. Increased cortical nitric oxide release after phencyclidine administration.

Studies of the NO system in the brain have for a long time been limited to secondary measures of NO release such as cGMP and metabolic by-products such as citrulline, nitrate and nitrite. In addition to the restricted specificity of these methods, the time resolution does not allow for dynamic assessment of NO signaling *in vivo*. The recent development of micro-electrochemical NO sensors has opened up new possibilities of real-time *in vivo* measurements of NO in the brain (Finnerty, 2008; Wang *et al*, 2006). In paper III, we measured NO levels in the rat prefrontal cortex using a NO selective amperometric microsensor with high selectivity and specificity. This specific setup is unique in that it allows measurements of NO levels in awake and behaving animals (Brown *et al*, 2005; Brown *et al*, 2003; Finnerty, 2008).

Systemic administration of PCP caused a robust increase in NO oxidation current. This increase was attenuated by pretreatment with the NOS inhibitor, L-NAME, at a dose identical to that which previously has been used to block several PCP-induced behavioral deficits in rats (Johansson *et al*, 1998; Klamer *et al*, 2005b; Klamer *et al*, 2005c; Wass *et al*, 2006a; Wass *et al*, 2006b; Wass *et al*, 2008b) (Fig 13).

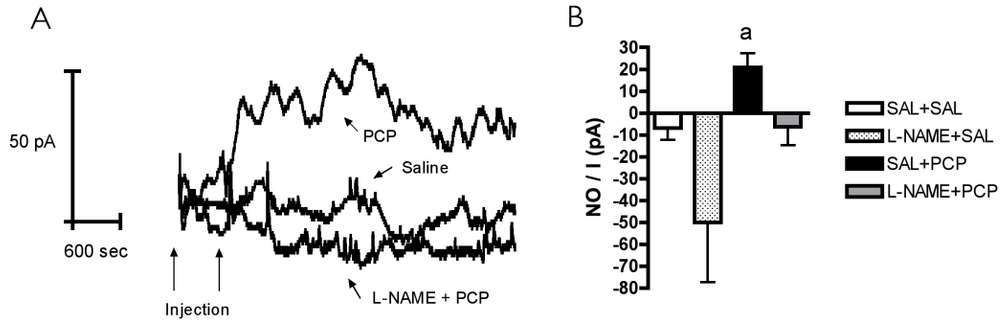

Figure 13. (A) Representative voltammograms showing change in NO oxidation current in the rat medial PFC after PCP (2 mg/kg, s.c.) and L-NAME (10 mg/kg, s.c.) treatment. Data is expressed as current (pA) over time (s). (B) Mean change in NO current compared to baseline following drug treament. Data expressed as mean +/− SEM change in current (15–45 min post injection) compared to saline. See Paper III for details.

Based on *in vitro* calibrations of the sensors, the rise in NO oxidation current caused by PCP in Paper III corresponds to a NO concentration in the range of about 13–24 nM. This suggests that the NO concentration in the vicinity of the sensor is at least ten times higher than what is believed to be the typical NO concentration in the synaptic cleft following continuous NMDA receptor stimulation (Garthwaite, 2008). An increase in NO levels of this magnitude is therefore not likely a consequence of exclusively synaptic transmission, but may possibly reflect the activation of additional sources of NO, such as eNOS. Given that most of the eNOS in the brain is found in the capillary circulation, which is devoid of smooth muscle cells, it is possible that eNOS-derived NO serves other purposes than dilating vessels such as "vasculoneuronal" communication (Garthwaite, 2008). This is supported to some extent by the fact that eNOS knockout mice have both altered GABA release and impaired synaptic plasticity in hippocampus, cortex and striatum (Doreulee *et al*, 2003; Haul *et al*, 1999; Kano *et al*, 1998; Wilson *et al*, 1999). In addition, both the magnitude (~10–20 nM) and temporal profile (maximal NO peak 30–40 min post injection) of the increases in NO levels resemble those of an earlier voltammetry study, which investigated the effects of systemic cocaine administration on prefrontal NO release in anesthesized rats (Sammut and West, 2008). Regardless of the source for the high NO levels observed in Paper III, it is clear that PCP stimulates NO release in the PFC, and that this increase may underlie the behavioral deficits induced by this drug.

These real-time measurements correspond to previous behavioral studies on the interaction between PCP and NO by using an identical dosing regime. Furthermore, the peak in NO levels at 30–40 min coincides with the peak effect of PCP on PPI (Klamer *et al*, 2005b). NO signaling may of course be altered in several brain regions following PCP administration. Given that PCP causes a substantial activation (as measured by pharmacological MRI) of cortico-limbo-thalamic circuitry (Gozzi *et al*, 2007), it cannot be excluded that other brain regions may follow the same pattern. Nevertheless, Paper III strongly supports the involvement of prefrontal NO signaling in the effects of PCP, and that *in vivo* voltammetry may become a useful biochemical tool when studying the role of NO for cognitive function.

Paper IV. Prefrontal GABAB receptor activation attenuates phencyclidine-induced impairments of prepulse inhibition: Involvement of nitric oxide.

Most NOS containing neurons in the PFC of both rats and primates synthesize GABA, indicating a close relation between these two transmitter systems (Gabbott and Bacon, 1995; Yan *et al*, 1996). Furthermore, GABAergic interneurons appear to rely on NMDA receptor signaling to a larger extent than pyramidal cells (Grunze *et al*, 1996; Jones *et al*, 1993) suggesting a high susceptibility to NMDA receptor antagonism. This theory is supported by numerous studies showing increase in cortical activity following acute administration of NMDA-receptor antagonists, which likely arises from a decrease in inhibitory power (Breier *et al*, 1997; Gozzi *et al*, 2007; Jackson *et al*, 2004; Lahti *et al*, 1995; Moghaddam *et al*, 1997).

In paper IV, the ability of the $GABA_B$ receptor agonist baclofen to restore PPI was investigated in animals treated with PCP. Pretreatment with systemic baclofen normalized both the PPI deficits and the hyperactivity caused by PCP. This attenuation of PCP-induced PPI deficits did not seem to be explained by a true interaction with PCP, as systemic baclofen treatment increased PPI *per se*. Interestingly, prefrontal microinjections of baclofen fully blocked the effects of PCP on PPI, without affecting baseline values (Fig 14A). This suggests that impairments in prefrontal $GABA_B$-mediated inhibition may be important for the effects of PCP on information processing and that restoration of inhibitory signaling through these receptors in the PFC is sufficient to normalize PPI.

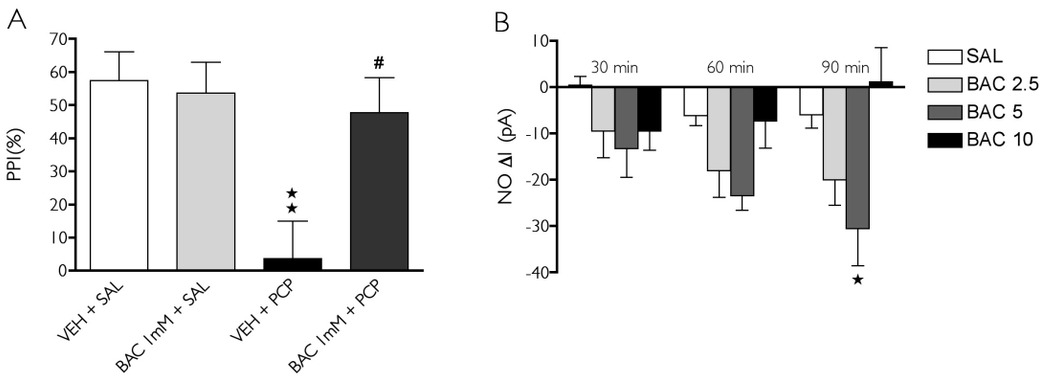

Figure 14. (A) The effects of bilateral baclofen treatment (BAC: 1 mM) in the mouse medial PFC followed by systemic PCP administration (5 mg/kg) on prepulse inhibition (PPI). (B) Change in prefrontal NO release 30, 60 and 90 min after systemic baclofen administration (2.5, 5, 10 mg/kg) in the rat. See Paper IV for details.

These results corroborate previous findings showing that baclofen attenuates both spontaneous PPI deficits in mice and deficits induced by the NMDA receptor antagonist MK-801 in rats and mice without affecting baseline PPI (Arai et al, 2008; Bortolato et al, 2004; Bortolato et al, 2007). However, systemic administration of baclofen increased basal PPI, which is at variance with studies from other laboratories. Tentatively, this may be the result of differences in the timing of baclofen administration in combination with strain- or species-dependent factors.

In combination with the above-mentioned studies, these findings point to a putative anti-psychotic potential of baclofen. In fact, baclofen was initially shown to have beneficial effects in the treatment of schizophrenia (Frederiksen, 1975; Schopf and Hucker, 1977) although later studies could not replicate this finding (Beckmann *et al*, 1977; Bigelow *et al*, 1977; Gulmann *et al*, 1976). Given the wide distribution of $GABA_B$ receptors in the brain both pre- and post-synaptically and their molecular diversity (Bettler *et al*, 2004; Bettler and Tiao, 2006; Blein *et al*, 2000; Bowery *et al*, 2002), it is not surprising that a general stimulation of these receptors may result in different findings depending on dosing regimes and output measures. In addition, it remains unlikely that systemic administration of $GABA_B$ receptor agonists would improve cognition, given that baclofen disrupts both recognition and spatial memory in the rodents (McNamara and Skelton, 1996; Pitsikas *et al*, 2003) and that $GABA_B$ receptor antagonists improve cognitive performance in various animal models (for review see Bowery *et al*, 2002) and humans (Froestl *et al*, 2004). However, genetic deletions of $GABA_B$ receptors in mice impair learning and memory, suggesting that these receptors also are essential for baseline cognitive function (Gassmann *et al*, 2004; Schuler *et al*, 2001). Furthermore, systemic administration of baclofen blocks amphetamine-induced deficits in successive discrimination in the rat, suggesting that baclofen may have beneficial effects on some aspects spatial ability (Ahlenius *et al*, 1975). Taken together, it is possible that both positive and negative modulation of the $GABA_B$ system may become useful in a clinical setting following the development of selective modulators that target distinct subclasses of these receptors.

In the present experiments, baclofen was primarily used as a tool to investigate the role of prefrontal $GABA_B$ receptors for the behavioral effects of PCP in relation to NO signaling. The combination of baclofen and the NOS inhibitor, L-NAME, was more effective than either compound by itself, both in attenuating the effects of PCP, and in increasing basal PPI. This opens up the possibility that these two drugs act on a common pathway involving glutamate, GABA and NO. In line with this, baclofen decreased NO levels in the PFC in a dose-dependent manner (Fig 14B) suggesting that NO release is under the influence of $GABA_B$ receptor signaling in this brain region. A relation between these two signaling systems has earlier been described where release of both glutamate and the formation of the effector of NO signaling, cGMP, are decreased by baclofen but increased by $GABA_B$ antagonists (Fedele *et al*, 1997; Harte and O'Connor, 2005; Waldmeier *et al*, 2008). Thus, antagonism at these receptors or removal of their endogenous agonist GABA may elevate NO levels. Given the earlier mentioned potent inhibitory effect of NMDA receptor antagonists on interneurons (see introduction), a possible consequence would be a decrease in GABA release and a subsequent decrease in $GABA_B$ receptor activation. Such a loss of inhibitory power (disinhibition) would in turn lead to an increased activity of pyramidal neurons, and stimulate glutamate release. This could elevate NO through the stimulation of Ca^{2+}-permeable non-NMDA receptors, such as AMPA receptors lacking the GluR2 subunit (see below "Glutamate, GABA, NO and disinhibition").

In summary, Paper IV proposes a role for $GABA_B$ receptor signaling in the effects of PCP, possibly with altered NO levels as a downstream mediator. Thus, NO may play an important role as an effector of a disinhibited cortex that can be of relevance for cognitive deficits in schizophrenia.

GENERAL CONSIDERATIONS

The PCP model of schizophrenia

Accumulating evidence suggests that both acute and chronic PCP administration can be used in rodents and primates to produce a pattern of neurochemical, structural and behavioral changes that closely resemble those observed in patients with schizophrenia. This implies that PCP acts on a similar neurocircuitry to that disturbed in the disease, and that use of the PCP model may elucidate pathophysiological mechanisms underlying the disease, or at least the dysregulated neurotransmission responsible for some of the symptoms.

Importantly, PCP given to rodents has been shown to induce neurotoxic effects such as vacuolization and degeneration in regions including the hippocampus, retrosplenial cortex, cingulate cortex (Ellison and Switzer, 1993; Gao *et al*, 1993; Olney *et al*, 1989; Schroeder *et al*, 1998), and at very high doses, the striatum (Mitchell *et al*, 1998). These alterations have not been observed in patients with schizophrenia, suggesting that long-term administration of high doses of PCP is not a suitable approach to model this disease (Morris *et al*, 2005). However, given that these effects are predominantly seen following sub-chronic or chronic treatment or at doses higher than used in the present thesis, neurotoxic effects of PCP are not likely to underlie the behavioral changes presented here. In addition, the concentration of PCP in the rat brain appears to peak approximately 30 min after s.c. or i.p. administration (Kalinichev *et al*, 2008; Schroeder *et al*, 1998), which coincides with the time they are tested for PPI. Behavioral deficits due to neurotoxic effects would likely emerge after, rather than during, this maximum response. Nevertheless, long-term effects involving neurotoxicity could explain part of the differences observed between acute and sub-chronic PCP administration.

Given that PCP also has affinity for D_2 receptors and the dopamine transporter, a reasonable question is whether behavioral disruption by PCP really can be attributed to its NMDA receptor antagonism. First, PPI deficits caused by NMDA receptor antagonists such as PCP or MK-801 are relatively resistant to antipsychotics with a strong D_2 receptor antagonism such as haloperidol (Fejgin *et al*, 2007; Keith *et al*, 1991; Linn *et al*, 2003) suggesting that the effects of PCP are not primarily mediated by the dopamine system. On the other hand, second-generation antipsychotics, that generally have a mixed pharmacological profile, block PCP-induced PPI deficits to a certain degree (Bakshi *et al*, 1995; Bakshi *et al*, 1994; Bubenikova *et al*, 2005; Fejgin *et al*, 2007; Wiley, 1994) lending further support for the involvement of transmitter systems other than dopamine. Second, the doses of NMDA receptor antagonists needed to disrupt PPI tend to reflect their affinities to this receptor, rather than their effects on the dopamine system (MK-801>PCP>ketamine) (Mansbach *et al*, 1989). Even if the involvement of dopamine signaling in the effects of PCP may depend on the behavioral paradigm investigated, increases in corticolimbic dopamine transmission do not appear to explain the effects of PCP on locomotor activity or working memory (Adams *et al*, 1998).

As mentioned above, the PCP-model is able to distinguish between first and second-generation antipsychotics, something dopaminergic models of schizophrenia fail to show. Furthermore, PCP differs in that it induces negative symptoms, cognitive deficits, auditory hallucinations and flattened affect in human subjects, thus mimicking a more comprehensive spectrum of schizophrenia symptoms than *e.g.* amphetamine (for review see Steinpreis, 1996). Since MK-801 is only used preclinically, current clinincal studies of the behavioral effects of NMDA receptor antagonists in humans have been restricted to the administration of ketamine. Ketamine produces somewhat similar effects to PCP in humans, such as hallucinations and cognitive deficits (for review see Gunduz-Bruce, 2008; Krystal *et al*, 1994). However, psychotomimetic doses of ketamine do not disrupt PPI in human subjects (Oranje *et al*, 2002; van Berckel *et al*, 1998), but have in fact been shown to increase PPI in several studies (Abel *et al*, 2003; Duncan *et al*, 2001; Heekeren *et al*, 2007). This is in contrast to the effects of ketamine in research animals, where PPI is disrupted in both rats and mice (Brody *et al*, 2003; Chan *et al*, 2008; Swerdlow *et al*, 2008), and raises questions regarding the translational value of preclinical studies on ketamine- and PCP-induced PPI deficits. However, ketamine has been shown to disrupt other measures of sensory gating as measured by EEG (Boeijinga *et al*, 2007) lending at least some support to a disruptive effect on information processing in humans. Importantly, several differences between the effects of ketamine and PCP in humans have been demonstrated. For example, ketamine has both a lower potency and a shorter duration of action than PCP, making continuous drug infusions necessary in clinical studies (Rainey and Crowder, 1974). Furthermore, ketamine induces visual rather than auditory hallucinations humans and thus does not mimic schizophrenia as well as PCP in this respect (Krystal *et al*, 1994). Finally, a higher degree of CNS depression is observed for ketamine than for PCP, which is probably explained by its effect in potentiating $GABA_A$ transmission in the cerebellum (Hevers *et al*, 2008). Whether PCP would disrupt PPI in a clinical setting will remain an unanswered question due to ethical considerations, but it is possible that the qualitative differences between ketamine and PCP also reflect differences in their ability to disrupt PPI.

Prepulse inhibition and cognition

A deficit in pre-attentive information processing may theoretically lead to a stimulus overload and a subsequent cognitive fragmentation in schizophrenia (Braff *et al*, 1978). However, PPI deficits are not pathognomonic for schizophrenia as suggested by their presence in other brain disorders and by the overlap in PPI levels between healthy controls and patients with schizophrenia (Swerdlow *et al*, 2008). As PPI is sensitive to parametrical differences, gender (Kumari *et al*, 2004; Swerdlow *et al*, 1993a), instructed attention to prepulses (Hazlett *et al*, 2003; Kedzior *et al*, 2007), antipsychotic medication (Quednow *et al*, 2006; Wynn *et al*, 2007), and a number of other factors, it is not surprising that robust relationships between PPI and specific symptoms of schizophrenia have been hard to detect. Furthermore, the neurocircuitry involved in the regulation of PPI is rather distributed, suggesting that deficits in several brain regions and transmitter systems may cause similar changes in PPI levels.

Interestingly, PPI deficits have been detected in prodromal patients and relatives of patients with schizophrenia (Kumari *et al*, 2005; Quednow *et al*, 2008), indicating that alterations in PPI may be more of a “trait” than a “state” phenomenon. Importantly, PPI has been shown

to correlate with several cognitive functions in patients with schizophrenia, including thought disturbance (Perry *et al*, 1994), and attention (Karper *et al*, 1996), although other studies have shown correlations with global functioning but not cognitive deficits (Swerdlow *et al*, 2006a). Adding to the relation between PPI and cognition, studies on healthy volunteers have shown associations to social cognition (Wynn *et al*, 2005), strategy formation (Bitsios *et al*, 2006) and execution times for cognitive tasks (Csomor *et al*, 2008).

Tentatively, some of these associations may be explained by alterations in the cortico-striato-pallido-thalamic circuitry since such a network is involved both in cognitive function and regulation of PPI. In support of this, a recent study by Kumari and coworkers shows positive correlations between PPI and grey matter volume in the dorsolateral prefrontal, middle frontal and orbital/medial prefrontal cortices of patients with schizophrenia (Kumari *et al*, 2008). Other indirect evidence for the relation of PFC signaling and PPI comes from studies showing that healthy controls with the val/val genotype for COMT display lower levels of PPI (Roussos *et al*, 2008). This polymorphism in the COMT gene has been associated with schizophrenia and appears to be functionally related to dopamine signaling in the PFC and cognitive functions such as working memory (see introduction "dopamine and schizophrenia"). In addition the COMT inhibitor tolcapone, improves both working memory and PPI in healthy subjects with the val/val genotype (Giakoumaki *et al*, 2008). This suggests that PFC function is important for both cognitive function and PPI in patients with schizophrenia and healthy controls, and that these interactions are well worth studying when trying to understand the pathophysiological mechanisms underlying cognitive deficits in this disease.

GENERAL DISCUSSION

Glutamate, GABA, NO and disinhibition

In the present thesis, evidence is presented that NO signaling in the PFC is important for the biochemical and behavioral effects of PCP. The observed increase in NO levels is suggested to be the consequence of an increased glutamate release resulting from disinhibited pyramidal cells. A putative chain of events that explain this phenomenon may be as follows:

1) GABAergic interneurons are particularly sensitive to NMDA antagonists such as PCP since they rely more on NMDA receptor signaling for their activity than pyramidal cells. In addition, a recent study of PFC function shows that inhibition of NMDA receptors preferentially decreases the activity of fast-spiking interneurons (Homayoun *et al*, 2007).

2) Such a removal of inhibitory power appears to cause a disinhibition of pyramidal cells as evidenced by the increase in cortical activity and glutamate levels following administration of NMDA receptor antagonists in both clinical and preclinical studies (Breier *et al*, 1997; Gozzi *et al*, 2007; Jackson *et al*, 2004; Lahti *et al*, 1995; Moghaddam *et al*, 1997).

3) An increase in cortical glutamate efflux, may then stimulate NO synthesis by increasing intracellular Ca^{2+} concentrations. This may be mediated by non-NMDA glutamate receptors with Ca^{2+} permeability such as AMPA receptors lacking the GluR2 subunit.

Interestingly, most neurons in the temporal and frontal cortex of rats and primates that express this subtype of AMPA receptor and/or produce NO are GABAergic interneurons (Gabbott *et al*, 1995; Jonas *et al*, 1994; Szabadits *et al*, 2007; Yan *et al*, 1996; Yin *et al*, 1994). A similar situation is seen in humans, where NOS expressing neurons of the temporal cortex are GABAergic, and express lower levels of GluR2 (Gonzalez-Albo *et al*, 2001) indicating that these cells may increase NO production following glutamate-induced Ca^{2+} influx through the AMPA receptor. This suggests a close interaction between glutamate, GABA and NO signaling in the cortex, and also that these circuits may be similar across species.

The attenuation of the disinhibitory effects of PCP on pyramidal cells by baclofen may have several possible explanations. The most obvious effect would be the activation of postsynaptic $GABA_B$ receptors situated on pyramidal cells leading to an increased inhibition of these cells. Another option is that baclofen activates presynaptic heteroreceptors, thus decreasing glutamate release and counteracting the increase in cortical activity.

Both these alternatives require pyramidal $GABA_B$ receptors to be more affected than the $GABA_B$ receptors on interneurons. Tentatively, the latter option could explain the dose-related "inverted U" shaped change in NO oxidation current observed in Paper IV. Low doses of baclofen may possibly engage pyramidal heteroreceptors that block glutamate release, whereas the highest dose of baclofen also engages autoreceptors on interneurons causing a decrease in GABA release that antagonizes the the effects of heteroreceptors on glutamate

efflux. Although GABA and glutamate release appears to be governed by different isoforms of presynaptic $GABA_B$ receptors (Waldmeier *et al*, 2008), all currently known modulators of the $GABA_B$ receptor bind to a domain that is shared by the two isoforms (Bettler *et al*, 2004). The future development of subunit-specific agonists will provide a tool for investigating this matter further.

The effect of the PCP-induced NO increase observed in Paper III provides biochemical support for NO acting as a mediator of a disinhibited PFC. The cognition-related behavioral effects of such an increase in NO signaling are likely to be mediated by the sGC/cGMP system, as inhibition of this pathway in the PFC completely blocks the disruptive effects of PCP on PPI (Paper II). Consequently, the apparent role of PFC-derived NO in the effects of PCP ties in with current theories regarding disinhibition in schizophrenia (for review see Lisman *et al*, 2008)), and may thus be informative of the aspects of cognitive dysfunction that are the consequence of a disrupted prefrontal circuitry in schizophrenia.

NO in schizophrenia

NO is unique in many aspects, given its ability to diffuse freely through membranes, and thereby has an important role in neurotransmission, regulation of blood flow and inflammation. This makes the interpretation of the effects of NO on biochemistry and behavior even more complicated, and creates difficulties when trying to pinpoint specific underlying mechanisms. Our research group and others have demonstrated that inhibition of NOS in rodents is sufficient to normalize schizophrenia-like behavioral deficits caused by PCP. These include deficits in PPI, habituation of acoustic startle, latent inhibition, spatial learning, reference memory, and working memory, which all can be prevented by interfering with the production of NO (Johansson *et al*, 1997; Johansson *et al*, 1998; Klamer *et al*, 2001, 2004a, b; Klamer *et al*, 2004c; Klamer *et al*, 2005c; Wass *et al*, 2006a; Wass *et al*, 2006b; Wiley, 1998)). Although the above findings suggest that an *increase* in NO may underlie these schizophrenia-like deficits, several studies have shown that also NOS *inhibition* may disrupt behavior. Acute pretreatment with NOS inhibitors may potentiate PCP-induced stereotypies and induce deficits in spatial learning (Bujas-Bobanovic *et al*, 2000; Chapman *et al*, 1992; Prendergast *et al*, 1997). Furthermore, neonatal treatment with NOS inhibitors may induce long-lasting deficits in PPI, social interaction, latent inhibition, and increased amphetamine sensitivity (Black *et al*, 1999; Black *et al*, 2002; Black *et al*, 2008; Morales-Medina *et al*, 2008). In summary, this underscores that both an abnormal increase and a decrease in NO signaling can underlie schizophrenia-like deficits.

The present preclinical findings are in line with the varying results observed in clinical studies, where NO metabolites have been shown to be increased (Atmaca *et al*, 2007; Das *et al*, 1996; Das *et al*, 1995; Herken *et al*, 2001; Taneli *et al*, 2004; Yanik *et al*, 2003; Yao *et al*, 2004; Yilmaz *et al*, 2007; Zoroglu *et al*, 2002) and in some studies decreased (Lee *et al*, 2008; Ramirez *et al*, 2004; Srivastava *et al*, 2001; Suzuki *et al*, 2003) in the plasma and CSF of patients with schizophrenia. Specific post-mortem investigations of nitrinergic neurons in the hypothalamus, the striatum and the PFC of patients with schizophrenia, have revealed abnormalities such as decreased levels of nitrinergic neurons, aberrant neuronal distribution, and decreased NOS activity (Akbarian *et al*, 1993a; Akbarian *et al*, 1993b; Bernstein *et al*, 2005; Fritzen *et al*, 2007; Lauer *et al*, 2005; Xing *et al*, 2002). At the same time an increase in nNOS mRNA in the PFC and increased cerebellar NOS levels have been detected in schizophrenia (Baba *et al*, 2004; Karson *et al*, 1996) indicating a hyperactive NO system.

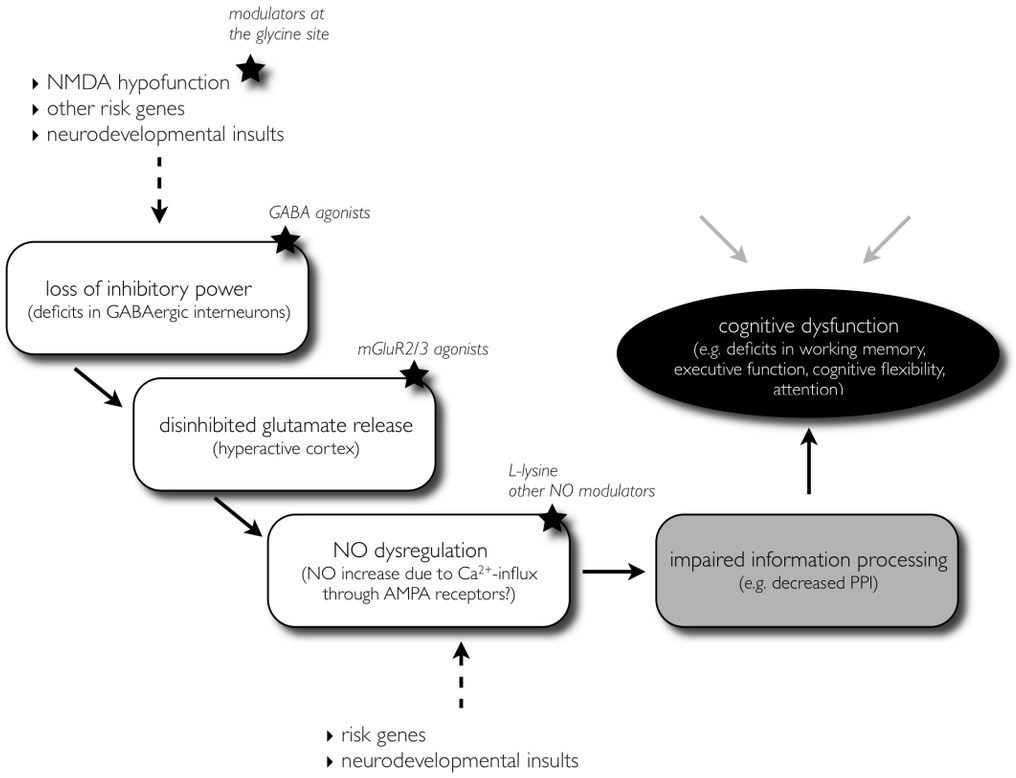

Figure 15. Hypothetical model of how a disinhibited cortex and a dysregulated NO system may converge to form cognitive deficits in schizophrenia. White areas represent pathophysiological changes, grey fields represent their functional consequences and black areas symptomatology. Black stars indicate novel possible treatment options for cognitive dysfunction along this pathway, that have been clinically validated to some extent.

Clinical studies have consistently found evidence for dysregulated NO system in schizophrenia that may have relevance for the pathophysiology and/or the symptomatology of this disabling brain disease. The underlying cause for such deficits in nitrinergic signaling is not known, but may originate in genetic factors, neurodevelopmental insults or even inflammatory processes. The present thesis suggests that an increase in prefrontal NO signaling may underlie some cognitive deficits present in schizophrenia, and that this increase may be secondary to a disinhibited glutamate system caused by deficits in the inhibition mediated by GABAergic interneurons due to NMDA hypofunction (Fig 15). However, the present results to not necessarily contradict the possibility that a loss in NO signaling due to neurodevelopmental insults may be an alternative route for the generation of similar deficits. Future clinical studies that target specific subgroups of patients while accounting for the confounding factors mentioned above, will prove helpful when trying to elucidate the nature of NO dysregulation in schizophrenia.

Measuring cognition in animal models

The term cognition is a widely used but vaguely defined term in science, and it's meaning is usually open for interpretation. Cognition generally refers to some aspect of attentive, higher-level information processing by the brain. The cognitive dysfunction in schizophrenia includes deficits in learning and memory, working memory, attention, concentration, executive function and cognitive flexibility, and at a more complex level social cognition (for review see Green, 2007; Green *et al*, 2005). Although many of these functions may be perceived as uniquely human when it comes to complexity and capacity, corresponding albeit simpler aspects of cognition can be found in other species such as rodents and certainly in primates. A useful animal model of cognition will never mirror the human situation perfectly, nor does it have to. Instead, the aim must be to model a corresponding function that serves a similar purpose in both human and research animal. For example, a rat digging for food rewards in a bowl while paying attention to dimensions such as odor, digging medium and texture is not identical to a human performing the WCST. Nevertheless, both tests can estimate the capacity for attentional set shifting and cognitive flexibility while engaging the prefrontal cortex. These tasks are different but measure similar mechanisms by putting each species in an appropriate salient context, suggesting that animal models of attentional set shifting may have both face and predictive validity. The translational value of any attempt to measure cognition depends on the choice of appropriate species, tasks and on the interpretation of the output. Thus, studies of a simpler system than the human brain may be valuable when trying to decipher general and evolutionary preserved cognitive mechanisms.

Another useful approach may be to study mechanisms that are not considered cognitive *per se*, but may be related to, or important for, cognitive function. In the present thesis, PPI was used to model pre-attentive gating of sensory information. The putative role of such a mechanism is to protect the brain from stimulus overload by gating out irrelevant stimuli. A filter mechanism like PPI may constitute important prerequisite for higher-order processing, but is also modulated in a top-down manner by higher brain regions. The combination of a suitable pharmacological challenge such as PCP administration with a translational output measure such as PPI, may constitute a useful model of information processing deficits in schizophrenia. However, the validity of such an approach is naturally limited in that the findings cannot be extrapolated to all cognitive deficits. One way of addressing this may be to validate hypotheses generated by PPI experiments in additional models for cognitive function. When investigating the role of NO signaling for the effects of PCP, we have tried to apply a "cognitive test battery" including habituation of acoustic startle, latent inhibition, spatial learning, and spatial reference memory to see if the NO system relates to cognition in a broader sense than PPI. The fact that inhibition of the NO system blocks PCP-induced deficits in all these domains, suggests that NO may be important for cognitive dysfunction in a general sense rather than limited to specific impairments.

Concluding remarks

To this date, available treatment options for schizophrenia have had limited effects on the disabling cognitive dysfunction that is shared by a majority of the patients. A small but important difference in treatment effect has been observed between typical and atypical antipsychotics, the latter class being more effective in ameliorating negative symptoms.

The exact relationship between positive symptoms, negative symptoms and cognitive dysfunction is still not known, although these symptom domains are generally considered to be separate and thus reflect distinct pathophysiological entities. If so, the likelihood of finding the "ideal" antipsychotic, which improves all aspects of the disease, is disappearingly small. A more pragmatic approach could be to develop cognitive enhancers that can be used as adjuvants to conventional antipsychotic treatment, thereby addressing additional aspects of the symptomatology in schizophrenia.

To discover novel mechanisms suitable for the development of such drugs, the schizophrenia research field has to abandon classical screening models predictive of antipsychotic effect, or continue to reinvent the wheel. For example, an animal model based on amphetamine-induced deficits will likely not uncover new principles that do not target the dopamine system, and a transgenic mice model with a schizophrenia-like phenotype that is normalized by clozapine will not necessarily have higher predictive validity for detecting new treatment targets, than a model where no improvement by clozapine can be shown.

If cognitive dysfunction is at the core of schizophrenia, the research efforts in the field should be even more focused on investigating the mechanisms underlying these deficits. A major challenge will be the development and application of a translational cognitive test battery with high test-retest validity. To this end, the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative may prove valuable, as it tries to categorize the cognitive deficits into different domains that to a large extent can be modeled in research animals. Finally, it is possible that beneficial effects of a drug on cognition cannot be expected to reach satisfactory levels without the simultaneous use of an appropriate cognitive training program. For example, cognitive remediation therapy where patients are taught information processing strategies through exercise, have been shown to improve cognitive performance (*e.g.* in WSCT, non-verbal memory, executive function) in both early-onset and chronic patients with schizophrenia (Penades *et al*, 2006; Wykes and van der Gaag, 2001). Possibly, patients would benefit from synergistic effects when subjected to a combination of strategy formation exercises and pro-cognitive pharmacological treatment. Given the amount of cognitive domains and the complexity of each cognitive function, it is not obvious that cognitive enhancers will facilitate cognition in a general sense. Perhaps, it is more likely that a specific pro-cognitive drug will target only distinct cognitive functions and that future cognition-improving treatment strategies will be tailored to the demands of the individual patient.

The present thesis proposes NO signaling in the PFC as a putative target when searching for novel treatment options for cognitive dysfunction in schizophrenia. This is based on the assumption that the behavioral and neurochemical effects of PCP in humans and animals relate to at least some aspects of the cognitive deficits in this brain disorder. The recently completed clinical pilot study where L-lysine, used as an adjuvant to antipsychotic treatment, was shown to improve psychopathology and cognitive impairments (Wass *et al*, 2008a, manuscript), underscores the translational value of the PCP model. Furthermore, this indicates that the NO/sGC/cGMP pathway constitutes a potential treatment target for cognitive deficits in schizophrenia.

SWEDISH SUMMARY

Sammanfattning riktad till familj och vänner

Bakgrund: Schizofreni är en allvarlig och ofta kronisk hjärnsjukdom som drabbar människor över hela världen och som har förödande konsekvenser för både patienter och deras familjer. Vanligtvis bryter sjukdomen ut i de sena tonåren – en kritisk period i livet för personlig utveckling, där identitetskapande och bildandet av sociala nätverk är avgörande för framtida utsikter i både relationer och arbetsliv. Diagnosen är baserad på fenomenologiska kliniska observationer eftersom inget objektivt test eller markör kan avgöra huruvida en person är drabbad, trots att det är känt att ärftligheten för denna sjukdom är mycket hög. Symptombilden brukar ofta delas in positiva symptom, negativa symptom och kognitiva funktionsnedsättningar. *Positiva symptom*, som i hög grad kan behandlas med idag tillgängliga antipsykotika, utgörs av exempelvis hallucinationer och vanföreställningar, det vill säga tillstånd som läggs till en persons vanliga beteende. *Negativa symptom* kan bara behandlas till en liten del och utgörs av ett frånfall av funktioner, som kan visa sig i en minskad drivkraft, svårigheter att förstå och förmedla känslor eller en oförmåga att känna glädje. *Kognitiva funktionsnedsättningar* yttrar sig ofta i problem med uppmärksamhet, svårigheter med olika typer av minne och inlärning samt försämrad koncentrationsförmåga och informationshantering. För dessa symptom finns det dessvärre inga effektiva behandlingsmetoder. Samtidigt påverkar de kognitiva funktionsnedsättningarna hur det går för patienten på lång sikt, till exempel vad beträffar möjligheter till att kunna leva självständigt i samhället genom att exempelvis arbeta eller ha egen bostad. Behovet av effektiva behandlingsmetoder som riktar in sig på denna symptomklass är därför mycket stort och det är också kognitiva funktionsnedsättningar som står i fokus för den här avhandlingen.

Metod: Ett sätt att försöka hitta nya farmakologiska angreppspunkter för behandling av kognitiva funktionsnedsättningar är att försöka skapa en modell av sjukdomen i försöksdjur. Det är såklart uppenbart att en råtta eller mus inte kan ha schizofreni, men vissa aspekter som relaterar till grundläggande kognitiva funktioner är väldigt lika i alla däggdjur. Den här avhandlingen baseras på en modell där gnagare ges en ”schizofrenihärmande” substans, fencyklidin, varefter de testas för sin förmåga att filtrera inkommande information (i form av ljudimpulser). Denna filtreringsmekanism kallas för prepulsinhibition (PPI) och tros vara ett viktigt sätt att begränsa mängden information som når högre hjärnområden. Personer med schizofreni har generellt en sänkt filtreringsförmåga, vilket tros kunna orsaka att hjärnan drabbas av en informationsöversvämning som i sin tur kan påverka den kognitiva förmågan i en negativ riktning.

Fencyklidin framkallar ett tillstånd som är mycket likt schizofreni när det ges till människor, med såväl positiva och negativa symptom som kognitiva funktionsnedsättningar. Dessa effekter beror framförallt på en hämning av en av de viktigaste aktiverande signalsubstanserna i hjärnan, glutamat, som kan ses som hjärnans ”gaspedal”. Antagandet är alltså att en substans som kan skapa ett såpass schizofrenilikt tillstånd hos människor också borde påverka de hjärnområden och signalsystem som är störda vid schizofreni. Eftersom fencyklidin orsakar liknande effekter hos försöksdjur, använder man det ofta som en modell inom schizofreniforskningen.

Kväveoxid (NO) är en signalmolekyl som är speciell eftersom den är gasformig och kan frisättas direkt från platsen där den bildas, det vill säga inte bara i synapser. Vår forskargrupp har under det senaste decenniet visat att fencyklidins kognitionshämmande effekter på försöksdjur kan motverkas om man hämmar hjärnans produktion av NO. Detta är i linje med ett flertal kliniska studier som tyder på att NO-systemet är stört hos patienter med schizofreni. Ett antal av dessa studier pekar också på specifika störningar i ett hjärnområde som kallas prefrontala kortex. Detta område är förknippat med högre kognitiva funktioner såsom arbetsminne, uppmärksamhet och olika aspekter av beteendekontroll och kan därför ses som hjärnans ”dirigent”. Störningar i prefrontala kortex har logiskt nog också visat sig vara en bidragande orsak till de kognitiva funktionsnedsättningar som patienter med schizofreni drabbas av.

Syfte: Det övergripande syftet med denna avhandling var att undersöka NO-systemets betydelse för förmedveten informationsbearbetning i en djurmodell för schizofreni, med särskilt fokus på ett hjärnområde som är viktigt för kognitiva funktioner. På sikt skulle ny kunskap om detta signalsystem kunna möjliggöra utvecklingen av nya läkemedel som särskilt riktar in sig på kognitiva funktionsnedsättningar vid schizofreni.

Resultat: I första artikeln visar vi att man genom att minska tillgången på den aminosyra (L-arginin) som behövs för att NO skall kunna bildas kan motverka fencyklidins effekter på informationsfiltrering. Detta görs genom att behandla möss med en annan aminosyra, L-lysin, som konkurrerar med L-arginin om att komma in i hjärnan och nervcellerna. Resultaten i denna artikel visar att NO är viktigt för fencyklidins effekter på informationsbearbetning och pekar också på ett helt nytt sätt att reglera nivåerna av NO i hjärnan. Dessa prekliniska fynd har lett till att vi har kunnat genomföra en liten klinisk studie, där patienter har fått L-lysin som tillskott till sin konventionella behandling med antipsykotiska läkemedel. Preliminärt verkar L-lysin förbättra den allmänna symptombilden hos dessa patienter och även vissa aspekter av kognitiv funktion.

I den andra artikeln visar vi att man, genom att endast påverka NO-systemet i prefrontala kortex, kan normalisera filtreringsförmågan hos möss som har fått fencyklidin. Samtidigt visar vi att en budbärare för NO-signalering ökar i denna region efter fencyklidinbehandling. Detta innebär att NO i prefrontala kortex spelar en viktig roll för fencyklidins effekter och möjligen också för kognitiva funktionsnedsättningar hos patienter med schizofreni.

I den tredje artikeln mäter vi NO-halterna direkt i prefrontala kortex på vakna, fritt rörliga råttor. Vi visar här att fencyklidin höjer NO i detta hjärnområde, samt att denna höjning kan motverkas genom att hämma enzymet som ansvarar för NO-produktion. Det har tidigare inte varit möjligt att mäta NO-nivåer direkt, bland annat på grund av att NO har så kort halveringstid, men utvecklingen av nya sensorer har löst detta problem. Effekterna vi såg på NO speglar tydligt våra tidigare fynd vad beträffar fencyklidin och beteende. Således utgör dessa resultat en biokemisk grund för vår hypotes om att NO-systemet i prefrontala kortex är stört vid schizofreni.

I den fjärde artikeln försöker vi koppla ihop NO:s betydelse med andra signalsystem i hjärnan. Vi visar här att det i prefrontala kortex verkar finnas ett samband mellan den aktiverande signalsubstansen glutamat, den hämmande signalsubstansen GABA och NO. Genom att injicera en substans i prefrontala kortex som stimulerar de receptorer som GABA verkar på kan vi normalisera den sänkta filtreringsförmåga som orsakas av fencyklidin. Vidare visar vi att samma substans sänker NO-nivåerna i prefrontala kortex och således att detta är en möjlig förklaring till de normaliserande effekter vi sett på filtreringsförmåga.

Slutsats: Sammantaget visar denna avhandling att NO-signalering i prefrontala kortex är viktigt för informationsbearbetning i en djurmodell för (aspekter av) schizofreni. Dessutom verkar NO i detta hjärnområde samverka med andra signalsystem som man sedan tidigare vet är rubbade vid schizofreni. Vi föreslår att NO-systemet kan spela en viktig roll för kognitiva funktionsnedsättningar vid schizofreni och att det därför också kan utgöra en ny och viktig angreppspunkt för utvecklingen av nya läkemedel. Våra preliminära kliniska fynd med L-lysin stöder denna hypotes, och bör verifieras i långtidsstudier med fler patienter och ett antal dosnivåer.

ACKNOWLEDGEMENTS

I would like to thank my eminent supervisors, Doctor Daniel Klamer, Associate Professor Lennart Svensson, and Professor Jörgen Engel, who took me on this journey and believed in me.

Daniel, for having more drive than is healthy in one individual, for always making me do my best, for convincing me that science is for me, and most of all for being a great friend.

Lennart, for patiently sharing endless hours in front of the computer with our dear colleages Prism and SPSS, and for holding me back when I use a scientific language that is more suitable in a life-style magazine than in a scientific paper.

Jörgen, for your broad scientific knowledge, your remarkable ability to pinpoint strengths and weaknesses in any hypothesis, and for always giving constructive and fair feedback.

Furthermore, a huge thanks to the fantastic members of our research group:

Caroline Wass, for all the support, for being the best possible roomie there is, and for laughing with me every day. **Erik Pålsson**, for a hundred ironic comments, a thousand lab favors, and a million questions answered. **Elisabet Jerlhag,** for always helping out, for teaching me that cats are intellectual, and for being a great colleague at all times. **Sara Landgren,** for making vicious cosmopolitans, for great company in France, and for many laughs. **Gun Andersson,** for teaching me the stereotax, for a 100 L of Ringer's solution, but most of all for being such a warm, caring person. **Ken Johannessen,** for solving a technical issue each day, for always joking and for many discussions on wildlife and kayaks. **Marianne Nyqvist,** for giving me help before I even knew I needed it, for beautiful eggplants from your garden, and for talking about things that are softer than science.

Present and past colleagues at the department of Pharmacology and other parts of "Berget". Without all of you it would not have been the same!

Special thanks to**: Petra S, Olle B, Jessica B, Kristina A, Susanne H, Lars W, Jonas M, Denny J, Jonas F, Daniel A, Daniel R, Rasmus J, Joel T, Elin L, Anna M**.

Eric , My, Ilse , Jocke, Therese, Jonny for surströmming, travel company and hard-core science.

Caroline, Susanne, Kerstin, Farhad, Erik, Hanna, Kristina for being great exam workers by asking smart questions, working hard and, when appropriate, actually doing what I say.

To our Irish collaborators **John, Niall and Fiachra** for great experiments, great Guinness, and for being the most motorically challenged skiers on this planet.

Rickard W and Emil E for our brilliant Tuesday-Thursday concept " a run in the woods – a lunch at Blå Huset – a destroyed lab schedule".

Uppsala-gänget: **Klas, Åsa, Lina, Karin** for sharing your exciting project, for a nice time in Uppsala and for teaching me that I know absolutely nothing about genetics.

Annika Dronge for helpful comments and support, and for teaching me not be such an academic nerd.

My sincere gratitude to **Joel**, **Ing-Marie, Peo** and **Rosa** at dpn, for help with cover picture, layout and professional advice despite my hopeless timing.

The Dellgrans at Rödvedsgatan 5, for happy times, and for always making me feel like home.

Rosa and **Jonne** for countless dinners and great company at “Spa Krogarne”.

All my fantastic friends.

Mamma, Pappa, Julia for being the best and warmest family there is, and for making me who I am.

My princesses, **Malin** and **Smilla,** for making me smile out of happiness a million times a day, for keeping me grounded and sky-high at the same time, and most of all for being all I really care for in the world.

The work in this thesis was supported by grants from Adlerbertska Forskningsstiftelsen, AstraZeneca, Sweden, the Swedish Medical Research Council (4247), Wilhelm och Martina Lundgrens Vetenskapsfond, Hjärnfonden, Jubileumsfonden, Konrad och Helfrid Johanssons fond, The Lundbeck Foundation, the Royal Society of Chemistry (Analytical Division), Schizofrenisällskapet, Stiftelsen Goljes Minne, Stiftelsen Tornspiran, Svenska Läkarsällskapet (the Swedish Society of Medicine), Svenska Sällskapet för Medicinsk Forskning (the Swedish Society for Medical Research), Åhlenstiftelsen and Åke Wibergs Stiftelse.

REFERENCES

Abdul-Monim Z, Neill JC, Reynolds GP (2007). Sub-chronic psychotomimetic phencyclidine induces deficits in reversal learning and alterations in parvalbumin-immunoreactive expression in the rat. *J Psychopharmacol* **21**(2): 198-205.

Abekawa T, Ito K, Nakagawa S, Koyama T (2007). Prenatal exposure to an NMDA receptor antagonist, MK-801 reduces density of parvalbumin-immunoreactive GABAergic neurons in the medial prefrontal cortex and enhances phencyclidine-induced hyperlocomotion but not behavioral sensitization to methamphetamine in postpubertal rats. *Psychopharmacology (Berl)* **192**(3): 303-316.

Abel K, Waikar M, Pedro B, Hemsley D, Geyer M (1998). Repeated testing of prepulse inhibition and habituation of the startle reflex: a study in healthy human controls. *J Psychopharmacol* **12**(4): 330-337.

Abel KM, Allin MP, Hemsley DR, Geyer MA (2003). Low dose ketamine increases prepulse inhibition in healthy men. *Neuropharmacology* **44**(6): 729-737.

Abi-Dargham A (2007). Alterations of serotonin transmission in schizophrenia. *Int Rev Neurobiol* **78**: 133-164.

Abi-Dargham A, Gil R, Krystal J, Baldwin RM, Seibyl JP, Bowers M, *et al* (1998). Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am J Psychiatry* **155**(6): 761-767.

Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, *et al* (2002). Prefrontal dopamine D1 receptors and working memory in schizophrenia. *J Neurosci* **22**(9): 3708-3719.

Adachi M, Reid G, Schuetz JD (2002). Therapeutic and biological importance of getting nucleotides out of cells: a case for the ABC transporters, MRP4 and 5. *Adv Drug Deliv Rev* **54**(10): 1333-1342.

Adams B, Moghaddam B (1998). Corticolimbic dopamine neurotransmission is temporally dissociated from the cognitive and locomotor effects of phencyclidine. *J Neurosci* **18**(14): 5545-5554.

Adler CM, Malhotra AK, Elman I, Goldberg T, Egan M, Pickar D, *et al* (1999). Comparison of ketamine-induced thought disorder in healthy volunteers and thought disorder in schizophrenia. *Am J Psychiatry* **156**(10): 1646-1649.

Adler LE, Olincy A, Cawthra EM, McRae KA, Harris JG, Nagamoto HT, *et al* (2004). Varied effects of atypical neuroleptics on P50 auditory gating in schizophrenia patients. *Am J Psychiatry* **161**(10): 1822-1828.

Afonso VM, Sison M, Lovic V, Fleming AS (2007). Medial prefrontal cortex lesions in the female rat affect sexual and maternal behavior and their sequential organization. *Behav Neurosci* **121**(3): 515-526.

Ahlenius S, Carlsson A, Engel J (1975). Antagonism by baclophen of the d-amphetamine-induced disruption of a successive discrimination in the rat. *J Neural Transm* **36**(3-4): 327-333.

Akbarian S, Bunney WE, Jr., Potkin SG, Wigal SB, Hagman JO, Sandman CA, *et al* (1993a). Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development. *Arch Gen Psychiatry* **50**(3): 169-177.

Akbarian S, Vinuela A, Kim JJ, Potkin SG, Bunney WE, Jr., Jones EG (1993b). Distorted distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase neurons in temporal lobe of schizophrenics implies anomalous cortical development. *Arch Gen Psychiatry* **50**(3): 178-187.

Aleman A, Kahn RS, Selten JP (2003). Sex differences in the risk of schizophrenia: evidence from meta-analysis. *Arch Gen Psychiatry* **60**(6): 565-571.

Anastasio NC, Johnson KM (2008). Differential regulation of the NMDA receptor by acute and sub-chronic phencyclidine administration in the developing rat. *J Neurochem* **104**(5): 1210-1218.

Andreasen NC (1995). Symptoms, signs, and diagnosis of schizophrenia. *Lancet* **346**(8973): 477-481.

Andreasen NC, Rezai K, Alliger R, Swayze VW, 2nd, Flaum M, Kirchner P, *et al* (1992). Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. Assessment with xenon 133 single-photon emission computed tomography and the Tower of London. *Arch Gen Psychiatry* **49**(12): 943-958.

Angrist BM, Gershon S (1970). The phenomenology of experimentally induced amphetamine psychosis--preliminary observations. *Biol Psychiatry* **2**(2): 95-107.

Anis NA, Berry SC, Burton NR, Lodge D (1983). The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. *Br J Pharmacol* **79**(2): 565-575.

APA (1994) Diagnostic and statistical manual of mental disorders (DSM-IV). Organization AP (ed).

Arai S, Takuma K, Mizoguchi H, Ibi D, Nagai T, Takahashi K, *et al* (2008). Involvement of Pallidotegmental Neurons in Methamphetamine- and MK-801-Induced Impairment of Prepulse Inhibition of the Acoustic Startle Reflex in Mice: Reversal by GABA(B) Receptor Agonist Baclofen. *Neuropsychopharmacology*.

Arango C, Summerfelt A, Buchanan RW (2003). Olanzapine effects on auditory sensory gating in schizophrenia. *Am J Psychiatry* **160**(11): 2066-2068.

Araque A, Sanzgiri RP, Parpura V, Haydon PG (1999). Astrocyte-induced modulation of synaptic transmission. *Can J Physiol Pharmacol* **77**(9): 699-706.

Arias-Carrion O, Poppel E (2007). Dopamine, learning, and reward-seeking behavior. *Acta Neurobiol Exp (Wars)* **67**(4): 481-488.

Atmaca M, Tezcan E, Ustundag B (2007). Plasma nitric oxide and leptin values in patients with olanzapine-induced weight gain. *J Psychiatr Res* **41**(1-2): 74-79.

Baba H, Suzuki T, Arai H, Emson PC (2004). Expression of nNOS and soluble guanylate cyclase in schizophrenic brain. *Neuroreport* **15**(4): 677-680.

Bailey DN (1979). Phencyclidine abuse. Clinical findings and concentrations in biological fluids after nonfatal intoxication. *Am J Clin Pathol* **72**(5): 795-799.

Bakshi VP, Geyer MA (1995). Antagonism of phencyclidine-induced deficits in prepulse inhibition by the putative atypical antipsychotic olanzapine. *Psychopharmacology (Berl)* **122**(2): 198-201.

Bakshi VP, Swerdlow NR, Geyer MA (1994). Clozapine antagonizes phencyclidine-induced deficits in sensorimotor gating of the startle response. *J Pharmacol Exp Ther* **271**(2): 787-794.

Ban TA (2004). Neuropsychopharmacology and the genetics of schizophrenia: a history of the diagnosis of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* **28**(5): 753-762.

Bannerman DM, Niewoehner B, Lyon L, Romberg C, Schmitt WB, Taylor A, *et al* (2008). NMDA receptor subunit NR2A is required for rapidly acquired spatial working memory but not incremental spatial reference memory. *J Neurosci* **28**(14): 3623-3630.

Barbas H, Blatt GJ (1995). Topographically specific hippocampal projections target functionally distinct prefrontal areas in the rhesus monkey. *Hippocampus* **5**(6): 511-533.

Barch DM, Carter CS, Braver TS, Sabb FW, MacDonald A, 3rd, Noll DC, *et al* (2001). Selective deficits in prefrontal cortex function in medication-naive patients with schizophrenia. *Arch Gen Psychiatry* **58**(3): 280-288.

Bauer D, Gupta D, Harotunian V, Meador-Woodruff JH, McCullumsmith RE (2008). Abnormal expression of glutamate transporter and transporter interacting molecules in prefrontal cortex in elderly patients with schizophrenia. *Schizophr Res* **104**(1-3): 108-120.

Beckman JS, Koppenol WH (1996). Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. *Am J Physiol* **271**(5 Pt 1): C1424-1437.

Beckmann H, Frische M, Ruther E, Zimmer R (1977). Baclofen (para-chlorphenyl-GABA) in schizophrenia. *Pharmakopsychiatr Neuropsychopharmakol* **10**(1): 26-31.

Behrens MM, Ali SS, Dao DN, Lucero J, Shekhtman G, Quick KL, *et al* (2007). Ketamine-induced loss of phenotype of fast-spiking interneurons is mediated by NADPH-oxidase. *Science* **318**(5856): 1645-1647.

Bernstein HG, Bogerts B, Keilhoff G (2005). The many faces of nitric oxide in schizophrenia. A review. *Schizophr Res* **78**(1): 69-86.

Bettler B, Kaupmann K, Mosbacher J, Gassmann M (2004). Molecular structure and physiological functions of GABA(B) receptors. *Physiol Rev* **84**(3): 835-867.

Bettler B, Tiao JY (2006). Molecular diversity, trafficking and subcellular localization of GABAB receptors. *Pharmacol Ther* **110**(3): 533-543.

Bigelow LB, Nasrallah H, Carman J, Gillin JC, Wyatt RJ (1977). Baclofen treatment in chronic schizophrenia: a clinical trial. *Am J Psychiatry* **134**(3): 318-320.

Bilder RM, Goldman RS, Robinson D, Reiter G, Bell L, Bates JA, *et al* (2000). Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *Am J Psychiatry* **157**(4): 549-559.

Bilder RM, Volavka J, Czobor P, Malhotra AK, Kennedy JL, Ni X, *et al* (2002). Neurocognitive correlates of the COMT Val(158)Met polymorphism in chronic schizophrenia. *Biol Psychiatry* **52**(7): 701-707.

Bird DC, Bujas-Bobanovic M, Robertson HA, Dursun SM (2001). Lack of phencyclidine-induced effects in mice with reduced neuronal nitric oxide synthase. *Psychopharmacology (Berl)* **155**(3): 299-309.

Bitsios P, Giakoumaki SG, Theou K, Frangou S (2006). Increased prepulse inhibition of the acoustic startle response is associated with better strategy formation and execution times in healthy males. *Neuropsychologia* **44**(12): 2494-2499.

Black MD, Selk DE, Hitchcock JM, Wettstein JG, Sorensen SM (1999). On the effect of neonatal nitric oxide synthase inhibition in rats: a potential neurodevelopmental model of schizophrenia. *Neuropharmacology* **38**(9): 1299-1306.

Black MD, Simmonds J, Senyah Y, Wettstein JG (2002). Neonatal nitric oxide synthase inhibition: social interaction deficits in adulthood and reversal by antipsychotic drugs. *Neuropharmacology* **42**(3): 414-420.

Black MD, Varty GB, Arad M, Barak S, De Levie A, Boulay D, *et al* (2008). Procognitive and antipsychotic efficacy of glycine transport 1 inhibitors (GlyT1) in acute and neurodevelopmental models of schizophrenia: latent inhibition studies in the rat. *Psychopharmacology (Berl)*.

Blein S, Hawrot E, Barlow P (2000). The metabotropic GABA receptor: molecular insights and their functional consequences. *Cell Mol Life Sci* **57**(4): 635-650.

Bleuler E (1911/1950). Dementia praecox; or, the group of schizophrenias. *International Universities Press, New York*.

Boeijinga PH, Soufflet L, Santoro F, Luthringer R (2007). Ketamine effects on CNS responses assessed with MEG/EEG in a passive auditory sensory-gating paradigm: an attempt for modelling some symptoms of psychosis in man. *J Psychopharmacol* **21**(3): 321-337.

Bortolato M, Frau R, Aru GN, Orru M, Gessa GL (2004). Baclofen reverses the reduction in prepulse inhibition of the acoustic startle response induced by dizocilpine, but not by apomorphine. *Psychopharmacology (Berl)* **171**(3): 322-330.

Bortolato M, Frau R, Orru M, Piras AP, Fa M, Tuveri A, *et al* (2007). Activation of GABA(B) receptors reverses spontaneous gating deficits in juvenile DBA/2J mice. *Psychopharmacology (Berl)*.

Boucher AA, Arnold JC, Duffy L, Schofield PR, Micheau J, Karl T (2007). Heterozygous neuregulin 1 mice are more sensitive to the behavioural effects of Delta9-tetrahydrocannabinol. *Psychopharmacology (Berl)* **192**(3): 325-336.

Bowery NG, Bettler B, Froestl W, Gallagher JP, Marshall F, Raiteri M, *et al* (2002). International Union of Pharmacology. XXXIII. Mammalian gamma-aminobutyric acid(B) receptors: structure and function. *Pharmacol Rev* **54**(2): 247-264.

Braff D, Stone C, Callaway E, Geyer M, Glick I, Bali L (1978). Prestimulus effects on human startle reflex in normals and schizophrenics. *Psychophysiology* **15**(4): 339-343.

Braff DL, Geyer MA, Swerdlow NR (2001). Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. *Psychopharmacology (Berl)* **156**(2-3): 234-258.

Bredt DS, Glatt CE, Hwang PM, Fotuhi M, Dawson TM, Snyder SH (1991). Nitric oxide synthase protein and mRNA are discretely localized in neuronal populations of the mammalian CNS together with NADPH diaphorase. *Neuron* **7**(4): 615-624.

Breier A, Malhotra AK, Pinals DA, Weisenfeld NI, Pickar D (1997). Association of ketamine-induced psychosis with focal activation of the prefrontal cortex in healthy volunteers. *Am J Psychiatry* **154**(6): 805-811.

Brekke J, Kay DD, Lee KS, Green MF (2005). Biosocial pathways to functional outcome in schizophrenia. *Schizophr Res* **80**(2-3): 213-225.

Brenner CA, Edwards CR, Carroll CA, Kieffaber PD, Hetrick WP (2004). P50 and acoustic startle gating are not related in healthy participants. *Psychophysiology* **41**(5): 702-708.

Brenner CA, Sporns O, Lysaker PH, O'Donnell BF (2003). EEG synchronization to modulated auditory tones in schizophrenia, schizoaffective disorder, and schizotypal personality disorder. *Am J Psychiatry* **160**(12): 2238-2240.

Brody SA, Geyer MA, Large CH (2003). Lamotrigine prevents ketamine but not amphetamine-induced deficits in prepulse inhibition in mice. *Psychopharmacology (Berl)* **169**(3-4): 240-246.

Brown FO, Finnerty NJ, Bolger FB, Millar J, Lowry JP (2005). Calibration of NO sensors for in-vivo voltammetry: laboratory synthesis of NO and the use of UV-visible spectroscopy for determining stock concentrations. *Anal Bioanal Chem* **381**(4): 964-971.

Brown FO, Lowry JP (2003). Microelectrochemical sensors for in vivo brain analysis: an investigation of procedures for modifying Pt electrodes using Nafion. *Analyst* **128**(6): 700-705.

Brown GC (2007). Mechanisms of inflammatory neurodegeneration: iNOS and NADPH oxidase. *Biochem Soc Trans* **35**(Pt 5): 1119-1121.

Brzustowicz LM, Simone J, Mohseni P, Hayter JE, Hodgkinson KA, Chow EW*, et al* (2004). Linkage disequilibrium mapping of schizophrenia susceptibility to the CAPON region of chromosome 1q22. *Am J Hum Genet* **74**(5): 1057-1063.

Bubenikova V, Votava M, Horacek J, Palenicek T, Dockery C (2005). The effect of zotepine, risperidone, clozapine and olanzapine on MK-801-disrupted sensorimotor gating. *Pharmacol Biochem Behav* **80**(4): 591-596.

Bubser M, Koch M (1994). Prepulse inhibition of the acoustic startle response of rats is reduced by 6-hydroxydopamine lesions of the medial prefrontal cortex. *Psychopharmacology (Berl)* **113**(3-4): 487-492.

Bujas-Bobanovic M, Robertson HA, Dursun SM (2000). Effects of nitric oxide synthase inhibitor N(G)-nitro-L-arginine methyl ester on phencyclidine-induced effects in rats. *Eur J Pharmacol* **409**(1): 57-65.

Burris KD, Molski TF, Xu C, Ryan E, Tottori K, Kikuchi T*, et al* (2002). Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Ther* **302**(1): 381-389.

Calkins ME, Iacono WG (2000). Eye movement dysfunction in schizophrenia: a heritable characteristic for enhancing phenotype definition. *Am J Med Genet* **97**(1): 72-76.

Callicott JH, Bertolino A, Mattay VS, Langheim FJ, Duyn J, Coppola R*, et al* (2000). Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. *Cereb Cortex* **10**(11): 1078-1092.

Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR (2003). Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *Am J Psychiatry* **160**(12): 2209-2215.

Carlsson A (1959). The occurrence, distribution and physiological role of catecholamines in the nervous system. *Pharmacol Rev* **11**(2, Part 2): 490-493.

Carlsson A, Lindqvist M (1963). Effect of Chlorpromazine or Haloperidol on Formation of 3methoxytyramine and Normetanephrine in Mouse Brain. *Acta Pharmacol Toxicol (Copenh)* **20**: 140-144.

Carlsson A, Lindqvist M, Magnusson T (1957). 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature* **180**(4596): 1200.

Carlsson A, Lindqvist M, Magnusson T, Waldeck B (1958). On the presence of 3-hydroxytyramine in brain. *Science* **127**(3296): 471.

Carlsson M, Carlsson A (1990). Schizophrenia: a subcortical neurotransmitter imbalance syndrome? *Schizophr Bull* **16**(3): 425-432.

Castellanos FX, Fine EJ, Kaysen D, Marsh WL, Rapoport JL, Hallett M (1996). Sensorimotor gating in boys with Tourette's syndrome and ADHD: preliminary results. *Biol Psychiatry* **39**(1): 33-41.

Castner SA, Williams GV (2007). Tuning the engine of cognition: a focus on NMDA/D1 receptor interactions in prefrontal cortex. *Brain Cogn* **63**(2): 94-122.

Catts SV, Shelley AM, Ward PB, Liebert B, McConaghy N, Andrews S*, et al* (1995). Brain potential evidence for an auditory sensory memory deficit in schizophrenia. *Am J Psychiatry* **152**(2): 213-219.

Chan MH, Chiu PH, Sou JH, Chen HH (2008). Attenuation of ketamine-evoked behavioral responses by mGluR5 positive modulators in mice. *Psychopharmacology (Berl)* **198**(1): 141-148.

Chapman PF, Atkins CM, Allen MT, Haley JE, Steinmetz JE (1992). Inhibition of nitric oxide synthesis impairs two different forms of learning. *Neuroreport* **3**(7): 567-570.

Cilia J, Hatcher P, Reavill C, Jones DN (2007). (+/-) Ketamine-induced prepulse inhibition deficits of an acoustic startle response in rats are not reversed by antipsychotics. *J Psychopharmacol* **21**(3): 302-311.

Claghorn J, Honigfeld G, Abuzzahab FS, Sr., Wang R, Steinbook R, Tuason V, *et al* (1987). The risks and benefits of clozapine versus chlorpromazine. *J Clin Psychopharmacol* **7**(6): 377-384.

Clapcote SJ, Lipina TV, Millar JK, Mackie S, Christie S, Ogawa F, *et al* (2007). Behavioral phenotypes of Disc1 missense mutations in mice. *Neuron* **54**(3): 387-402.

Closs EI, Basha FZ, Habermeier A, Forstermann U (1997). Interference of L-arginine analogues with L-arginine transport mediated by the y+ carrier hCAT-2B. *Nitric Oxide* **1**(1): 65-73.

Cochran SM, Fujimura M, Morris BJ, Pratt JA (2002). Acute and delayed effects of phencyclidine upon mRNA levels of markers of glutamatergic and GABAergic neurotransmitter function in the rat brain. *Synapse* **46**(3): 206-214.

Cochran SM, Kennedy M, McKerchar CE, Steward LJ, Pratt JA, Morris BJ (2003). Induction of metabolic hypofunction and neurochemical deficits after chronic intermittent exposure to phencyclidine: differential modulation by antipsychotic drugs. *Neuropsychopharmacology* **28**(2): 265-275.

Cohen JD, Braver TS, O'Reilly RC (1996). A computational approach to prefrontal cortex, cognitive control and schizophrenia: recent developments and current challenges. *Philos Trans R Soc Lond B Biol Sci* **351**(1346): 1515-1527.

Corbett R, Camacho F, Woods AT, Kerman LL, Fishkin RJ, Brooks K, *et al* (1995). Antipsychotic agents antagonize non-competitive N-methyl-D-aspartate antagonist-induced behaviors. *Psychopharmacology (Berl)* **120**(1): 67-74.

Coyle JT, Tsai G, Goff DC (2002). Ionotropic glutamate receptors as therapeutic targets in schizophrenia. *Curr Drug Targets CNS Neurol Disord* **1**(2): 183-189.

Creese I, Burt DR, Snyder SH (1976). Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science* **192**(4238): 481-483.

Csomor PA, Yee BK, Feldon J, Theodoridou A, Studerus E, Vollenweider FX (2008). Impaired Prepulse Inhibition and Prepulse-Elicited Reactivity but Intact Reflex Circuit Excitability in Unmedicated Schizophrenia Patients: a Comparison With Healthy Subjects and Medicated Schizophrenia Patients. *Schizophr Bull*.

Cunningham MO, Hunt J, Middleton S, LeBeau FE, Gillies MJ, Davies CH, *et al* (2006). Region-specific reduction in entorhinal gamma oscillations and parvalbumin-immunoreactive neurons in animal models of psychiatric illness. *J Neurosci* **26**(10): 2767-2776.

Curtis VA, Bullmore ET, Morris RG, Brammer MJ, Williams SC, Simmons A, *et al* (1999). Attenuated frontal activation in schizophrenia may be task dependent. *Schizophr Res* **37**(1): 35-44.

Daniel DG, Weinberger DR, Jones DW, Zigun JR, Coppola R, Handel S, *et al* (1991). The effect of amphetamine on regional cerebral blood flow during cognitive activation in schizophrenia. *J Neurosci* **11**(7): 1907-1917.

Das I, Khan NS, Puri BK, Hirsch SR (1996). Elevated endogenous nitric oxide synthase inhibitor in schizophrenic plasma may reflect abnormalities in brain nitric oxide production. *Neurosci Lett* **215**(3): 209-211.

Das I, Khan NS, Puri BK, Sooranna SR, de Belleroche J, Hirsch SR (1995). Elevated platelet calcium mobilization and nitric oxide synthase activity may reflect abnormalities in schizophrenic brain. *Biochem Biophys Res Commun* **212**(2): 375-380.

Daskalakis ZJ, Christensen BK, Chen R, Fitzgerald PB, Zipursky RB, Kapur S (2002). Evidence for impaired cortical inhibition in schizophrenia using transcranial magnetic stimulation. *Arch Gen Psychiatry* **59**(4): 347-354.

Davidson LL, Heinrichs RW (2003). Quantification of frontal and temporal lobe brain-imaging findings in schizophrenia: a meta-analysis. *Psychiatry Res* **122**(2): 69-87.

Davis M, Gendelman DS, Tischler MD, Gendelman PM (1982). A primary acoustic startle circuit: lesion and stimulation studies. *J Neurosci* **2**(6): 791-805.

Davis M, Svensson TH, Aghajanian GK (1975). Effects of d- and l-amphetamine on habituation and sensitization of the acoustic startle response in rats. *Psychopharmacologia* **43**(1): 1-11.

Day-Wilson KM, Jones DN, Southam E, Cilia J, Totterdell S (2006). Medial prefrontal cortex volume loss in rats with isolation rearing-induced deficits in prepulse inhibition of acoustic startle. *Neuroscience* **141**(3): 1113-1121.

de Jong IE, van den Buuse M (2006). SCH 23390 in the prefrontal cortex enhances the effect of apomorphine on prepulse inhibition of rats. *Neuropharmacology* **51**(3): 438-446.

Delay J, Deniker P, Harl JM (1952). [Therapeutic use in psychiatry of phenothiazine of central elective action (4560 RP).]. *Ann Med Psychol (Paris)* **110**(2:1): 112-117.

Deutsch SI, Rosse RB, Schwartz BL, Fay-McCarthy M, Rosenberg PB, Fearing K (1997). Methylene blue adjuvant therapy of schizophrenia. *Clin Neuropharmacol* **20**(4): 357-363.

Diaz-Asper CM, Goldberg TE, Kolachana BS, Straub RE, Egan MF, Weinberger DR (2008). Genetic variation in catechol-O-methyltransferase: effects on working memory in schizophrenic patients, their siblings, and healthy controls. *Biol Psychiatry* **63**(1): 72-79.

Dolan RJ, Fletcher P, Frith CD, Friston KJ, Frackowiak RS, Grasby PM (1995). Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia. *Nature* **378**(6553): 180-182.

Doreulee N, Sergeeva OA, Yanovsky Y, Chepkova AN, Selbach O, Godecke A*, et al* (2003). Cortico-striatal synaptic plasticity in endothelial nitric oxide synthase deficient mice. *Brain Res* **964**(1): 159-163.

Duncan EJ, Madonick SH, Parwani A, Angrist B, Rajan R, Chakravorty S*, et al* (2001). Clinical and sensorimotor gating effects of ketamine in normals. *Neuropsychopharmacology* **25**(1): 72-83.

Egerton A, Reid L, McGregor S, Cochran SM, Morris BJ, Pratt JA (2008). Subchronic and chronic PCP treatment produces temporally distinct deficits in attentional set shifting and prepulse inhibition in rats. *Psychopharmacology (Berl)* **198**(1): 37-49.

Egerton A, Reid L, McKerchar CE, Morris BJ, Pratt JA (2005). Impairment in perceptual attentional set-shifting following PCP administration: a rodent model of set-shifting deficits in schizophrenia. *Psychopharmacology (Berl)* **179**(1): 77-84.

Ellenbroek BA, Budde S, Cools AR (1996). Prepulse inhibition and latent inhibition: the role of dopamine in the medial prefrontal cortex. *Neuroscience* **75**(2): 535-542.

Ellenbroek BA, Knobbout DA, Cools AR (1997). The role of mesolimbic and nigrostriatal dopamine in latent inhibition as measured with the conditioned taste aversion paradigm. *Psychopharmacology (Berl)* **129**(2): 112-120.

Ellison G, Switzer RC, 3rd (1993). Dissimilar patterns of degeneration in brain following four different addictive stimulants. *Neuroreport* **5**(1): 17-20.

Elvevag B, Goldberg TE (2000). Cognitive impairment in schizophrenia is the core of the disorder. *Crit Rev Neurobiol* **14**(1): 1-21.

Engel JA, Zhang J, Bergstrom T, Conradi N, Forkstam C, Liljeroth A*, et al* (2000). Neonatal herpes simplex virus type 1 brain infection affects the development of sensorimotor gating in rats. *Brain Res* **863**(1-2): 233-240.

Erhardt S, Blennow K, Nordin C, Skogh E, Lindstrom LH, Engberg G (2001). Kynurenic acid levels are elevated in the cerebrospinal fluid of patients with schizophrenia. *Neurosci Lett* **313**(1-2): 96-98.

Farde L, Nordstrom AL, Nyberg S, Halldin C, Sedvall G (1994). D1-, D2-, and 5-HT2-receptor occupancy in clozapine-treated patients. *J Clin Psychiatry* **55 Suppl B**: 67-69.

Farde L, Wiesel FA, Stone-Elander S, Halldin C, Nordstrom AL, Hall H*, et al* (1990). D2 dopamine receptors in neuroleptic-naive schizophrenic patients. A positron emission tomography study with [11C]raclopride. *Arch Gen Psychiatry* **47**(3): 213-219.

Fearon P, Kirkbride JB, Morgan C, Dazzan P, Morgan K, Lloyd T*, et al* (2006). Incidence of schizophrenia and other psychoses in ethnic minority groups: results from the MRC AESOP Study. *Psychol Med* **36**(11): 1541-1550.

Featherstone RE, Rizos Z, Kapur S, Fletcher PJ (2008). A sensitizing regimen of amphetamine that disrupts attentional set-shifting does not disrupt working or long-term memory. *Behav Brain Res* **189**(1): 170-179.

Fedele E, Varnier G, Raiteri M (1997). In vivo microdialysis study of GABA(A) and GABA(B) receptors modulating the glutamate receptor/NO/cyclic GMP pathway in the rat hippocampus. *Neuropharmacology* **36**(10): 1405-1415.

Fejgin K, Safonov S, Palsson E, Wass C, Engel JA, Svensson L*, et al* (2007). The atypical antipsychotic, aripiprazole, blocks phencyclidine-induced disruption of prepulse inhibition in mice. *Psychopharmacology (Berl)* **191**(2): 377-385.

ffrench-Mullen JM, Rogawski MA (1989). Interaction of phencyclidine with voltage-dependent potassium channels in cultured rat hippocampal neurons: comparison with block of the NMDA receptor-ionophore complex. *J Neurosci* **9**(11): 4051-4061.

Finnerty N (2008). Electrochemical Sensors: In-vitro and in-vivo analysis of brain nitric oxide and regional cerebral blood flow. National University of ireland Maynooth, Maynooth.

Fox JE (1979). Habituation and prestimulus inhibition of the auditory startle reflex in decerebrate rats. *Physiol Behav* **23**(2): 291-297.

Franklin KBJ, Paxinos G (1996). *The Mouse Brain in Stereotaxic Coordinates* Academic Press, New York.

Frederiksen PK (1975). Letter: Baclofen in the treatment of schizophrenia. *Lancet* **1**(7908): 702.

Friebe A, Koesling D (2003). Regulation of nitric oxide-sensitive guanylyl cyclase. *Circ Res* **93**(2): 96-105.

Fries P, Reynolds JH, Rorie AE, Desimone R (2001). Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* **291**(5508): 1560-1563.

Friston KJ, Liddle PF, Frith CD, Hirsch SR, Frackowiak RS (1992). The left medial temporal region and schizophrenia. A PET study. *Brain* **115 (Pt 2)**: 367-382.

Fritzen S, Lauer M, Schmitt A, Topner T, Strobel A, Lesch KP*, et al* (2007). NO synthase-positive striatal interneurons are decreased in schizophrenia. *Eur Neuropsychopharmacol* **17**(9): 595-599.

Froestl W, Gallagher M, Jenkins H, Madrid A, Melcher T, Teichman S*, et al* (2004). SGS742: the first GABA(B) receptor antagonist in clinical trials. *Biochem Pharmacol* **68**(8): 1479-1487.

Furchgott RF (1999). Endothelium-derived relaxing factor: discovery, early studies, and identification as nitric oxide. *Biosci Rep* **19**(4): 235-251.

Fuster JM (1997). Network memory. *Trends Neurosci* **20**(10): 451-459.

Gabbott PL, Bacon SJ (1995). Co-localisation of NADPH diaphorase activity and GABA immunoreactivity in local circuit neurones in the medial prefrontal cortex (mPFC) of the rat. *Brain Res* **699**(2): 321-328.

Galderisi S, Quarantelli M, Volpe U, Mucci A, Cassano GB, Invernizzi G*, et al* (2008). Patterns of structural MRI abnormalities in deficit and nondeficit schizophrenia. *Schizophr Bull* **34**(2): 393-401.

Galletly CA, Clark CR, McFarlane AC (2005). Clozapine improves working memory updating in schizophrenia. *Eur Neuropsychopharmacol* **15**(6): 601-608.

Gallinat J, Winterer G, Herrmann CS, Senkowski D (2004). Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing. *Clin Neurophysiol* **115**(8): 1863-1874.

Gao XM, Shirakawa O, Du F, Tamminga CA (1993). Delayed regional metabolic actions of phencyclidine. *Eur J Pharmacol* **241**(1): 7-15.

Garey RE, Heath RG (1976). The effects of phencyclidine on the uptake of 3H-catecholamines by rat striatal and hypothalamic synaptosomes. *Life Sci* **18**(10): 1105-1110.

Garthwaite J (1985). Cellular uptake disguises action of L-glutamate on N-methyl-D-aspartate receptors. With an appendix: diffusion of transported amino acids into brain slices. *Br J Pharmacol* **85**(1): 297-307.

Garthwaite J (2008). Concepts of neural nitric oxide-mediated transmission. *Eur J Neurosci* **27**(11): 2783-2802.

Garthwaite J, Garthwaite G (1987). Cellular origins of cyclic GMP responses to excitatory amino acid receptor agonists in rat cerebellum in vitro. *J Neurochem* **48**(1): 29-39.

Gassmann M, Shaban H, Vigot R, Sansig G, Haller C, Barbieri S*, et al* (2004). Redistribution of GABAB(1) protein and atypical GABAB responses in GABAB(2)-deficient mice. *J Neurosci* **24**(27): 6086-6097.

Geyer MA, Krebs-Thomson K, Braff DL, Swerdlow NR (2001). Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. *Psychopharmacology (Berl)* **156**(2-3): 117-154.

Geyer MA, Wilkinson LS, Humby T, Robbins TW (1993). Isolation rearing of rats produces a deficit in prepulse inhibition of acoustic startle similar to that in schizophrenia. *Biol Psychiatry* **34**(6): 361-372.

Giakoumaki SG, Roussos P, Bitsios P (2008). Improvement of prepulse inhibition and executive function by the COMT inhibitor tolcapone depends on COMT Val158Met polymorphism. *Neuropsychopharmacology* **33**(13): 3058-3068.

Girault JA, Greengard P (2004). The neurobiology of dopamine signaling. *Arch Neurol* **61**(5): 641-644.

Goldberg TE, Goldman RS, Burdick KE, Malhotra AK, Lencz T, Patel RC*, et al* (2007). Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? *Arch Gen Psychiatry* **64**(10): 1115-1122.

Goldberg TE, Weinberger DR (1996). Effects of neuroleptic medications on the cognition of patients with schizophrenia: a review of recent studies. *J Clin Psychiatry* **57 Suppl 9**: 62-65.

Goldberg TE, Weinberger DR (2004). Genes and the parsing of cognitive processes. *Trends Cogn Sci* **8**(7): 325-335.

Goldman-Rakic PS, Castner SA, Svensson TH, Siever LJ, Williams GV (2004). Targeting the dopamine D1 receptor in schizophrenia: insights for cognitive dysfunction. *Psychopharmacology (Berl)* **174**(1): 3-16.

Gonzalez-Albo MC, Elston GN, DeFelipe J (2001). The human temporal cortex: characterization of neurons expressing nitric oxide synthase, neuropeptides and calcium-binding proteins, and their glutamate receptor subunit profiles. *Cereb Cortex* **11**(12): 1170-1181.

Gotti S, Sica M, Viglietti-Panzica C, Panzica G (2005). Distribution of nitric oxide synthase immunoreactivity in the mouse brain. *Microsc Res Tech* **68**(1): 13-35.

Gozzi A, Large CH, Schwarz A, Bertani S, Crestan V, Bifone A (2007). Differential Effects of Antipsychotic and Glutamatergic Agents on the phMRI Response to Phencyclidine. *Neuropsychopharmacology*.

Green MF (2007). Stimulating the development of drug treatments to improve cognition in schizophrenia. *Annu Rev Clin Psychol* **3**: 159-180.

Green MF, Kern RS, Braff DL, Mintz J (2000). Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull* **26**(1): 119-136.

Green MF, Olivier B, Crawley JN, Penn DL, Silverstein S (2005). Social cognition in schizophrenia: recommendations from the measurement and treatment research to improve cognition in schizophrenia new approaches conference. *Schizophr Bull* **31**(4): 882-887.

Greene JR, Kerkhoff JE, Guiver L, Totterdell S (2001). Structural and functional abnormalities of the hippocampal formation in rats with environmentally induced reductions in prepulse inhibition of acoustic startle. *Neuroscience* **103**(2): 315-323.

Grima G, Benz B, Do KQ (1997). Glutamate-induced release of the nitric oxide precursor, arginine, from glial cells. *Eur J Neurosci* **9**(11): 2248-2258.

Grima G, Cuenod M, Pfeiffer S, Mayer B, Do KQ (1998). Arginine availability controls the N-methyl-D-aspartate-induced nitric oxide synthesis: involvement of a glial-neuronal arginine transfer. *J Neurochem* **71**(5): 2139-2144.

Grunze HC, Rainnie DG, Hasselmo ME, Barkai E, Hearn EF, McCarley RW*, et al* (1996). NMDA-dependent modulation of CA1 local circuit inhibition. *J Neurosci* **16**(6): 2034-2043.

Gulmann NC, Bahr B, Andersen B, Eliassen HM (1976). A double-blind trial of baclofen against placebo in the treatment of schizophrenia. *Acta Psychiatr Scand* **54**(4): 287-293.

Gunduz-Bruce H (2008). The acute effects of NMDA antagonism: From the rodent to the human brain. *Brain Res Rev*.

Harrison PJ, Law AJ, Eastwood SL (2003). Glutamate receptors and transporters in the hippocampus in schizophrenia. *Ann N Y Acad Sci* **1003**: 94-101.

Harrison PJ, Weinberger DR (2005). Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry* **10**(1): 40-68; image 45.

Harte M, O'Connor WT (2005). Evidence for a selective prefrontal cortical GABA(B) receptor-mediated inhibition of glutamate release in the ventral tegmental area: a dual probe microdialysis study in the awake rat. *Neuroscience* **130**(1): 215-222.

Hashimoto K, Engberg G, Shimizu E, Nordin C, Lindstrom LH, Iyo M (2005). Elevated glutamine/glutamate ratio in cerebrospinal fluid of first episode and drug naive schizophrenic patients. *BMC Psychiatry* **5**: 6.

Hashimoto T, Volk DW, Eggan SM, Mirnics K, Pierri JN, Sun Z, *et al* (2003). Gene expression deficits in a subclass of GABA neurons in the prefrontal cortex of subjects with schizophrenia. *J Neurosci* **23**(15): 6315-6326.

Haul S, Godecke A, Schrader J, Haas HL, Luhmann HJ (1999). Impairment of neocortical long-term potentiation in mice deficient of endothelial nitric oxide synthase. *J Neurophysiol* **81**(2): 494-497.

Hazlett EA, Levine J, Buchsbaum MS, Silverman JM, New A, Sevin EM, *et al* (2003). Deficient attentional modulation of the startle response in patients with schizotypal personality disorder. *Am J Psychiatry* **160**(9): 1621-1626.

Heckers S, Rauch SL, Goff D, Savage CR, Schacter DL, Fischman AJ, *et al* (1998). Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. *Nat Neurosci* **1**(4): 318-323.

Heekeren K, Neukirch A, Daumann J, Stoll M, Obradovic M, Kovar KA, *et al* (2007). Prepulse inhibition of the startle reflex and its attentional modulation in the human S-ketamine and N,N-dimethyltryptamine (DMT) models of psychosis. *J Psychopharmacol* **21**(3): 312-320.

Herken H, Uz E, Ozyurt H, Akyol O (2001). Red blood cell nitric oxide levels in patients with schizophrenia. *Schizophr Res* **52**(3): 289-290.

Hertel P, Fagerquist MV, Svensson TH (1999). Enhanced cortical dopamine output and antipsychotic-like effects of raclopride by alpha2 adrenoceptor blockade. *Science* **286**(5437): 105-107.

Hevers W, Hadley SH, Luddens H, Amin J (2008). Ketamine, but not phencyclidine, selectively modulates cerebellar GABA(A) receptors containing alpha6 and delta subunits. *J Neurosci* **28**(20): 5383-5393.

Holzman PS (2000). Eye movements and the search for the essence of schizophrenia. *Brain Res Brain Res Rev* **31**(2-3): 350-356.

Homayoun H, Moghaddam B (2007). NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. *J Neurosci* **27**(43): 11496-11500.

Honey GD, Bullmore ET, Sharma T (2002). De-coupling of cognitive performance and cerebral functional response during working memory in schizophrenia. *Schizophr Res* **53**(1-2): 45-56.

Honey RA, Turner DC, Honey GD, Sharar SR, Kumaran D, Pomarol-Clotet E, *et al* (2003). Subdissociative dose ketamine produces a deficit in manipulation but not maintenance of the contents of working memory. *Neuropsychopharmacology* **28**(11): 2037-2044.

Howard MW, Rizzuto DS, Caplan JB, Madsen JR, Lisman J, Aschenbrenner-Scheibe R, *et al* (2003). Gamma oscillations correlate with working memory load in humans. *Cereb Cortex* **13**(12): 1369-1374.

Huang CS, Shi SH, Ule J, Ruggiu M, Barker LA, Darnell RB, *et al* (2005). Common molecular pathways mediate long-term potentiation of synaptic excitation and slow synaptic inhibition. *Cell* **123**(1): 105-118.

Huerta I, McCullumsmith RE, Haroutunian V, Gimenez-Amaya JM, Meador-Woodruff JH (2006). Expression of excitatory amino acid transporter interacting protein transcripts in the thalamus in schizophrenia. *Synapse* **59**(7): 394-402.

Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G (1987). Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proc Natl Acad Sci U S A* **84**(24): 9265-9269.

Ingvar DH, Franzen G (1974). Distribution of cerebral activity in chronic schizophrenia. *Lancet* **2**(7895): 1484-1486.

Ison JR, McAdam DW, Hammond GR (1973). Latency and amplitude changes in the acoustic startle reflex of the rat produced by variation in auditory prestimulation. *Physiol Behav* **10**(6): 1035-1039.

Itil T, Keskiner A, Kiremitci N, Holden JM (1967). Effect of phencyclidine in chronic schizophrenics. *Can Psychiatr Assoc J* **12**(2): 209-212.

Jackson ME, Homayoun H, Moghaddam B (2004). NMDA receptor hypofunction produces concomitant firing rate potentiation and burst activity reduction in the prefrontal cortex. *Proc Natl Acad Sci U S A* **101**(22): 8467-8472.

Javitt DC (2007). Glutamate and Schizophrenia: Phencyclidine, N-Methyl-d-Aspartate Receptors, and Dopamine-Glutamate Interactions. *Int Rev Neurobiol* **78**: 69-108.

Javitt DC (2008). Glycine transport inhibitors and the treatment of schizophrenia. *Biol Psychiatry* **63**(1): 6-8.

Javitt DC, Zukin SR (1991). Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry* **148**(10): 1301-1308.

Jedlitschky G, Burchell B, Keppler D (2000). The multidrug resistance protein 5 functions as an ATP-dependent export pump for cyclic nucleotides. *J Biol Chem* **275**(39): 30069-30074.

Jentsch JD, Redmond DE, Jr., Elsworth JD, Taylor JR, Youngren KD, Roth RH (1997a). Enduring cognitive deficits and cortical dopamine dysfunction in monkeys after long-term administration of phencyclidine. *Science* **277**(5328): 953-955.

Jentsch JD, Roth RH (1999). The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology* **20**(3): 201-225.

Jentsch JD, Tran A, Le D, Youngren KD, Roth RH (1997b). Subchronic phencyclidine administration reduces mesoprefrontal dopamine utilization and impairs prefrontal cortical-dependent cognition in the rat. *Neuropsychopharmacology* **17**(2): 92-99.

Johansson C, Deveney AM, Reif D, Jackson DM (1999). The neuronal selective nitric oxide inhibitor AR-R 17477, blocks some effects of phencyclidine, while having no observable behavioural effects when given alone. *Pharmacol Toxicol* **84**(5): 226-233.

Johansson C, Jackson DM, Svensson L (1997). Nitric oxide synthase inhibition blocks phencyclidine-induced behavioural effects on prepulse inhibition and locomotor activity in the rat. *Psychopharmacology (Berl)* **131**(2): 167-173.

Johansson C, Jackson DM, Zhang J, Svensson L (1995). Prepulse inhibition of acoustic startle, a measure of sensorimotor gating: effects of antipsychotics and other agents in rats. *Pharmacol Biochem Behav* **52**(4): 649-654.

Johansson C, Magnusson O, Deveney AM, Jackson DM, Zhang J, Engel JA*, et al* (1998). The nitric oxide synthase inhibitor, L-NAME, blocks certain phencyclidine-induced but not amphetamin-induced effects on behaviour and brain biochemistry in the rat. *Prog Neuro-Psychopharmacol & Biol Psychiat* **22**: 1341-1360.

Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L (1976). Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet* **2**(7992): 924-926.

Jonas P, Racca C, Sakmann B, Seeburg PH, Monyer H (1994). Differences in Ca2+ permeability of AMPA-type glutamate receptor channels in neocortical neurons caused by differential GluR-B subunit expression. *Neuron* **12**(6): 1281-1289.

Jones EG (1987). Ascending inputs to, and internal organization of, cortical motor areas. *Ciba Found Symp* **132**: 21-39.

Jones GH, Marsden CA, Robbins TW (1990). Increased sensitivity to amphetamine and reward-related stimuli following social isolation in rats: possible disruption of dopamine-dependent mechanisms of the nucleus accumbens. *Psychopharmacology (Berl)* **102**(3): 364-372.

Jones RS, Buhl EH (1993). Basket-like interneurones in layer II of the entorhinal cortex exhibit a powerful NMDA-mediated synaptic excitation. *Neurosci Lett* **149**(1): 35-39.

Judd LL, McAdams L, Budnick B, Braff DL (1992). Sensory gating deficits in schizophrenia: new results. *Am J Psychiatry* **149**(4): 488-493.

Kahn RS, Harvey PD, Davidson M, Keefe RS, Apter S, Neale JM*, et al* (1994). Neuropsychological correlates of central monoamine function in chronic schizophrenia: relationship between CSF metabolites and cognitive function. *Schizophr Res* **11**(3): 217-224.

Kalinichev M, Robbins MJ, Hartfield EM, Maycox PR, Moore SH, Savage KM*, et al* (2008). Comparison between intraperitoneal and subcutaneous phencyclidine administration in Sprague-Dawley rats: a locomotor activity and gene induction study. *Prog Neuropsychopharmacol Biol Psychiatry* **32**(2): 414-422.

Kamiya A, Kubo K, Tomoda T, Takaki M, Youn R, Ozeki Y*, et al* (2005). A schizophrenia-associated mutation of DISC1 perturbs cerebral cortex development. *Nat Cell Biol* **7**(12): 1167-1178.

Kane J, Honigfeld G, Singer J, Meltzer H (1988). Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* **45**(9): 789-796.

Kane JM, Carson WH, Saha AR, McQuade RD, Ingenito GG, Zimbroff DL*, et al* (2002). Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry* **63**(9): 763-771.

Kano T, Shimizu-Sasamata M, Huang PL, Moskowitz MA, Lo EH (1998). Effects of nitric oxide synthase gene knockout on neurotransmitter release in vivo. *Neuroscience* **86**(3): 695-699.

Kapur S, Remington G, Jones C, Wilson A, DaSilva J, Houle S*, et al* (1996). High levels of dopamine D2 receptor occupancy with low-dose haloperidol treatment: a PET study. *Am J Psychiatry* **153**(7): 948-950.

Kapur S, Seeman P (2002). NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D(2) and serotonin 5-HT(2)receptors-implications for models of schizophrenia. *Mol Psychiatry* **7**(8): 837-844.

Karatinos J, Rosse RB, Deutsch SI (1995). The nitric oxide pathway: potential implications for treatment of neuropsychiatric disorders. *Clin Neuropharmacol* **18**(6): 482-499.

Karlsson P, Farde L, Halldin C, Sedvall G (2002). PET study of D(1) dopamine receptor binding in neuroleptic-naive patients with schizophrenia. *Am J Psychiatry* **159**(5): 761-767.

Karper LP, Freeman GK, Grillon C, Morgan CA, 3rd, Charney DS, Krystal JH (1996). Preliminary evidence of an association between sensorimotor gating and distractibility in psychosis. *J Neuropsychiatry Clin Neurosci* **8**(1): 60-66.

Karson CN, Griffin WS, Mrak RE, Husain M, Dawson TM, Snyder SH*, et al* (1996). Nitric oxide synthase (NOS) in schizophrenia: increases in cerebellar vermis. *Mol Chem Neuropathol* **27**(3): 275-284.

Keck PE, Jr., McElroy SL (2003). Aripiprazole: a partial dopamine D2 receptor agonist antipsychotic. *Expert Opin Investig Drugs* **12**(4): 655-662.

Kedzior KK, Koch M, Basar-Eroglu C (2007). Auditory-evoked EEG oscillations associated with prepulse inhibition (PPI) of auditory startle reflex in healthy humans. *Brain Res* **1163**: 111-118.

Keefe RS, Bilder RM, Davis SM, Harvey PD, Palmer BW, Gold JM*, et al* (2007a). Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry* **64**(6): 633-647.

Keefe RS, Sweeney JA, Gu H, Hamer RM, Perkins DO, McEvoy JP*, et al* (2007b). Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry* **164**(7): 1061-1071.

Kegeles LS, Abi-Dargham A, Zea-Ponce Y, Rodenhiser-Hill J, Mann JJ, Van Heertum RL*, et al* (2000). Modulation of amphetamine-induced striatal dopamine release by ketamine in humans: implications for schizophrenia. *Biol Psychiatry* **48**(7): 627-640.

Keilhoff G, Becker A, Grecksch G, Wolf G, Bernstein HG (2004). Repeated application of ketamine to rats induces changes in the hippocampal expression of parvalbumin, neuronal nitric oxide synthase and cFOS similar to those found in human schizophrenia. *Neuroscience* **126**(3): 591-598.

Keith VA, Mansbach RS, Geyer MA (1991). Failure of haloperidol to block the effects of phencyclidine and dizocilpine on prepulse inhibition of startle. *Biol Psychiatry* **30**(6): 557-566.

Kessler M, Terramani T, Lynch G, Baudry M (1989). A glycine site associated with N-methyl-D-aspartic acid receptors: characterization and identification of a new class of antagonists. *J Neurochem* **52**(4): 1319-1328.

Kim JS, Kornhuber HH, Schmid-Burgk W, Holzmuller B (1980). Low cerebrospinal fluid glutamate in schizophrenic patients and a new hypothesis on schizophrenia. *Neurosci Lett* **20**(3): 379-382.

Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J*, et al* (2006). Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study. *Arch Gen Psychiatry* **63**(3): 250-258.

Klamer D, Engel JA, Svensson L (2001). The nitric oxide synthase inhibitor, L-NAME, blocks phencyclidine-induced disruption of prepulse inhibition in mice. *Psychopharmacology (Berl)* **156**(2-3): 182-186.

Klamer D, Engel JA, Svensson L (2004a). Phencyclidine-induced behaviour in mice prevented by methylene blue. *Basic Clin Pharmacol Toxicol* **94**(2): 65-72.

Klamer D, Engel JA, Svensson L (2004b). The neuronal selective nitric oxide synthase inhibitor, Nomega-propyl-L-arginine, blocks the effects of phencyclidine on prepulse inhibition and locomotor activity in mice. *Eur J Pharmacol* **503**(1-3): 103-107.

Klamer D, Engel JA, Svensson L (2005a). Effects of phencyclidine on acoustic startle and prepulse inhibition in neuronal nitric oxide synthase deficient mice. *Eur Neuropsychopharmacol* **15**(5): 587-590.

Klamer D, Palsson E, Fejgin K, Zhang J, Engel JA, Svensson L (2005b). Activation of a nitric-oxide-sensitive cAMP pathway with phencyclidine: elevated hippocampal cAMP levels are temporally associated with deficits in prepulse inhibition. *Psychopharmacology (Berl)* **179**(2): 479-488.

Klamer D, Palsson E, Revesz A, Engel JA, Svensson L (2004c). Habituation of acoustic startle is disrupted by psychotomimetic drugs: differential dependence on dopaminergic and nitric oxide modulatory mechanisms. *Psychopharmacology (Berl)* **176**(3-4): 440-450.

Klamer D, Palsson E, Wass C, Archer T, Engel JA, Svensson L (2005c). Antagonism of the nitric oxide synthase inhibitor, L-NAME, of the effects of phencyclidine on latent inhibition in taste aversion conditioning. *Behav Brain Res* **161**(1): 60-68.

Klamer D, Zhang J, Engel JA, Svensson L (2005d). Selective interaction of nitric oxide synthase inhibition with phencyclidine: behavioural and NMDA receptor binding studies in the rat. *Behav Brain Res* **159**(1): 95-103.

Koch M (1999). The neurobiology of startle. *Prog Neurobiol* **59**(2): 107-128.

Kraepelin E (1907). *Text book of psychiatry (7th ed) (trans. A.R. Diefendorf)* London: Macmillan.

Kraepelin E, Robertson G (1919). Dementia praecox an paraphrenia. *Livingstone Edinburgh*.

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD*, et al* (1994). Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* **51**(3): 199-214.

Kumari V, Aasen I, Sharma T (2004). Sex differences in prepulse inhibition deficits in chronic schizophrenia. *Schizophr Res* **69**(2-3): 219-235.

Kumari V, Das M, Zachariah E, Ettinger U, Sharma T (2005). Reduced prepulse inhibition in unaffected siblings of schizophrenia patients. *Psychophysiology* **42**(5): 588-594.

Kumari V, Fannon D, Geyer MA, Premkumar P, Antonova E, Simmons A*, et al* (2008). Cortical grey matter volume and sensorimotor gating in schizophrenia. *Cortex* **44**(9): 1206-1214.

Lahti AC, Holcomb HH, Medoff DR, Tamminga CA (1995). Ketamine activates psychosis and alters limbic blood flow in schizophrenia. *Neuroreport* **6**(6): 869-872.

Lahti AC, Weiler MA, Tamara Michaelidis BA, Parwani A, Tamminga CA (2001). Effects of ketamine in normal and schizophrenic volunteers. *Neuropsychopharmacology* **25**(4): 455-467.

Laitinen JT, Laitinen KS, Tuomisto L, Airaksinen MM (1994). Differential regulation of cyclic GMP levels in the frontal cortex and the cerebellum of anesthetized rats by nitric oxide: an in vivo microdialysis study. *Brain Res* **668**(1-2): 117-121.

Laitinen KS, Salovaara K, Severgnini S, Laitinen JT (1997). Regulation of cyclic GMP levels in the rat frontal cortex in vivo: effects of exogenous carbon monoxide and phosphodiesterase inhibition. *Brain Res* **755**(2): 272-278.

Larsson A, Engel JA (2004). Neurochemical and behavioral studies on ethanol and nicotine interactions. *Neurosci Biobehav Rev* **27**(8): 713-720.

Laruelle M (1998). Imaging dopamine transmission in schizophrenia. A review and meta-analysis. *Q J Nucl Med* **42**(3): 211-221.

Laruelle M, Abi-Dargham A (1999). Dopamine as the wind of the psychotic fire: new evidence from brain imaging studies. *J Psychopharmacol* **13**(4): 358-371.

Laruelle M, Frankle WG, Narendran R, Kegeles LS, Abi-Dargham A (2005). Mechanism of action of antipsychotic drugs: from dopamine D(2) receptor antagonism to glutamate NMDA facilitation. *Clin Ther* **27 Suppl A**: S16-24.

Laruelle M, Kegeles LS, Abi-Dargham A (2003). Glutamate, dopamine, and schizophrenia: from pathophysiology to treatment. *Ann N Y Acad Sci* **1003**: 138-158.

Lauer M, Johannes S, Fritzen S, Senitz D, Riederer P, Reif A (2005). Morphological abnormalities in nitric-oxide-synthase-positive striatal interneurons of schizophrenic patients. *Neuropsychobiology* **52**(3): 111-117.

Lee BH, Kim YK (2008). Reduced plasma nitric oxide metabolites before and after antipsychotic treatment in patients with schizophrenia compared to controls. *Schizophr Res* **104**(1-3): 36-43.

Lei S, McBain CJ (2002). Distinct NMDA receptors provide differential modes of transmission at mossy fiber-interneuron synapses. *Neuron* **33**(6): 921-933.

Leonard CM (1969). The prefrontal cortex of the rat. I. Cortical projection of the mediodorsal nucleus. II. Efferent connections. *Brain Res* **12**(2): 321-343.

Levine MS, Li Z, Cepeda C, Cromwell HC, Altemus KL (1996). Neuromodulatory actions of dopamine on synaptically-evoked neostriatal responses in slices. *Synapse* **24**(1): 65-78.

Levy DL, Holzman PS, Matthysse S, Mendell NR (1994). Eye tracking and schizophrenia: a selective review. *Schizophr Bull* **20**(1): 47-62.

Lewis DA, Cho RY, Carter CS, Eklund K, Forster S, Kelly MA*, et al* (2008). Subunit-Selective Modulation of GABA Type A Receptor Neurotransmission and Cognition in Schizophrenia. *Am J Psychiatry*.

Lewis DA, Hashimoto T, Volk DW (2005). Cortical inhibitory neurons and schizophrenia. *Nat Rev Neurosci* **6**(4): 312-324.

Lewis DA, Moghaddam B (2006). Cognitive dysfunction in schizophrenia: convergence of gamma-aminobutyric acid and glutamate alterations. *Arch Neurol* **63**(10): 1372-1376.

Lewis G, David A, Andreasson S, Allebeck P (1992). Schizophrenia and city life. *Lancet* **340**(8812): 137-140.

Li D, He L (2007). Association study between the NMDA receptor 2B subunit gene (GRIN2B) and schizophrenia: a HuGE review and meta-analysis. *Genet Med* **9**(1): 4-8.

Liddle PF (1987). The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. *Br J Psychiatry* **151**: 145-151.

Lieberman JA (1999). Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. *Biol Psychiatry* **46**(6): 729-739.

Light GA, Braff DL (2001). Measuring P50 suppression and prepulse inhibition in a single recording session. *Am J Psychiatry* **158**(12): 2066-2068.

Light GA, Braff DL (2005). Mismatch negativity deficits are associated with poor functioning in schizophrenia patients. *Arch Gen Psychiatry* **62**(2): 127-136.

Light GA, Hsu JL, Hsieh MH, Meyer-Gomes K, Sprock J, Swerdlow NR*, et al* (2006). Gamma band oscillations reveal neural network cortical coherence dysfunction in schizophrenia patients. *Biol Psychiatry* **60**(11): 1231-1240.

Lindstrom LH, Gefvert O, Hagberg G, Lundberg T, Bergstrom M, Hartvig P*, et al* (1999). Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(beta-11C) DOPA and PET. *Biol Psychiatry* **46**(5): 681-688.

Lingenhohl K, Friauf E (1994). Giant neurons in the rat reticular formation: a sensorimotor interface in the elementary acoustic startle circuit? *J Neurosci* **14**(3 Pt 1): 1176-1194.

Linn GS, Javitt DC (2001). Phencyclidine (PCP)-induced deficits of prepulse inhibition in monkeys. *Neuroreport* **12**(1): 117-120.

Linn GS, Negi SS, Gerum SV, Javitt DC (2003). Reversal of phencyclidine-induced prepulse inhibition deficits by clozapine in monkeys. *Psychopharmacology (Berl)* **169**(3-4): 234-239.

Lipska BK (2004). Using animal models to test a neurodevelopmental hypothesis of schizophrenia. *J Psychiatry Neurosci* **29**(4): 282-286.

Lisman JE, Coyle JT, Green RW, Javitt DC, Benes FM, Heckers S*, et al* (2008). Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends Neurosci* **31**(5): 234-242.

Liu Y, Wong TP, Aarts M, Rooyakkers A, Liu L, Lai TW*, et al* (2007). NMDA receptor subunits have differential roles in mediating excitotoxic neuronal death both in vitro and in vivo. *J Neurosci* **27**(11): 2846-2857.

Loebel AD, Lieberman JA, Alvir JM, Mayerhoff DI, Geisler SH, Szymanski SR (1992). Duration of psychosis and outcome in first-episode schizophrenia. *Am J Psychiatry* **149**(9): 1183-1188.

Lopes MC, Cardoso SA, Schousboe A, Carvalho AP (1994). Amino acids differentially inhibit the L-[3H]arginine transport and nitric oxide synthase in rat brain synaptosomes. *Neurosci Lett* **181**(1-2): 1-4.

Lowry JP, Boutelle MG, Fillenz M (1997). Measurement of brain tissue oxygen at a carbon past electrode can serve as an index of increases in regional cerebral blood flow. *J Neurosci Methods* **71**(2): 177-182.

Luby ED, Cohen BD, Rosenbaum G, Gottlieb LS, Kelly R (1959). Study of a new schizophrenomimetic drug-sernyl. *Arch Neurol Psychiatry* **81**: 363-369.

Lynch DR, Guttmann RP (2001). NMDA receptor pharmacology: perspectives from molecular biology. *Curr Drug Targets* **2**(3): 215-231.

Maccabe JH (2008). Population-based Cohort Studies on Premorbid Cognitive Function in Schizophrenia. *Epidemiol Rev.*

Macdonald RL, Olsen RW (1994). GABAA receptor channels. *Annu Rev Neurosci* **17**: 569-602.

Mackeprang T, Kristiansen KT, Glenthoj BY (2002). Effects of antipsychotics on prepulse inhibition of the startle response in drug-naive schizophrenic patients. *Biol Psychiatry* **52**(9): 863-873.

Malaspina D, Harkavy-Friedman J, Corcoran C, Mujica-Parodi L, Printz D, Gorman JM*, et al* (2004). Resting neural activity distinguishes subgroups of schizophrenia patients. *Biol Psychiatry* **56**(12): 931-937.

Manoach DS (2003). Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. *Schizophr Res* **60**(2-3): 285-298.

Manoach DS, Gollub RL, Benson ES, Searl MM, Goff DC, Halpern E*, et al* (2000). Schizophrenic subjects show aberrant fMRI activation of dorsolateral prefrontal cortex and basal ganglia during working memory performance. *Biol Psychiatry* **48**(2): 99-109.

Manoach DS, Press DZ, Thangaraj V, Searl MM, Goff DC, Halpern E*, et al* (1999). Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. *Biol Psychiatry* **45**(9): 1128-1137.

Mansbach RS, Brooks EW, Sanner MA, Zorn SH (1998). Selective dopamine D4 receptor antagonists reverse apomorphine-induced blockade of prepulse inhibition. *Psychopharmacology (Berl)* **135**(2): 194-200.

Mansbach RS, Geyer MA (1989). Effects of phencyclidine and phencyclidine biologs on sensorimotor gating in the rat. *Neuropsychopharmacology* **2**(4): 299-308.

Markram H, Toledo-Rodriguez M, Wang Y, Gupta A, Silberberg G, Wu C (2004). Interneurons of the neocortical inhibitory system. *Nat Rev Neurosci* **5**(10): 793-807.

McGowan S, Lawrence AD, Sales T, Quested D, Grasby P (2004). Presynaptic dopaminergic dysfunction in schizophrenia: a positron emission tomographic [18F]fluorodopa study. *Arch Gen Psychiatry* **61**(2): 134-142.

McGrath J, Saha S, Chant D, Welham J (2008). Schizophrenia: A Concise Overview of Incidence, Prevalence, and Mortality. *Epidemiol Rev.*

McGurk SR (1999). The effects of clozapine on cognitive functioning in schizophrenia. *J Clin Psychiatry* **60 Suppl 12**: 24-29.

McNamara RK, Skelton RW (1996). Baclofen, a selective GABAB receptor agonist, dose-dependently impairs spatial learning in rats. *Pharmacol Biochem Behav* **53**(2): 303-308.

Meltzer HY, Gudelsky GA (1992). Dopaminergic and serotonergic effects of clozapine. Implications for a unique clinical profile. *Arzneimittelforschung* **42**(2A): 268-272.

Menon V, Anagnoson RT, Mathalon DH, Glover GH, Pfefferbaum A (2001). Functional neuroanatomy of auditory working memory in schizophrenia: relation to positive and negative symptoms. *Neuroimage* **13**(3): 433-446.

Meyer-Lindenberg A, Miletich RS, Kohn PD, Esposito G, Carson RE, Quarantelli M*, et al* (2002). Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. *Nat Neurosci* **5**(3): 267-271.

Michie PT (2001). What has MMN revealed about the auditory system in schizophrenia? *Int J Psychophysiol* **42**(2): 177-194.

Mitchell IJ, Cooper AJ, Griffiths MR, Barber DJ (1998). Phencyclidine and corticosteroids induce apoptosis of a subpopulation of striatal neurons: a neural substrate for psychosis? *Neuroscience* **84**(2): 489-501.

Miyakawa T, Leiter LM, Gerber DJ, Gainetdinov RR, Sotnikova TD, Zeng H, *et al* (2003). Conditional calcineurin knockout mice exhibit multiple abnormal behaviors related to schizophrenia. *Proc Natl Acad Sci U S A* **100**(15): 8987-8992.

Moghaddam B (2004). Targeting metabotropic glutamate receptors for treatment of the cognitive symptoms of schizophrenia. *Psychopharmacology (Berl)*.

Moghaddam B, Adams B, Verma A, Daly D (1997). Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci* **17**(8): 2921-2927.

Moghaddam B, Homayoun H (2008). Divergent plasticity of prefrontal cortex networks. *Neuropsychopharmacology* **33**(1): 42-55.

Mohn AR, Gainetdinov RR, Caron MG, Koller BH (1999). Mice with reduced NMDA receptor expression display behaviors related to schizophrenia. *Cell* **98**(4): 427-436.

Molteni R, Pasini M, Moraschi S, Gennarelli M, Drago F, Racagni G, *et al* (2008). Reduced activation of intracellular signaling pathways in rat prefrontal cortex after chronic phencyclidine administration. *Pharmacol Res* **57**(4): 296-302.

Monaghan DT, Cotman CW (1985). Distribution of N-methyl-D-aspartate-sensitive L-[3H]glutamate-binding sites in rat brain. *J Neurosci* **5**(11): 2909-2919.

Morales-Medina JC, Mejorada A, Romero-Curiel A, Aguilar-Alonso P, Leon-Chavez BA, Gamboa C, *et al* (2008). Neonatal administration of N-omega-nitro-l-arginine induces permanent decrease in NO levels and hyperresponsiveness to locomotor activity by d-amphetamine in postpubertal rats. *Neuropharmacology*.

Morris BJ, Cochran SM, Pratt JA (2005). PCP: from pharmacology to modelling schizophrenia. *Curr Opin Pharmacol* **5**(1): 101-106.

Murotani T, Ishizuka T, Hattori S, Hashimoto R, Matsuzaki S, Yamatodani A (2007). High dopamine turnover in the brains of Sandy mice. *Neurosci Lett* **421**(1): 47-51.

Nakanishi S, Nakajima Y, Masu M, Ueda Y, Nakahara K, Watanabe D, *et al* (1998). Glutamate receptors: brain function and signal transduction. *Brain Res Brain Res Rev* **26**(2-3): 230-235.

Nesvag R, Lawyer G, Varnas K, Fjell AM, Walhovd KB, Frigessi A, *et al* (2008). Regional thinning of the cerebral cortex in schizophrenia: effects of diagnosis, age and antipsychotic medication. *Schizophr Res* **98**(1-3): 16-28.

Newcomer JW, Farber NB, Jevtovic-Todorovic V, Selke G, Melson AK, Hershey T, *et al* (1999). Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. *Neuropsychopharmacology* **20**(2): 106-118.

Nilsson LK, Linderholm KR, Engberg G, Paulson L, Blennow K, Lindstrom LH, *et al* (2005). Elevated levels of kynurenic acid in the cerebrospinal fluid of male patients with schizophrenia. *Schizophr Res* **80**(2-3): 315-322.

O'Donnell P, Lewis BL, Weinberger DR, Lipska BK (2002). Neonatal hippocampal damage alters electrophysiological properties of prefrontal cortical neurons in adult rats. *Cereb Cortex* **12**(9): 975-982.

O'Kane RL, Vina JR, Simpson I, Zaragoza R, Mokashi A, Hawkins RA (2006). Cationic amino acid transport across the blood-brain barrier is mediated exclusively by system y+. *Am J Physiol Endocrinol Metab* **291**(2): E412-419.

Ohnuma T, Sakai Y, Maeshima H, Hatano T, Hanzawa R, Abe S, *et al* (2008). Changes in plasma glycine, l-serine, and d-serine levels in patients with schizophrenia as their clinical symptoms improve: Results from the Juntendo University Schizophrenia Projects (JUSP). *Prog Neuropsychopharmacol Biol Psychiatry*.

Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, *et al* (1997). Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. *Nature* **385**(6617): 634-636.

Olney JW, Farber NB (1995). NMDA antagonists as neurotherapeutic drugs, psychotogens, neurotoxins, and research tools for studying schizophrenia. *Neuropsychopharmacology* **13**(4): 335-345.

Olney JW, Labruyere J, Price MT (1989). Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science* **244**(4910): 1360-1362.

Oranje B, Gispen-de Wied CC, Verbaten MN, Kahn RS (2002). Modulating sensory gating in healthy volunteers: the effects of ketamine and haloperidol. *Biol Psychiatry* **52**(9): 887-895.

Oranje B, van Berckel BN, Kemner C, van Ree JM, Kahn RS, Verbaten MN (1999). P50 suppression and prepulse inhibition of the startle reflex in humans: a correlational study. *Biol Psychiatry* **45**(7): 883-890.

Palmer RM, Ferrige AG, Moncada S (1987). Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* **327**(6122): 524-526.

Palsson E, Fejgin K, Wass C, Klamer D (2008). Agmatine attenuates the disruptive effects of phencyclidine on prepulse inhibition. *Eur J Pharmacol* **590**(1-3): 212-216.

Palsson E, Klamer D, Wass C, Archer T, Engel JA, Svensson L (2005). The effects of phencyclidine on latent inhibition in taste aversion conditioning: differential effects of preexposure and conditioning. *Behav Brain Res* **157**(1): 139-146.

Park S, Holzman PS (1992). Schizophrenics show spatial working memory deficits. *Arch Gen Psychiatry* **49**(12): 975-982.

Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV*, et al* (2007). Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. *Nat Med*.

Paxinos G, Watson C (2005). *The Rat Brain in Stereotaxic Coordinates* Academic Press, New York.

Penades R, Catalan R, Salamero M, Boget T, Puig O, Guarch J*, et al* (2006). Cognitive remediation therapy for outpatients with chronic schizophrenia: a controlled and randomized study. *Schizophr Res* **87**(1-3): 323-331.

Penn DL, Corrigan PW, Bentall RP, Racenstein JM, Newman L (1997). Social cognition in schizophrenia. *Psychol Bull* **121**(1): 114-132.

Pepicelli O, Brescia A, Gherzi E, Raiteri M, Fedele E (2004). GABA(A), but not NMDA, receptors modulate in vivo NO-mediated cGMP synthesis in the rat cerebral cortex. *Neuropharmacology* **46**(4): 480-489.

Peralta V, Cuesta MJ (2003). The nosology of psychotic disorders: a comparison among competing classification systems. *Schizophr Bull* **29**(3): 413-425.

Perlstein WM, Carter CS, Noll DC, Cohen JD (2001). Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. *Am J Psychiatry* **158**(7): 1105-1113.

Perry W, Braff DL (1994). Information-processing deficits and thought disorder in schizophrenia. *Am J Psychiatry* **151**(3): 363-367.

Pifarre P, Garcia A, Mengod G (2007). Species differences in the localization of soluble guanylyl cyclase subunits in monkey and rat brain. *J Comp Neurol* **500**(5): 942-957.

Pilowsky LS, Bressan RA, Stone JM, Erlandsson K, Mulligan RS, Krystal JH*, et al* (2006). First in vivo evidence of an NMDA receptor deficit in medication-free schizophrenic patients. *Mol Psychiatry* **11**(2): 118-119.

Pilz PK, Schnitzler HU (1996). Habituation and sensitization of the acoustic startle response in rats: amplitude, threshold, and latency measures. *Neurobiol Learn Mem* **66**(1): 67-79.

Pitsikas N, Rigamonti AE, Cella SG, Muller EE (2003). The GABAB receptor and recognition memory: possible modulation of its behavioral effects by the nitrergic system. *Neuroscience* **118**(4): 1121-1127.

Pletnikov MV, Rubin SA, Vogel MW, Moran TH, Carbone KM (2002). Effects of genetic background on neonatal Borna disease virus infection-induced neurodevelopmental damage. I. Brain pathology and behavioral deficits. *Brain Res* **944**(1-2): 97-107.

Poulopoulou C, Nowak LM (1998). Extracellular 3',5' cyclic guanosine monophosphate inhibits kainate-activated responses in cultured mouse cerebellar neurons. *J Pharmacol Exp Ther* **286**(1): 99-109.

Pouzet B, Andersen MP, Hogg S (2004). Effects of acute treatment with antidepressant drugs on sensorimotor gating deficits in rats. *Psychopharmacology (Berl)*.

Prast H, Philippu A (2001). Nitric oxide as modulator of neuronal function. *Prog Neurobiol* **64**(1): 51-68.

Pratt JA, Winchester C, Egerton A, Cochran SM, Morris BJ (2008). Modelling prefrontal cortex deficits in schizophrenia: implications for treatment. *Br J Pharmacol* **153 Suppl 1**: S465-470.

Prendergast MA, Buccafusco JJ, Terry AV, Jr. (1997). Nitric oxide synthase inhibition impairs spatial navigation learning and induces conditioned taste aversion. *Pharmacol Biochem Behav* **57**(1-2): 347-352.

Pubill D, Canudas AM, Sureda FX, Camins A, Pallas M, Escubedo E, *et al* (1998). Effect of PCP and sigma ligands on both noradrenaline- and electrically-induced contractions and on [3H]-noradrenaline uptake in rat vas deferens. *J Auton Pharmacol* **18**(4): 239-244.

Quednow BB, Frommann I, Berning J, Kuhn KU, Maier W, Wagner M (2008). Impaired sensorimotor gating of the acoustic startle response in the prodrome of schizophrenia. *Biol Psychiatry* **64**(9): 766-773.

Quednow BB, Wagner M, Westheide J, Beckmann K, Bliesener N, Maier W, *et al* (2006). Sensorimotor gating and habituation of the startle response in schizophrenic patients randomly treated with amisulpride or olanzapine. *Biol Psychiatry* **59**(6): 536-545.

Raedler TJ, Bymaster FP, Tandon R, Copolov D, Dean B (2007). Towards a muscarinic hypothesis of schizophrenia. *Mol Psychiatry* **12**(3): 232-246.

Rainey JM, Jr., Crowder MK (1974). Letter: Ketamine or phencyclidine. *JAMA* **230**(6): 824.

Rakic P (2002). Evolving concepts of cortical radial and areal specification. *Prog Brain Res* **136**: 265-280.

Ramirez J, Garnica R, Boll MC, Montes S, Rios C (2004). Low concentration of nitrite and nitrate in the cerebrospinal fluid from schizophrenic patients: a pilot study. *Schizophr Res* **68**(2-3): 357-361.

Ramsey NF, Koning HA, Welles P, Cahn W, van der Linden JA, Kahn RS (2002). Excessive recruitment of neural systems subserving logical reasoning in schizophrenia. *Brain* **125**(Pt 8): 1793-1807.

Reif A, Herterich S, Strobel A, Ehlis AC, Saur D, Jacob CP, *et al* (2006). A neuronal nitric oxide synthase (NOS-I) haplotype associated with schizophrenia modifies prefrontal cortex function. *Mol Psychiatry* **11**(3): 286-300.

Reis DJ, Regunathan S (2000). Is agmatine a novel neurotransmitter in brain? *Trends Pharmacol Sci* **21**(5): 187-193.

Rodefer JS, Nguyen TN, Karlsson JJ, Arnt J (2008). Reversal of subchronic PCP-induced deficits in attentional set shifting in rats by sertindole and a 5-HT(6) receptor antagonist: comparison among antipsychotics. *Neuropsychopharmacology* **33**(11): 2657-2666.

Rothman RB, Reid AA, Monn JA, Jacobson AE, Rice KC (1989). The psychotomimetic drug phencyclidine labels two high affinity binding sites in guinea pig brain: evidence for N-methyl-D-aspartate-coupled and dopamine reuptake carrier-associated phencyclidine binding sites. *Mol Pharmacol* **36**(6): 887-896.

Roussos P, Giakoumaki SG, Rogdaki M, Pavlakis S, Frangou S, Bitsios P (2008). Prepulse inhibition of the startle reflex depends on the catechol O-methyltransferase Val158Met gene polymorphism. *Psychol Med* **38**(11): 1651-1658.

Roy K, Murtie JC, El-Khodor BF, Edgar N, Sardi SP, Hooks BM, *et al* (2007). Loss of erbB signaling in oligodendrocytes alters myelin and dopaminergic function, a potential mechanism for neuropsychiatric disorders. *Proc Natl Acad Sci U S A* **104**(19): 8131-8136.

Saha S, Chant D, Welham J, McGrath J (2005). A systematic review of the prevalence of schizophrenia. *PLoS Med* **2**(5): e141.

Saha S, Welham J, Chant D, McGrath J (2006). Incidence of schizophrenia does not vary with economic status of the country: evidence from a systematic review. *Soc Psychiatry Psychiatr Epidemiol* **41**(5): 338-340.

Salinas E, Sejnowski TJ (2000). Impact of correlated synaptic input on output firing rate and variability in simple neuronal models. *J Neurosci* **20**(16): 6193-6209.

Sammut S, West AR (2008). Acute cocaine administration increases NO efflux in the rat prefrontal cortex via a neuronal NOS-dependent mechanism. *Synapse* **62**(9): 710-713.

Sams-Dodd F (1995). Distinct effects of d-amphetamine and phencyclidine on the social behaviour of rats. *Behav Pharmacol* **6**(1): 55-65.

Sartorius N, Jablensky A, Korten A, Ernberg G, Anker M, Cooper JE, *et al* (1986). Early manifestations and first-contact incidence of schizophrenia in different cultures. A preliminary report on the initial evaluation phase of the WHO Collaborative Study on determinants of outcome of severe mental disorders. *Psychol Med* **16**(4): 909-928.

Sawaguchi T, Goldman-Rakic PS (1994). The role of D1-dopamine receptor in working memory: local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. *J Neurophysiol* **71**(2): 515-528.

Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, Stafiniak P*, et al* (1994). Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. *Arch Gen Psychiatry* **51**(2): 124-131.

Schneider M, Koch M (2005). Behavioral and morphological alterations following neonatal excitotoxic lesions of the medial prefrontal cortex in rats. *Exp Neurol* **195**(1): 185-198.

Schopf J, Hucker H (1977). Baclofen in the treatment of schizophrenia: a pilot study. *Pharmakopsychiatr Neuropsychopharmakol* **10**(2): 89-91.

Schroeder U, Schroeder H, Darius J, Grecksch G, Sabel BA (1998). Simulation of psychosis by continuous delivery of phencyclidine from controlled-release polymer implants. *Behav Brain Res* **97**(1-2): 59-68.

Schuler V, Luscher C, Blanchet C, Klix N, Sansig G, Klebs K*, et al* (2001). Epilepsy, hyperalgesia, impaired memory, and loss of pre- and postsynaptic GABA(B) responses in mice lacking GABA(B(1)). *Neuron* **31**(1): 47-58.

Schwabe K, Koch M (2004). Role of the medial prefrontal cortex in N-methyl-D-aspartate receptor antagonist induced sensorimotor gating deficit in rats. *Neurosci Lett* **355**(1-2): 5-8.

Schwarcz R, Rassoulpour A, Wu HQ, Medoff D, Tamminga CA, Roberts RC (2001). Increased cortical kynurenate content in schizophrenia. *Biol Psychiatry* **50**(7): 521-530.

Schwarzkopf SB, Lamberti JS, Smith DA (1993). Concurrent assessment of acoustic startle and auditory P50 evoked potential measures of sensory inhibition. *Biol Psychiatry* **33**(11-12): 815-828.

Sedvall G, Farde L, Hall H, Pauli S, Persson A, Wiesel FA (1988). PET scanning--a new tool in clinical psychopharmacology. *Psychopharmacol Ser* **5**: 27-33.

Seeman MV (1982). Gender differences in schizophrenia. *Can J Psychiatry* **27**(2): 107-112.

Seeman P, Lasaga M (2005). Dopamine agonist action of phencyclidine. *Synapse* **58**(4): 275-277.

Seeman P, Lee T (1975). Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. *Science* **188**(4194): 1217-1219.

Seeman P, Tallerico T (1998). Antipsychotic drugs which elicit little or no parkinsonism bind more loosely than dopamine to brain D2 receptors, yet occupy high levels of these receptors. *Mol Psychiatry* **3**(2): 123-134.

Sergi MJ, Rassovsky Y, Nuechterlein KH, Green MF (2006). Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. *Am J Psychiatry* **163**(3): 448-454.

Shenton ME, Dickey CC, Frumin M, McCarley RW (2001). A review of MRI findings in schizophrenia. *Schizophr Res* **49**(1-2): 1-52.

Shi L, Fatemi SH, Sidwell RW, Patterson PH (2003). Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. *J Neurosci* **23**(1): 297-302.

Shinkai T, Ohmori O, Hori H, Nakamura J (2002). Allelic association of the neuronal nitric oxide synthase (NOS1) gene with schizophrenia. *Mol Psychiatry* **7**(6): 560-563.

Shoemaker JM, Saint Marie RL, Bongiovanni MJ, Neary AC, Tochen LS, Swerdlow NR (2005). Prefrontal D1 and ventral hippocampal N-methyl-D-aspartate regulation of startle gating in rats. *Neuroscience* **135**(2): 385-394.

Slifstein M, Kolachana B, Simpson EH, Tabares P, Cheng B, Duvall M*, et al* (2008). COMT genotype predicts cortical-limbic D1 receptor availability measured with [11C]NNC112 and PET. *Mol Psychiatry* **13**(8): 821-827.

Southam E, Garthwaite J (1993). The nitric oxide-cyclic GMP signalling pathway in rat brain. *Neuropharmacology* **32**(11): 1267-1277.

Srivastava N, Barthwal MK, Dalal PK, Agarwal AK, Nag D, Srimal RC*, et al* (2001). Nitrite content and antioxidant enzyme levels in the blood of schizophrenia patients. *Psychopharmacology (Berl)* **158**(2): 140-145.

Steinpreis RE (1996). The behavioral and neurochemical effects of phencyclidine in humans and animals: some implications for modeling psychosis. *Behav Brain Res* **74**(1-2): 45-55.

Sullivan PF, Kendler KS, Neale MC (2003). Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry* **60**(12): 1187-1192.

Suzuki E, Nakaki T, Nakamura M, Miyaoka H (2003). Plasma nitrate levels in deficit versus non-deficit forms of schizophrenia. *J Psychiatry Neurosci* **28**(4): 288-292.

Swerdlow NR, Auerbach P, Monroe SM, Hartston H, Geyer MA, Braff DL (1993a). Men are more inhibited than women by weak prepulses. *Biol Psychiatry* **34**(4): 253-260.

Swerdlow NR, Benbow CH, Zisook S, Geyer MA, Braff DL (1993b). A preliminary assessment of sensorimotor gating in patients with obsessive compulsive disorder. *Biol Psychiatry* **33**(4): 298-301.

Swerdlow NR, Geyer MA (1998). Using an animal model of deficient sensorimotor gating to study the pathophysiology and new treatments of schizophrenia. *Schizophr Bull* **24**(2): 285-301.

Swerdlow NR, Geyer MA, Braff DL (2001). Neural circuit regulation of prepulse inhibition of startle in the rat: current knowledge and future challenges. *Psychopharmacology (Berl)* **156**(2-3): 194-215.

Swerdlow NR, Light GA, Cadenhead KS, Sprock J, Hsieh MH, Braff DL (2006a). Startle gating deficits in a large cohort of patients with schizophrenia: relationship to medications, symptoms, neurocognition, and level of function. *Arch Gen Psychiatry* **63**(12): 1325-1335.

Swerdlow NR, Paulsen J, Braff DL, Butters N, Geyer MA, Swenson MR (1995). Impaired prepulse inhibition of acoustic and tactile startle response in patients with Huntington's disease. *J Neurol Neurosurg Psychiatry* **58**(2): 192-200.

Swerdlow NR, Shoemaker JM, Bongiovanni MJ, Neary AC, Tochen LS, Saint Marie RL (2005). Reduced startle gating after D1 blockade: effects of concurrent D2 blockade. *Pharmacol Biochem Behav* **82**(2): 293-299.

Swerdlow NR, Shoemaker JM, Crain S, Goins J, Onozuka K, Auerbach PP (2004). Sensitivity to drug effects on prepulse inhibition in inbred and outbred rat strains. *Pharmacol Biochem Behav* **77**(2): 291-302.

Swerdlow NR, Talledo J, Sutherland AN, Nagy D, Shoemaker JM (2006b). Antipsychotic effects on prepulse inhibition in normal 'low gating' humans and rats. *Neuropsychopharmacology* **31**(9): 2011-2021.

Swerdlow NR, Weber M, Qu Y, Light GA, Braff DL (2008). Realistic expectations of prepulse inhibition in translational models for schizophrenia research. *Psychopharmacology (Berl)* **199**(3): 331-388.

Szabadits E, Cserep C, Ludanyi A, Katona I, Gracia-Llanes J, Freund TF*, et al* (2007). Hippocampal GABAergic synapses possess the molecular machinery for retrograde nitric oxide signaling. *J Neurosci* **27**(30): 8101-8111.

Szoke A, Trandafir A, Dupont ME, Meary A, Schurhoff F, Leboyer M (2008). Longitudinal studies of cognition in schizophrenia: meta-analysis. *Br J Psychiatry* **192**(4): 248-257.

Tamminga CA, Carlsson A (2002). Partial dopamine agonists and dopaminergic stabilizers, in the treatment of psychosis. *Curr Drug Targets CNS Neurol Disord* **1**(2): 141-147.

Tan HY, Chen Q, Goldberg TE, Mattay VS, Meyer-Lindenberg A, Weinberger DR*, et al* (2007). Catechol-O-methyltransferase Val158Met modulation of prefrontal-parietal-striatal brain systems during arithmetic and temporal transformations in working memory. *J Neurosci* **27**(49): 13393-13401.

Taneli F, Pirildar S, Akdeniz F, Uyanik BS, Ari Z (2004). Serum nitric oxide metabolite levels and the effect of antipsychotic therapy in schizophrenia. *Arch Med Res* **35**(5): 401-405.

Tjornhammar ML, Lazaridis G, Bartfai T (1986). Efflux of cyclic guanosine 3',5'-monophosphate from cerebellar slices stimulated by L-glutamate or high K+ or N-methyl-N'-nitro-N-nitrosoguanidine. *Neurosci Lett* **68**(1): 95-99.

Tkachev D, Mimmack ML, Huffaker SJ, Ryan M, Bahn S (2007). Further evidence for altered myelin biosynthesis and glutamatergic dysfunction in schizophrenia. *Int J Neuropsychopharmacol* **10**(4): 557-563.

Toda M, Abi-Dargham A (2007). Dopamine hypothesis of schizophrenia: making sense of it all. *Curr Psychiatry Rep* **9**(4): 329-336.

Touyz RM, Picard S, Schiffrin EL, Deschepper CF (1997). Cyclic GMP inhibits a pharmacologically distinct Na+/H+ exchanger variant in cultured rat astrocytes via an extracellular site of action. *J Neurochem* **68**(4): 1451-1461.

Trinh JV, Nehrenberg DL, Jacobsen JP, Caron MG, Wetsel WC (2003). Differential psychostimulant-induced activation of neural circuits in dopamine transporter knockout and wild type mice. *Neuroscience* **118**(2): 297-310.

Tsai G, Passani LA, Slusher BS, Carter R, Baer L, Kleinman JE*, et al* (1995). Abnormal excitatory neurotransmitter metabolism in schizophrenic brains. *Arch Gen Psychiatry* **52**(10): 829-836.

Tseng KY, Lewis BL, Lipska BK, O'Donnell P (2007). Post-pubertal disruption of medial prefrontal cortical dopamine-glutamate interactions in a developmental animal model of schizophrenia. *Biol Psychiatry* **62**(7): 730-738.

Tsuang M (2000). Schizophrenia: genes and environment. *Biol Psychiatry* **47**(3): 210-220.

Uylings HB, Groenewegen HJ, Kolb B (2003). Do rats have a prefrontal cortex? *Behav Brain Res* **146**(1-2): 3-17.

Uylings HB, van Eden CG (1990). Qualitative and quantitative comparison of the prefrontal cortex in rat and in primates, including humans. *Prog Brain Res* **85**: 31-62.

van Berckel BN, Oranje B, van Ree JM, Verbaten MN, Kahn RS (1998). The effects of low dose ketamine on sensory gating, neuroendocrine secretion and behavior in healthy human subjects. *Psychopharmacology (Berl)* **137**(3): 271-281.

Van Horn JD, McManus IC (1992). Ventricular enlargement in schizophrenia. A meta-analysis of studies of the ventricle:brain ratio (VBR). *Br J Psychiatry* **160**: 687-697.

van Rossum JM (1966). The significance of dopamine-receptor blockade for the mechanism of action of neuroleptic drugs. *Arch Int Pharmacodyn Ther* **160**(2): 492-494.

Venables PH (1964). Input Dysfunction in Schizophrenia. *Prog Exp Pers Res* **72**: 1-47.

Vincent JP, Bidard JN, Lazdunski M, Romey G, Tourneur Y, Vignon J (1983). Identification and properties of phencyclidine-binding sites in nervous tissues. *Fed Proc* **42**(9): 2570-2573.

Vincent SR, Kimura H (1992). Histochemical mapping of nitric oxide synthase in the rat brain. *Neuroscience* **46**(4): 755-784.

Vincent SR, Williams JA, Reiner PB, el-Husseini Ae-D (1998). Monitoring neuronal NO release in vivo in cerebellum, thalamus and hippocampus. *Prog Brain Res* **118**: 27-35.

Volk D, Austin M, Pierri J, Sampson A, Lewis D (2001). GABA transporter-1 mRNA in the prefrontal cortex in schizophrenia: decreased expression in a subset of neurons. *Am J Psychiatry* **158**(2): 256-265.

Vollenweider FX, Barro M, Csomor PA, Feldon J (2006). Clozapine enhances prepulse inhibition in healthy humans with low but not with high prepulse inhibition levels. *Biol Psychiatry* **60**(6): 597-603.

Volz H, Gaser C, Hager F, Rzanny R, Ponisch J, Mentzel H*, et al* (1999). Decreased frontal activation in schizophrenics during stimulation with the continuous performance test--a functional magnetic resonance imaging study. *Eur Psychiatry* **14**(1): 17-24.

Waldmeier PC, Kaupmann K, Urwyler S (2008). Roles of GABA(B) receptor subtypes in presynaptic auto- and heteroreceptor function regulating GABA and glutamate release. *J Neural Transm*.

Wallén-Mackenzie Å, Fejgin K, Lagerström M, Nordenankar K, Emilsson L, Fredriksson R*, et al* (2008). Restricted cortical and amygdaloid removal of vesicular glutamate transporter 2 in pre-adolescent mice disrupts dopaminergic activity and neuronal circuitry of higher brain function. *Manuscript*.

Wang S, Paton JF, Kasparov S (2006). The challenge of real-time measurements of nitric oxide release in the brain. *Auton Neurosci* **126-127**: 59-67.

Wass C, Archer T, Palsson E, Fejgin K, Alexandersson A, Klamer D*, et al* (2006a). Phencyclidine affects memory in a nitric oxide-dependent manner: working and reference memory. *Behav Brain Res* **174**(1): 49-55.

Wass C, Archer T, Palsson E, Fejgin K, Klamer D, Engel JA*, et al* (2006b). Effects of phencyclidine on spatial learning and memory: Nitric oxide-dependent mechanisms. *Behav Brain Res* **171**(1): 147-153.

Wass C, Klamer D, Katsarogiannis E, Svensson L, Fejgin K, Pålsson E*, et al* (2008a). An open study investigating L-lysine as an add-on treatment in patients with schizophrenia. *Manuscript*.

Wass C, Svensson L, Fejgin K, Palsson E, Archer T, Engel JA*, et al* (2008b). Nitric oxide synthase inhibition attenuates phencyclidine-induced disruption of cognitive flexibility. *Pharmacol Biochem Behav* **89**(3): 352-359.

Weinberger DR (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* **44**(7): 660-669.

Weinberger DR, Berman KF, Illowsky BP (1988). Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. III. A new cohort and evidence for a monoaminergic mechanism. *Arch Gen Psychiatry* **45**(7): 609-615.

Weinberger DR, Berman KF, Zec RF (1986). Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow evidence. *Arch Gen Psychiatry* **43**(2): 114-124.

Weiner I, Lubow RE, Feldon J (1984). Abolition of the expression but not the acquisition of latent inhibition by chronic amphetamine in rats. *Psychopharmacology (Berl)* **83**(2): 194-199.

Weiss AP, Dewitt I, Goff D, Ditman T, Heckers S (2005). Anterior and posterior hippocampal volumes in schizophrenia. *Schizophr Res* **73**(1): 103-112.

White MF, Gazzola GC, Christensen HN (1982). Cationic amino acid transport into cultured animal cells. I. Influx into cultured human fibroblasts. *J Biol Chem* **257**(8): 4443-4449.

WHO (1992) The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Organization WH (ed). WHO.

Wiesinger H (2001). Arginine metabolism and the synthesis of nitric oxide in the nervous system. *Prog Neurobiol* **64**(4): 365-391.

Wiley JL (1994). Clozapine's effects on phencyclidine-induced disruption of prepulse inhibition of the acoustic startle response. *Pharmacol Biochem Behav* **49**(4): 1025-1028.

Wiley JL (1998). Nitric oxide synthase inhibitors attenuate phencyclidine-induced disruption of prepulse inhibition. *Neuropsychopharmacology* **19**(1): 86-94.

Wiley JL, Kogut CP, Witherell JR (1999). Effects of acute and repeated dosing with PCP on locomotion in nNOS knockout mice. *29th Annual Meeting, Society for Neuroscience (Miami Beach: Society for Neuroscience)*: pp 946.

Willner P (1984). The validity of animal models of depression. *Psychopharmacology (Berl)* **83**(1): 1-16.

Wilson RI, Godecke A, Brown RE, Schrader J, Haas HL (1999). Mice deficient in endothelial nitric oxide synthase exhibit a selective deficit in hippocampal long-term potentiation. *Neuroscience* **90**(4): 1157-1165.

Woo TU, Kim AM, Viscidi E (2008). Disease-specific alterations in glutamatergic neurotransmission on inhibitory interneurons in the prefrontal cortex in schizophrenia. *Brain Res* **1218**: 267-277.

Woo TU, Walsh JP, Benes FM (2004). Density of glutamic acid decarboxylase 67 messenger RNA-containing neurons that express the N-methyl-D-aspartate receptor subunit NR2A in the anterior cingulate cortex in schizophrenia and bipolar disorder. *Arch Gen Psychiatry* **61**(7): 649-657.

Woodward ND, Purdon SE, Meltzer HY, Zald DH (2005). A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. *Int J Neuropsychopharmacol* **8**(3): 457-472.

Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET (2000). Meta-analysis of regional brain volumes in schizophrenia. *Am J Psychiatry* **157**(1): 16-25.

Wykes T, van der Gaag M (2001). Is it time to develop a new cognitive therapy for psychosis--cognitive remediation therapy (CRT)? *Clin Psychol Rev* **21**(8): 1227-1256.

Wynn JK, Green MF, Sprock J, Light GA, Widmark C, Reist C*, et al* (2007). Effects of olanzapine, risperidone and haloperidol on prepulse inhibition in schizophrenia patients: a double-blind, randomized controlled trial. *Schizophr Res* **95**(1-3): 134-142.

Wynn JK, Sergi MJ, Dawson ME, Schell AM, Green MF (2005). Sensorimotor gating, orienting and social perception in schizophrenia. *Schizophr Res* **73**(2-3): 319-325.

Xi ZX, Baker DA, Shen H, Carson DS, Kalivas PW (2002). Group II metabotropic glutamate receptors modulate extracellular glutamate in the nucleus accumbens. *J Pharmacol Exp Ther* **300**(1): 162-171.

Xing G, Chavko M, Zhang LX, Yang S, Post RM (2002). Decreased calcium-dependent constitutive nitric oxide synthase (cNOS) activity in prefrontal cortex in schizophrenia and depression. *Schizophr Res* **58**(1): 21-30.

Yan XX, Jen LS, Garey LJ (1996). NADPH-diaphorase-positive neurons in primate cerebral cortex colocalize with GABA and calcium-binding proteins. *Cereb Cortex* **6**(3): 524-529.

Yanik M, Vural H, Kocyigit A, Tutkun H, Zoroglu SS, Herken H*, et al* (2003). Is the arginine-nitric oxide pathway involved in the pathogenesis of schizophrenia? *Neuropsychobiology* **47**(2): 61-65.

Yao JK, Leonard S, Reddy RD (2004). Increased nitric oxide radicals in postmortem brain from patients with schizophrenia. *Schizophr Bull* **30**(4): 923-934.

Yee BK, Keist R, von Boehmer L, Studer R, Benke D, Hagenbuch N, *et al* (2005). A schizophrenia-related sensorimotor deficit links alpha 3-containing GABAA receptors to a dopamine hyperfunction. *Proc Natl Acad Sci U S A* **102**(47): 17154-17159.

Yesavage JA, Freman AM (1978). Acute phencyclidine (PCP) intoxication: psychopathology and prognosis. *J Clin Psychiatry* **39**(8): 664-666.

Yilmaz N, Herken H, Cicek HK, Celik A, Yurekli M, Akyol O (2007). Increased levels of nitric oxide, cortisol and adrenomedullin in patients with chronic schizophrenia. *Med Princ Pract* **16**(2): 137-141.

Yin H, Turetsky D, Choi DW, Weiss JH (1994). Cortical neurones with Ca2+ permeable AMPA/kainate channels display distinct receptor immunoreactivity and are GABAergic. *Neurobiol Dis* **1**(1-2): 43-49.

Yui K, Goto K, Ikemoto S, Ishiguro T, Angrist B, Duncan GE, *et al* (1999). Neurobiological basis of relapse prediction in stimulant-induced psychosis and schizophrenia: the role of sensitization. *Mol Psychiatry* **4**(6): 512-523.

Zakzanis KK, Hansen KT (1998). Dopamine D2 densities and the schizophrenic brain. *Schizophr Res* **32**(3): 201-206.

Zhang J, Engel JA, Ericson M, Svensson L (1999). Involvement of the medial geniculate body in prepulse inhibition of acoustic startle. *Psychopharmacology (Berl)* **141**(2): 189-196.

Zheng Y, Li H, Qin W, Chen W, Duan Y, Xiao Y, *et al* (2005). Association of the carboxyl-terminal PDZ ligand of neuronal nitric oxide synthase gene with schizophrenia in the Chinese Han population. *Biochem Biophys Res Commun* **328**(4): 809-815.

Zipursky RB, Christensen BK, Daskalakis Z, Epstein I, Roy P, Furimsky I, *et al* (2005). Treatment response to olanzapine and haloperidol and its association with dopamine D receptor occupancy in first-episode psychosis. *Can J Psychiatry* **50**(8): 462-469.

Zoroglu SS, Herken H, Yurekli M, Uz E, Tutkun H, Savas HA, *et al* (2002). The possible pathophysiological role of plasma nitric oxide and adrenomedullin in schizophrenia. *J Psychiatr Res* **36**(5): 309-315.