

Cognition and social behaviour in schizophrenia

*An animal model investigating the potential role of
nitric oxide*

Caroline Wass
2007



Institute of Neuroscience and Physiology
Section for Pharmacology
The Sahlgrenska Academy at Göteborgs University
Sweden

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ISBN 978-91-628-7360-8

ABSTRACT

Cognition and social behaviour in schizophrenia

An animal model investigating the potential role of nitric oxide

Caroline Wass

Institute of Neuroscience and Physiology, Section for Pharmacology, the Sahlgrenska Academy at Göteborg University, Sweden

Cognitive deficits are the single strongest predictor of functional outcome in patients with schizophrenia. Furthermore, these deficits are not satisfactorily alleviated by available antipsychotic treatment. Functional outcome is also dependent upon social functioning and patients with schizophrenia display social dysfunctions including specific impairment in social cognition. Thus, cognitive deficits and social dysfunctions make up core symptoms of schizophrenia that needs to be further investigated in order to find novel treatment targets. Phencyclidine (PCP) is a psychotomimetic compound that produces symptoms in humans that closely resemble schizophrenia. Consequently, the PCP-model is consistently used for studying schizophrenia in experimental animals. Previous studies from our lab demonstrate that PCP-induced deficits in several translational animal models of schizophrenia can be blocked by inhibition of nitric oxide (NO) production. Such PCP-induced deficits range from impairment in pre-cognitive (pre-attentive) sensory information processing and habituation of acoustic startle to selective attention. In addition, several clinical studies indicate that the NO-signalling pathway may be involved in the pathophysiology of schizophrenia.

The overall aim of this thesis was to investigate the effects of PCP and NO synthase (NOS) inhibition on higher order cognitive functions, i.e. memory, and social interaction. Therefore, we investigated the effects of PCP and the NOS-inhibitor, *N*^G-nitro-L-arginine methyl ester (L-NAME) on; (1) spatial learning, working memory, long-term memory, and cognitive flexibility using different versions of the Morris water maze, and (2) social function and memory using a social interaction paradigm.

The results demonstrate that acute PCP-treatment impaired spatial learning, working memory, long-term memory, and cognitive flexibility in rats. These PCP-induced deficits were normalized by pretreatment with the

NOS-inhibitor, L-NAME. Furthermore, PCP-treatment decreased time spent in social interaction, a deficit that was independent of motor activity and frequency of interactions. This social interaction deficit was blocked by NOS-inhibition.

Taken together these results suggest that the effects of PCP, on cognitive functioning and social interaction, depend on the NO-signalling system. In addition, several studies from our research group show that systemic PCP-treatment in fact seems to increase NO production in the rodent brain. Based on these findings, in addition to the results from this thesis, we propose a “NO-dysregulation hypothesis for schizophrenia”. Moreover, this hypothesis suggests that the NO-signalling pathway may be a potential new treatment target for schizophrenia.

Key words: schizophrenia, cognition, memory, Morris water maze, social function, social interaction, phencyclidine, nitric oxide, L-NAME, rat.

ISBN 978-91-628-7360-8

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

- I. Effects of phencyclidine on spatial learning and memory: Nitric oxide-dependent mechanisms. Wass C, Arher T, Palsson E, Fejgin K, Klamer D, Engel J. A. & Svensson L. Behavioural Brain Research 2006 Jul 15; 171(1): 147-53
- II. Phencyclidine affects memory in a nitric oxide-dependent manner: Working and reference memory. Wass C, Arher T, Palsson E, Fejgin K, Alexandersson A, Klamer D, Engel J. A. & Svensson L. Behavioural Brain Research 2006 Nov 1; 174(1):49-55
- III. Effects of phencyclidine on cognitive load: Targeting the nitric oxide system. Wass C, Svensson L, Fejgin K, Palsson E, Arher T, Engel J. A. & Klamer D. Submitted.
- IV. The importance of nitric oxide in social dysfunction. Wass C, Fejgin K, Palsson E, Engel J. A., Arher T, Svensson L & Klamer D. Manuscript.

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Schizofreni – en obalans i kväveoxidsystemet?. Fel! Bokmärket är inte definierat.

ABBREVIATIONS

AMPA/R	α -amino-3-hydroxy-5-hydroxy-5-methyl-4-isoxazolepropionate/receptor
Ca ²⁺	calcium
cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
COMT	catechol-O-methyltransferase
CA1	<i>cornu ammonis</i> 1
DA/R	dopamine/receptor
D1R	dopamine D1 receptor
D2R	dopamine D2 receptor
D5R	dopamine D5 receptor
eNOS	endothelial nitric oxide synthase
GABA/R	γ -amino-butyric acid/receptor
GTP	guanosine triphosphate
iNOS	inducible nitric oxide synthase
L-NAME	N ^G -nitro-L-arginine methyl ester
LTP	long-term potentiation
mGlu/R	metabotropic glutamate/receptor
MWM	Morris water maze
nNOS	neuronal nitric oxide synthase
NADPH	nicotinamide adenine dinucleotide phosphate-oxidase
NMDA/R	<i>N-methyl-D-aspartate</i> /receptor
NO	nitric oxide
NOS	nitric oxide synthase
PCP	phencyclidine
PFC	prefrontal cortex
PPI	prepulse inhibition
SAL	saline (sodium chloride)
sGC	soluble guanylyl cyclase
5-HT/R	5-hydroxytryptamine, <i>i.e.</i> serotonin/receptor

BACKGROUND

Dementia praecox, i.e.” premature dementia” was first described by Czechoslovakian psychiatrist Arnold Pick in a case study of a patient that displayed a hebephrenic type of psychosis (Pick, 1891). Psychiatrist Emil Kraepelin, was the first to acknowledge psychiatric disorders from a biological perspective, and further established the term *dementia praecox*. In 1911, the Swiss psychiatrist Paul Eugen Bleuler renamed dementia praecox as “the group of schizophrenias” and described it as a cluster of disorders rather than one coherent disease (Adityanjee et al., 1999). The name schizophrenia stems from Greek and implies “split mind”. The group of schizophrenias was characterized as sharing basic symptoms, such as splitting or fragmentation of the mind, disordered train of mental associations and derangement of thoughts. Thus, there has been an emphasis on both the cognitive aspects, as well as the heterogeneity, of this disorder, or group of disorders, since it was first described.

Schizophrenia affects approximately 1% of the population worldwide and is a chronic, severe disorder, lacking curative treatment. The suicide rate is as high as 9-13%, with the incidence of suicide attempt reaching 50% of diagnosed patients over a lifetime (Caldwell and Gottesman, 1990, Perenyi and Forlano, 2005). The onset of schizophrenia usually occurs around 18-25 years of age and is often preceded by premorbid behavioural deviations, such as social withdrawal and affective changes (Keshavan et al., 2005). Furthermore, most patients diagnosed with schizophrenia never return to school or work (Marwaha and Johnson, 2004).

Symptoms

The symptoms of schizophrenia are commonly divided into three categories namely; positive symptoms, negative symptoms, and cognitive deficits (Green, 1996, Fuller, 2003).

Positive symptoms

Positive symptoms are characterized by functions and behaviours that are displayed in addition to normal functioning, thereof the term “positive” meaning “extra”. Hallucinations, delusions and disorganized behaviour are often the type of symptom that brings the patient to the emergency room and qualify her or him as ill. Hallucinations most often occur within the auditory domain, such as “hearing voices” that are often of an unpleasant and disparaging nature. Delusions may be grandiose or paranoid and can

become very disabling, as they are incorporated in, and govern, daily living. The positive symptoms are cyclic in nature and are alleviated reliably by available antipsychotic treatment (Capuano et al., 2002).

Negative symptoms

In contrast to the positive symptoms, negative symptoms are characterized by loss of “normal” functioning, are chronic, and include anhedonia (loss of pleasurable feelings), flattened affect (e.g. blunted emotions), avolition (lack of initiative), and social withdrawal. Social withdrawal and lack of social cognition may in fact be a symptom category of its own. These losses of functioning closely resemble the symptoms apparent in states of clinical depression. In general, negative symptoms are at best only partially alleviated by available antipsychotic treatment (Murphy et al., 2006, Stahl and Buckley, 2007). It has even been suggested that negative symptoms are worsened by antipsychotic treatment (*i.e.* neuroleptic-induced dysphoria) as blockade of the dopamine (DA)ergic reward system seems to attenuate feelings of reward (Kirsch et al., 2007).

There has previously been some deliberation in the literature as to whether or not negative symptoms include cognitive deficits. Extensive research indicates that cognitive deficits should be regarded as a separate group of deficits. Compared to *e.g.* affective changes, cognitive deficits have a distinct neuroanatomical basis (Menon et al., 2001, Honey et al., 2003).

Cognitive deficits

As early as the late 19th century, Kraepelin emphasized the importance of cognitive deficits as a significant part of schizophrenia, indicated by the term “premature dementia”. This important core deficit was then somewhat ignored in the favour of positive symptoms, since the positive symptoms were treated successfully with chlorpromazine. After the breakthrough of chlorpromazine, psychotic symptoms could be treated pharmacologically instead of using ethically questionable strategies such as lobotomy and insulin shock. In this last decade, there has been an increasing interest in studying cognitive dysfunctions, as they have been found to be predictive of both disease outcome and treatment response (Green, 1996, Green, 2006, Helldin et al., 2007, Lewis, 2004). Cognitive deficits include difficulties with attention, language, several aspects of memory, executive functioning, cognitive flexibility, and interpretation of social cues (Conklin et al., 2005, Couture et al., 2006, Green, 2006, Hill et

al., 2004, Karilampi et al., 2007, Swerdlow et al., 1996). Cognitive deficits are not satisfactorily alleviated by available antipsychotic treatment. Hence, there is a pressing need to develop effective pharmacological interventions for treating this category of disabling deficits (Green and Braff, 2001).

Aetiology

The aetiology of schizophrenia remains unknown and given the heterogeneous nature of the disorder it is likely that there are multiple contributing aetiological factors. The single strongest predictive factor for developing schizophrenia is a family history including a first degree relative with the disorder (Hallmayer, 2000). Monozygotic twins show a 48% concordance rate for schizophrenia and having a parent with schizophrenia means a 13% risk of developing the disorder. So far no single predictive gene has been discovered, but there are several candidate genes that predispose an individual to the disorder (see Table 1 adapted from Stahl, 2007, McClellan et al., 2007).

Susceptibility genes for schizophrenia	
AKT1	D3R
BDNF	MUTED
CHRNA7	MRDS1
COMT	MAO-A
DAAO	Nur77
DAOA	Neuregulin
DISC-1	PPP3CC
Dysbindin	PRODH2
GAD1	RGS4
GRM3	Tyrosine hydroxylase
Erb-B4	Spinophylin
D2R	FEZ1

Table 1: Susceptibility genes for schizophrenia, adopted from Stahl (2007).

Several environmental risk factors for developing schizophrenia have been proposed, such as urban living, immigrant status, and expressed emotion within the family, with varying results (Kavanagh, 1992, Freeman, 1994, McDonald and Murray, 2000). Moreover, seasonal birth, maternal influenza, delivery complications, and nutritional restriction are predictors

of increased risk for schizophrenia in adult life. These risk factors support a neurodevelopmental theory of schizophrenia (see “Neurodevelopmental hypothesis”, page 19, Lewis and Levitt, 2002).

Another possible aetiological factor for schizophrenia may be cannabis abuse. Patients seeking help for cannabis-dependence were found to have an increased incidence of previous psychiatric diagnosis, *e.g.* schizophrenia, in comparison to controls, indicating co-morbidity of these disorders (Arendt et al., 2007). In another Danish register study, cannabis-induced psychotic disorder was found to predispose individuals to develop long lasting psychotic disorders in almost 50% of the patients (Arendt et al., 2005). Furthermore, several studies have established a causal association between cannabis abuse and development of psychosis (Palsson et al., 1982, Andreasson et al., 1987, Arseneault et al., 2004), an association that is further influenced by allelic composition of the catechol-O-methyltransferase (COMT) gene (Caspi et al., 2005).

Dopamine hypothesis

In 1947, the French surgeon Henri Laborit, discovered the antipsychotic effect of chlorpromazine in patients with schizophrenia (Coirault et al., 1956). The mechanism of action of chlorpromazine however, was going to remain unknown for almost two decades. In 2000, Arvid Carlsson was awarded the Nobel Prize for his discoveries concerning DA as a neurotransmitter essential for motor function and as the main target transmitter system of antipsychotic treatment (Carlsson, 1959, Carlsson and Lindqvist, 1963). The role of DA in the central nervous system was first described by Arvid Carlsson and co-workers in 1950s' (Carlsson et al., 1958, Carlsson et al., 1957, Carlsson, 1959). Since then, DA has been found to be involved in several other brain functions, such as reward mechanisms and cognition. Dysfunctions of the DA systems may cause diseases such as addictive behaviours, including compulsive over eating, pathological gambling, drug addiction, but also Parkinsons' disease (Carlson, 1959, Engel and Carlsson, 1977, Ehringer and Hornykiewicz, 1960, Jerlhag et al., 2007, Liljequist et al., 1977, Volkow et al., 2003).

In the central nervous system, the catecholamine DA, is most abundant in the corpus striatum, limbic system, and the hypothalamus. It is less abundant in other areas such as the prefrontal cortex (PFC). The four major DA pathways are the nigrostriatal-, tuberoinfundibular-, mesocortical- and mesolimbic pathways, which all mediate different effects

of DA (Stahl, 2002). DA exerts its effects through G-protein coupled receptors that are classified into two categories; DA D1 type receptors (D1R) and DA D2 type receptors (D2R). The D1R family include D1 and D5 receptors and activation of these receptors lead to an activation of adenylate cyclase and an increase in adenosine monophosphate (cAMP) production. The D2R family includes D2, D3, and D4 receptors and activation results in inhibition of adenylate cyclase resulting in reduction of cAMP production and/or increase in inositol triphosphate production (Garau et al., 1978, Gingrich and Caron, 1993, Keabian and Calne, 1979, Keabian and Greengard, 1971).

The DAergic hypothesis of schizophrenia rests mainly on the fact that the clinical effects of all antipsychotic medications are blockade of the D2R (Nordstrom et al., 1993, Seeman et al., 1976). Further evidence for a hyperDAergic state, underlying schizophrenia, comes from observations that d-amphetamine can lead to psychosis in healthy subjects (Angrist and Gershon, 1970). D-amphetamine exacerbates positive symptoms in patients with schizophrenia, which is accompanied by an elevated increase in DA release, and over activity of striatal D2Rs, compared to controls (Abi-Dargham et al., 1998, Laruelle et al., 2000). Thus, DA is a key player in the pathophysiology of schizophrenia specifically regarding the positive symptoms.

The “original” DA hypothesis states that schizophrenia stems from a hyperDAergic state. There is however accumulating evidence that schizophrenia is a DA-dysregulation disorder. Striatal DA activity, mediated by D2R, is increased while prefrontal DA activity, transmitted by D1R activity, is decreased in schizophrenia (Abi-Dargham, 2004). The imbalance in the DA system results from a dysfunctional interplay between several neurotransmitter systems, including the γ -amino-butyric acidergic (GABA) and the glutamatergic system (Carlsson et al., 2001).

Glutamate hypothesis

Clinical observations from the 1950's, and onward, showed that the dissociative anaesthetic compound Sernyl[®], *i.e.* phencyclidine (PCP), induces symptoms in humans that closely resemble schizophrenia. These symptoms incorporate positive symptoms, negative symptoms, and cognitive deficits (Allen and Young, 1978, Luby et al., 1959, Yesavage and Freman, 1978). PCP mainly exerts its pharmacological effects through the glutamatergic system. Based on these findings, PCP is thought to induce

some of the underlying pathophysiological mechanisms involved in schizophrenia (Javitt and Zukin, 1991, Olney et al., 1999).

Glutamate is the most abundant excitatory amino acid transmitter of the brain (Curtis et al., 1959, Watkins, 2000). Glutamate, besides serving as an important metabolic contributor, exerts its effect as a neurotransmitter via acting on four different kinds of receptors, namely *N*-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), kainate and metabotropic (mGlu) receptors. The NMDA, AMPA and kainate receptors are ionotropic receptors, permeable to Ca^{2+} , Na^{+} and K^{+} , while the metabotropic receptor acts via intracellular second messenger systems that mediate *e.g.* intracellular Ca^{2+} release (Schoepp, 2001, Thornberg and Saklad, 1996).

The NMDA receptor (NMDAR), in cooperation with the AMPA receptor (AMPA), play an important role in cognitive functioning such as learning and memory (Robbins and Murphy, 2006). These two receptors are furthermore associated with schizophrenia (as reviewed in Kristiansen et al., 2007). Moreover, several susceptibility genes, regulating neurodevelopmental molecular processes, synaptogenesis and NMDAR functioning in schizophrenia have been discovered (Stahl, 2007). These findings suggest a coherent hypothesis merging genetic susceptibility, neurodevelopmental abnormalities, pathological neurocircuitry changes, and information processing deficits together with glutamateric abnormality, in revealing schizophrenia.

NMDARs are widely distributed throughout the brain, with the highest density in the hippocampus, nucleus accumbens, and the PFC (Monaghan and Cotman, 1985). NMDARs are localized on both neurons and glial cells (Verkhatsky and Kirchhoff, 2007) and are involved in several essential neural functions such as cerebrovascular dilation (Busija et al., 2007) and neuronal plasticity including long-term synaptic changes (Lau and Zukin, 2007, Rao and Finkbeiner, 2007). The psychotomimetic compounds, PCP and ketamine, are non-competitive NMDAR antagonists that bind the PCP site in the ion channel and thereby block cation passage.

Further support for the hypoglutamatergic hypothesis of schizophrenia, was produced by Kim and co-workers (1980), as they found lower levels of glutamate in cerebrospinal fluid of patients with schizophrenia compared to controls. These findings have not been consistently replicated and therefore remain controversial (Hashimoto et al., 2005a).

A new interesting hypoglutamatergic hypothesis has been proposed involving the endogenous NMDAR antagonist, kynurenic acid, in schizophrenia (Erhardt et al., 2007). Patients with schizophrenia are found to have increased levels of kynurenic acid both in the brain and in cerebrospinal fluid in comparison with controls (Erhardt et al., 2001, Nilsson, 2005 #377, Nilsson et al., 2005, Schwarcz et al., 2001).

Evidently there is accumulated support for a dysregulated glutamatergic system involved in schizophrenia. However, it is not clear whether a dysfunctional glutamatergic system is the primary cause of the disease, giving rise to the DAergic imbalance, or vice versa.

Glutamate-dopamine imbalance

Glutamatergic and DAergic pathways make up an intricate network of subcortical – cortical connections, in which subcortical DA release is modulated by *e.g.* glutamate. The midbrain ventral tegmental area and substantia nigra DAergic activity is modulated by both activation and inhibition of projections ascending from the PFC (Sesack and Carr, 2002). The activating PFC projections are glutamatergic and synapse right on to DAergic neurons, while the inhibiting pathways are glutamatergic modulations of DA cells via GABAergic interneurons (Carlsson et al., 1999, Carlsson and Carlsson, 1990, Carlsson et al., 2001). From the hippocampus there are excitatory afferent projections to the PFC (Carr and Sesack, 1996) and these projections are abnormal in patients with schizophrenia (Arnold et al., 1995).

Thus, a dysregulation hypothesis of these cortical-subcortical, DAergic and glutamatergic projections, including the PFC, striatum and hippocampus, is proposed for schizophrenia (Schultz and Andreasen, 1999, Arnold et al., 1995, Carlsson et al., 1997, Javitt, 2007)

Besides DA and glutamate, several other neurotransmitter systems are involved in the pathophysiology of schizophrenia, such as the 5-HT-, noradrenaline-, acetylcholine-, and nitric oxide (NO) signalling system.

Neurodevelopmental hypothesis

Neuroanatomical studies of patients with schizophrenia have consistently shown enlarged ventricles, reduced brain volume, abnormal hippocampal volume, and deviant layering of the cortex (Bogerts et al., 1990, Chana et al., 2003, Chance et al., 2004, Weinberger et al., 1979). A study by Susser and Lin (1992) showed that children of pregnant mothers who were victims of starvation during the Dutch famine, 1944-45, displayed an increased incidence of schizophrenia in adult life. These findings have been replicated in a Chinese cohort study (St Clair et al., 2005). Birth complications such as hypoxia and maternal influenza, during the second trimester of pregnancy, have been found to correlate with increased incidence of schizophrenia in offspring (Mednick et al., 1988, Cannon et al., 2000, Rosso et al., 2000). Such findings have led to a neurodevelopmental hypothesis for schizophrenia, suggesting that schizophrenia is a disorder of abnormal perinatal neurodevelopment, although no certain causal relationships have been established between these risk factors and the development of schizophrenia. None of the risk factors seem to be sufficient or necessary for developing schizophrenia later in life, but in combination with other vulnerability factors, *e.g.* genetic heritability, the risk may be increased (Figure 1).

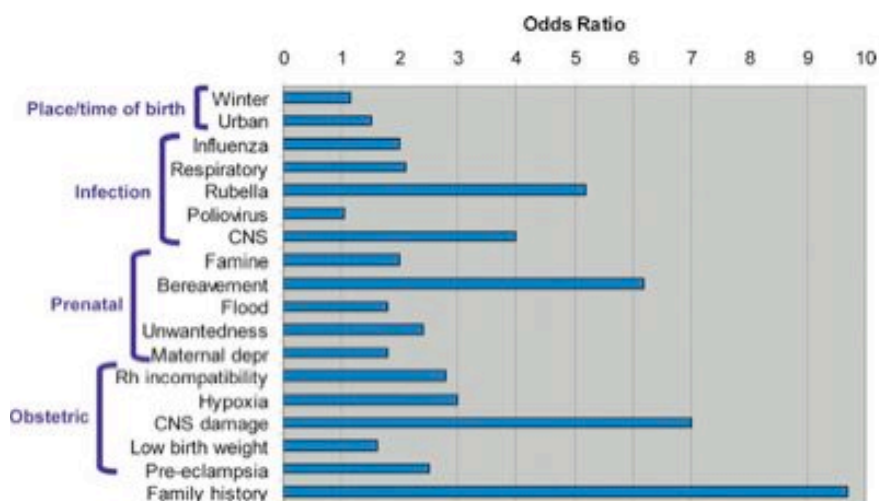


Figure 1: Risk factors adding to genetic predisposition for developing schizophrenia, adapted from Sullivan (2005).

Nitric oxide and schizophrenia

NO is a gaseous molecule involved in several important physiological functions, such as immunological response, platelet aggregation, dilation of smooth muscle, neuroplasticity, neurotransmitter release, and neurodevelopment (Ignarro, 1989, Gruetter et al., 1979, Bernstein et al., 2005). NO is a reactive gas with a half-life in the range of seconds, that can diffuse freely through membranes. Thus, NO may act as both an intra and extra cellular communicator. The synthesis of NO occurs through a NO synthase (NOS) and calcium-calmodulin-activated chemical reaction using L-arginine as the substrate for synthesis, along with oxygen. Synthesis involves several cofactors, including NADPH as an essential electron donor in the oxidation of L-arginine to NO and L-citrulline (Griffith and Stuehr, 1995, Figure 2).

There are three different isoforms of the NOS enzyme; endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS). The iNOS synthesizes NO that is important for immune response and expressed in *e.g.* macrophages and neutrophils. The endothelial form of NOS is primarily expressed in vascular endothelial cells, and regulates vascular tone (Prickaerts et al., 2004), while the nNOS is mainly expressed in neurons (Bredt and Snyder, 1994).

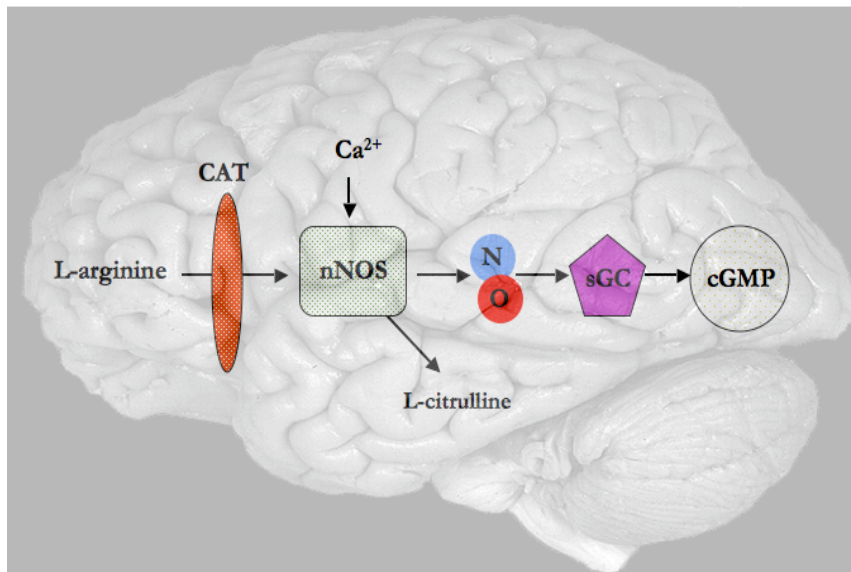


Figure 2: NO synthesis and its signalling pathway.

Preferentially, NO exerts its function through binding to a heme group, *i.e.* the “NO receptor”, on soluble guanylyl cyclase (sGC) and induces the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP, Figure 2). In brain slices, it has been shown that NO-cGMP signal transduction is activated by NMDARs (Hopkins et al., 1996).

Regarding long-term potentiation (LTP) in the hippocampus, cGMP exerts its effects by regulating cGMP-dependent ion channels and activating cGMP-dependent protein kinases, that in turn phosphorylate various proteins and affects cAMP concentrations (Leinders-Zufall et al., 1995). Endogenous NO also modulates the release of several neurotransmitters throughout the brain and exerts modulator effects on 5-HT and DA release in *e.g.* the hippocampus (Wegener et al., 2000, Strasser et al., 1994).

It has been suggested that NO is involved in several aspects of cognition, *e.g.* learning and memory (Bernstein et al., 2005, Zhuo et al., 1994). Behavioural studies show that inhibitors of NOS disrupts spatial learning (Chapman et al., 1992, Zou et al., 1998) and furthermore, that NOS is expressed in *e.g.* pyramidal neurons of the hippocampus *cornu ammonis* 1 (CA1), (Pepicelli et al., 2004). Moreover, the NO-cGMP pathway seems to be particularly important for hippocampus-dependent memory (Ingram et al., 1998, Mamiya et al., 2000, Zou et al., 1998) as nNOS is co-localized with NMDARs and sGC in the CA1 region (Burette et al., 2002). Taken together, the NMDAR mediated NO-cGMP signalling pathway of the hippocampus seems to be important for learning and memory.

Interestingly, there is accumulating evidence from clinical studies suggesting that the NO signalling system is involved in the pathophysiology of schizophrenia (Bernstein et al., 2005, for further information see “Proposed clinical relevans”, page 57).

Disrupted filtering mechanism in schizophrenia: A unifying theory?

Schizophrenia is a heterogeneous disorder encompassing deficits in several brain functions reflecting its complex underlying pathophysiology. Although there is no proven unifying aetiological hypothesis, a model integrating developmental abnormalities with physiological network dysfunction and expression of schizophrenic symptoms has been proposed. Patients with schizophrenia consistently show deficits in sensory information processing, measured by prepulse inhibition (PPI) and habituation of acoustic startle (Braff et al., 1992, Swerdlow et al., 1994). PPI is a measure of reflexive pre-attentive information processing whereby a weak pre-stimulus inhibits the startle response to a following stronger stimuli. Habituation is a measure of response learning, as one stimulus elicits a progressively weaker startling response when consistently repeated (Braff, 1993, Braff et al., 1992). The primary PPI circuit consists of a complex network, including cortico-striato-pallido-thalamic neural circuitry that is dependent on *e.g.* DA and glutamate transmission (Johansson et al., 1994, Koch, 1999, Swerdlow et al., 1994, Zhang et al., 1999).

The hypothesis proposes that pre-attentive sensory information processing, measured by *e.g.* PPI, is necessary for an adequate filtering of incoming sensory information. Thus, filtering out irrelevant sensory information on a subcortical, pre-attentive level is necessary for the brains' capacity to further process relevant information. Hence, an abnormal filtering mechanism, *e.g.* decreased PPI, could lead to an inability to distinguish "relevant" from "irrelevant" sensory information. This could cause an overflow of inappropriate information, reaching higher cortical areas, resulting in deficits in attention and cognitive abnormalities (Andreasen, 2000, Braff, 1993, Geyer, 2006). It is furthermore possible that such information overflow could result in additional psychotic symptoms, including hallucinations and delusions.

This point is further elucidated in the reply given by John Forbes Nash Jr, Nobel Prize Winner in Economics 1994, diagnosed with schizophrenia, when asked by professor George Mackey:

“How could you, a mathematician, a man devoted to reason and logical proof. How could you believe that extraterrestrials are sending you messages? How could you believe that you were being recruited by aliens from outer space to save the world?”.

John Nash Jr replied:

“ ...the ideas I had about supernatural beings came to me the same way that my mathematical ideas did. So I took them seriously”. (Nasar, 1998)

The unifying hypothesis states that environmental and genetic risk factors interact during the perinatal period, affecting neurodevelopmental physiological processes such as neurogenesis, neuronal migration synaptogenesis, and apoptosis. An abnormal neurodevelopment would lead to anatomical deviations and inappropriate neuronal networks in the adolescent brain. This abnormal physiology could create a vulnerability that, later in life and in combination with various environmental factors, could lead to development of schizophrenia, Figure 3 (Andreasen, 2000, Braff, 1993, Klamer, 2004).

Working model

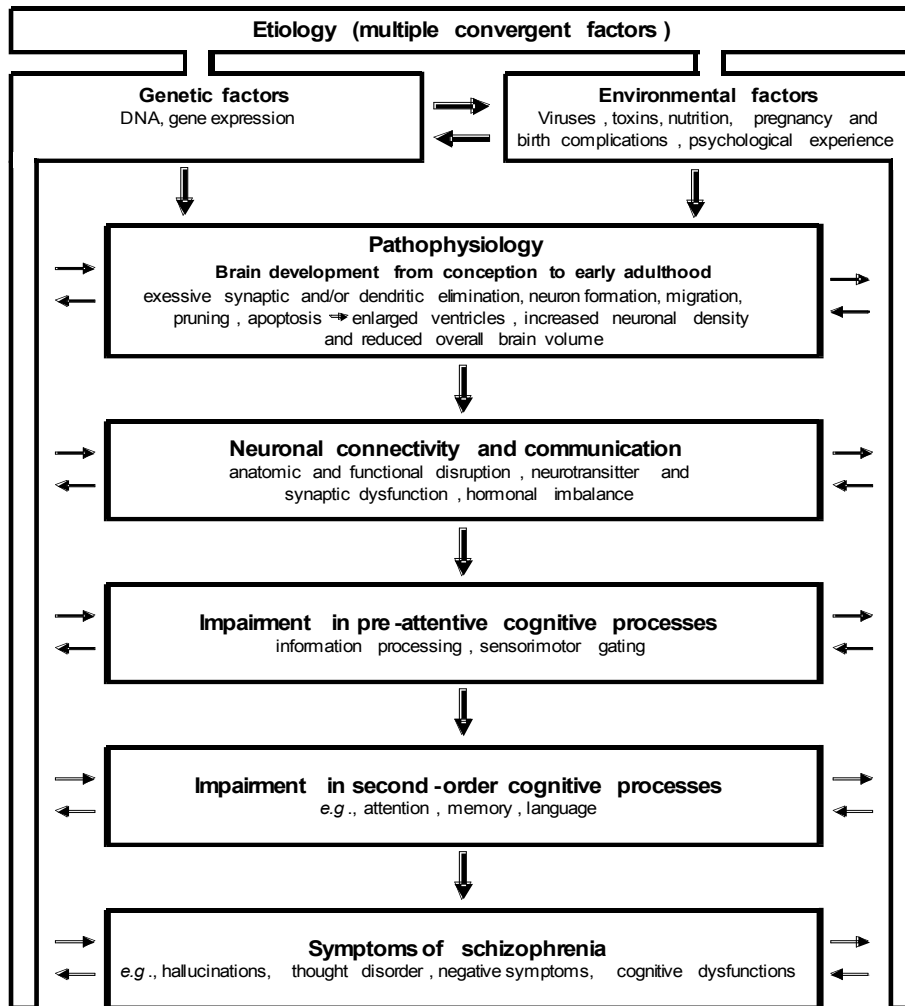


Figure 3: Working hypothesis of schizophrenia unifying developmental abnormalities, sensory information processing and symptoms of schizophrenia Reference: Klammer (2004) modified after Andreasen (2000) and Braff (1993).

Learning memory and schizophrenia

Division of memory

Memory has traditionally been divided into two components; short-term and long-term memory. Short-term memory has been defined as transient storage, in the range of seconds, with the capacity of holding 7 ± 2 items. The items in short-term memory with repeated exposure would transform into long-term memory. Long-term memory could hold an unlimited amount of memory for an indefinite amount of time (Miller, 1956, Atkinson, 1968). Baddeley and Hitch (1974) further developed this two-component model into a unifying working memory model, integrating short- with long-term memory. Working memory was defined as a three-component model where phonologic, visual and spatial information would be processed under the influence of an attention-steering central executive component (Baddeley, 1974). Thus, working memory converged short-term and long-term memory, involving manipulation of information and highlighting the importance of cognitive functioning in memory. Working memory is dependent on PFC functioning (Baddeley, 2004).

In 1957, Scoville and Milner described a patient that had lost the capacity to form new memories. Patient H.M. had gone through bilateral hippocampectomy due to severe epilepsy. H.M was soon found to be unable to form so-called explicit memories, *i.e.* memories of events and facts. However, his implicit memory, *i.e.* motor learning, was still intact. H.M. displayed anterograde but not retrograde amnesia for explicit memories. Consequently, the hippocampus was discovered to be necessary for the storage of new explicit memories, but not for retrieval of old memories.

Long-term memory is divided up in two main categories of memories; explicit (or declarative) and implicit (or non-declarative) memories, Figure 4. Explicit memories include facts and events, *i.e.* memories that can be “declared” or talked about (Tulving, 2002). This type of memory is, dependent upon the medial temporal lobe, as illustrated by H.M. Implicit memory includes priming, procedural learning (*i.e.* motor learning), associative learning (*e.g.* classical conditioning) and non-associative learning (such as response habituation, (Squire, 1987).

Figure 4: Long-term memory, its subdivisions and the structural anatomy governing these functions, adapted from (Squire, 1994).

Physiology of memory

The basis for learning and memory is the remarkable plasticity of the brain and its inherent capacity to change its structure at the synaptic level. Donald O. Hebb's Law illustrates this point as he described the neural basis for long-term memory:

“When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased”

(Hebb, 1949)

Thus, Donald O. Hebb was one of the first people to describe activity-dependent neural plasticity.

The neural basis, underlying memory formation, is proposed to be due to changes in synaptic strength, *i.e.* long-term potentiation (LTP) (Bliss and Collingridge, 1993, Bliss and Lomo, 1973, Kandel, 2004). Kandel and co-workers have contributed tremendously to the understanding of the molecular basis for storage of (1) implicit memory by investigation of the *Aplysia* motor and sensory neurons, and (2) explicit memory by studying synaptic plasticity of the mammalian hippocampal pyramidal cells (Kandel, 2004). In mammals, LTP has been most extensively studied in the hippocampal pyramidal neurons known to be essential for the encoding of explicit memories, *e.g.* spatial memory (Kandel, 1999).

Glutamate and memory

The hippocampal pyramidal cells, known as “place cells”, are essential for spatial learning and memory since these cells encode extra-personal space (O'Keefe, 1979). Spatial learning is dependent upon NMDAR functioning in the hippocampus. Treatment with NMDAR antagonists block both spatial memory and hippocampal place cell LTP, in rodents (Morris, 1989, Morris et al., 1986). Studies of spatial learning and memory in rodents, are some of the most well established ways of studying explicit memory in experimental animals (Morris, 1984, Smith and Mizumori, 2006).

The process of LTP can be divided into early phase LTP (E-LTP) and late phase LTP (L-LTP) (Frey et al., 1993, Nguyen et al., 1994). E-LTP is the initial synaptic facilitation, lasting 1 to 3 hours, thought to underlie short-term memory. E-LTP is induced by increased presynaptic glutamate release stimulating postsynaptic influx of Ca^{2+} through NMDARs, resulting in phosphorylation and insertion of AMPARs into the synapse. Thus, E-LTP does not require *de novo* protein synthesis (Malenka and Nicoll, 1997, Frey et al., 1993).

By contrast, L-LTP lasts up to days, and occurs when there is a stronger facilitation of the synapse such that the postsynaptic intracellular Ca^{2+} levels are high enough, or facilitated by a modulatory DAergic input, to activate cAMP. The cAMP activation in turn activates a cascade of kinases and transcription factors resulting in *de novo* protein synthesis of *e.g.* growth factor brain-derived neurotrophic factor (Nguyen et al., 1994, Frey et al., 1993, Huang and Kandel, 1995, Kovalchuk et al., 2002). In the hippocampus, NMDARs can induce LTP, however, their activity is tightly regulated by D1/D5Rs (Huang and Kandel, 1995), AMPARs, and

GABARs (as reviewed in Collingridge et al., 2004). Furthermore, NO may act as a retrograde messenger during both the early phase E-LTP and L-LTP (Lu et al., 1999, O'Dell et al., 1991, Zhuo et al., 1994).

Memory in schizophrenia

Patients with schizophrenia display deficits in several different explicit memory domains (Gold et al., 1992), such as verbal memory (Toulopoulou et al., 2003, Hill et al., 2004), spatial memory (Fleming et al., 1997, Hanlon et al., 2006), and episodic memory (Clare et al., 1993, Rushe et al., 1999). Furthermore, this patient group has a fundamental disruption of working memory and executive functioning, mediated by the PFC (Bertolino et al., 2006, Gold et al., 1997, Goldman-Rakic et al., 2004). Hippocampal abnormalities, governed by glutamatergic and acetylcholinergic imbalance, are consistently found in patients with schizophrenia (Freedman et al., 2000, Lahti et al., 1995, Tamminga, 2006) and such abnormalities are further associated with declarative memory deficits (Preston et al., 2005). Among the working memory deficits are *e.g.* problems with spatial working memory (Park and Holzman, 1992, Piskulic et al., 2007). Deficient working memory is attributed to an imbalance in GABAergic, glutamatergic and DAergic interactions of the PFC (Lewis and Moghaddam, 2006, Castner and Williams, 2007). Thus, there are fundamental memory deficits present in patients with schizophrenia and these deficits determine both functional outcome and treatment response (Green, 1996, Green, 2006).

Social cognition

Increasing attention has recently been paid to social cognition deficits in patients with schizophrenia (Bertrand et al., 2007, Burns, 2006a, Green et al., 2005). Traditionally, social withdrawal in schizophrenia has been considered a negative symptom. Lately however, there has been a focus on elucidating the underlying cognitive dysfunctions as they *e.g.* predict functional outcome (Couture et al., 2006, Green et al., 2005). Social cognitive deficits include low social cue recognition, impaired facial recognition as well as problems with theory of mind (Hall et al., 2004, Sprong et al., 2007, Zhu et al., 2007). In summary, dysfunctions in social cognition include several domains, such as memory impairments, affective disturbances, and executive functional deficits in patients with schizophrenia. For further discussion see “Social cognition in schizophrenia: The road ahead”, page 59.

Treatment

With the revolution of chlorpromazine in the 1950's came the introduction of the first generation antipsychotics. First generation antipsychotics are characterized by high D2R affinity, occupying approximately 65-89% of D2Rs, in clinically effective doses (Farde et al., 1988). This treatment alleviates the psychotic positive symptoms very well. However, the high D2R affinity results in aversive side effects including extrapyramidal side effects. The second generation antipsychotics were developed in the 1970's and display a D2R occupancy of 40-65% (Farde et al., 1989). The second generation antipsychotics induce less DA-dependent side effects than the first generation antipsychotics. The "prototype" of second generation antipsychotic is clozapine. In addition to its D2R antagonist activity, it also has affinity for the serotonin (5-HT)_{2A} receptor (5-HT_{2A}R), the histamine type-1 receptor, adrenergic type-1 receptor, and the muscarinic type-1 receptor (Capuano et al., 2002). Although inducing less extrapyramidal side effects than most of the effective second generation compounds, clozapine treatment can lead to agranulocytosis, diabetes, and obesity (Schultz and Andreasen, 1999). Besides improving positive symptoms, second generation antipsychotics have been reported to have some, although modest, beneficial effects on negative symptoms and cognitive deficits (Murphy et al., 2006). The most recently developed approved antipsychotic treatment is the DA-stabilizer, *i.e.* the third generation antipsychotic, aripiprazole. Aripiprazole is a partial DA agonist, proposed to primarily stabilize the striatal-cortical DA-dysregulation underlying schizophrenia (Carlsson et al., 2004, Nilsson et al., 2004).

Until recently, all antipsychotics have displayed DA affinity. However, a recent phase-2 trial showed that mGlu receptor 2 and 3 (mGluR_{2/3}) agonists, LY2140023, have clinical efficacy comparable to olanzapine. LY2140023 treatment was found to significantly improve schizophrenia symptoms in comparison to controls (Patil et al., 2007). Metabotropic glutamate agonists of this kind exert their effects on the limbic system by decreasing presynaptic release of glutamate (Schoepp, 2001).

Another approach in targeting the glutamate system is to use NMDAR partial agonists, glycine, D-serine, and D-cycloserine. These modulators have been investigated as adjunctive treatments in schizophrenia with variable results. Clinical trials of these agonists show that D-serine, as an additive treatment, has the most beneficial effect in alleviating otherwise treatment-refractory schizophrenia (Heresco-Levy et al., 2005).

Furthermore, other trials have shown that sarcosine, a glycine transporter inhibitor, is effective as an add-on therapy to antipsychotic treatment (Tsai et al., 2004, Heresco-Levy, 2006).

Taken together there are some new promising drug candidates for treating schizophrenia on the rise. Moreover, perhaps in the future we will have the option of designing more symptom specific treatment regimens for schizophrenia.

The phencyclidine model

The PCP model of schizophrenia emerged in the 1950's as the anaesthetic compound, Sernyl[®], was tried in healthy volunteers. PCP induced a psychosis-like state in healthy volunteers, including sensory perceptual delusions, affective changes, stereotypies and cognitive deficits. PCP was therefore described as a "schizophrenomimetic drug" (Allen and Young, 1978, Luby et al., 1959, Yesavage and Freman, 1978). When PCP was given in a single dose to patients with schizophrenia, their symptoms were exacerbated up to several weeks, compared to healthy controls in which the drug effects wore off in a matter of hours (Luby et al., 1959). In the 1960's PCP, or "angel dust", became a drug of abuse where by a one time exposure to the drug could induced psychotic states. Repeated use of PCP could cause a more persistent drug-induced psychotic state (Rainey and Crowder, 1975). PCP has since been used to model aspects of schizophrenia in experimental animals. Although PCP is no longer used to mimic schizophrenia in humans, ketamine is used for this purpose (Krystal et al., 1994). Ketamine, as well as PCP, works by decreasing NMDAR-mediated neurotransmission, and although less potent, displays a similar receptor profile to PCP (Kapur and Seeman, 2002).

The main pharmacological property of PCP is non-competitive antagonism of the NMDAR. However, PCP also has affinity for *e.g.* the D2R, the 5-HT₂R, the sigma receptor, as well as potassium channels (Rothman, 1994, Kapur and Seeman, 2002). Furthermore, acute administration of PCP leads to increased DA release in rats (Hertel et al., 1995, Jentsch et al., 1997a), while subchronic PCP-treatment decrease DA release in monkey and rat PFC (Jentsch et al., 1998, Jentsch et al., 1997b). Thus, PCP administration leads to an imbalance in the prefrontal DA system in accordance with the pathophysiology of schizophrenia (as reviewed in Jentsch et al., 1997b and Jentsch, 1999). Long-term PCP abuse leads to decreased frontal blood flow (Hertzmann et al., 1990, Wu et al., 1991), which is in alignment with clinical findings of "hypofrontality, that

is further associated with cognitive deficits in schizophrenia (Goldman-Rakic, 1990, Ingvar and Franzen, 1974, Weinberger et al., 1986). Acute PCP administration causes an increase in glutamate overflow in the PFC (Adams and Moghaddam, 1998, Takahata and Moghaddam, 2003) as well as increased cerebral blood flow in the basal ganglia, thalamus, hippocampus and PFC in the rat (Gozzi et al., 2007). Such abnormalities most likely contribute to the disruption of cognitive functions observed after acute PCP administration (Jentsch, 1999).

In experimental animals, PCP is used to model a NMDAR hypofunctioning and produce deficits in several translational behavioural animal models for schizophrenia, such as locomotor activity, social interaction, sensory information processing, selective attention and working memory (Adams and Moghaddam, 1998, Egerton et al., 2005, Geyer et al., 1984, Javitt, 2007, Jentsch and Anzivino, 2004, Klamer, 2004, Ogren and Goldstein, 1994, Palsson et al., 2005, Sams-Dodd, 1995). Thus, the PCP-model mimics aspects of behavioural and neurophysiological deficits observed in schizophrenia.

Phencyclidine-induced behavioural deficits: Role of nitric oxide

Some of the behavioural effects of PCP can be blocked by second generation antipsychotics (Fejgin et al., 2007b, Hashimoto et al., 2005b, Johansson et al., 1994). The PCP model is proposed to display heuristic potential to identify new treatment targets against cognitive deficits observed in patients with schizophrenia (Lipska and Weinberger, 2000). However, available antipsychotics lack the ability to fully improve the cognitive dysfunctions and hence the need for novel cognitive enhancing treatments. One potentially new treatment target may be the NO signalling pathway. Previous animal studies from our research group have shown that PCP-induced disruption of several translational behaviours, on different levels of cognitive demand, can be blocked by pretreatment with a NOS inhibitor. These translational behaviours include hyperlocomotion, decreased prepulse inhibition of acoustic startle, low response habituation of acoustic startle, and abnormal latent inhibition, Figure 5. These findings suggest a potentially new treatment approach of particular interest, since there is accumulating clinical evidence for involvement of NO in the pathophysiology of schizophrenia (Bernstein et al., 2005, Palsson, 2006).

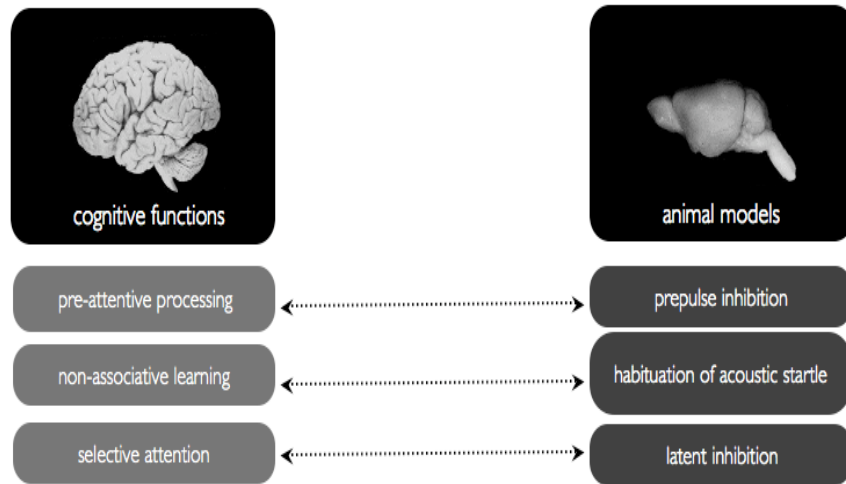


Figure 5: On the left are cognitions behaviours deficient in schizophrenia and on the right are the translational animal models used to measure these cognitive functions. Acute PCP treatment disrupts all the behaviours displayed in the figure. Furthermore, the PCP-induced deficits are ameliorated by NOS-inhibition (Johansson et al., 1997, Klamer et al., 2001, Klamer et al., 2004c, Klamer et al., 2004d, Klamer et al., 2005a, Klamer et al., 2005b).

NO production is regulated by three different isoenzymes of NOS (for further information see "Nitric oxide and schizophrenia", page 18). Previous studies from our research group suggest that the neuronal version of NOS is mediating the PCP-induced behaviours. As such, PCP-induced disruption of both PPI and locomotor activity was normalized in rats and mice by a selective nNOS inhibitor (Johansson et al., 1999, Johansson et al., 1997, Klamer et al., 2004b). Furthermore, mice lacking the nNOS isoenzyme did not display PCP-induced hyperlocomotion (Bird et al., 2001). We thus hypothesize that PCP-induced deficits ameliorated by NOS-inhibition are mediated via nNOS.

Phencyclidine-induced behavioural deficits: What can we expect from animal models?

Extensive schizophrenia research has provided us with increasing knowledge regarding this complex disorder. However, the aetiological factors and underlying pathophysiology still remains unknown. The complex diversity in the clinical picture of schizophrenia probably pinpoints the many different mechanisms resulting in its characteristic symptoms. Several different animal models have been proposed to model schizophrenia, including neurodevelopmental lesions and pharmacological models, social isolation paradigms, and acute pharmacological psychotomimetic interventions (Carlsson et al., 2004, Geyer et al., 1993, Javitt, 2007, Lipska, 2004). Still, no single existing animal model has so far proved to fully mimic schizophrenia.

Given the heterogeneity of the schizophrenic disorder and its unknown aetiology, it is currently highly unlikely to find an animal model that completely mimics the disorder in all its regards. However, optimally animal models of psychiatric disorders should be evaluated according to its face, construct, and predictive validity as a schizophrenia model.

Animal models of psychiatric disorders can be classified as having construct, face or predictive validity (Willner, 1984):	
Construct validity	similar underlying neurophysiological concept
Face validity	similar endpoint measurements in clinical and experimental models
Predictive validity	similar pharmacological profile in clinical and experimental studies

The PCP model of schizophrenia displays high face validity as PCP induces the same type of behavioural deficits as observed in schizophrenia, both in humans and in experimental animal (Figure 5, Javitt, 2007, Jentsch, 1999). PCP mimics some of the aberrant neurochemical findings of schizophrenia such as *e.g.* hyperDAergia (for more information see “The phencyclidine model”, page 28). Since schizophrenia seems to be a neurodevelopmental disorder, acute pharmacological manipulations will not fully mimic the disorder. In spite of this limitation, PCP mimics some of the symptoms of schizophrenia, and can thus be used to model certain schizophrenia-like features.

AIM OF THESIS

The overall purpose of this research was to investigate the role of NO-signalling as a potential new treatment target to eliminate cognitive deficits in schizophrenia. In this thesis the role of NOS-inhibition on PCP-induced deficits in higher order cognitive functions and social behaviour, was studied in animal models.

Specific aims

- I. To investigate the NO-dependent effects of PCP on spatial learning, working memory, long-term memory, and cognitive flexibility using different versions of the Morris water maze (MWM).
- II. To elucidate the NO-dependent effects of PCP on social interaction and recognition memory.

MATERIALS AND METHODS

Animals

In all the experiments, male Sprague-Dawley rats with a body weight of 250 grams were purchased from B&K Universal AB, Sollentuna, Sweden. Upon arrival to the animal facility the animals were housed in cages (Macrolon IV, 24 x 42 x 15 cm) of maximum four animals per cage. The rats were housed in a colony room for one to two weeks before testing started in order to habituate. Food (Harlan Teklad, Norfolk, England) and tap water was available *ad libitum*, room temperature ($20 \pm 1^\circ \text{C}$) and humidity (55%) was kept constant. The daylight cycle was maintained artificially, lights went off at 18:00 till 7:00 h and experiments were performed during the light phase. The studies were all approved by the Ethics Committee for Animal Experiments, Göteborg, Sweden.

Drugs

Drugs used were phencyclidine (1-(1-phenylcyclohexyl)piperidine HCL, PCP) (RBI, Natick, USA) and *N*^G-nitro-L-arginine methyl ester (L-NAME) (RBI, Natick, USA). Both PCP and L-NAME were dissolved in saline (0.9% NaCl dissolved in distilled water) and injected in a volume of 2 ml/kg subcutaneously (sc). Saline (SAL) was used as vehicle. In all experiments L-NAME was injected 10 minutes prior to PCP, and 25 minutes before behavioural testing began (*i.e.* before the first swim of each training day and before the social interaction test on day 1). The doses were selected based previous findings within the research group (Johansson et al., 1997, Klamer et al., 2005a)

Behavioural models

Apparatus

Morris water maze

A circular pool with a diameter of 1.4 m and a circular Plexiglas platform (HVS Image, UK) with a diameter of 10 cm was used. The pool was filled with water of a temperature of $24 \pm 1^\circ \text{C}$ and the water surface was kept 2 cm above the platform. Water soluble paint (Allmogefarg, Panduro, Göteborg, Sweden) was used to make the water opaque. The pool was placed in a room with external cues (geometric black shapes on white background), mounted on the walls. These cues were kept in a constant position throughout the whole experiment (Figure 6). A camera mounted in the ceiling recorded the behaviour using the 2020 Plus Tracking System (HVS Image, UK).

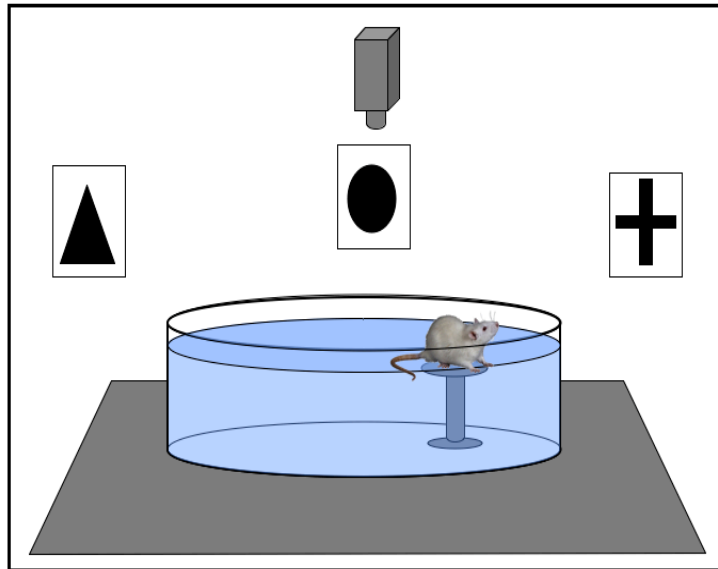


Figure 6: Schematic drawing of the MWM setup.

Social interaction

The social interaction test was carried out in eight sound attenuated locomotor activity boxes (70x70x40cm, Plexiglas, Kungsbacka mät- och reglerteknik AB, Fjärås, Sweden). Locomotor activity was assessed by the number of crossings of eight by eight photocell beams directed across the floor of the box. Animal behaviour was also recorded by a video camera (Canon MV900). The luminescence inside the box was set to 3.5-7 lux. The boxes were carefully cleaned between test sessions to minimise distracting odours.

Experimental procedure

Morris water maze

The MWM paradigm was first established by Richard Morris in the 1980's and has since been consistently used to assess rodent spatial memory (Morris, 1984). A novel paradigm of the MWM that allowed the estimation of both spatial learning, working memory, and long-term memory (*i.e.* reference memory), on each of the acquisition days, was developed by Baldi and co-workers (2005). In Paper I, the original MWM paradigm was applied and in Paper II, the Baldi paradigm was used. Paper III was based on a combination of the Baldi paradigm and a version of the MWM in which platform positions were varied between days (Steele and Morris, 1999).

In all water maze experiments animals were given an acclimatization session two days before the acquisition period started. During the acclimatization session each rat was allowed 30 s to swim around in the maze without the platform present. Depending on what type of memory that was investigated, the paradigms varied between the different experiments. The different experimental procedures are summarized in Table 2. In all experiments each acquisition session consisted of five or ten consecutive swimmings for four to five consecutive days. During acquisition the animal was let into the pool from one of eight positions (N, E, SE, S, SW, W, NW, NE), facing the wall of the pool. The platform was always held in a constant position within days, but varied between days in Paper III. During acquisition sessions, mean time to find the platform (s) of all trials in one day and swim speed (m/s) were recorded. When an animal located the platform, or was guided to it (this occurred when the

platform was not located within the limited search period), the animal was allowed a platform rest before the next swimming started.

Probe trials were executed in order to measure memory of the previous platform position. During probe trials the platform was removed and the animals memory for the previous platform position was assessed during a 60 s swimming trial. Memory for the previous platform position was measured as either; % of time spent in the quadrant of the pool where the platform had previously been located (*i.e.* the target quadrant) or, by assessing mean distance (m) to the previous platform position. After each swimming session the animal was washed and allowed to dry under a fan heater before put back into the home cage.

PAPER	ACQUISITION					PROBE		
	Days	# of Swimmings/day	Swimming length (s)	Platform position	Platform rest (s)	Days	# of trials/day	Length of trial
I: exp 1	1- 4	5	90	constant	30	7	2	60
I: exp 2	1- 4	5	90	constant	30	7	1	60
II	1- 5	10	60	constant	20	1 to 5	2	60
III	1- 4	10	60	varied bw days	20	1 to 5	2	60

Table 2: Summary of experimental procedure for Papers I, II, and III. Category for “Days” imply days over a period of 7 consecutive days (Day 1 to 7) (bw= between).

Paper I

In the first two experiments, of Paper I, the design was arranged in order to study spatial learning and long-term (*i.e.* reference) memory in the water maze.

Dose-dependent effects of PCP

In experiment 1 the effect of PCP dose was evaluated as rats were injected with PCP in a dose of 0.5, 1.0 or 2.0 mg/kg or SAL (n=10), 15 min prior to the first swim on each of the four acquisition days. The platform was kept in the NE quadrant throughout the whole acquisition period. After the last day of acquisition the animals were allowed to rest for two days and then on the third day they went through a drug-free probe test. During probe trials the % of time spent in the target quadrant was measured over the 60 s period.

State-dependency effects

After the initial probe test in experiment 1, the state dependent effects of PCP were evaluated as the rats, right after the initial probe test were

injected with the same dose of PCP (2 mg/kg, n=10) as during acquisition and then allowed to swim in the pool for another 60 s, platform removed. The second probe trial was done in order to control for state dependency effects on search behaviour for the platform and the % of time spent in the target quadrant was assessed.

Effects of L-NAME on PCP-induced deficits

In experiment 2, the effect of pretreatment with L-NAME on the PCP-induced effects was investigated. On each of the acquisition days the rats were pretreated with L-NAME (10 mg/kg) or SAL prior to the PCP (2 mg/kg) or SAL injection. The platform was maintained in the SW quadrant throughout the acquisition period. The probe trial was performed in a drug-free state.

Paper II

To further investigate NO-dependent effects of PCP on spatial learning, working memory, and reference memory, a novel MWM paradigm was applied (Baldi et al., 2005). Using this paradigm it was possible to acquire more information on each acquisition day than when using the paradigm in Paper I. Right before and after each acquisition session there was a probe trial on each of the five acquisition days, making it a total of 12 swimming trials per day. The first probe trial of each day served to measure what the rat remembered from the previous day (*i.e.* reference memory), while the probe trial carried out right after the last acquisition swim of each test day, served to assess working memory. Between the acquisition swim and probe trials rats were allowed a 20 s platform rest as described above, followed by a 20 s cage rest before the next swim trial. This 20 s cage rest was carried out in order for the experimenter to eliminate any possible odour traces by gently stirring the water or to allow time to put the platform back into the water after the probe trial.

On each of the acquisition days the rats were pretreated with L-NAME (10 mg/kg) or SAL, before the PCP (2 mg/kg) or SAL (n=8) injection. Mean distance to platform during the 60 s probe trial (Gallagher proximity measure, m) was recorded on each of the five acquisition days.

Paper III

The final MWM experiment, of this thesis, was designed to investigate higher order cognitive functioning, such as cognitive flexibility and executive functioning. Based on a MWM paradigm modified after Steele and Morris (1999) we evaluated the effects of PCP and NOS inhibition on cognitive flexibility. On each of the acquisition days the rats were

pretreated with L-NAME (10 mg/kg) or SAL before the PCP (2 mg/kg) or SAL (n=8) injection. Each swimming session consisted of a total of 11 swimming trials, the last swim being a probe trial (platform removed). Each swimming lasted for a maximum of 60 s followed by a 20 s platform rest (except on probe trails) and then a 20 s rest in a plastic cage, followed by the subsequent swimming. The platform position was held constant **within** each of the acquisition days but varied **between** acquisition days, such that each animal was to find the platform in a novel position on the first swim of each day. During probe trials Gallagher proximity measure was assessed.

Social interaction

Paper IV

Two days before the first social interaction test, each animal was introduced to the activity box for 10 minutes, one by one, as to habituate to the new test environment and thereby eliminate explorative behaviour of the environment on the test day. The social interaction test consisted of two tests performed on two consecutive days. On the first day, two unfamiliar animals were drug-treated with the same treatment and put in the same box for 10 minutes. During this 10-minute period, the rats' behaviour was recorded in order to investigate the effects of PCP and L-NAME on social interaction. Twenty-four hours later the same animals were tested according to the same procedure, but without any drug treatment, in order to investigate their memory of the social interaction from the previous day. On both days of testing, each animal was individually put in a plastic cage for 30 minutes before testing began. The design of the social interaction test was partly adopted from File and co-workers (2001) and Sams-Dodd (1995). Social interaction included sniffing, licking, following, playing, wrestling, and social supporting (the two rats sitting in close proximity, $\leq 3\text{cm}$, to each other without interacting). Both the frequency (number of interactions) and the time (total time in seconds interacting) engaging in social interaction were assessed. Locomotor activity was recorded as the total counts of horizontal activity (*i.e.* number of times a photocell beam was interrupted in the horizontal plane).

On the first social interaction test, the rats were pretreated with L-NAME (10 mg/kg) or SAL prior to the PCP (2 mg/kg) or SAL injection (*i.e.* the main treatment). Five pairs of rats in each of the four treatment groups (SAL+SAL, SAL+PCP, L-NAME+SAL, L-NAME+PCP, n=10) were used.

Statistics

Paper I

The acquisition sessions were analysed using a repeated measures two-way ANOVA with treatment as between-subjects factor and trial as within-subjects factor followed by Bonferroni's Multiple Comparison Test.

Analysis of probe trials were done separately using a one-way ANOVA with treatment as between-subjects factor followed by Dunnett's Multiple Comparison Test. One sample t-tests were used to separately analyse preference for the target quadrant and state dependent effects related to drug treatment.

Paper II

The acquisition trials were analysed using a repeated measures two-way ANOVA with treatment as between-subjects factor and acquisition session as within-subjects factor, followed by Bonferroni's Multiple Comparison Test. Analysis of probe trials was carried out separately using a two-way ANOVA with treatment as between-subjects factor and the trial as within-subjects factor, followed by Bonferroni's Multiple Comparison Test.

Paper III

In Paper III, acquisition trials were analysed using a repeated measures three-way ANOVA with pretreatment (SAL or L-NAME) and treatment (SAL or PCP) as between-subjects factors and acquisition session as within-subjects factor. Post hoc analysis was performed by Bonferroni's Multiple Comparison Test when appropriate.

Paper IV

Two- or three-way ANOVA followed by Tukey's HSD test for comparison between treatment groups were used to analyse the experimental data. Two-way ANOVA using pretreatment (SAL or L-NAME) and treatment (SAL or PCP) as between-subjects factors assessed drug effects on time in social interaction, number of interactions and locomotor activity on test-Day 1. Three-way ANOVA was used to evaluate treatment effects on social interaction using pretreatment (SAL or L-NAME) and treatment (SAL or PCP) as between-subjects factors, and test day as within-subjects factor (test-Day 1 and 2).

Two-tailed levels of significance were used in all the above mentioned analyses and $P < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Paper I: Effects of phencyclidine on spatial learning and memory: Nitric oxide-dependent mechanisms.

Cognitive deficits of schizophrenia are predictive of disease outcome as well as functional level and are not alleviated by antipsychotic treatment (Green, 2006, Green, 1996). Therefore, methods for studying cognitive deficits with relevance for schizophrenia are needed in order to find better pharmacological treatments. Previous findings within the research group show that PCP-induced deficits in sensory information processing, *i.e.* prepulse inhibition, habituation of acoustic startle and selective attention, can be ameliorated by NOS-inhibition (Klamer et al., 2004b, Klamer et al., 2004d, Johansson et al., 1997). Based on these findings, the present study was carried out in order to evaluate the NO-dependent effects of PCP on higher order cognitive functions, such as spatial learning and reference memory, *i.e.* spatial long-term memory, using the MWM paradigm as adopted from Morris (1984).

The dose-response experiment showed that PCP (2 mg/kg) disrupted (*i.e.* delayed) spatial learning as indicated by significantly increased time to find the platform over the four training days. Furthermore, PCP administration also impaired reference memory as displayed by significantly less amount of time spent in the target quadrant compared to controls. The time to find the platform in rats treated with the lower doses of PCP (0.5 and 1.0 mg/kg) did not differ from control animals. Therefore PCP 2 mg/kg was chosen as the appropriate dose to use, which was in accordance with previous studies by our research group (Klamer et al., 2005b, Klamer et al., 2005a, Johansson et al., 1997, Palsson et al., 2005). No state-dependent effects of PCP were detected on time spent searching for the platform during probe test. This indicates that PCP does not function as a cue to initiate search for the platform in rats that were treated with PCP during acquisition. Moreover, control animals displayed a significant decrease of searching behaviour in the target quadrant on the second probe test. The behaviour of the control animals implicates learning that the platform is not in the previous position, in only one probe trial.

Surprisingly, in the first experiment, PCP (2 mg/kg), delayed spatial learning significantly during the first two days of acquisition. However, on the third and fourth day there was no difference in time to find the platform between treatment groups. In experiment two, PCP-treatment

not only delayed but also impaired spatial learning significantly over the whole four-day acquisition period. The explanation for this discrepancy remains unknown. A possible explanation could be that the discrepancy is due to differences in batches of animals, or to the increased experience of the researcher carrying out the second experiment.

Furthermore, in experiment two, pretreatment with the NOS inhibitor, L-NAME, completely restored the PCP-induced spatial learning deficit, however did not manage to restore the reference memory dysfunction as measured on the probe test, Figure 7. The lack of restoration of the PCP-induced reference memory deficit was surprising given that rats treated with L-NAME+PCP seemed to have learned the position of the platform as well as control animals during acquisition, and therefore were expected to remember the platform position equally well on probe test. These effects indicate that some PCP-induced deficits of spatial learning and memory are NO-dependent, while others are not (Knepper and Kurylo, 1998, Kesner et al., 1993). PCP, besides being a NMDAR antagonist, also display affinity for the 5-HT₂R, the sigma receptor and the D₂R. Consequently it is possible that some of the effects of PCP on these receptors may contribute to some of its NO-independent effects (Kapur and Seeman, 2002).

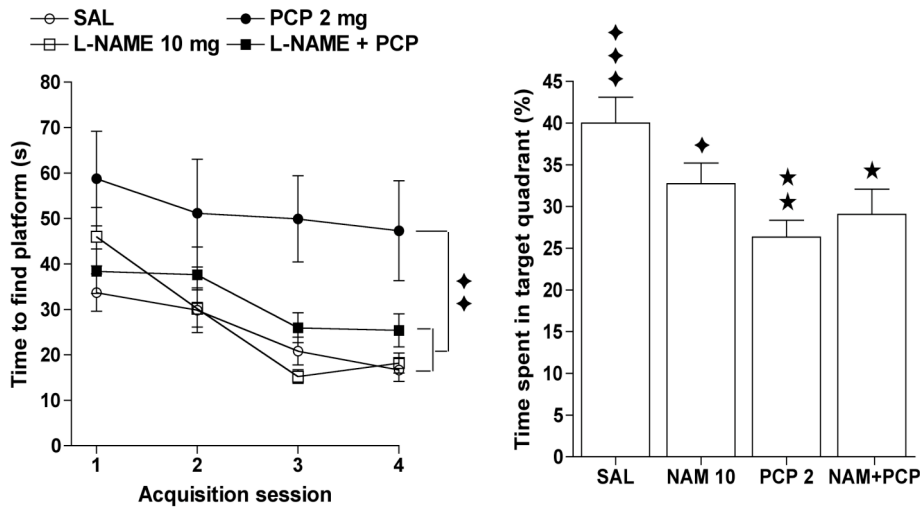


Figure 7: Left: The effects of PCP and L-NAME on acquisition of a spatial learning task using the MWM (◆◆ p<0.01). Right: The effects of L-NAME (NAM) and PCP on long-term memory. ★★ p<0.01 and ★ p<0.05 compared to saline (SAL)-treated rats, ◆◆◆ p<0.001 and ◆ p<0.05 vs. 25% time spent in the target quadrant. For details see Paper I.

Interestingly, patients with schizophrenia display the same type of deficits in a virtual version of the MWM (Hanlon et al., 2006), as observed in Paper I. Thus, patients with schizophrenia showed a delayed time to find the platform during acquisition and less time spent in the target quadrant during probe test. This indicates high face validity for our experimental animal model for spatial learning and memory in schizophrenia.

Paper II: Phencyclidine affects memory in a nitric oxide-dependent manner: Working and reference memory.

Patients with schizophrenia consistently display deficits in different types of working memory, such as spatial working memory (Carter et al., 1996, Park and Holzman, 1992). These spatial working memory deficits can be attenuated by some second generation antipsychotics (*i.e.* risperidone) but worsened by others, such as clozapine (McGurk et al., 2005). Hence these deficits are not consistently alleviated by available antipsychotic treatments and therefore new pharmacological tools are needed. Based on the findings from Paper I, we wanted to further investigate the effects of NOS-inhibition on PCP-induced deficits on working- and reference memory.

The paradigm used in this paper tested spatial learning, working memory, and reference memory within the same session, on each of the five acquisition days. In this way a continuous measure of these different aspects of memory over the whole testing period was obtained. The results from Paper II show that PCP disrupts spatial learning as PCP-treated animals took significantly longer time to find the platform on each of the five acquisition days. The probe test carried out right after the last acquisition trial of each day assessed working memory. PCP treatment disrupted working memory as these rats showed a significantly longer mean distance to the previous platform position (*i.e.* a higher Gallaghers' proximity index), compared to control rats. Reference memory was measured on the first probe test of each acquisition day. PCP-treated animals showed significant reference memory deficits compared to controls. On Day 1, all animals displayed the same results on the reference memory test. This indicates that PCP had no motor side effects that disrupted the behaviour required for probe testing (Figure 8). Thus, PCP had no effects on probe test behaviour before any learning had occurred on Day 1. This further strengthens the treatment effects on learning and memory on the following acquisition days.

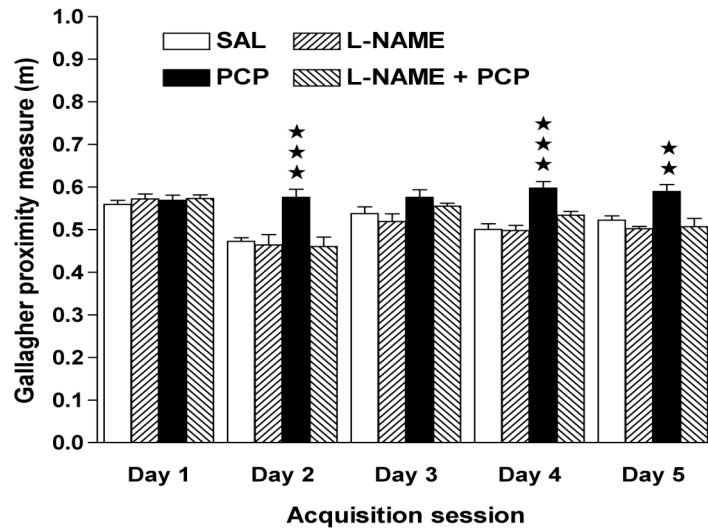


Figure 8: The effect of PCP and L-NAME on reference memory using the MWM. ★★ $p < 0.01$, ★★★ $p < 0.001$ compared to SAL-treated rats. For details see Paper II.

The results further demonstrate that blocking the synthesis of NO, by pretreatment with L-NAME completely restored the PCP-induced deficits on spatial learning, working memory, and reference memory to control levels. L-NAME, by itself, had no effects on any of the measured behaviours.

Analysis of swim speed showed that there was a significant effect of PCP on this measure during acquisition training such that PCP-treated animals swam faster than all other treatment groups. This finding is probably due to induction of thigmotaxis (aimless forward-only swimming along the edges of the pool, for example see Figure 10) in PCP-treated animals. Interestingly, this increase in swim speed was normalized by L-NAME pretreatment. In line with these findings, we have previously shown that also PCP-induced locomotor stimulation can be blocked by NOS-inhibition (Johansson, 1997). Hyperlocomotion has been linked to increased DA efflux in the nucleus accumbens (Engel and Carlsson, 1977). However, PCP-induced hyperlocomotion was not found to be temporally associated with DA overflow in the rat nucleus accumbens whereas such

an association between glutamate efflux in the rat nucleus accumbens and hyperlocomotion was obtained (Adams and Moghaddam, 1998). Moreover, in our own studies PCP-induced increase in DA overflow in the rat nucleus accumbens was significantly ameliorated by L-NAME pre-treatment. Amphetamine-induced hyperlocomotion and DA overflow in the rat nucleus accumbens on the other hand, was not affected by L-NAME pretreatment (Johansson, 1998). Thus, the NO-dependent effects of PCP on locomotor activity may primarily be related to changes in glutamate function.

Taken together, the results from Paper II show that PCP induces deficits in several learning and memory domains consistently found to be impaired in patients with schizophrenia. Moreover, all these PCP-induced memory impairments were attenuated by interfering with NO production. In sum, there seems to be a NO-dependent mechanism underlying PCP-induced disruption of spatial learning and memory.

Paper III: Effects of phencyclidine on cognitive load: Targeting the nitric oxide system.

Functions dependent on the PFC, such as working memory, executive functioning, and planning are often impaired in patients with schizophrenia (Castner et al., 2004, Gold et al., 1997, Semkowska et al., 2004). Lack of these functions may lead to cognitive stereotypy (perseveration or lack of cognitive flexibility) observed in schizophrenia (as reviewed in Drake and Lewis, 2003). In Paper III, we wanted to investigate the effects of PCP and NOS inhibition on cognitive functioning dependent upon the PFC, *i.e.* cognitive flexibility.

In order to investigate cognitive flexibility we used a paradigm that required the rat to deal with a new situation of the same task, each testing day. The idea here was that rats would have to develop an efficient search strategy trying to find the new platform position between days.

The results showed that control animals displayed a significantly decrease in time to find the platform Day 1 compared to Day 2 and 3. However, on the fourth day, as the platform was moved a fourth time, the animals showed an increase in time to find the platform, Figure 9. Thus, one advantage with this model is that it estimates the limits of the rats' cognitive ability.

PCP treatment disrupted learning on the three first days of testing compared to all other treatment groups. Furthermore, excluding the PCP group there was no significant difference between any of the other treatment groups. Thus, pretreatment with L-NAME normalized the PCP-induced inability to learn to find the platform.

Analysis of swim speed showed no significant effects of treatment and analysis of probe trials showed no significant treatment or training effect.

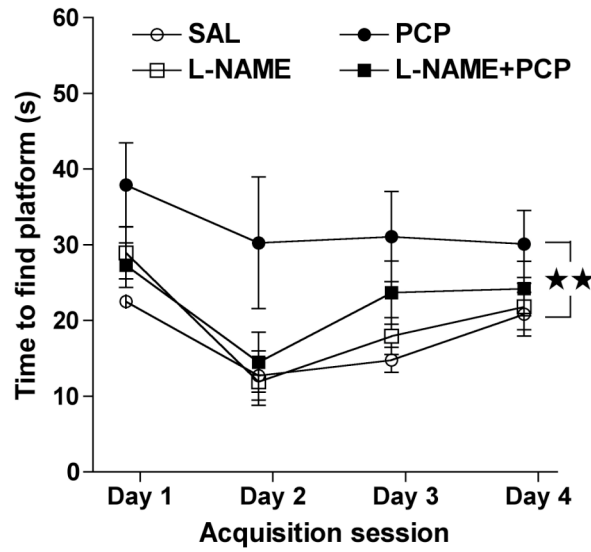


Figure 9: The effect of PCP and L-NAME on acquisition during a “constant spatial reversal” using the MWM. PCP impaired acquisition (★★ $p < 0.01$). L-NAME pretreatment normalized the PCP-induced deficits. For details see Paper III.

The swimming pattern diagram is a representative drawing of how PCP and/or L-NAME treatment affects search strategy, Figure 10. The illustration present swim patterns of ten consecutive swimming trials from one animal on Day 2. The diagram indicates that the PCP-treated rat show pronounced thigmotaxis (swimming along the edges of the pool) and a chaotic pattern indicating aimless swimming. Interestingly, animals pretreated with L-NAME, before PCP, displayed a swimming pattern that very much looked like the control rats’ as these rats found the platform on a majority of the trials.

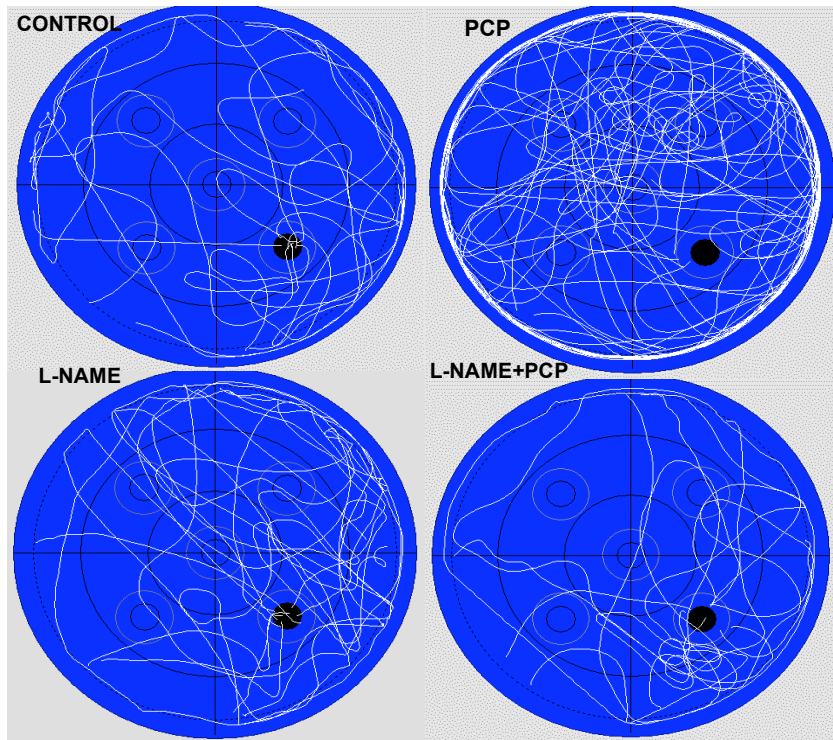


Figure 10: Swimming pattern diagram. Swimming trails are drawn in white and platform position in black. PCP induced aimless swimming and thigmotaxis. The PCP-induced impairment was normalized by NOS-inhibition. For details see Paper IV.

Taken together, this data could be interpreted as though the control rats showed an understanding of the purpose of the task, *i.e.* finding the escape platform, on the first three days of testing. Saline-, L-NAME-, and L-NAME+PCP-treated animals all demonstrated a significant decrease in search time on Day 2 and 3, Figure 9. As the task became more demanding, however, the rats did not manage to cope with the task, which was displayed by increased time to find platform on Day 4. Based on these findings this test does assess the animals' capacity to learn the purpose of the task (*i.e.* searching for the platform in a new position each day).

In summary, the results from this study show that PCP disrupted the searching behaviour as measured by time to find the platform as well as by gross observation of the swimming pattern analysis, compared to control

animals. Furthermore, pretreatment with NOS inhibitor, L-NAME, restored the PCP-induced disruption in searching behaviour to control levels both quantitatively, as measured by time to find the platform, but also qualitatively, as observed in swim pattern diagram. Taken together, this may be interpreted as though PCP decrease cognitive flexibility, a deficit that is normalized by decreasing NO production, in rats.

In conclusion, the results from Paper I, II, and III suggest that PCP-induced disruption in learning and memory is dependent on NO-signalling. This may imply that NO-modulation could be a potential treatment target for alleviating learning and memory deficits in schizophrenia.

Paper IV: The importance of nitric oxide in social dysfunction

Patients with schizophrenia often suffer from negative symptoms, such as anhedonia, avolition and social withdrawal. Negative symptoms are chronic in nature and poorly alleviated by available antipsychotics (Stahl and Buckley, 2007). Deficits within the social domain are paid increasing attention as they are attributed to depend upon an underlying cognitive dysfunction (Green et al., 2005). The social interaction model is *e.g.* used as an experimental animal model for studying PCP-induced schizophrenia-like negative symptoms (Ellenbroek and Cools, 2000, Sams-Dodd, 1999). Rats display a pronounced social interactive behaviour that is disrupted by PCP, but not amphetamine, indicating that this model is a particularly suitable model for evaluating schizophrenia-like negative symptoms induced by PCP (Sams-Dodd, 1999). In Paper IV we investigated the effects of NOS-inhibition on PCP-induced social interaction deficits, in rats. Furthermore, a drug-free memory test was carried out twenty-four hours after the initial social interaction test.

The results show that PCP induced deficits in social interaction behaviour, by significantly reducing the time spent in social interaction, compared to control rats. Pretreatment with a NOS inhibitor, L-NAME, attenuated the PCP-induced decrease in time of social interaction to control levels, Figure 11. Furthermore, no treatment effect on locomotor activity or number of social interactions was found, this observation suggests that the PCP-induced reduction in time of social interaction did not depend on drug-effects on motor behaviour, *e.g.* stereotypies.

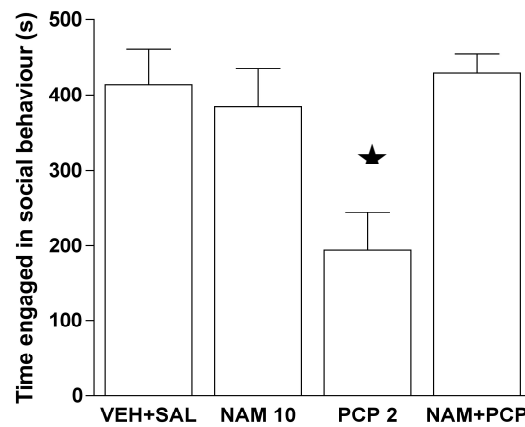


Figure 11: The effects of L-NAME and PCP on social interaction. PCP significantly decreased time spent in social interaction (★ $p < 0.05$) in comparison to controls. L-NAME pretreatment restored the PCP-induced disruption to control levels. For details see Paper IV.

Several other studies have evaluated the effects of antipsychotic compounds on PCP-induced social interaction deficits, with varying results. Sams-Dodd (1997) showed that remoxipride, risperidone, sertindole, olanzapine and quetiapine all produced an attenuating effect on PCP-induced social interaction deficits. However, all these drugs also had an effect on social interaction in control animals. In recent studies, two different compounds with both 5-HT_{1A}R receptor agonist and D₂R antagonistic properties, but not clozapine and haloperidol, reversed PCP-induced social interaction deficits, in rats (Boulay et al., 2004, Depoortere et al., 2007). The attenuating effects were attributed to the 5HT_{1A} profile of these compounds. Taken together, there remains uncertainty in the literature as to what effects different antipsychotic compounds do have on PCP-induced social interaction deficits. The best candidates for alleviating such deficits in rats seem to be atypical antipsychotic compounds, preferably with some 5-HT_{1A}R affinity. In the clinic, available antipsychotic do not fully alleviate the negative symptoms in patients with schizophrenia. Thus, this indicates that the PCP-model for social interaction may be used as an experimental model for social withdrawal.

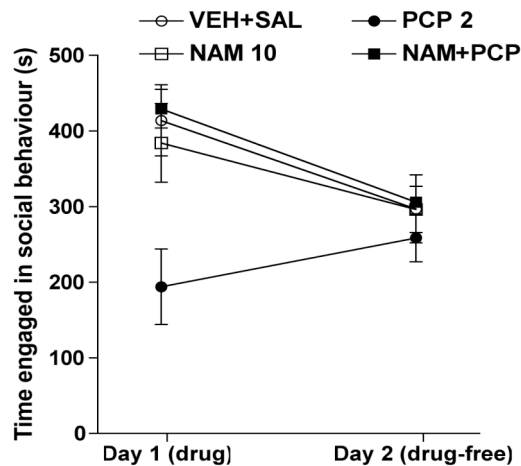


Figure 12: The effect of treatment L-NAME 10 mg/kg (NAM 10), and PCP 2mg/kg (PCP 2) on time of social interaction test Day 1 (with drug treatment) and Day 2 (no drug treatment). There was a significant effect of pretreatment (SAL or L-NAME) and main treatment (SAL or PCP) ($p < 0.01$), pretreatment and test day ($p < 0.05$) and main treatment and test day ($p < 0.05$).

Our results show that pretreatment with a NOS inhibitor can block PCP-induced deficits in social interaction. The rats' social memory of the first social interaction (Day 1) was assessed on the second day, Figure 12. These results showed that PCP-treated rats increased their time of interaction on Day 2, while all other treatment groups decreased their time interacting on Day 2, compared to Day 1. These results lack the proper control groups to be able to eliminate possible state-dependency effects of PCP on social memory. Any interpretation of the data ought therefore to be speculative. It is possible that the increase in time of interaction on Day 2 compared to Day 1, in PCP-treated rats, was due to a perceived novelty to the other rat, as the PCP effect was gone. Rats that spent more time in interaction on Day 1 (*i.e.* SAL+SAL, L-NAME+SAL, L-NAME+PCP- treated rats) did decrease their time in interaction on Day 2, thus signalling a decreased novelty to the other rat. This decrease in interaction possibly represent memory of the interaction from Day 1. It is however possible that the PCP-treated animals did learn to recognize the rat on Day 1, despite less time spent in social interaction that day. This might explain why they interacted the same amount of time on Day 2 as control animals. The latter interpretation could possibly mean that PCP inhibited the executive

functioning, or proper motivation, needed to carry out the social interaction on Day 1, although learning still occurred.

Taken together the results from Paper IV show that PCP-induced deficits in social interaction may be ameliorated effectively by NOS-inhibition, in rats. These findings reinforce current notions pertaining to negative symptom profiles in schizophrenia and the putative role of NO.

GENERAL DISCUSSION

The results presented in this thesis demonstrate that cognitive deficits and social dysfunction, studied in experimental animal models of schizophrenia, can be ameliorated by interfering with the NO signalling system.

PCP disrupts spatial learning, working memory, long-term memory, and cognitive flexibility assessed by different versions of the Morris water maze paradigm. Using a social interaction paradigm PCP decreased time spent in social interaction. Furthermore, all these PCP-induced deficits were normalized by pretreatment with a NOS-inhibitor.

PCP increases production of nitric oxide

In this thesis we used PCP to model schizophrenia-like deficits in rats. PCP exerts its effects by blocking the ion channel of the NMDAR thus prohibiting Ca^{2+} influx. This would in turn decrease intracellular NO production since constitutive NOS such as nNOS and eNOS are dependent on Ca^{2+} for their activation. It is therefore controversial that blocking NOS, and thus decreasing NO production, would normalize PCP-induced deficits. We have in this thesis presented several findings indicating that inhibition of the NO production normalized PCP-induced deficits in rodents. Therefore we hypothesize that PCP induces an **increase** in NO production in critical brain regions.

Firstly we have, using a microelectrochemical sensor that allows measurements of NO levels in living tissue, recently obtained important evidence supporting this hypothesis. An increase in NO was demonstrated in the PFC and nucleus accumbens in awake, freely moving rats after systemic administration of PCP. Furthermore, the increase in NO in the PFC was attenuated by pretreatment with L-NAME (Lowry JP et al in collaboration, unpublished data).

Further indirect evidence for an activation of NO-dependent signalling pathways following acute PCP administration was also recently obtained. Thus, a NO-dependent increase in cGMP levels in the mouse PFC was shown following acute PCP treatment. As described above (in “Nitric oxide in schizophrenia”, page 18), cGMP is the main effector of NO and consequently these results imply that the increase in cGMP observed after PCP administration is linked to an increase in NO production. It should

also be noted that blocking NO-dependent cGMP production with a sGC inhibitor locally administered into the mouse PFC normalized PCP-induced deficits in PPI (Fejgin et al., 2007a).

Another way to interfere with the NO signalling system is to reduce NO synthesis by decreasing the availability of L-arginine, the precursor of NO. The transportation of L-arginine over the blood brain barrier occurs through a cationic amino acid transporter (CAT). The same CAT is also responsible for transportation of L-lysine. Consequently, L-lysine and L-arginine compete for the same membrane transporter. In fact, treatment with L-lysine has been shown to reduce intracellular stores of L-arginine and production of NO in vitro (Carter et al., 2004, Closs et al., 1997). Based on these findings we used L-lysine to saturate the CAT in mice and found that subchronic treatment with L-lysine reduced PCP-induced disruption of PPI (Palsson et al., 2007).

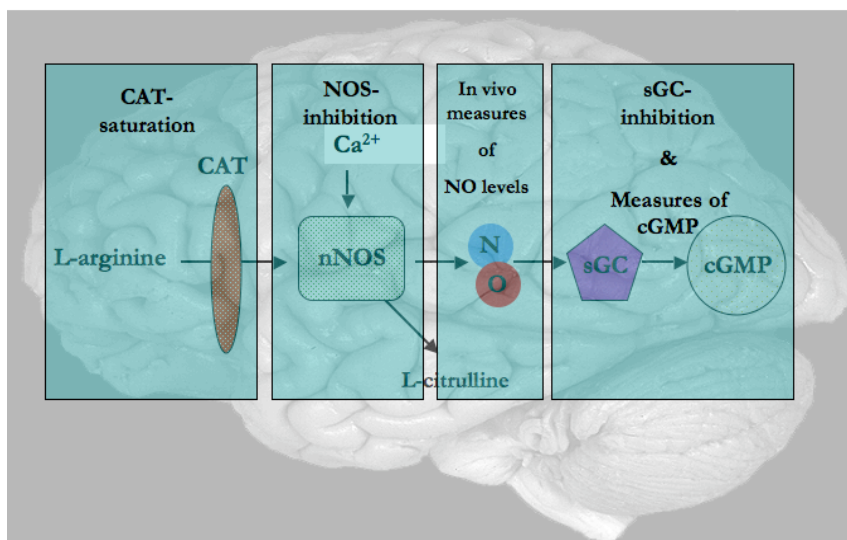


Figure 13: The NO-signalling pathway and the strategies we have used to interfere with the pathway (Fejgin et al., 2007, Johansson et al., 1997, Johansson et al., 1999, Klamer et al., 2004a, Klamer et al., 2004b, Klamer et al., 2004c, Klamer et al., 2005a, Klamer et al., 2005b, Lowry JP et al, unpublished data, Palsson et al., 2007, Paper I, II, III, IV).

Taken together, these results imply that acute PCP treatment increases NO production in critical regions of the brain. Furthermore, inhibiting the NO signalling cascade on several different levels normalize PCP-induced behavioural deficits in a number of translational animal models for

schizophrenia (Figure 13). Thus, the NO signalling system may constitute a new treatment target for schizophrenia. In order to test our hypothesis clinically we are currently setting up a pilot study evaluating the effects of adjunctive L-lysine treatment on cognitive deficits and PPI in patients with schizophrenia.

Possible mechanisms of phencyclidine on nitric oxide production

At present, we have accumulated data demonstrating that PCP treatment increases levels of NO in the rodent brain. However, the mechanism by which this happens remains to be elucidated. On the level of neuronal networks, PCP has been demonstrated to alter activity in PFC, hippocampus, amygdala, and thalamus. These regions form the cortico-limbo-thalamic loop, which is considered to make up an important network in the pathophysiology of schizophrenia (Gozzi et al., 2007). Furthermore, it is hypothesized that a blockade of the NMDAR by PCP could result in a complex circuit imbalance as a consequence of disinhibition of excitatory pathways which in turn could cause a hyperstimulation of primary corticolimbic neurons (Farber, 2003, Olney et al., 1999, Thornberg and Saklad, 1996). Even though PCP is generally regarded as a NMDAR antagonist it should be emphasized that it also interferes with several other neurotransmitter systems, such as the noradrenergic, 5-HTergic, DAergic, and GABAergic systems (Etou et al., 1998, Jones et al., 1987, Yonezawa et al., 1998). Furthermore, PCP has affinity for the D2R and the 5-HT2R and it is hence possible that some of the NO-related effects of PCP are mediated via direct interactions with these receptors (Kapur and Seeman, 2002).

One tentative explanation, provided that the observed effect is predominately nNOS mediated, may be as follows. Acute systemic administration of a NMDAR antagonist (i.e. PCP) in rodents has proved to increase glutamate release accompanied by working memory impairments (Abekawa et al., 2006, Moghaddam and Adams, 1998, Takahata and Moghaddam, 2003). Although the most well established NO-inducing signalling pathway is mediated via glutamate acting on NMDARs, there are other glutamate receptors that may contribute to Ca²⁺-dependent NO production. One such receptor candidate may be the Ca²⁺-permeable AMPAR (containing e.g. the GluR1 subunit but not the GluR2 subunit) known to regulate long-term synaptic plasticity and neurotransmission. These AMPARs are expressed in e.g. the CA1 region of

the hippocampus and in GABAergic cortical interneurons (Isaac et al., 2007, Yin et al., 1994). Furthermore, AMPAR GluR1 subunits have been found to co-localize with the NMDAR type 1 subunit and nNOS in rat brain (Lin and Talman, 2002). Additional evidence for the involvement of AMPARs may be derived from a study showing that PCP-induced decrease in electroencephalographic power in the rat PFC is inhibited by treatment with an AMPAR antagonist (Sebban et al., 2002). Thus, it is possible some of the effects of PCP on NO production may be mediated via glutamate acting on these Ca²⁺-permeable AMPARs. The merit of this explanation will need to be tested experimentally, but the very formulation of such hypothesis is necessary if the role of NO in the schizophrenia-like effects of PCP is to be fully determined.

Taken together, these results suggest that the psychotomimetic properties of PCP most likely result from neurochemical alterations encompassing several neurotransmitter systems and interacting brain regions.

Proposed clinical relevance

Accumulating evidence from clinical studies indicate that the NO signalling system is involved in the pathophysiology of schizophrenia (Bernstein et al., 2005). Genetic studies show associations between several NO-associated proteins (e.g. nNOS, tetrahydrobiopterin, synapsin 2) and schizophrenia (Reif et al., 2006, Xing et al., 2002, Saviouk et al., 2007, Xu et al., 2005, Richardson et al., 2005). Moreover, NO metabolite levels in cerebrospinal fluid were found to be decreased while serum NO and post mortem NO metabolites and sGC levels were shown to be increased in patients with schizophrenia compared to controls (Ramirez et al., 2004, Baba et al., 2004, Yilmaz et al., 2007, Yao et al., 2004). These findings indicate that there may be a dysregulation of the NO-signalling pathway in schizophrenia. This is further supported by a treatment study showing that patients with schizophrenia improved their overall psychopathology when treated with methylene blue, a NO/sGC inhibitor (Volke et al., 1999), in addition to conventional antipsychotic treatment (Deutsch et al., 1997). Interestingly, methylene blue also blocks the PCP-induced disruption of PPI in mice (Klamer et al., 2004a).

Memory and cognitive flexibility in schizophrenia

Cognitive deficits are the single strongest predictor of functional outcome in patients with schizophrenia (Green, 1996). Among the cognitive deficits observed are impairments in long-term spatial memory (Reeder et al., 2006), spatial working memory deficits (Piskulic et al., 2007), and cognitive flexibility (Addington and Addington, 1999). In this thesis spatial learning, spatial long-term memory, spatial working memory, and cognitive flexibility were studied using different versions of the MWM. Interestingly, there is a direct translational correlation between the results from Paper I and II and a clinical study in patients with schizophrenia. Using a virtual version of the MWM patients displayed longer time to find the platform during acquisition and spent less time in the target quadrant during probe test compared to controls (Hanlon et al., 2006). These clinical findings are in accordance with the results from Paper I and II, since rats treated with PCP showed the same type of impairments as the schizophrenic patients.

Spatial learning and memory depends mainly on the hippocampus (Morris et al., 1982, Smith and Mizumori, 2006) and blockade of NMDAR impairs these cognitive functions (Morris, 1989, Morris et al., 1986). The hippocampus has been found to be abnormal in both function and structure in patients with schizophrenia (Bogerts et al., 1990, Arnold et al., 1995, Tamminga et al., 1992). We have recently published evidence from our research group that suggests an involvement of hippocampal NO in PCP-induced deficits. Results showed a temporal correlation between PCP-induced deficits in PPI and increased levels of cAMP in the rat ventral hippocampus. These behavioural and neurochemical effects were blocked by pretreatment with a NOS-inhibitor, (Klamer et al., 2004c). Taken together there are few studies investigating the effects of acute PCP administration on NO signalling in the hippocampus. However, conflicting research reports have found that PCP and ketamine induce both increased, reduced, and no change in NOS expression in the rodent hippocampus (Keilhoff et al., 2004, Miyamoto et al., 2000, Noda et al., 1996).

Impairments in working memory are one of the most well established cognitive deficits of schizophrenia. Working memory is dependent upon the functional integrity of the PFC and several studies have demonstrated PFC hypofunctioning in patients with schizophrenia (Callicott et al., 2000, Gold et al., 1997, Goldman-Rakic, 1999, Ingvar and Franzen, 1974). Working memory is often assessed using the Wisconsin Card Sorting Test, a test that also taps into executive function and cognitive flexibility (Shad

et al., 2006). It thus becomes difficult to separate these different aspects of cognitive functioning and perhaps they are too interdependent to be measured independently, even in humans. Regardless of the exact relationship between these functions, they are probably unified by the dependence upon dorsolateral PFC functioning. In Paper II and III working memory and cognitive flexibility were assessed. Although the specific role of the PFC was not investigated in these experiments we have demonstrated the importance of the PFC for mediating the NO-dependent effects of PCP on PPI (Fejgin et al., 2007a) and acute PCP treatment increases the production of NO in the rat PFC (Lowry JP et al, unpublished data). Evaluating the specific role of the rodent PFC in working memory and cognitive flexibility by e.g. using a sGC inhibitor would add further information on the role of NO in PFC for cognitive functions.

As mentioned above, cognitive deficits are predictive of functional outcome, such as social functioning. However, it is argued that social cognitive deficits may constitute a symptom category of their own, different from other cognitive deficits observed in schizophrenia (Burns, 2006a, Lancaster et al., 2003). Furthermore, cognitive flexibility, working memory, and visuo-spatial long-term memory are associated with social functioning skills in patients with schizophrenia. On the other hand, several cognitive functions implicated in schizophrenia show no correlation with social functioning (Addington and Addington, 1999, Reeder et al., 2006).

Social cognition in schizophrenia: The road ahead

Schizophrenia, despite being a heritable disorder with several clear survival disadvantages, still remains within the human population. According to Darwinian laws of evolution, schizophrenia should have vanished from the population if it was not associated with some advantageous trait. Thus, an “evolutionary paradox of schizophrenia” has been proposed as schizophrenia survived despite both reduced fecundity and increased mortality (Burns, 2006b, Huxley et al., 1964). Such a favourable inherited trait could be expressed in individuals carrying some of the heritability for schizophrenia without expressing the phenotype. This is the case in first-degree relatives of patients with schizophrenia, displaying e.g. high academic performance (Burns, 2006b, Karlsson, 2004).

The social brain hypothesis states that the evolution of the *Homo sapiens* brain has evolved due to high social selective pressure. Living in a complex social environment along with the advantage of forming intense pair bonds

have been put forward as the strongest evolutionary forces driving human brain evolution (Dunbar and Shultz, 2007). Although a high degree of shared genes with primates, humans display specialized social cognitive skills, separate from that of our closest primate relatives (Herrmann et al., 2007).

Social cognition includes functions such as theory of mind (*i.e.* ability to understand other peoples' beliefs and intentions), social perception, emotional processing, and working memory (Burns, 2006a, Green et al., 2005). The neuroanatomical basis for social cognition includes several cortical networks, including the prefrontal, parietal, and temporal association cortices (Burns, 2006a). Patients with schizophrenia consistently show deficits in several aspects of social cognition that have been functionally associated with abnormal activation of *e.g.* the dorsolateral PFC (Russell et al., 2000), the orbitofrontal cortex (Sigmundsson et al., 2001), the amygdala, and the hippocampus (Gur et al., 2002). Thus, schizophrenia is proposed to be a disorder of functional and structural connectivity in neuronal networks essential for social cognition that remain as a disadvantageous by-product of human brain evolution (Burns, 2006b). Given the evolutionary frame of reference, social cognitive deficits in schizophrenia might make up a core symptom category of its own.

In 1920, Eugene Bleuler wrote that “*schizophrenia... is characterized by a specific kind of alternation of thinking and feeling, and of the relations with the outer world that occur nowhere else*”.

(As reviewed in Burns, 2006a)

In accordance with Bleuler, cognitive deficits, and social cognition in particular, pinpoints the core features of schizophrenia that still remain the greatest treatment challenge today. Perhaps the inability of patients to apply an appropriate theory of mind makes them detached from the social rules and norms that so strictly govern daily living in the social world for most of us. Maybe it is not lack of interest or motivation that fails these patients, but the mere lack of a functional prefrontal – temporal connection that makes it impossible for them to interpret social cues and make inferences based upon them. As discussed above, social cognition depends upon an intricate relationship between several functional cognitive domains and several brain areas. Available antipsychotics may worsen cognition and also induce negative symptoms (Castner et al., 2000, Lewander, 1994) and thus further adds to the complexity of this disorder.

These side effects, such as anhedonia and lack of drive, may in turn enhance the social dysfunction. This complex and intriguing deficit of social cognition in schizophrenia, still not affectively treated by antipsychotics, needs extensive investigation, as it seems to constitute an important core deficit.

A nitric oxide dysregulation hypothesis for schizophrenia

In summary, the findings of this thesis demonstrate a NO-dependent mechanism of PCP-induced cognitive and social dysfunctions. Together with previous findings from the research group, we demonstrate that NOS-inhibition ameliorates PCP-induced deficits in several translational animal models of schizophrenia, ranging from pre-attentive information processing to social interaction, Figure 14.

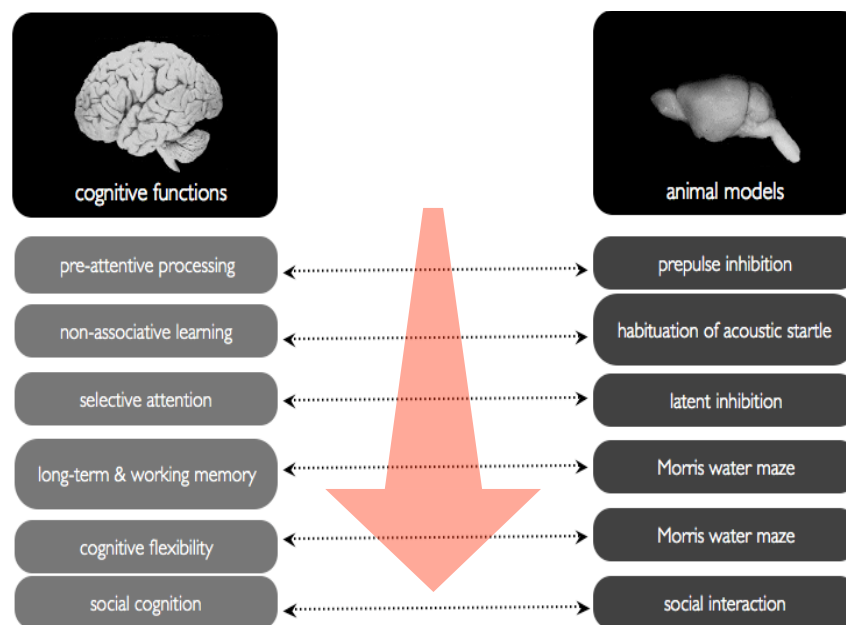


Figure 14: On the left are cognitions/behaviours deficient in schizophrenia and on the right are the translational animal models used to measure these cognitive functions. The arrow indicates increasing degree of cognitive complexity. Acute PCP treatment disrupts all the behaviours displayed in the figure. Furthermore, the PCP-induced deficits are ameliorated by NOS-inhibition (Johansson et al., 1997, Klamer et al., 2001, Klamer et al., 2004c, Klamer et al., 2004d, Klamer et al., 2005a, Klamer et al., 2005b, Paper I, II, III, and IV).

Based on our preclinical findings, together with clinical evidence supporting an involvement of the NO signalling system in the pathophysiology of schizophrenia, we propose a “NO-dysregulation hypothesis for schizophrenia”. Available antipsychotics are doubtlessly important for managing psychosis. Although second generation antipsychotics do have some, however modest, effect on cognitive deficits, they far from satisfactorily alleviate these deficits (Gray and Roth, 2007, Mishara and Goldberg, 2004). New treatments for alleviating cognitive deficits and social dysfunctions are needed in order to capture what seems to be one of the core deficits of schizophrenia. In order to effectively screen and find new cognitive treatments for schizophrenia, the National Institute of Mental Health has developed a consensus battery Measures And Treatment Research to Improve Cognition in Schizophrenia (MATRICS) evaluating seven different cognitive domains (Green et al., 2004, Green et al., 2005, Keefe et al., 2006, Nuechterlein et al., 2004). This initiative further highlights the importance of finding new ways of targeting the cognitive deficits and social dysfunctions of schizophrenia. Ongoing studies are evaluating the effects of several potential cognitive treatments targeting *e.g.* the DA, 5-HT, acetylcholine and GABA systems (Table 3).

Mechanism of action	Example Compound
D1 agonists	Dihydropyridine
D4 antagonists	Sonepiprazole
D4 agonists	A-412997
COMT inhibitors	Tolcapone
5-HT _{2A} antagonists	M100907
5-HT _{1A} agonists	Tandospirone
5-HT _{1A} antagonists	WAY100635
5-HT ₄ agonists	Tegaserod
5-HT ₆ antagonists	SB-271046
5-HT ₇ agonists	No selective ligands
Cholinesterase inhibitors	Donepezil
Nicotinic α 7 agonists	DMXB-A
Nicotinic α 4 β 2 agonists	RJR2403
M1 agonists	NDMC (nonselective)
M4 agonists	No selective ligands
M5 antagonists	No selective ligands
NMDA enhancers	Glycine
GlyT inhibitors	Org-24598
Ampakines	CX-516
mGluR _{2/3} agonists	Unknown
mGluR ₅ agonists	CDPPB
α 2-adrenergic antagonists	Guanfacine
GABAA (α 2) agonists	TPA023
GABAA (α 5) antagonists	L-655708
Sigma agonists	No selective ligands

Table 3: Potential new treatment targets for enhancing cognitive deficits in schizophrenia. Modified from Gray and Roth (2007).

Schizophrenia remains an enigma encompassing the different aetiological factors including several different susceptibility genes, multiple neurochemical system implications, and diverse clinical symptoms. Thus it might be beneficial to treat different aspects of this disorder according to the nature of the symptoms using a symptom-specific approach. Such an approach would be to find a treatment that targets the core signalling system underlying a specific group of symptoms. Available antipsychotics mainly targeting the DAergic system that seems to be the underlying core signalling system for positive symptoms. Regarding cognitive deficits, and perhaps also social dysfunctions, the core signalling system to target may be the NO signalling pathway as supported by the findings providing the basis for our “NO-dysregulation hypothesis for schizophrenia”.

ACKNOWLEDGMENTS

Firstly, my warmest and most sincere thanks to my supervisors; Associate Professor Lennart Svensson, Professor Jörgen A Engel, Professor Trevor Archer, and Dr Daniel Klamer. I will forever be thankful to all of you for making this achievement possible.

Lennart - thank You for always taking the time to answer all my questions and concerns. Thank You also for guiding me in the plethora of behavioural pharmacology. I am extra thankful for Your expertise in statistics and the way in which You make it all seem so easy.

Jörgen - thank You for taking me under Your wings, both financially and scientifically. Thank You also for all the constructive feedback and Your valuable expertise on everything. Last but not least, thanks for our long conversations about life in general, and clinical work in particular.

Trevor - thank You for guiding me into the arms of “Farmakolgen”. Thank You also for taking the time to discuss science, You always have new ideas. Further Thanks for educating me in history, exercise, whiskey, and many other important things under the sun.

Thank You Daniel for loads of encouragement and constructive feedback. You always answer my many questions and have always been a role model. I hope we will continue to make great science AND laugh together.

I am also very grateful to ALL other previous and present colleges and friends working at Department of Pharmacology, Göteborgs University.

THANK YOU

Gun and Kenn for all lab expertise. For helping out with calculations, solutions, guide cannulas, HPLC-problems, but also for a good time!

Marianne for always being professional, friendly, and very helpful, whatever the request is. You are the best secretary around!

Erik Pålsson for being my lab mentor. Thank you for taking special care of me the first 6 months at EBM, and for making me laugh even in the midst of the “neurodevelopmental graveyard”. Furthermore, thanks for all literary beauty and the good wine.

Kim Fejgin for being the best of roommates. Thank you for always being so engaged in everything from scientific concerns to iPods. You are a great companion and a dear friend.

Elisabeth for many great laughs, lots of support, and help.
Staffan for excellent help with the layout and cover.
Sara for your lovely laugh and energy.

Petra for taking great care of Eskil, Jessica for being a perfect study partner, Anna M and Elin for being my heroes.

Karin, Erik, and Kerstin for all the love and support.

Anna-Carin, Sofi, Anna E, Maria V, Lovisa, Eva-Lotta, Christopher, Åsa, Clin, and Carlotta for being the best of friends.

pappa for helping me move too many times.
the Egnahemsfamily for taking great care of Eskil.

Erik – min Erik for keeping me grounded and loved.

all of my family and friends - without You I would not be
here

*mamma Marie
for everything*

for the financial support; Swedish Research Council (4247), Tornspirans forskningsstiftelse, Lindhés Advokatbyrå: Till minne av Irma and Arvid Larsson-Röst, Wilhelm and Martina Lundgren Forskningsstiftelse, Adlerbertska Forsknings-stiftelse, Theodore and Vada Stanley Stiftelse, Magnus Bergvalls Stiftelse, Stiftelsen Clas Groschinskys Minnesfond, Göteborgs Läkare-sällskap, Filip Lunberg/Eirs 50-års Stiftelse, Stiftelsen Bengt Dahréns fond, Svenska Stiftelsen för Medicinsk Forskning, the Swedish Society of Medicine, Åke Wibergs Stiftelse, Fredrik och Ingrid Thuring's Stiftelse, Åhlén Stiftelsen, Lundbeck Stiftelsen, Schizofreni-sällskapet, Stiftelsen Söderström-Königskas Sjukhemmet and Svenska Lundbeckstiftelsen, The Stanely Medical Research Foundation, Jubileumsfonden, Kungliga Vetenskaps och Vitterhetsstiftelsen, CD Carlssons Stiftelse, Syskonen Bergmans fond, Stiftelsen Lars Hiertas Minne, Sven och Dagmar Saléns Stiftelse, Konrad och Helgfrid Johanssons Fond.

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