A frightening view on schizophrenia. Combining fear conditioning and ketamine administration to investigate emotional blunting in an animal model of schizophrenia

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Chapter 1

Introduction

1 Schizophrenia

Schizophrenia is a common disorder, occurring in all races and cultures, afflicting men and woman alike. It has been described as a chronic, severe and disabling disorder and can persist throughout ones life (Tsai and Coyle, 2002). It has therefore been ranked as one of the world's top ten causes of disability (Mueser and McGurk, 2004). Schizophrenia is a relatively old disorder, having being described by Shakespeare, where some of his characters exhibit behaviour typical of schizoaffective disorder e.g. Ophelia in Hamlet (Andreasen, 1976). Falvet first described schizophrenia in 1851 as a cyclical madness. Twenty years later, Hecker discovered the same group of symptoms and named it after the goddess of frivolity, Hebe i.e. Hebephrenia. The first comprehensive description was, however, only provided by Kraeplin around the end of the 19th century. He called it dementia praecox. Bleuler (1911) coined the term schizophrenia, which literally means split mind. Schizophrenia is not, however, a multiple personality disorder, as so many would think, but rather a fragmentation of thought or a disassociation between subjective feeling and thought. Modern day psychiatry classifies schizophrenic symptoms into 3 main categories: positive symptoms, negative symptoms and cognitive symptoms (Tsai and Coyle, 2002). Positive symptoms refer to delusions, hallucinations, and thought disorder. Negative symptoms include apathy, social incompetence and emotional blunting. General cognitive functions are also distorted, resulting in impairments in attention, memory and executive function.

One finds both structural and functional brain abnormalities in schizophrenia. Studies have shown that there is significant atrophy in the parahippocampal region (Sim et al., 2005) often associated with schizophrenic symptomology (Prasad et al., 2004), while other studies associate schizophrenia with significant atrophy of the cerebral cortex (Tsai and Coyle, 2002). Most data suggest, however, that abnormalities are mainly distributed throughout the thalamo-cortico-limbic brain regions (Tsai and Coyle, 2002; Snitz et al., 2005), areas typically involved in the processing of emotions and motivation. Among these, perhaps the most important are the amygdala, prefrontal cortex (anterior cingulate cortex) and hippocampus (Fig. 1).

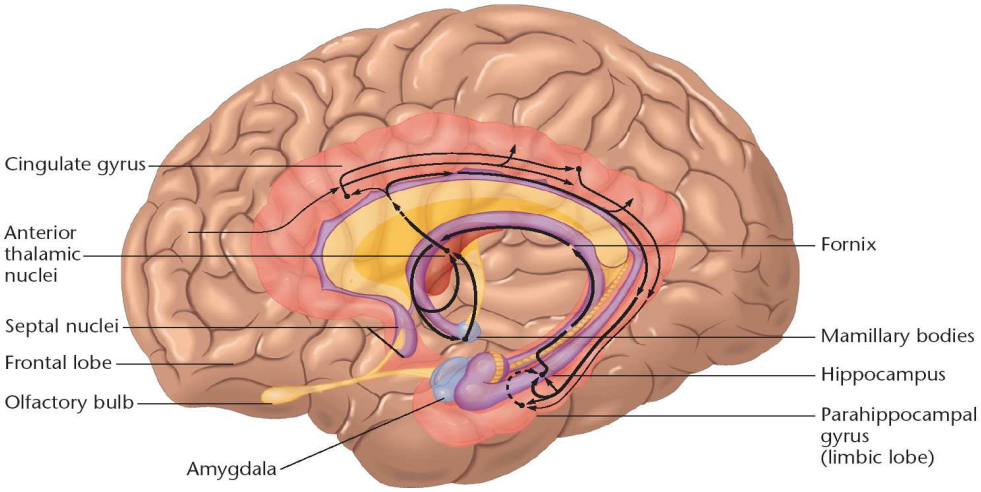


Figure 1: *Human brain circuits of the limbic system. The limbic system plays a pivotal role in emotional processing. Disruption of limbic processing networks has been centrally implicated in the pathophysiology of negative schizophrenic symptoms. From http://cti.itc.virginia.edu/~psyc220.*

2 Structural and functional abnormalities in schizophrenia

2.1 Amygdala

A key component of the limbic system is the amygdala (Fig. 2). The amygdala is a group of interconnected nuclei located in the temporal lobe of mammals (Walker and Davis, 2002) and plays an important role in the acquisition and expression of conditioned fear (Maren and Fanselow, 1996; LeDoux, 1998; LeDoux, 2000; Maren, 2001). Results of imaging studies suggest that the amygdala might be the link between the visual representation of fear (fearful faces) and the concept of fear (Adolphs et al., 2005). In line with this theory, it has been shown that bilateral amygdala damage in humans impairs the processing of fearful facial expressions (Adolphs et al., 1995). Schizophrenics themselves showed reduced activation of the left amygdala and bilateral hippocampal areas in a task requiring discrimination of positive from negative facial affect valence (Gur et al., 2002). These patients failed to activate limbic areas involved in valence discrimination, even though they performed just as well as healthy subjects verbally (Gur et al., 2002). Dysfunction in the amygdala could therefore underlie one of the negative symptoms characterising schizophrenia: emotional blunting. There is still, however, considerable controversy as to whether deficits in recognising affective states in faces are due to generalised problems in face processing, dysfunctional emotional processing, or to the general cognitive dysfunction seen in schizophrenia (see Fullam and Dolan, 2006 and references therein).

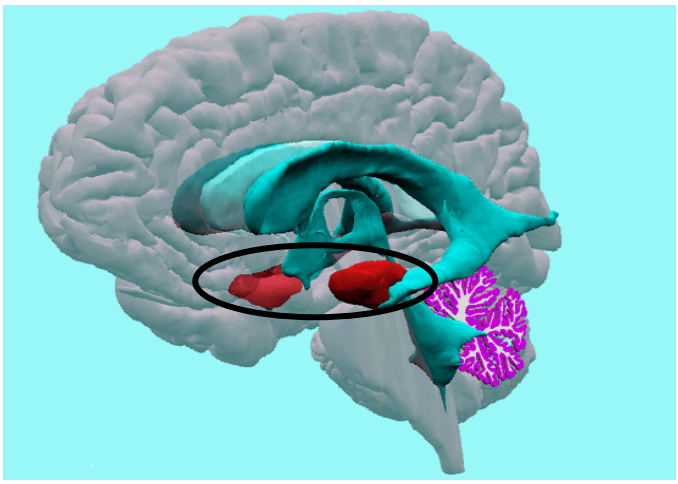


Figure 2: *Location of the left and right amygdala in the human brain. Lesions to the amygdala may underlie disturbances in attributing emotional significance to sensory stimuli and cognitive states. Abnormalities in amygdala functioning have also been implicated in schizophrenia. One of the major goals of the current thesis will be to examine the role of amygdala in a putative animal model of negative schizophrenic symptoms. Taken from http://www.liebermanparkinsonclinic.com.*

2.2 Prefrontal cortex

The prefrontal cortex (PFC) consists of the prelimbic, dorsal and anterior cingulate cortex (ACC) and medial pre-central cortices (Ananth et al., 2001). These areas form part of the broader prefrontal-limbic circuit, which includes the amygdala and orbitofrontal cortex. This entire system plays an important role in anticipating aversive stimuli and seems to mediate anticipatory planning and emotional regulation, particularly within social contexts (Veit et al., 2002). Emotional expression and perception are therefore considered to be a subcategory of social cognition (Pinkham et al., 2003). Dysregulation of this system could be the source of the social incompetence displayed by schizophrenics.

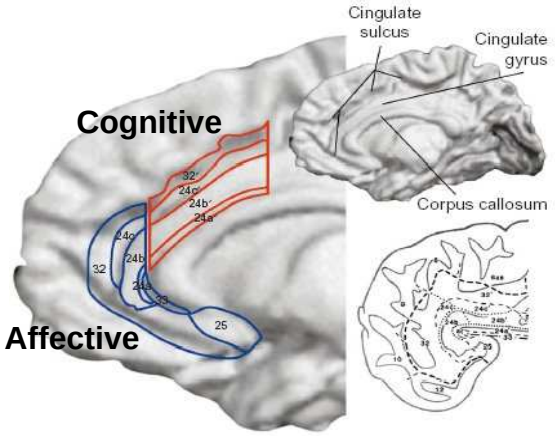


Figure 3: *Cognitive and affective subdivisions of the anterior cingulate cortex (ACC) in the human brain. Recent research suggests that abnormalities in ACC function may underlie several behavioural and cognitive disorders, such as schizophrenia. From Bush et al. (2000).*

The ACC (Fig. 3), a subsection of the PFC, has been shown to play a crucial role in

motivation (Devinsky et al., 1995) and acts primarily by influencing activity in other brain regions involved in cognitive, motor, endocrine and visceral responses (Bush et al., 2000). Consistent with this notion, lesions of the ACC produce symptoms including apathy, inattention, dysregulation of autonomic function, akinetic mutism and emotional instability (Bush et al., 2000), symptoms similar to those seen in the schizophrenic patient. The ACC includes specific modules for the processing of sensory, cognitive, and emotional information (Bush et al., 2000). The cognitive subdivision is part of a distributed attentional network and is connected to lateral PFC and motor areas, while the affective subdivision is connected to the amygdala, PAG, nucleus accumbens, hypothalamus, anterior insula, hippocampus and orbitofrontal cortex (Bush et al., 2000). These two subdivisions demonstrate reciprocal suppression during cognitively demanding tasks and intense emotional states (Bush et al., 2000). On the other hand, some studies have reported that recognition of emotional states correlates with cognitive functioning, especially memory processes and executive functioning (Kee et al., 1998; Sachs et al., 2004), implicating interactions between affective and cognitive subdivisions on some tasks. A recent report has also demonstrated an association between facial affect recognition and cognitive tasks, such as memory, executive functioning and psychomotor speed (Bozikas et al., 2004). Reduced activation of the ACC was also noted during an affect discrimination task with faces in schizophrenics (Hempel et al., 2003). The ACC therefore integrates input from various sources including motivation, evaluation of error, and representations from cognitive and emotional networks.

2.3 Hippocampus

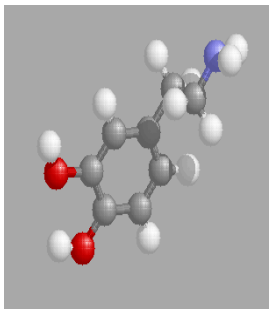
Together with the amygdala, ACC, and orbitofrontal cortex, the hippocampus (Fig. 1) is thought to be part of a circuit involved in cognitive-emotional information processing (Poldrack and Gabrieli, 1997; Shu et al., 2003), where it is primarily involved in the formation of declarative memory and memory consolidation (Eichenbaum, 1999, 2000). The hippocampus plays a role in relational and complex conditional learning in both animals and humans (Phillips and LeDoux, 1992; Peper et al., 2001; Sanders et al., 2003). Huff et al. (2006), for example, found increased levels of cFos and Arc mRNA (immediate early genes, markers of neuronal activity; see Section 10.1) in the hippocampus after context exposure and/or shock. Inactivation of the basolateral amygdala (BLA) in this experiment attenuated this

increase during the context plus shock condition (contextual fear conditioning) suggesting that the BLA plays an important role in regulating gene expression induced in the hippocampus by contextual fear conditioning (Huff et al., 2006). As shock alone has little impact on the expression of immediate early genes, (Hall et al., 2000), the context exposure itself must be the main trigger for immediate early gene expression in the hippocampus (Huff et al., 2006). Another study by Bechara et al. (1995) showed that a patient with damage to the amygdala failed to acquire conditioned autonomic responses to visual or auditory fear-inducing stimuli, but could still recall the factual content (which stimulus was paired with the unconditioned stimulus). Patients with damage to the hippocampus, in contrast, acquired conditioning, but could not recall the factual content (Bechara et al., 1995). A clinical study also showed that patients with amygdala damage could still report which US was associated with a CS, indicating that the declarative (hippocampal) knowledge of the US-CS association was intact and that these two memory systems are able to operate independently (Phelps and Anderson, 1997). More specifically, it seems that the CA3 (specific area of the hippocampus involved in learning) NMDA receptors (see Section 3.2.1 for full description) are critical for learning a novel paired-associates problem, especially for rapid concurrent acquisition of multiple, novel stimuli (Rajji et al., 2006). This suggests that antagonism of the NMDA receptor in the hippocampus could cause a deficit in contextual information processing by disrupting CA3-dependent acquisition of meaningful cues (Rajji et al., 2006).

3 Abnormalities associated with neurotransmitter systems

Functional neurotransmitter abnormalities have long been known to be present in the schizophrenic brain. Several neurotransmitter theories have been postulated in order to describe the symptoms present in patients. These neurotransmitter systems include dopamine, glutamate, serotonin and noradrenalin. The two main hypotheses that continue to attract most research, and therefore will be discussed here at length, are the dopamine and glutamate hypotheses.

3.1 Dopamine



The dominant theory of schizophrenia is that of a dysregulated dopaminergic system (Tsai and Coyle, 2002). There are three main dopaminergic pathways in the brain. The first originates from the ventral tegmental area and projects to the nucleus accumbens and the medial PFC and several other parts of the mesolimbic system. The second arises from within the substantia nigra and projects to the dorsal striatum, and is primarily involved in movement. A third runs from the hypothalamus to the pituitary and most likely has an endocrine function (Fig. 4). There are also two main dopamine receptor groups, D_1 and D_2, out of five in total (up to D_5). D_1 receptors tend to be distributed in cortical regions, while D_2 are subcortical (Williamson, 2006).

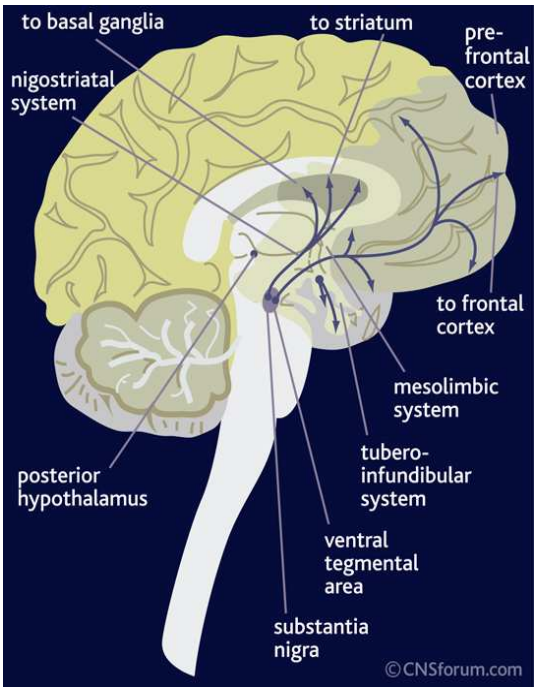
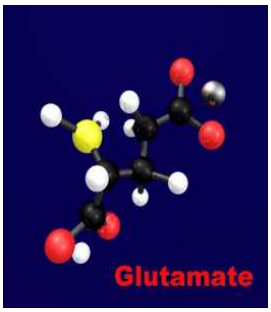


Figure 4: *Projections of the major dopamine pathways in the human brain. Dopamine has long been implicated in the pathophysiology of schizophrenia. Particular attention has been paid to dopamine midbrain projections (ventral tegmental area) to prefrontal cortex. From www.CNSforum.com.*

The dopamine hypothesis has its origins in the observation that typical antipsychotics (dopamine D_2 receptor antagonists) tend to ameliorate positive symptoms (Peroutka and Snyder, 1980; Jones and Pilowsky, 2002), whereas dopamine receptor agonists, such as amphetamine, augment the central dopaminergic system, inducing a schizophrenic-type psychosis (Robinson and Becker, 1986; Laruelle et al., 1999). An emerging theory involving dopamine is that its system is hypoactive in the cortex, while in subcortical areas it is hyperactive (Deutch, 1992). In particular, Weatherspoon et al. (1996) propose that dopaminergic hyperactivity in the nucleus

accumbens mediates positive symptoms, while dopaminergic hypoactivity in the PFC underlies negative symptomology. Dopaminergic dysfunction has also been implicated in abnormal cognitive functioning (Jentsch et al., 2000). By modulating dopamine receptors in the PFC, one can influence working memory (Castner et al., 2004). A study by Verma and Moghaddam (1996) showed that both acute and chronic deficiencies in dopamine neurotransmission disrupt the associative functions of the PFC. In a review by Moore et al. (1999), however, the authors state that dopamine transmission is not altered in schizophrenia as a result of a primary defect in the dopamine neurons, but rather as a result of abnormalities in their regulation by prefrontal and limbic cortical regions, where other neurotransmitters, such as glutamate, are also involved. Thus the dopamine hypothesis alone cannot fully explain all the functional abnormalities leading to the various symptoms of schizophrenia.

3.2 Glutamate



Glutamate is the main excitatory neurotransmitter and is used in more than 40% of all synapses. It is also the main neurotransmitter of the pyramidal cells that connect the cerebral cortex and limbic system (Tsai and Coyle, 2002), although it is found almost everywhere in the brain. Glutamate receptors can be either metabotropic or ionotropic (Fig. 5) (Goff and Coyle, 2001). Ionotropic receptors open calcium channels, and overactivity in these receptors can lead to excitotoxicity (Williamson, 2006). NMDA glutamate receptors are an example of a voltage-gated ionotropic receptor group (Tsai and Coyle, 2002). They are concentrated in the hippocampus, ACC and other parts of the limbic system (Williamson, 2006). Other ionotropic receptors include the AMPA/kainate subtype. Metabotropic receptors are G-protein mediated and found mostly in the forebrain areas (Moghaddam, 2004). It has been suggested that a pathological disruption of the glutamatergic input from afferent cortical systems could be responsible for the increase in dopamine responsivity in schizophrenic patients (Grace, 2000).

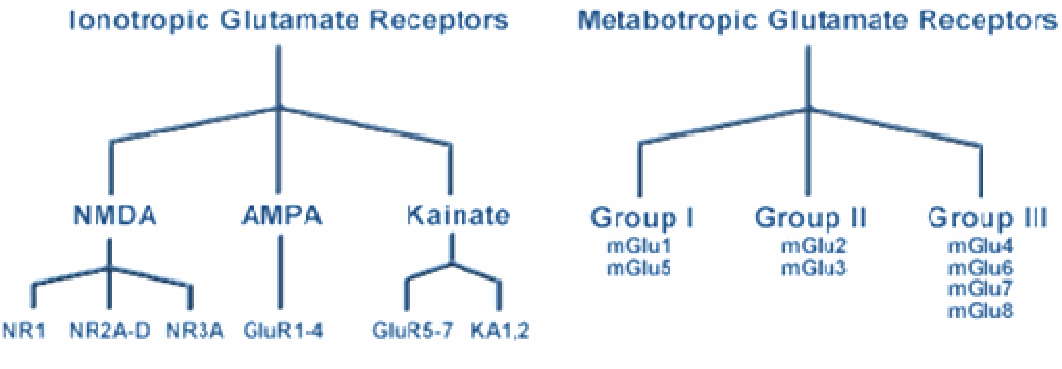


Figure 5: *Ionotropic and metabotropic glutamate receptor families. Antagonists of NMDA ionotropic receptors, such as ketamine, have proven particularly useful in studying both positive and negative symptoms of schizophrenia.*

3.2.1 NMDA (N-methyl-d-aspartate) receptors

The glutamate hypothesis originates from investigations showing that glutamate NMDA receptor antagonists induce psychosis in healthy volunteers, or elicits psychotic symptoms in refractory schizophrenic patients (Tsai and Coyle, 2002). Some studies (Moghaddam et al., 1997; Krystal et al., 2000; Abel et al., 2003) suggest that a hypofunctioning glutamatergic system could be specifically related to both the cognitive and emotional deficits displayed by schizophrenic patients (see Riedel et al., 2003, for a review of cognitive deficits). For example, a study investigating NAAG (N-acetylaspartylglutamate), a neuropeptide found in the NMDA receptors (Tsai et al., 1995), showed that levels of NAAG were increased in the schizophrenic brain, whereas its peptidase (enzyme) activity and glutamate levels were decreased (Tsai et al., 1995). Ibrahim et al. (2000) also found NMDA receptor hypoactivity in the limbic thalamus of schizophrenic patients, consistent with the attenuated glutamate activity hypothesis. An inverse correlation between negative symptoms and glutamate concentration has also been noted (van der Heijden et al., 2004). One proposed mechanism for how glutamate hypofunction might occur is via an excitotoxic process in early life that destroys postsynaptic cells that house the glutamate receptor system, thereby rendering the glutamate neural network defective (Heresco-Levy, 2003; Aleman and Kahn, 2005).

3.2.2 AMPA (amino-3-hydroxy-5-methyl-4-isoxazole)/Kainate receptors

NMDA receptors usually coexist with AMPA or kainate receptors and may be involved in augmentation of the glutamate signal (Bergink et al., 2004). Both these receptors mediate fast excitatory synaptic transmission (Cotman et al., 1995) and

promote the activation of the NMDA receptor. As they are co-localised, the distributions of the AMPA/kainate receptors are similar to the NMDA receptor (Bergink et al., 2004). These receptors are therefore typically located in the cortex and limbic system and exhibit effects on cognition, perception and mood (Krystal et al., 1999).

3.2.3 Metabotropic mGlu 2/3: LY 379268

G-protein-coupled glutamate receptors were discovered in the 1980s (Pin and Duvoisin, 1995) and to date 8 subtypes have been cloned (Bergink et al., 2004). It was found that these receptor subtypes were often located together on the same neurons and interacted within complex neural networks (Bergink et al., 2004). Metabotropic glutamate receptors are divided into 3 subgroups. Group one is connected to phospholipase C-related cellular cascades, while groups 2 and 3 are negatively coupled to adenylate cyclase (Nakanishi, 1992; Conn and Pin, 1997). Glutamate receptors 2/3 belong to the second subgroup and are highly expressed in the forebrain regions, although agonists of these receptors have been shown to work in the hippocampus, locus coeruleus, amygdala and PFC (Ohishi et al., 1993; Cartmell et al., 1999). Unlike the fast-acting ionotropic glutamate receptors, mGluR subtypes exert long-lasting effects through intracellular signals (Bergink et al., 2004).

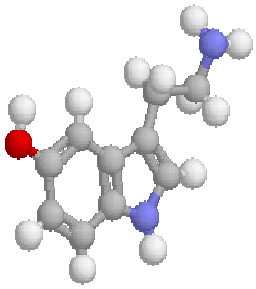
3.3 Interactions between dopamine and glutamate

Interactions between these neurotransmitter systems are known to occur. For example, MK-801, a glutamate NMDA receptor antagonist, exerts an effect on dopamine metabolism in the medial PFC and striatum (Dai et al., 1995), while NMDA receptor antagonists in general increase the firing rate of dopamine neurons in the ventral tegmental area (French and Ceci, 1990). Stimulation of metabotropic glutamate receptors by ACPD ((+/-)-trans-1-aminocyclopentane-1,3-dicarboxylic acid) dose-dependently increases the release of dopamine in the striatum (Verma and Moghaddam, 1998). Stimulation of AMPA or kainate glutamate receptors also leads to the increased release of dopamine in the PFC (Jedema and Moghaddam, 1996). Conversely, treatment with typical antipsychotics, which act primarily on dopamine receptors, results in a significant increase in glutamate levels in schizophrenic patients (van der Heijden et al., 2004). Such findings suggest that the dopamine and glutamate systems function in an antagonistic fashion, and that an

imbalance in the normal interactions between these systems may give rise to schizophrenic symptoms (de Bartolomeis et al., 2005).

In order to investigate the interaction between the two main neurotransmitter hypotheses of schizophrenia, Krystal et al. (2005) administered both amphetamine and ketamine (see Section 4.2) to healthy volunteers in a randomised double-blind psychopharmacological trial. While both drugs alone led to positive symptoms, combined administration was less severe than the sum of the effects of each drug individually. Their combination did, however, produce additive effects on euphoria and thought disorder (Krystal et al., 2005). Amphetamine attenuated the disruption of working memory induced by ketamine. In addition to positive symptoms, ketamine also led to negative symptoms and impairments in attention, working memory and declarative memory. Conversely, amphetamine mostly led to positive symptoms and psychomotor activation, rather than negative and cognitive symptoms (Krystal et al., 2005). This study therefore provides evidence of interactions between the dopaminergic and glutamatergic neurotransmitter systems, while also elucidating their own unique profiles.

3.4 Serotonin



Another neurochemical model of schizophrenia is that of the LSD/serotonin $5HT_2$ receptor hypothesis. It is interesting to note that the amygdala possesses moderate to high levels of 5 subtypes of serotonin receptors, with the $5HT_2$ receptors located in the basolateral nucleus, and the $5HT_{1A}$ receptors in the central nucleus (Pralong et al., 2002). An intimate relationship between the serotonergic (Fig. 6) and glutamatergic systems has also been established (Aghajanian and Marek, 2000). Evidence for this lies in the fact that $5HT_2$ antagonists are able to block both the behavioural effects of NMDA antagonists and psychedelic hallucinogens that make use of the serotonin system (Aghajanian and Marek, 2000). These hallucinogens, acting via $5HT_2$ receptors, also appear to enhance glutamatergic transmission in the locus coeruleus and cerebral cortex (Aghajanian and Marek, 2000).

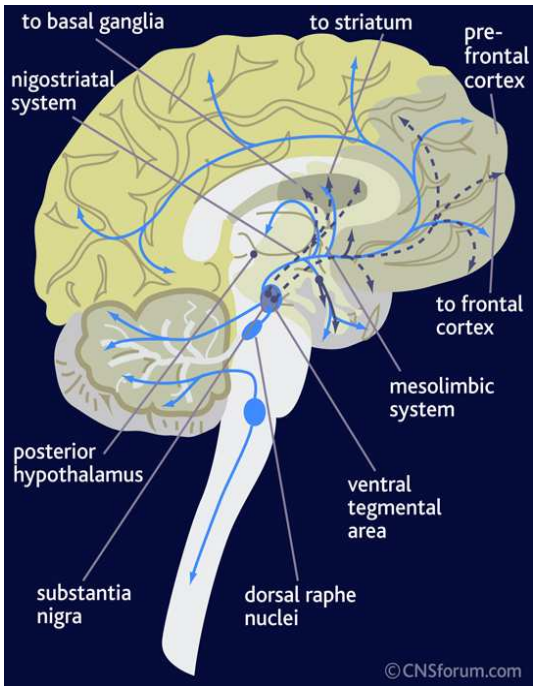
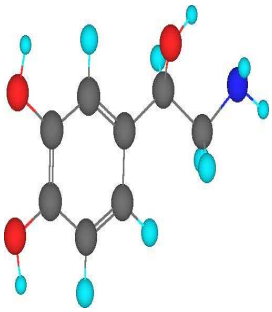


Figure 6: *Serotonin pathways in the human brain. There is some evidence to implicate pathophysiology of serotonin and its receptors in schizophrenia. From www.CNSforum.com.*

Post-mortem schizophrenic brains show increased $5HT_{1A}$ receptor density in the PFC (Bantick et al., 2001). Atypical antipsychotics also affect the serotonin $5HT_{2A}$ receptor, lending support to the serotonin hypothesis. Clozapine, an example of an atypical antipsychotic, combines D_2 receptor antagonism and $5HT_{1A}$ agonism (Bantick et al., 2001). Olanzapine, another atypical antipsychotic, also significantly increases the HVA/5HIAA (dopamine/serotonin metabolites) ratio in the cerebral spinal fluid of schizophrenic patients (Scheepers et al., 2001).

3.5 Noradrenalin



Noradrenalin innervates the human neocortex and limbic forebrain substantially (Fig. 7) (Yamamoto and Hornykiewicz, 2004) and has been proposed to play a role in the neurobiology of schizophrenia as early as 1971 (Stein and Wise, 1971).

Modulation of noradrenergic activity leads to similar symptoms as those seen in schizophrenia, including attention impairments, stress sensitivity and social avoidance (see references in Yamamoto and Hornykiewicz, 2004). Higher than normal concentrations of noradrenalin have been found in the cerebral spinal fluid of schizophrenic patients (Gomes et al., 1980; Sternberg et al., 1981; Kemali et al., 1990), mainly associated with paranoid symptoms.

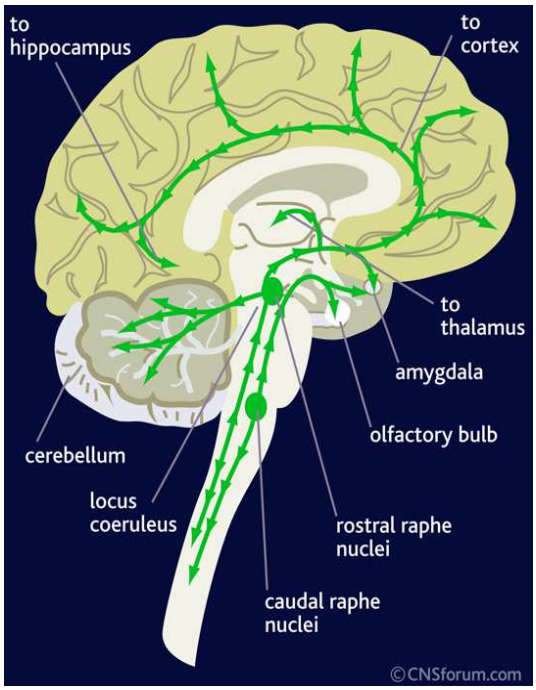


Figure 7: *Noradrenergic pathways in the human brain. Although noradrenaline has been implicated in schizophrenic pathology, its role has not been studied as extensively as dopamine and glutamate. From www.CNSforum.com.*

Noradrenalin also has effects on emotional learning. Within the BLA noradrenalin enhances glutamatergic synaptic plasticity (Ferry et al., 1997), which is thought to underlie learning and memory functions (Huang and Kandel, 1996). Alone, it exerts both inhibitory and excitatory effects via the α_2 and β adrenoreceptors respectively (Pralong et al., 2002), both of which are found in the BLA. It has been shown that noradrenalin was released in the amygdala after foot shock, and the concentration increased as the intensity of the footshock increased (Galvez et al., 1996), indicating a role for noradrenalin in fear learning. Noradrenergic projections from the locus coeruleus to the amygdala have also been shown to influence memory storage, as noradrenalin infused directly into the amygdala attenuated memory impairment (Liang et al., 1995).

4 Drugs acting on the glutamate system that mimic schizophrenic symptoms

4.1 PCP

Amongst the NMDA receptor antagonists, phencyclidine (PCP) and ketamine have been used in several studies investigating the hypothesis of glutamate hypofunction in schizophrenia. PCP has been extensively validated as a model of schizophrenia in animals and elicits both positive and negative symptomology (Javitt and Zukin, 1991). It has been found to dose-dependently induce stereotyped behaviour and

social withdrawal in rats (Sams-Dodd, 1999). It also produces deficits in working memory (spatial and object), which is reversed by clozapine (Jentsch et al., 1997; Castner et al., 2004). As well as being a glutamate receptor antagonist, PCP also acts on the dopaminergic system. It acts to reduce dopamine metabolism in the prefrontal, orbital and limbic frontal cortical regions in monkeys, thus mimicking the hypofrontality seen in schizophrenics (Jentsch et al., 1999).

4.2 Ketamine

Ketamine has been described as a phencyclidine hydrochloride derivative, dissociative anaesthetic and a non-competitive antagonist of the glutamate NMDA receptor (Krystal et al., 1994). Dissociative anaesthetics typically replicate the negative symptoms and cognitive impairments of schizophrenia, unlike the amphetamine model (which involves dopamine receptors), which recreates only the positive symptoms (Coyle and Tsai, 2004). Sub-anaesthetic doses of ketamine in healthy individuals lead to paranoia, perceptual alterations and memory loss, as well as positive and negative symptoms of schizophrenia (Krystal et al., 1994; Malhotra et al., 1997a; Abi-Saab et al., 1998). In the rat, ketamine administration is generally associated with behavioural symptoms, such as hyperlocomotion and stereotypy (Irifune et al., 1991; Uchihashi et al., 1992), and leads to PPI disruption, which is also seen in schizophrenic patients (Braff et al. 2001). In considering ketamine as an appropriate model for schizophrenia, Becker et al. (2003) noted alterations in social behaviour and a long-lasting disruption of latent inhibition (see below) up to 4 weeks after sub-chronic ketamine treatment. Ketamine also affects with learning and memory. In a study by Krystal et al. (2000), the authors showed that ketamine appeared to interfere with the acquisition, but not the expression, of functions related to abstract procedural learning in healthy volunteers. These impairments were found on tasks associated with frontal and cortical activities. In another study, ketamine administered to healthy volunteers significantly reduced changes in fMRI BOLD response in the posterior cingulate, preuncus, and ACC during retrieval of episodic memories (Northoff et al., 2005).

With regards to its effects on neurotransmitter systems, ketamine tends to exert a biphasic influence on the outflow of glutamate in the PFC: low sub-anaesthetic doses

increase these levels, whereas an anaesthetic dose decreases these levels (Moghaddam et al., 1997). It also has a stimulatory effect on the PFC dopamine release, which can be reduced by local application of an AMPA/kainate receptor antagonist (Moghaddam et al., 1997). Other studies showed that ketamine administration resulted in increased dopamine and serotonin secretion, as well as glutamate release, (perhaps through non-NMDA receptors, e.g. AMPA receptors) in the rat PFC (Lindefors et al., 1997; Lorrain et al., 2003). A recent study has shown that these effects of ketamine are in fact due to a *direct* stimulation of the D_2 and $5HT_2$ receptors (Kapur and Seeman, 2002). It could therefore be said that ketamine affects most of the neurotransmitter systems involved in the pathophysiology of schizophrenia.

5 Antipsychotics

Antipsychotic treatment began in the 1950s with the discovery of chlorpromazine (Willamson, 2006). Many more antipsychotics have been developed since then. Fewer than half of the patients receiving these medications however, reach full remission, and only 70 to 80% would be characterised as responding well to neuroleptics (Kane, 1989). As chlorpromazine is a D_2 receptor antagonist, this led to the development of other drugs known as typical antipsychotics such as haloperidol, which also act on the D_2 receptor (Jones and Pilowsky, 2002). It also supported the dopamine hypothesis. These drugs, however, have severe (extra-pyramidal) side effects, with patients often displaying parkinsonian-type symptoms. These antipsychotic treatments also have negative effects on cognition (Tsai and Coyle, 2002). When clozapine was developed in 1961, it was found that it did not fit in with other antipsychotics in terms of its receptor binding profile, and therefore other mechanisms of action were investigated (Pilowsky et al., 1992), signifying the discovery of atypicals. Both typical and atypical antipsychotics have been found to preferentially act on D_2 receptors in the cortex (Xiberas et al., 2001). Atypical antipsychotics, however, differ from typical psychotics in their limbic-specific affinity to dopamine D_2 receptors and in their high ratio of serotonin $5HT_2$ receptor to dopamine D_2 receptor binding (Meltzer et al., 1989; Worrel et al., 2000). Examples of atypical antipsychotics are clozapine, risperidone, quetiapine, and olanzapine. Atypical antipsychotics have subsequently been shown to be more effective in the treatment of schizophrenic symptoms than typical neuroleptics, and provide a greater beneficial

effect on cognition and negative symptoms (Worrel et al., 2000). Today, clozapine is a standard treatment for forms of schizophrenia that have not responded to other forms of treatment (Worrel et al., 2000).

5.1 Clozapine and haloperidol

In addition to being an NMDA and D_2 antagonist, clozapine also has an affinity for $5HT_{2A}$ as well as muscarinic cholinergic and adrenergic receptors (Duncan et al., 1998; Johnson et al., 2005; Ma et al., 2006). In relation to the dopaminergic system, clozapine has the greatest affinity for the D_4 receptor and haloperidol, the D_2 receptor (Meltzer, 1996; Duncan et al., 1998). Taken together with the fact that clozapine is a potent $5HT_2$ antagonist, this could contribute to the differences noted in the actions of these drugs (Duncan et al., 1998). Clozapine also differs from conventional neuroleptics in its cardinal effects on the glutamate system (Heresco-Levy, 2003). An increase in glutamate concentrations has been found after administration of clozapine in several studies (Goff et al., 1996; Evins et al., 1997). Animal studies have also shown this increase in the medial prefrontal cortical glutamate concentrations, an effect not associated with haloperidol (Daly and Moghaddam, 1993; Yamamoto and Cooperman, 1994). Clozapine has also been shown to be the most potent of the antipsychotic agents in blocking NMDA receptor antagonist-induced neurotoxicity (Farber et al., 1993; Olney and Farber, 1994).

The effects of haloperidol and clozapine on the glutamate NMDA receptor also differ. A study by Sams-Dodd (1996) showed that haloperidol did not selectively antagonise the effects produced by PCP in rats, while chronic clozapine treatment inhibited PCP-induced stereotypical behaviour and social isolation. In another study, clozapine (5 or 10 mg/kg) abolished the increased metabolism (2-deoxyglucose uptake) in the prelimbic cortex and nucleus accumbens, anterior ventral thalamic nucleus and hippocampal formation induced by ketamine administration (Duncan et al., 1998). This finding is consistent with the notion that clozapine's blocking/reversal of glutamate receptor antagonists is primarily via the NMDA receptor (Duncan et al., 1998). In the same study, haloperidol was administered 45 minutes prior to ketamine administration (0.5 mg/kg), but failed to alter the behavioural response or metabolic activation induced by ketamine (Duncan et al., 1998), consistent with its putative D_2

mechanism of action. An *in vitro* study has also shown clozapine to displace MK-801 from striatal tissue samples (Lidsky et al., 1993). Clinically, ketamine increases positive and negative symptoms in schizophrenics, an effect that is reduced with clozapine treatment (Malhotra et al., 1997a,b). There is still, however, the need for novel antipsychotics that counteract negative symptoms and cognitive deficits associated with chronic schizophrenia, particularly emotional blunting. These results of clozapine (atypicals) working on the NMDA receptor has led to a shift in research from modulating dopaminergic to glutamatergic systems (Heresco-Levy, 2003).

5.2 mGLu2/3 receptor agonists: LY 354740 and LY 379268

In an attempt to develop antipsychotics acting at the metabotropic glutamate receptor, it was found that novel glutamate receptor (2/3) agonists, LY354740 and LY379268, effectively reversed PCP-evoked motor activations, without impairment to the animals' motor capabilities (Cartmell et al., 1999). LY354740 was able to block ketamine-induced cognitive impairment in normal human volunteers (Swanson et al., 2005). In another study investigating the Glu2/3 agonist, LY379268, this compound increased dopamine levels in the PFC (Cartmell et al., 2000). This effect was, however, less than that of clozapine, and was evoked only after a longer time period.

6 Cognition and emotion

6.1 Cognitive and negative symptoms of schizophrenia

Memory functioning is the largest cognitive deficit seen in schizophrenia (Aleman, et al., 1999). As prefrontal regions are implicated as the origin of cognitive disorders and are involved in emotional regulation, memory functioning may be relevant for some negative symptoms. In a study by Sanfilipo et al. (2002), the authors found that cognitive deficits were strongly related to negative symptoms and/or disorganised behaviour. This study illustrates that schizophrenic patients show marked impairment in age-adjusted cognitive performance (Sanfilipo et al., 2002), relative to control subjects, of which memory and verbal processing are most affected. Patients also had significantly smaller bilateral volumes in grey, but not white matter, in the PFC (Sanfilipo et al., 2002). The authors therefore hypothesised that negative symptoms may involve the disruption of frontal-subcortical connections (Sanfilipo et al., 2002). The schizophrenic group also showed relationships between cognitive performance

and negative symptoms (Sanfilipo et al., 2002) with global negative symptoms (and particularly affective blunting) inversely related to cognitive flexibility.

6.2 Emotional learning

Emotional arousal is thought to have immediate effects during encoding that are interpreted to reflect attentional influences on memory (Labar and Cabeza, 2006). Such concepts of emotional modulation on learning and memory have rarely been explored, despite its well-known importance in human memory (Lang et al., 2000). Affective space is theoretically divided into two dimensions, arousal and valence. Arousal and valence affect the two different forms of memory - declarative and non-declarative (Labar and Cabeza, 2006). Declarative memory includes memory for events, or episodic memory, while non-declarative memory includes fear conditioning, an associative learning paradigm (Eysenck, 1988; Labar and Cabeza, 2006).

6.3 Association

Bleuler (1911) believed that a general “loosening of associations” represented the core deficit in schizophrenia. Indeed, it has been shown that some forms of associative learning (e.g. eyelid conditional discrimination) are disrupted in schizophrenic patients (O’Carroll, 1995; Rushe et al., 1999; Hofer et al., 2001). Furthermore, in an animal study mimicking schizophrenic symptoms with NMDA antagonists, Enomoto et al. (2005) treated mice for 14 days with PCP, which impaired pavlovian fear conditioning up to 8 days after cessation of PCP treatment (Enomoto et al., 2005). Repeated olanzapine for 7 days, but not haloperidol, reversed the associative learning impairment caused by PCP (Enomoto et al., 2005). Such findings suggest that a breakdown in simple associative processes could underlie some of the negative symptoms, such as emotional blunting, seen in schizophrenia. One way to combine examining emotional blunting and associative learning in an animal model is through fear conditioning, as fear is at present one of the most documented emotions in laboratory animals. The association network involved in emotional modulation of memory differs from declarative memory (hippocampus) as it has direct connections to primary motivation-related brain areas (Lang et al., 2000). Brain areas involved in emotional regulation are therefore typically activated by appetitive or aversive stimuli, resulting either in approach or

withdrawal behaviours respectively (Lang et al., 2000).

7 Fear conditioning

Classical fear conditioning is used throughout the literature to study fear circuits in the brain (Maren, 2001; Gerrits et al., 2003; Li et al, 2004). It involves the pairing of a neutral conditioned stimulus with an aversive unconditioned stimulus (Fig. 8). After a few trials, the conditioned stimulus elicits the same response as the aversive stimulus (Walker and Davis, 2002). The aversive stimulus can be visual, auditory, tactile, gustatory or olfactory. In animal models, such as the mouse or rat, measuring the freezing behaviour of animals in response to the conditioned stimulus can allow one to determine whether fear conditioning was acquired or not. Fear conditioning is also considered to be stress inducing (Sotty et al., 1996; Suzuki et al., 2002). Accordingly, the stress the animal experiences may be a good indicator of arousal, with the aversive stimulus eliciting the negatively-valenced emotional response. This response can then be measured after conditioning, in the absence of physical stressors (e.g. in the 5 minutes following a conditioning session).

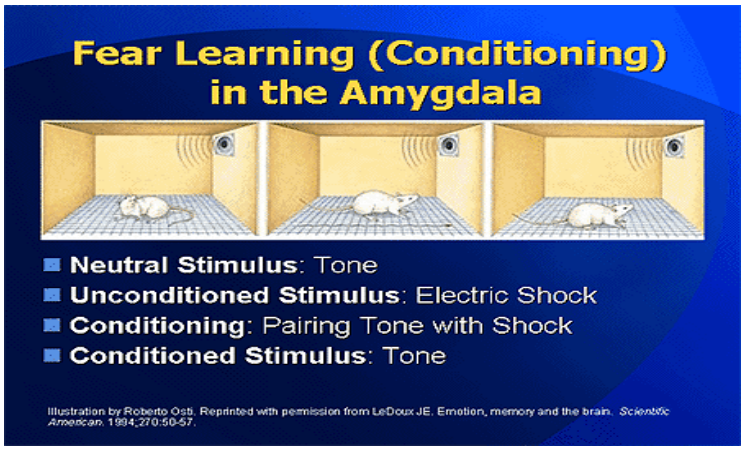


Figure 8: *Fear conditioning takes place in the amygdala. An emotionally-neutral stimulus (e.g. tone) is repeatedly paired with an emotionally-valent stimulus (e.g. shock). The tone then acquires some of the emotional valence associated with the shock, as expressed in various behavioural and neural assays. The fear conditioning paradigm is utilized extensively throughout the current thesis to assess an animal model of negative schizophrenic symptoms. After authors LeDoux et al. (1994), taken from www.medscape.com.*

7.1 Fear conditioning and schizophrenia

There has also been some evidence that fear conditioning is deficient in the schizophrenic patient. In a simple conditioning task combined with aversive emotional stimuli, schizophrenic patients failed to develop an increase in response

frequency to aversively reinforced trials, whereas healthy volunteers acquired a differential response to reinforced vs. unreinforced trials (Hofer et al., 2001). In another study, schizophrenics displayed a continuous deficit in emotional learning tasks after remission of symptoms, while performance on the non-emotional learning tasks was improved and no longer differed from controls (Exner et al., 2004). In the same study, schizophrenic patients also manifested diminished right amygdala volume (Exner et al., 2004). The authors therefore proposed that deficits of schizophrenics in emotional processing could be related to defective amygdala function. Conditioned inhibition (CI), another form of pavlovian conditioning, occurs when the CI stimulus in fact inhibits the prediction of the US by the CS. In a study investigating the relationship between CI and schizotypy scores (a prediction for the development of schizophrenia), Migo et al. (2006) found a negative correlation between these two elements, suggesting impaired learning capabilities in those susceptible to developing schizophrenia.

Taken together, one could suggest that a deficit in associative learning, such as fear conditioning, is in fact present in schizophrenia. Investigating the neural mechanisms thereof in an animal model could therefore elicit new information with regards to the mechanisms underlying the cognitive deficits seen in schizophrenia.

7.2 Brain circuits of fear conditioning

In Pavlovian conditioning, the neural mechanisms are highly conserved across species (Labar and Cabeza, 2006). Fear conditioning induces long-term potentiation, a form of synaptic plasticity that is thought to underlie learning, along both subcortical and cortical routes of information processing to the amygdala (Rogan et al., 1997; Tsvetkov et al., 2002). Brain regions that mediate the acquisition of fear in humans include the anterior cingulate cortex, insula, thalamus, sensory neocortex and amygdala (Buchel and Dolan, 2000; Birbaumer et al., 2005; Labar and Cabeza,

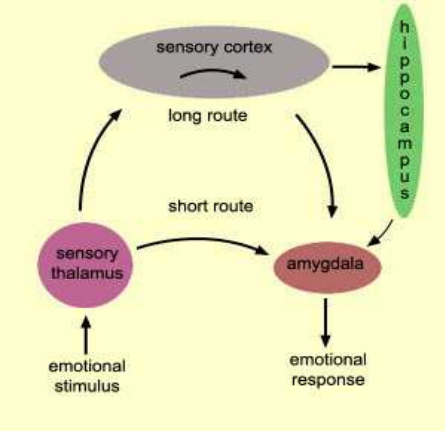


Figure 9: *Circuit underlying fear conditioning in the rat brain. The present study will examine neural activity in several regions of the rat brain following fear conditioning. Taken from* http://www.thebrain.mcgill.ca.

2006). The hippocampus also plays a role in conditioning (Maren, 2001; Sanders et al., 2003), especially in trace conditioning studies (Buchel and Dolan, 2000). The hippocampal formation provides inputs to the basolateral nuclei of the amygdala (Maren, 2001) and also has projections that extend to the PFC (Grace, 2000). According to Thiels and Klann (2002), the hippocampus, although important in contextual fear conditioned memory, does not play a part in tone-dependent fear conditioning, whereas the amygdala does (Phillips and LeDoux, 1992). LeDoux (1998) has previously illustrated a general overview of this fear circuitry in the rat brain in his review (Fig. 9).

According to this scheme, a conditioned stimulus, such as a tone (noise) is first processed by the auditory system, whereafter the information can take two routes to the amygdala (LeDoux, 1998). In rats, it has been shown that the lateral nucleus of the amygdala receives auditory input via 2 mechanisms: rapid, but impoverished input from the auditory thalamus and slow, rich input from the auditory cortex. The amygdala then integrates the 2 pathways during the acquisition and expression of conditioned fear responses (Li et al., 1996).

7.2.1 Amygdala, learning and memory in humans

The contributions of the amygdala, PFC, and the medial temporal lobe in memory are well characterised. This system participates both in the initial period of memory consolidation and the later retrieval of emotional memories, including those from the personal past (Labar and Cabeza, 2006). The amygdala is also involved in the ability to attribute mental states to others (Shaw et al., 2004) and in the processing of social cues (Adolphs et al., 1998).

A rare disease, called Urbach-Wiethe syndrome, involves selective amygdala pathology. These patients provide an important information source in trying to understand the workings and influences of the amygdala. They typically show impairments in long-term recall or recognition of emotional words, pictures and stories (Markowitsch et al., 1994; Adolphs et al., 1997). A later study by Adolphs et al. (1999) showed that bilateral amygdala damage also impaired fearful face recognition (as seen in schizophrenia) and attributed this deficit to the dysfunction of a general fear circuit in which the amygdala plays a central role. In addition, these

patients were inconsistent in recognising emotions. The authors suggested that this impairment is due to an inability to retrieve emotional knowledge, especially with negative emotions (Adolphs et al., 1999). Patients with amygdala lesions (unilateral temporal lobectomy) do, however, remember words that are affectively valent, but low in arousal (unlike fearful stimuli) relative to neutral ones (Phelps et al., 1997). Emotional arousal may therefore play an important role in amygdala-related memory formation (Phelps and Anderson, 1997). Conversely, patients with amygdala damage also exhibited intact responses to arousing events. The authors claim that these deficits in emotional processing are perhaps not specifically related to perception, but rather are memory-based (Phelps and Anderson, 1997).

Evidence for this proposal is found in PET studies, which established that the amount of amygdala activation during encoding of memory correlates positively with delayed recall of aversive, but not neutral, film clips, as well as delayed recognition of emotionally arousing pictures that are both positive and negative in valence (Cahill et al., 1996). One PET study has found a positive correlation between brain glucose metabolic rate in the right amygdala during memory encoding and the number of emotional films recalled three weeks later (Hamann et al., 1999). This finding was not significant for neutral films. Left and right amygdala activity was also related to episodic memory for aversive (and pleasant) stimuli (Hamann et al., 1999).

7.2.2 Amygdala and fear conditioning

Damage to the amygdala consistently impairs fear conditioning and fear-potentiated startle responses (paradigms used to investigate associative emotion-based learning) in non-human animals (Peper et al., 2001; Buchanan et al., 2004). In humans, it has been shown that the amygdala's strongest response to conditioned fear is during the acquisition phase, when emotional associations are initially formed (Buchel et al., 1998; LaBar et al., 1998). This finding is similar to the electrophysiological response profiles of some lateral amygdala neurons during fear conditioning in rats (Quirk et al., 1995). In animals, bilateral excitotoxic amygdala lesions in rats result in a blockade of mesocortical monoaminergic responses to stress induced by re-exposure to stimuli previously paired with an unconditioned stressor (Goldstein et al., 1996). These lesions also attenuated associated

adrenocortical activation, freezing, ultrasonic vocalisation, and defecation (Goldstein et al., 1996). The authors suggest that the amygdala is critical in linking aversive stimuli to the normally contingent behavioural, neuroendocrine, and cortical monoamine responses to stress (Fig. 10) (Goldstein et al., 1996).

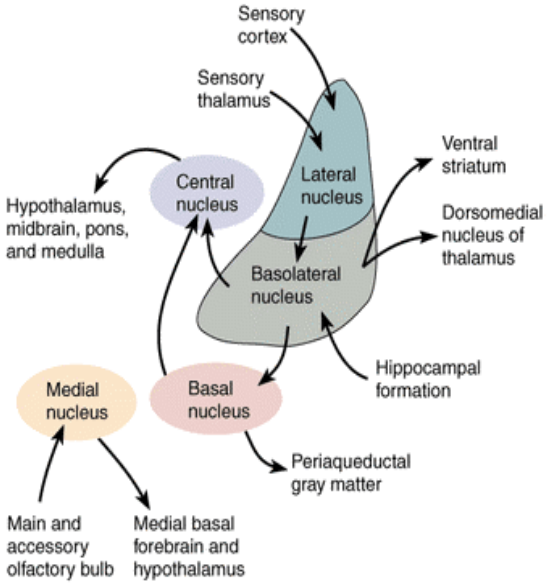


Figure 10: *The amygdala and its major input and output projections. The amygdala receives projections from sensory cortex and provides outputs to brain areas involved in autonomic, endocrine, motor, memory and cognitive functions. The amygdala several major nuclei, perhaps the most important (from a fear conditioning perspective) being the basolateral and lateral nuclei and the central nucleus. The respective function of the regions is a topic of ongoing research and will be an important consideration in the present study. From* [*http://homepage.psy.utexas.edu*](http://homepage.psy.utexas.edu)*.*

A study investigating patients with unilateral amygdala lesions demonstrated impairments in the conditioned startle potentiation (see below) by aversive and threatening stimulation, revealing an important role for the amygdaloid complex in this response (Weike et al., 2005). This response was also lateralised, with right hemisphere lesioned-patients showing accurate startle reflex during an instructed fear paradigm, but an impaired one when no instructions were given regarding the pairings of aversive stimuli and CS. The opposite pattern was noted in patients with left hemisphere lesions (Weike et al., 2005). Morris et al. (1998) also noted lateralisation effects when they investigated the amygdala's response to fear conditioning in humans by making use of a masking paradigm. Activity in the right amygdala was enhanced significantly during presentation of masked conditioned faces, whereas activity in the left amygdala was relatively enhanced when the conditioned angry face was clearly seen (unmasked). In this context, Markowitsch (1998) suggests that the left amygdala be more closely related to the encoding and

extraction of detailed stimulus features, whereas the right amygdala is involved in retrieval, with a special affinity for pictorial emotional material. Meta-analysis has also revealed that left amygdala (more than right) activation is related to cognitive processing of emotional stimuli (Wager et al., 2003). Further research needs to be undertaken to fully explore lateralisation effects of the amygdala.

The amygdala, being composed of several nuclei (Fig. 10), has various functions depending on the nucleus. According to an fMRI study, which involved the pairing of a red light with an electrical shock, the central amygdala (CEA) is primarily involved in the execution of autonomic responses to fearful events, whereas the basolateral nuclei are involved in the connection of the event to the fearful stimulus. Data from several animal studies agree with this statement. For example, Fanselow and Kim (1994) found that bilateral administration of AP5, a glutamate antagonist, into the BLA prior to fear conditioning prevented fear acquisition, but infusions into the central nucleus did not. Similar results were found in a study by Shors and Matthew (1998). In the study by Killcross et al. (1997), lesions made within the basolateral nucleus of the amygdala prevented the animals from being able to learn to avoid the shock, while the lesions in the central nucleus did not do so. The study by Koo et al. (2004) showed that the fibres that run through the central nucleus from the basolateral nucleus, and not the neurons within the central nucleus itself, are responsible for fear conditioning, thus implicating the basolateral nucleus alone in the fear conditioning process. It has also been shown that lesions in the BLA that are given 28 days after training produce deficits in expression of conditioned fear, indicating storage of the association between CS and US in the BLA (Lee et al., 1996; Maren et al., 1996).

The convergence of the sensory pathways within the basolateral nucleus of the amygdala (Fig. 10) has in the past made it an interesting site to investigate fear conditioning (Walker and Davis, 2002). According to Huff and Rudy (2004), the basolateral region of the amygdala modulates memory formation in other regions of the brain and is a storage site for CS-US association (Schauz and Koch, 2000, Gale et al., 2004). Gale et al. (2004) investigated the role of the BLA in expression of fear memories varying from 1 day to 16 months. Lesions of the basolateral nuclei, made

shortly before or after training, produced profound deficits in fear conditioning to auditory, visual and contextual stimuli. Lesioned rats also showed robust deficits during all recent and remote memory tests. In particular, post-training lesions produced robust freezing deficits to contextual and auditory stimuli, independently of training-to-lesion interval (Gale et al., 2004), indicating a role for the BLA in memory storage of both auditory and contextual fear (Gale et al., 2004). BLA lesions, however, did not interfere with the general ability to freeze (Gale et al., 2004). This evidence suggests that the BLA plays a specialized role in encoding the emotional aspects of fear conditioning, perhaps coordinating the consolidation of declarative memory in extra-amygdala regions (Grace, 2000; Gale et al., 2004). Over-training can, however, allow contextual training to occur independent of the BLA (Gale et al., 2004), indicating that other regions can compensate for loss of BLA activity. While direct fear responses to specific threats are primarily mediated by the amygdala, sustained anxiety responses that persist beyond the immediate threat include structures other than the amygdala for mediation (Walker and Davis, 2002).

7.2.3 Glutamate NMDA receptors, fear learning and the amygdala

It has already been established in this Introduction that the amygdala, in particular the BLA, is critical for fear conditioning. In this process, the glutamate receptors, especially those located on the BLA, play an important role. In fact, NMDA receptors are more highly concentrated in the basolateral nucleus than in the central nucleus of the amygdala (Monaghan and Cotman, 1985) reinforcing the BLA's role in fear conditioning. Amygdala NMDA receptors have been shown to participate in the initial acquisition of Pavlovian fear memories, and may also participate in post-training consolidation processes important for avoidance learning (Walker and Davis, 2002). One study showed that pre-training infusion of the NMDA antagonist, APV (2-amino-5 phosphonovalerate), into the BLA, impairs the acquisition of the two-way active avoidance reaction: animals failed to acquire the directionality of the escape reaction and showed deficits in attention to conditioned stimuli (Savonenko et al., 2003). APV did not retard the acquisition of freezing to contextual cues, however, but did dramatically deteriorate the retention of contextual fear (Savonenko et al., 2003). This deficit coincided with a significant attenuation of cFos activation in the amygdala (Savonenko et al., 2003): cFos is associated with the acquisition of new memories in this particular paradigm (Radwanska et al., 2002). cFos expression in the amygdala

has also been correlated with measures of emotional learning, but not with sensory stimulation (e.g. during foot shock) (Savonenko et al., 1999). Savonenko et al. (2003) conclude that the blockade of NMDA receptors in the BLA during their paradigm represents a disrupted CS-US association in pavlovian fear conditioning. Another study also indicated that when the NMDA antagonist, AP5, is infused into the BLA prior to fear conditioning (light-shock), fear learning is disrupted, as assessed 1 week later (Miserendino et al., 1990). Infusions 5 days after training, and 1 week before testing, had no effect on the fear-potentiated startle reflex. These findings were replicated using auditory and olfactory cues as CS (Walker and Davis, 2002).

7.2.4 Prefrontal cortex

7.2.4.1 Learning and conditioning

A variety of cognitive abnormalities have been described in schizophrenia, including disturbances in selective attention and working memory. Hypofrontality in the PFC is also a robust finding in schizophrenia research (Williamson, 1987; Lewis et al., 2004), and likely provides a neural basis for many of the cognitive deficits (Castner et al., 2004; Lewis et al., 2004). One fMRI study showed learning-related changes in activation within the ACC (Knight et al., 1999). Within the ACC itself, the amount of active tissue increased as a function of repeated CS-US trials, but did not change with unpaired light and shock presentations (Knight et al., 1999), providing evidence for a role in associative learning. The authors did, however, suggest that the ACC may facilitate, but not necessarily be critical, in learning affective behaviour, as determined by lesion and physiological studies (Knight et al., 1999). It has recently been suggested that one possible mechanism of how this facilitation is achieved is through connections between the ACC and the amygdala (Tang et al., 2005). In fact, many ACC neurons have been found to project directly to the amygdala (Aggleton et al., 1980). It has also been suggested that the amygdala relays signals to the ACC that could be important for adjusting motivational levels or for forming reward expectations in the ACC (Sugase-Miyamoto and Richmond, 2005). In line with this idea, an animal study showed that auditory fear memory produced by pairing ACC stimulation with a tone was blocked by an NMDA receptor antagonist, AP5, administered locally into the amygdala (Tang et al., 2005). This was not the case for contextual fear memory, which may be mediated by other structures, such as the

hippocampus (Tang et al., 2005).

7.2.4.2 Pain

As well as being involved in associative learning, the ACC is also involved in the processing of both pain sensation and pain emotion (Gao et al., 2004). Pain could therefore be a confounding variable in a shock-related fear conditioning paradigm, as it also involves the ACC. Historically, it has been shown that surgical ablation of the ACC and surrounding cortical tissue decreased pain-related unpleasantness without affecting the patient's ability to discriminate the intensity or localization of the noxious stimuli (Foltz and White, 1962). An animal study investigating the magnitude of formalin-induced conditioned place avoidance showed that this behaviour was reduced in ACC and amygdala lesioned rats, indicating that different neural substrates underlie pain affect and pain sensation (Gao et al., 2004). The authors suggested that lesions in the ACC cause a decrease in aversion or perceived unpleasantness to the noxious stimulus (Gao et al., 2004). They also proposed that the ACC may be specifically involved in pain-related negative emotion, rather than aversive associative learning, as ACC lesions did not affect the foot shock induced avoidance, but did block pain related avoidance (Gao et al., 2004).

7.2.4.3 NMDA receptors, fear learning and the ACC

Glutamate receptors in the ACC also contribute to emotional learning. Activation of metabotropic glutamate receptors in the ACC facilitates behavioural responses in both the tail-flick reflex and hot-plate tests, providing direct evidence for the involvement of glutamate in pain mediation in the ACC (Tang et al., 2005). mGlu receptors have also been shown to be involved in learning in the ACC, as demonstrated by the enhanced the escape response due to chemical activation of these receptors (Tang et al., 2005)

7.2.5 Use of NMDA antagonists in the disruption of fear conditioning

As some NMDA receptor antagonists induce sensory distortions in humans, the use of these antagonists in a fear conditioning (emotional learning) paradigm has been questioned. Walker and Davis (2002) claim that the effects of NMDA receptor blockade cannot be attributed to a general disruption of amygdala activity, or to a specific inability of the rat to process the CS. Observations have been made that

NMDA receptor-mediated currents contribute minimally to synaptic transmission, but in fact play a more active role in triggering intracellular cascades, such as those involved in neural plasticity (Walker and Davis, 2002). Could the NMDA antagonist (AP-5)-induced learning impairments then be attributed to a disruption of the US processing? Miserendino (1990) has reported that reactions to foot shocks between controls and AP5 rats (injected into the amygdala) were indistinguishable, even at a dose four times that required to impair learning. Subsequent studies have confirmed this result (Campeau et al., 1992). Therefore there is no evidence for the analgesic influence of this treatment. Walker and Davis (2002) also claim that the ability of AP5 to disrupt learning could not be attributed to the disruption of neural transmission in pathways that convey footshock information to the amygdala. The disruption must therefore involve the impaired association of a US and a CS (Walker and Davis, 2002).

8 Animal models of schizophrenia

8.1 Latent inhibition and blocking

Animal models of schizophrenia typically combine either pharmacological treatments, adult lesions or neonatal lesions, with some form of conditioning paradigm (Marcotte et al., 2001). Attentional (cognitive) deficits in schizophrenia are often investigated by a type of conditioned fear response, known as latent inhibition (e.g. Sotty et al., 1996). This phenomenon is elicited when the conditioned stimulus is presented in the absence of the unconditioned aversive stimulus prior to conditioning, which then delays the learning process (Sotty et al., 1996; Escobar et al., 2002). Radulovic et al. (1998) described latent inhibition as a decrease in attentional processing during the encounter of a stimulus. These tests are reputed to reflect the normal functioning of attention, which has repeatedly been shown to be disrupted in acute schizophrenics (Escobar et al., 2002). Kamin blocking is defined as a procedure involving a pre-exposure stage, where an association between a conditioned stimulus CS and an unconditioned stimulus US is made. A second series of pairings are then presented with the same US as before. Kamin blocking is then indicated by a decreased rate of learning of the second pairing exhibited by the subjects exposed to the original CS-US relationship (Jones et al., 1997).

Schizophrenic patients and their schizotypal and non-schizotypal relatives display disrupted latent inhibition and Kamin-blocking effects (Martins Serra et al., 2001). In another study, latent inhibition was also not observed in acute unmedicated patients, while it was observed in chronic, medicated patients and controls (Vaitl et al., 2002). Animal models have also shown disrupted latent inhibition with drugs known to induce schizophrenic-type psychotic states, such as NMDA antagonists. In a conditioned emotional response model in rats for example, MK-801 led to abnormally persistent latent inhibition during the conditioning stage (Gaisler-Salomon and Weiner, 2003). This effect was subsequently reversed by clozapine, but not haloperidol, administered during pre-exposure (Gaisler-Salomon and Weiner, 2003). One shortcoming of the attentional model prevalent in studies of latent inhibition and blocking is that it only explains changes occurring in response to the conditioned stimulus (Escobar et al., 2002) and not the association of the US and CS.

8.2 PPI

The startle reflex consists of a collection of physiological responses in response to a sudden intense stimulus. The major advantage of the startle reflex paradigm is that the resulting behavioural responses can be studied in a variety of species including both humans and rodents (Braff and Geyer, 1990; Koch, 1996). It therefore serves as a valuable tool to assess different forms of information processing, such as fear-potentiation and prepulse inhibition.

Schizophrenia patients are deficient in the normal inhibition of the startle reflex that occurs when the startling stimulus is preceded by a weak pre-stimulus (for a review, see Braff et al. 2001). This loss of normal prepulse inhibition (PPI) is thought to be a measure of the deficient sensorimotor gating (Braff and Geyer, 1990) that underlies sensory flooding and cognitive fragmentation in these patients (McGhie and Chapman, 1961). Similar deficits in PPI can be produced in rodents by pharmacological or developmental manipulation, which provide models of sensorimotor gating deficits in schizophrenic patients with face, predictive and construct validity (Geyer et al., 2001; Swerdlow et al., 2001). Yet, PPI remains primarily a model of attentional processing, and does not explore the emotional modulation of cognitive processes.

9 Fear processing and anxiety disorders

9.1 Basic features

Fear/stress is considered to be a normal response to threatening or potentially threatening stimuli, as seen in the fear conditioning paradigm. Fear is defined as a reaction to an aversive or threatening stimulus leading towards behaviour directed at escape or avoidance (Lang et al., 2000). This reaction typically utilises the fear conditioning circuit mentioned above. Fear responses include not only the classic three “cannonical” options of fight, flight, or freeze (Cannon, 1929) but also anticipatory fear and increased levels of arousal (Yerkes, 1921), which can be measured in the absence of the aversive stimulus in order to gauge the emotional arousal. Anxiety, however, is defined as a more general and longer lasting state of distress, involving physiological arousal, but sometimes without functional behaviour (Lang et al., 2000). It has been suggested that this emotional state makes more use of the bed nucleus stria terminalis than the CEA, although these two areas project onto the same end substrates (Lang et al., 2000). If these responses become maladaptive i.e. if the response is incongruent to the situation, they may constitute a disorder. Anxiety disorders incorporate panic disorder, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder and generalized anxiety disorder.

9.2 Brain circuits

The brain circuit involved in anxiety disorders is the equivalent of the fear conditioning circuit (Davidson, 2002; see section 7.2). It was suggested in Davidson (2002) that disinhibition of the PFC’s control of the amygdala could lead to maintenance of a learned aversive response, leading to anxiety disorder.

9.3 mGlu receptors and anxiety

As glutamate is the main excitatory neurotransmitter in the brain, and since anxiety disorders may involve overexcitation of the fear circuit, it is logical that new therapeutic approaches towards anxiety disorders include drugs that modulate glutamate functioning. Disruption of the glutamate system is therefore not only associated with schizophrenia, but also with anxiety disorders. In particular, both NMDA and AMPA/kainate receptor antagonists have shown anxiolytic properties (Jardim et al., 2005; Alt et al., 2006; Boyce-Rustay and Holmes, 2006). In the clinical

setting, however, these drugs have not been convenient in treating anxiety disorders, due to memory impairment and central nervous system depression (Danysz and Parsons, 1998). The direction of the search for anxiolytics has therefore turned to the metabotropic glutamate receptors, as mGlu receptors do not have the profound negative effects of the ionotropic receptors on the nervous system (Fig. 11). The group II mGlu (2/3) receptor agonists, in particular, have been shown to be potential anxiolytics through inhibition of glutamate release. Of particular interest, these agonists suppress excitatory neurotransmission in the amygdala (Swanson et al., 2005).

One study has shown that pre-treatment with LY354740, an mGlu 2/3 agonist, prevents stress-induced cFos induction in the hippocampal regions, but does not modify the elevated-plus-maze-induced cFos induction seen in the CEA nucleus (Linden et al., 2004). As indicated previously, it is well known that the hippocampus is primarily involved in contextual conditioning (Labar and Disterhoft, 1998; Holland and

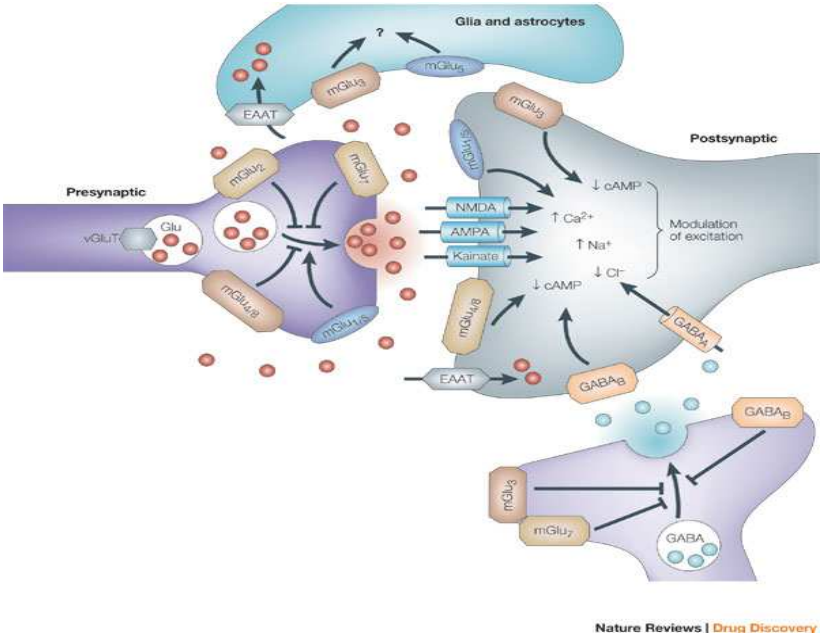


Figure 11: *Localisation and function of glutamate receptors on a hypothetical synapse according to Swanson et al. (2005). Ionotropic glutamate receptors have not been successful in the clinic, and therefore focus has switched to the mGlu receptors. mGlu (2/3) receptor agonists, in particular, have been shown to be potential anxiolytics through inhibition of glutamate release*

Bouton, 1999; Gewirtz et al., 2000; Maren and Holt, 2000; Anagnostaras et al., 2001). In anxiety disorders, contextual factors contribute more to fear generalisation, traumatic memory retrieval and relapse after exposure therapy (Mineka et al., 1999) than possibly sensory conditioning, the latter involving primarily the amygdala (Thiels and Klann, 2002). Psychological stress, dysregulation of central monoamine systems, and dysfunction of the amygdala have, however, been proposed to play a role in the development of post-traumatic stress disorder (Charney et al., 1993; Goldstein et al., 1994).

10 Schizophrenia, fear conditioning and ketamine: a novel approach to negative symptoms

In patients suffering from negative symptoms, we often find the opposite phenomenon to anxiety disorder, with an absence of emotional response to fear-inducing stimuli (emotional blunting), including diminished functional and structural integrity of amygdala and other important fear and motivation areas. As summarized above, the functional integrity of the amygdala and related brain regions is critically dependent on normal glutamate NMDA functioning.

In the present study, we wish to develop an animal model to study emotional blunting, a key negative symptom in schizophrenia. We therefore make use of a fear conditioning paradigm. Although this paradigm is usually used to investigate anxiety disorders, as pointed out by Aleman and Kahn (2005), anxiety and schizophrenia are interlinked. Studies have shown that anxiety often precedes the onset of hallucinations (Delespaul et al., 2002) and higher levels of anxiety are related to a predisposition for hallucinations (Allen et al., 2005). Neuro-imaging studies suggest that positive symptoms are associated with increased amygdala activity, whereas negative symptoms are associated with hypoactivation (Taylor et al., 2002; Fahim et al., 2005). Anxiety is present in the onset stages of schizophrenia, yet largely absent in the longer-term stages of the disorder (Cutting, 2003). Aleman and Kahn (2005) propose a two-hit model of amygdala abnormalities in schizophrenia. They speculate that prolonged activation of the amygdala during psychotic states in the onset stages of schizophrenia could lead to glutamate excitoxicity resulting in amygdala lesions and long-term hypofunctioning (see also Heresco-Levy, 2003). A decrease in amygdala grey matter density is also noted in schizophrenics over the course of the disorder (Hulshoff Pol et al., 2001). Here we simulate glutamate excitotoxicity through glutamate antagonism, namely through ketamine administration, leading to hypofunctioning of the amygdala and other brain areas involved in fear conditioning. Accordingly, we combine a conditioning paradigm (Chapter 2) with ketamine (Chapter 3), and examine conventional measures of fearful behaviour (e.g. freezing) and neural activity (see below) in a putative rat model of emotional blunting (Chapters 3-5).

10.1 cFos expression as a measure of functional integrity

cFos is an immediate-early gene that can be used as an index of neuronal activity, since it is speculated to occur as a consequence of synaptic activity (Sagar et al., 1988). Immediate-early genes are so-called because of their direct transcriptional activation due to neurotransmitters or drugs (Sagar et al., 1988; Ananth et al., 2001). At rest, Fos is produced in small quantities in the neuron. In response to a stimulus, cFos mRNA is produced *en masse* and translocated into the cytoplasm to be translated into protein (Ananth et al., 2001). If cFos is induced, the time period when the protein product is maximal is between 1 and 4 hours post-experimentation (Sharp, 1997).

As mentioned earlier, glutamate NMDA receptor antagonists are reputed to induce several symptoms characterising schizophrenia. cFos studies would therefore be helpful in pinpointing their locus of action in the rat brain. For example, induction of cFos mRNA was noted 1 hour after injection of PCP (0.86 mg/kg or 8.6 mg/kg i.p.) in the anterior and posterior cingulate areas and in the thalamus (Gao et al., 1998). This activation was sustained up to 3 hours after injection. In the same experiment, MK-801 (0.1 mg/kg; 1 mg/kg i.p.) also induced cFos mRNA expression (at both dosages) in limbic and cortical areas, including the medial prefrontal, parietal and cingulate cortices (Gao et al., 1998). If cFos induction can be measured with respect to drugs that induce negative schizophrenic symptoms (e.g. ketamine), then logically the capacity of antipsychotics to relieve or block these symptoms can also be measured in terms of cFos expression (e.g. Nguyen et al., 1992; Chapter 4).

10.2 Central hypotheses of the thesis and their significance

The present model is aimed at elucidating the putative glutamate-regulated breakdown in fear processing, and related cognitive-emotional processes, observed in patients suffering from schizophrenia, and similarly, in healthy controls following ketamine administration (Krystal et al., 2000; Abel et al., 2003). As fear conditioning involves basic associative learning and memory processes, we wish to investigate whether emotional blunting (a negative symptom) is caused by an interruption of basic emotional processing in the amygdala and other brain areas in the fear circuit. We therefore combine the paradigm of fear conditioning with ketamine administration

in order to develop an animal model of the negative symptoms of schizophrenia.

Based on the above, we therefore propose the following logical sequence of hypotheses:

1) Fear conditioning will lead to:
    a. Increase in behaviour associated with fear (e.g. freezing).
    b. Increase in cFos expression in those brain areas involved in fear conditioning, including the ACC and BLA.
    c. Increased glutamate release and dopamine modulation in those same brain areas.
2) Ketamine administration will abolish all the above-mentioned effects of fear conditioning to baseline levels of behaviour, cFos expression and neurotransmitter levels.
3) Administration of clozapine, but not haloperidol or LY 379268 (an anxiolytic), will block the effects of ketamine in all measured output parameters, either fully or partially.

Evidence in favour of all three hypotheses would support the notion that glutamatergic hypofunctioning in the amygdala and related brain areas underlies negative schizophrenic symptoms, thereby paving the way for future studies to explore novel drug treatments of these notoriously drug-resistant symptoms.

10.3 The emotional-cognitive perspective

The putative model may shed light on the emergence of cognitive symptoms through the breakdown of normal interactions between emotional and cognitive processing, as proposed in the theory of Grossberg (2000) (Fig. 12). According to this theory, brain regions involved in emotion and motivational learning, such as the amygdala, interact with cognitive brain regions that selectively focus attention on sensory features relevant to a conditioning task. A deficit in motivational learning can lead to problems in attentional focusing by means of the bi-directional linkage between brain areas subserving these functional roles. Cardinal et al. (2002) have proposed that the rodent BLA performs the role of motivational learning, while the ACC selects specific

sensory features associated with a conditioned stimulus. Based on these hypotheses, we speculate that ketamine will lead to the abolition of fear-related activity in the BLA and the ACC, which in the present study may represent the cognitive-emotional breakdown predicted in Grossberg's (2000) theory of schizophrenia.

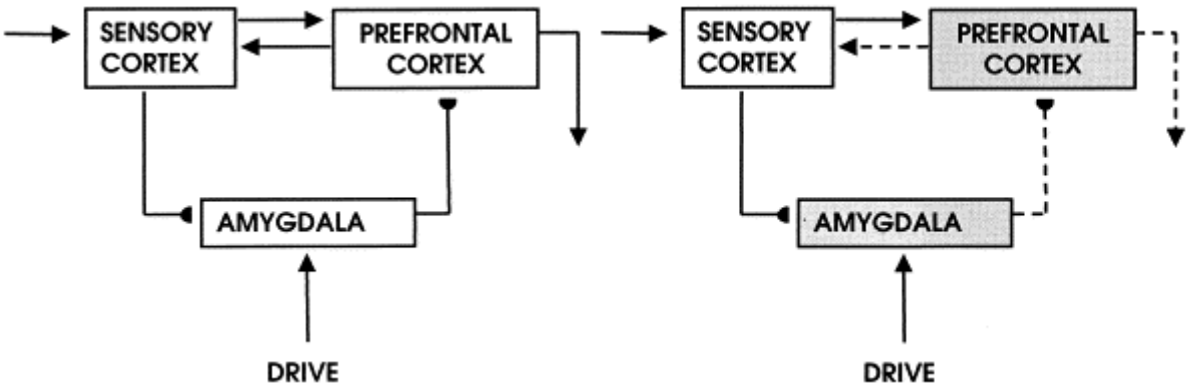


Figure 12: *Grossberg's (2000) emotional-cognitive model of schizophrenia. In the normal case, the amygdala is hypothesised to facilitate motivated behaviour through interactions with the prefrontal cortex and the sensory cortex (left). When the activities of drive representations in the amygdala are compromised (right), say through excitotoxic lesions, processing of emotionally-valent sensory and cognitive (in prefrontal cortex) information is compromised, leading to problems in associative linking of sensory, emotional and cognitive states. This breakdown may correspond to the negative schizophrenic syndrome.*

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