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“Sometimes I think people take reality for granted.”

— Francesca Zappia

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Abstract

Much about the mechanisms behind psychotic symptoms and syndromes is yet unknown. Studying the development of psychotic disorders remains difficult, because of confounding factors such as treatment side effects, effects of hospitalization and that most patients are seen in later stages of illness. Here, model systems can be useful. When employing model systems, it is important to explore both their strengths and their limitations in order to define which conclusions can be drawn from them.

The research presented in this thesis provides insight into the strengths and limitations of two frequently used model systems of psychosis – acute ketamine administration as a state-model and high levels of schizotypy as a trait-model. Executive functions and declarative memory have been reliably demonstrated to be impaired in psychosis and smooth pursuit eye movements (SPEM) are a promising biomarker of psychosis. To better understand ketamine as a model of psychosis, research must focus on the effect of ketamine on biomarkers and cognitive symptoms and possible changes in neuronal activity during their execution. The literature on cognitive impairments in individuals with high levels of schizotypy is inconsistent. To better understand high levels of schizotypy as a model of psychosis, it is important to quantitatively assess the available literature and shape a clearer view of the current state of research in this domain. To investigate the strengths and weaknesses of these models, the work I report in this dissertation combines the methods of functional resonance imaging, eye-movement recording, computerized cognitive tasks and meta-analysis.

Results reported in this thesis show that while acute ketamine administration led to impairments and neuronal alterations in SPEM and emotional memory that have been reported in psychosis, it did not impair antisaccade performance as reported in psychosis and did not lead to the neuronal changes during antisaccade performance that have been reported in psychosis. The meta-analysis of schizotypy and executive functions reported in this thesis indicates that schizotypy mimics Inhibition and Updating deficits which are also consistently reported in psychosis, but they do not lead to alterations in Shifting function, which is generally reported in psychosis. In conclusion, the research presented in this thesis suggest that ketamine and schizotypy, while being incomplete models, can be viewed as parts in a puzzle that may help to further our understanding of the etiology and pathophysiology of psychosis.

Zusammenfassung

Die Mechanismen hinter psychotischen Symptomen und Erkrankungen sind noch nicht vollständig verstanden. Da Patienten häufig erst in späteren Erkrankungsstadien gesehen werden und die Behandlung zu Nebenwirkungen führt, bleibt es schwierig die Entstehung psychotischer Störungen zu erforschen. Hier können Modellsysteme hilfreich sein. Bei ihrem Einsatz ist es wichtig ihre Stärken und Limitationen zu beschreiben um zu definieren welche Schlüsse aus vorliegenden Daten gezogen werden können.

Die Ergebnisse, die in dieser Dissertation berichtet werden, beschreiben Stärken und Limitationen zweier häufig verwendeter Modellsysteme: Akute Ketamininfusion als Kurzzeit-Modell und hohe Schizotypiewerte als Langzeit-Modell. Exekutive Funktionen und das deklarative Langzeitgedächtnis sind bei Psychose-Patienten reliabel beeinträchtigt und glatte Augenfolgebewegungen sind ein vielversprechender Biomarker der Psychose. Um Ketamin als Psychosemodell besser zu verstehen, ist es wichtig den Effekt von Ketamininfusion auf Biomarker und kognitive Symptome, sowie deren neuronale Korrelate zu untersuchen. Die Literatur bezüglich der kognitiven Beeinträchtigungen von Personen mit einem hohen Schizotypielevel ist inkonsistent. Um hohe Schizotypiewerte als Psychose-Modell besser zu verstehen, ist es wichtig die Literatur zu diesem Thema quantitativ zu untersuchen und ein klareres Bild der aktuellen Forschung abzubilden. Um die Stärken und Limitationen der beschriebenen Modelle zu untersuchen, kombiniert die Forschungsarbeit in dieser Dissertation funktionelle Magnetresonanztomographie, Augenbewegungsaufzeichnungen, computerbasierte kognitive Aufgaben und meta-analytische Methoden.

Die berichteten Ergebnisse zeigen, dass während akute Ketamininfusion zu Beeinträchtigungen und neuronalen Veränderungen bei glatten Augenfolgebewegungen und emotionalem Gedächtnis führte, keine entsprechenden Veränderungen bei der Ausführung von Antisakkaden auftraten. Die Meta-Analyse zu dem Zusammenhang zwischen Schizotypie und Exekutiven Funktionen legt nahe, dass das Schizotypie-Modell Defizite in „Inhibition“ und „Updating“, jedoch nicht in der „Shifting“-Funktion von Psychose-Patienten abbildet. Die Forschungsergebnisse, die in dieser Arbeit berichtet werden, legen nahe, dass Ketamin und Schizotypie als unvollständige Modelle ein hilfreicher Baustein sein können, um die Ätiologie und Pathophysiologie der Psychose besser zu verstehen.

1 General Introduction

"The scariest thing of all is never knowing what you're suddenly going to believe."

- Neal Shusterman

1.1 Model Systems of Psychosis

1.1.1 Psychosis Spectrum and Schizophrenia

Key features of psychotic disorders are positive symptoms such as hallucinations, delusions, disorganized thinking, disorganized motor behavior and negative symptoms, such as diminished emotional expression, anhedonia and avolition (American Psychiatric Association, 2013). Cognitive impairments are common in psychotic disorders and these symptoms seem to play a key role in the global functioning of patients (Barch et al., 2013; Heckers et al., 2013).

There is strong evidence in the literature of a psychosis spectrum: This conceptualization assumes the existence of a continuum, ranging from mild psychotic symptoms to severe psychosis, taking into account that psychotic symptoms appear not only in schizophrenia, but in the general population (Linscott & van Os, 2013; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009) as well as across diverse disorders (Mancuso et al., 2015; Murray et al., 2004). However, most psychosis research focuses on schizophrenia, although only 30% of patients suffering from a psychotic disorder meet all criteria for schizophrenia (Perälä et al., 2007). Accordingly, a majority of the research that is the foundation of this thesis will concern schizophrenia patients (Guloksuz & van Os, 2018).

The lifetime prevalence of psychotic disorders is 3.5% (Perälä et al., 2007) and leads to a multitude of mental, social, economic and physical challenges. At over €90 billion per year, the cost of psychotic disorders is currently the third highest of any brain disorder in Europe (DiLuca & Olesen, 2014; Olesen, Gustavsson, Svensson, Wittchen, & Jönsson, 2012). Two thirds of these costs result from the secondary effects of these disorders connected to global functioning deficits of patients, such as high unemployment rates among patients (Evensen et al., 2016; Olesen et al., 2012).

Empirical evidence of heritability (Ripke et al., 2013) of schizophrenia saw the emergence of genetic research focused on identifying underlying genetic causes. In the 1990s, especially made possible though the completion of the HapMap project (International HapMap Consortium, 2003), genome wide association studies (GWAS) identified many single nucleotide polymorphisms (SNPs) associated with schizophrenia (Ripke et al., 2013). Still, the identified SNPs only account for up to 23% of variation (Lee et al., 2012). Among 100 of the identified SNPs seem to have notable genome wide significance. Notably, many of these are related to glutamate receptor function and plasticity at glutamate synapses, such as SNPs associated with dopamine receptor function (Friston, Brown, Siemerkus, & Stephan, 2016; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). In addition to these SNPs, some putatively damaging mutations in multiple genes related to glutamate receptor function have been associated with schizophrenia (Timms et al., 2013). Other studies of healthy parents of schizophrenia patients indicate that those parents carried a higher burden for de novo SNPs which increased the psychosis risk of their children (Girard et al., 2011; Kong et al., 2012; Xu et al., 2011). Some copy number variants (CNVs) have also been associated with risk of schizophrenia: Most notably the DiGeorge syndrome (22q11.2 deletion syndrome), 25-30% of carriers of which suffer from schizophrenia (Kirov et al., 2014; Murphy, Jones, & Owen, 1999). Again, a number of the CNVs linked to psychosis are associated with glutamate receptor function (Rujescu et al., 2009). In light of all this work, it seems likely that the interaction of multiple genetic changes (many relating to glutamate receptor functioning and plasticity at glutamate synapses) may play a role in the etiology of schizophrenia. The high heritability may be caused by alleles that individually are not necessary or sufficient to cause schizophrenia (Friston et al., 2016).

In light of the possible role of glutamate receptor functioning and plasticity at glutamate synapses in psychosis, aberrant neuromodulation of synaptic efficacy mediating context-sensitive influence of intrinsic and extrinsic connectivity has been proposed as the key pathophysiology of psychosis (Corlett, Honey, Krystal, & Fletcher, 2011; Fletcher & Frith, 2009; Powers, Gancsos, Finn, Morgan, & Corlett, 2015; Teufel, Kingdon, Ingram, Wolpert, & Fletcher, 2010) as described in the dysconnection hypothesis (Friston et al., 2016; Friston & Frith, 1995). The dysconnection hypothesis rests on the theoretical frameworks of the Baysian brain and predictive coding (Clark, 2013; Dayan, Hinton, Neal, & Zemel, 1995; Friston, Kilner, & Harrison, 2006; Lee & Mumford, 2003) for understanding connectivity and the functional, computational architecture of the brain (Friston et al., 2016). The basic idea is that neural activity encodes beliefs about states of the world which cause sensations. To this end, higher level representations generate predictions of representations of lower levels. These predictions are

then compared with lower level representations. The difference (termed prediction error and represented by superficial pyramidal cell activity), in turn is used to update higher representations (Friston et al., 2016). In addition, the precision of these predictions is predicted via modulation of the gain/excitability of neuronal populations reporting prediction error (Feldman & Friston, 2010; Iglesias et al., 2013; Moran et al., 2013) which is in line with the fact that the superficial levels have many synaptic gain mechanisms (Braver, Barch, & Cohen, 1999; Goldman-Rakic, Lidow, Smiley, & Williams, 1992). An inability for this precision weighting of predictions on lower, sensory levels, would explain sensory aspects of psychosis, such as reduced mismatch negativity (Dima, Frangou, Burge, Braeutigam, & James, 2012; Zarchi et al., 2013), SPEM deficits (Beedie, Benson, & St Clair, 2011) and resistance to illusions (Barch et al., 2012; Brown, Adams, Parees, Edwards, & Friston, 2013; Jardri & Denève, 2013). The failure to attenuate sensory precision in motor control may lead to psychomotor poverty and reduce sensitivity to sensory consequences of self-made acts (Feldman & Friston, 2010; Friston et al., 2016; Jiang, Summerfield, & Egner, 2013). What is more, when sensory predictions are unattenuated, the brain may try to compensate by increasing the confidence in high-level beliefs so that they become more resistant to sensory evidence (Teufel et al., 2015), which may be an explanation for delusions (as false beliefs about behavior, action, agency and intention of oneself and others) (Adams, Stephan, Brown, Frith, & Friston, 2013; Corlett et al., 2011; Fletcher & Frith, 2009; Friston et al., 2016; Powers et al., 2015; Teufel et al., 2010). This mechanism would especially explain the emergence of paranoid delusions, as unattenuated sensory signals might suggest that an action is not self-generated, but top-down beliefs might suggest self-generation of the same action (Friston et al., 2016). In these cases, logically, one would have to believe in an outside agency preventing the action one believes one is trying to execute (Friston et al., 2016).

1.1.2 Model Systems and Their Benefits

Much about the mechanisms behind psychotic symptoms and syndromes is yet unknown (Javitt, Zukin, Heresco-Levy, & Umbricht, 2012). Studying the development of psychotic disorders remains difficult, because of confounding factors such as treatment side effects, effects of hospitalization and that most patients are seen in later stages of illness (Barrantes-Vidal, Grant, & Kwapil, 2015; Mason, 2015). Model systems of psychosis lack the confounds of patient research, such as medication and hospitalization (Lenzenweger, 2010) and can help to further our understanding of the pathophysiology of psychotic disorders (Stone, 2011; Stone, Raffin, Morrison, & McGuire, 2010). In addition, currently available antipsychotic compounds (Dunlop & Brandon, 2015; Jann, 2014; Köster, Carbon, & Correll, 2014; Rothschild, 2013; Sommer et al., 2012) have proven to be ineffective in treating negative symptoms, such as

avolition and anhedonia, as well as cognitive symptoms, such as reduced executive function and reduced attention (Chou, Twamley, & Swerdlow, 2012; Hill, Bishop, Palumbo, & Sweeney, 2010; Keefe et al., 2013; Köster et al., 2014; Nielsen et al., 2015; Remington et al., 2016). Seeing as both negative and cognitive symptoms are linked to global functioning of patients (Chang, Hui, Chan, Lee, & Chen, 2016; Green, 2016; Rabinowitz et al., 2012), it is vital to develop new pharmacological treatments that are able to target these symptom domains. Translational model systems of psychosis constitute a well-established method to inform the development of treatments for psychotic disorders (Breier, 2005; Carpenter & Koenig, 2008; Chavez-Noriega, Schaffhauser, & Campbell, 2002; Javitt et al., 2018, 2012; Kola & Landis, 2004; Koychev et al., 2012; Krystal et al., 2003; Stone, 2011).

Numerous model systems of psychosis, both in humans and in other animals, have been developed. They can be grouped into state and trait model systems. State model systems employ short-term conditions, such as acute N-Methyl-D-Aspartate Receptor (NMDAR) blockage, whereas trait model systems employ long-term conditions, such as high levels of schizotypy. Table 1 gives an overview of currently available psychosis model systems.

Table 1. Currently Available Psychosis Model Systems

		Human Model	Other Animal Model
Surrogate Populations	Schizotypy	x	
	Low Performers	x	
Pharmacological Intervention	Ketamine	x	x
	Cannabis	x	x
	Lysergic Acid Diethylamide (LSD)	x	x
	Amphetamine	x	x
Genetic	D1 receptor knockout		x
Anatomic/Lesions	Lesions in ventral hippocampus		x
Developmental	Social Isolation		x
Behavioral	Sleep Deprivation	x	x

Naturally, an ideal model would both mimic the biological changes which drive pathogenesis and reliably predict the efficacy of novel therapeutic compounds (Steeds, Carhart-Harris, &

Stone, 2015). However, considering the complexity of psychosis, it might be challenging for one single model to mimic all features of this heterogeneous disorder spectrum (Carhart-Harris, Brugger, Nutt, & Stone, 2013; van Os & Kapur, 2009). Hence, furthering our understanding of both the strengths and limitations of existing model systems is crucial for their effective application in research.

In this thesis, I focus on ketamine as a prominent state model of psychosis (Javitt et al., 2012), and schizotypy as a prominent trait model of psychosis (Nelson, Seal, Pantelis, & Phillips, 2013), respectively. I will touch only briefly on works concerning other model systems of psychosis, as an in-depth discussion would be beyond the scope of this work.

1.1.3 Acute Ketamine Administration as a State Model System of Psychosis

Glutamate is the main excitatory neurotransmitter in the human brain (Orser, Pennefather, & MacDonald, 1997). The types of glutamate receptors can be divided into ionotropic receptors (which open to allow ions to pass through the membrane in response to binding of a ligand) and metabotropic receptors (which act through a second messenger) (Mori & Mishina, 1995; Orser et al., 1997). The ionotropic receptors can be subdivided into the NMDAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate receptors (Orser et al., 1997). The NMDAR requires the binding of both glutamate and the coagonist glycine for channel activation (Johnson & Ascher, 1987). There are known competitive, non-competitive and uncompetitive NMDAR antagonists. The different mechanisms of antagonism are illustrated in figure 1.

Ketamine (2-O-chlorophenyl-2-methylamino cyclohexanone) is a derivate of phencyclidine (PCP) (Poels et al., 2014). Like PCP, it is an NMDAR antagonist (Joules et al., 2015). Blockage by ketamine is dependent on an open receptor channel because the binding site is located inside the channel pore. Therefore, ketamine is an un-competitive NMDAR antagonist (Pennefather & Quastel, 1992). Ketamine is among the most selective NMDAR antagonists available for human studies (Driesen et al., 2013).

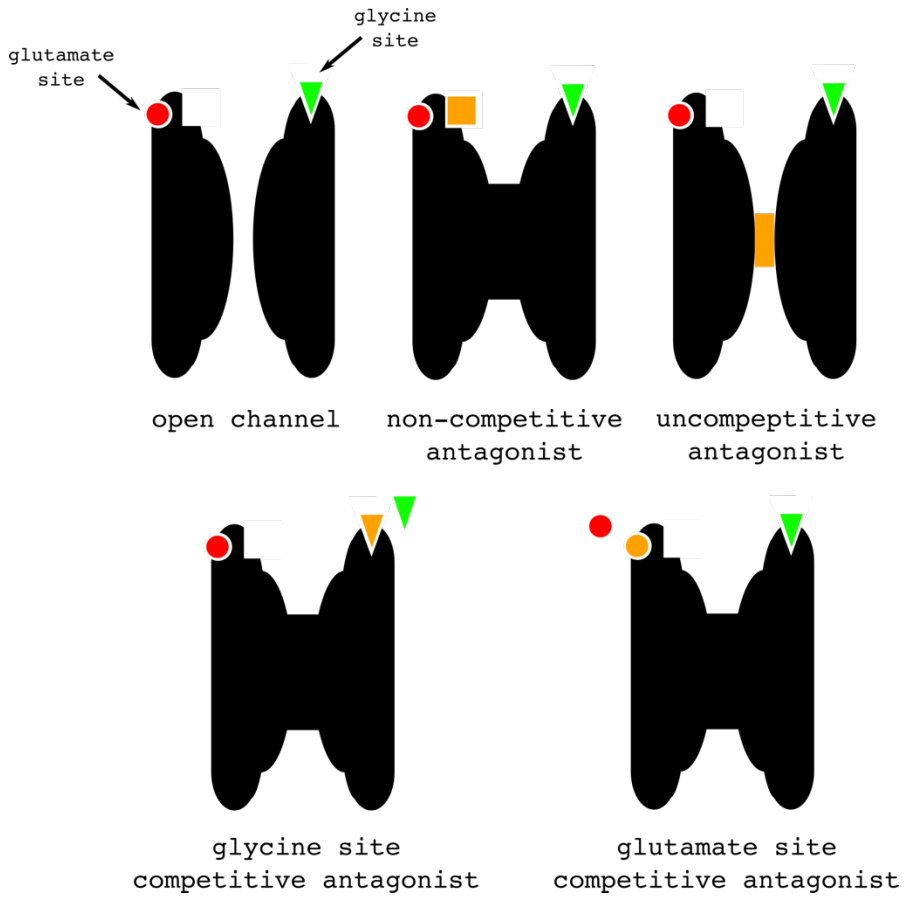

Figure 1. Antagonists of the NMDAR.
Glutamate (red) and glycine (green) bind to their respective binding sites to open the NMDAR Ca^{2+} channel. Different antagonists (orange) can bind to the NMDAR. Non-competitive antagonists bind to an allosteric binding site, uncompetitive antagonists block the Ca^{2+} channel, competitive antagonists bind to the glutamate or the glycine binding site.

Blockage of the NMDAR via compounds such as PCP or ketamine evokes transient symptoms which mimic a wide spectrum of psychosis symptoms (Krystal et al., 1994; Lahti et al., 2001; Schmechtig, Lees, Perkins, et al., 2013). Early observations of these effects led to the rise of glutamatergic theories of psychosis. These theories postulate that NMDAR hypofunction plays a fundamental role in the pathophysiology of psychosis (Kantrowitz & Javitt, 2010; Krystal et al., 2003; Poels et al., 2014) and may explain the full spectrum of psychosis symptoms better than other existing models, such as the highly influential dopamine hypothesis (Javitt et al., 2012). In the early 1960s, the dopamine hypothesis was developed in the wake of the discovery of strong antipsychotic effects of some dopaminergic agents (Javitt et al., 2012). It has since been reconceptualized to reflect that dopamine dysfunction may simply be the final common pathway of psychosis rather than the single underlying psychopathological mechanism (Howes & Kapur, 2009). Dopamine dysfunction cannot account for all features of psychosis, especially on the negative and cognitive symptom domains (Javitt et al., 2012).

In contrast, the glutamate hypothesis seems better equipped to explain the wide spread symptoms of psychosis (Kantrowitz & Javitt, 2010). This hypothesis proposes that dopaminergic dysfunction and associated positive symptoms are a downstream consequence of NMDAR pathophysiology. This could explain why dopaminergic treatments have not been able to target negative and cognitive symptom domains as well as positive symptoms – some of these symptoms may simply be mediated via non-dopaminergic pathways (Kantrowitz & Javitt, 2010). NMDAR dysfunction would predict a number of widespread symptoms, located especially in regions of the brain with high NMDAR density (Javitt et al., 2012), a prediction that is, so far, supported by current research (Friston et al., 2016; Javitt, 2010; Javitt et al., 2012). The glutamate hypothesis would suggest that some symptoms of psychosis are a direct consequence of altered NMDAR function, or more generally, altered glutamate signaling (Friston et al., 2016; Javitt et al., 2012). These should be mimicked by state models such as ketamine administration, which induces transient, acute NMDAR hypofunction. Other symptoms, such as auditory hallucinations, however, could be secondary consequences of chronically altered glutamate signaling (Javitt et al., 2012) and can therefore not be expected to emerge during a one-off ketamine administration. The dysconnectivity hypothesis, as summarized in chapter 1.1.1, suggests that in psychosis, different pathways (among them NMDAR structure and function and dopaminergic neuromodulation of NMDAR), may lead to altered glutamate signaling and, functionally, the failure to encode the relative confidence which should be placed in sensory evidence compared to prior beliefs (Friston et al., 2016). NMDAR hypofunction has been linked to disrupted formation of dendritic spines and the disruption of the growth of dendritic trees, as well as impaired myelination of axons (Fields, 2015; Monfils & Teskey, 2004; Sin, Haas, Ruthazer, & Cline, 2002). NMDAR dysfunction could therefore be casually linked to structural (white matter) changes which can be seen in psychosis. This is in line with the observation that anatomical and structural connectivity abnormalities, which are common in psychosis, evolve over time (Sun et al., 2016; van Haren et al., 2011).

The pure s- and r-enantiomers of ketamine have different affinity for the NMDAR. S-ketamine has a four to five times higher affinity for the NMDAR (Vollenweider, Leenders, Oye, Hell, & Angst, 1997). Studies show that psychotomimetic effects of the enantiomers correspond with their NMDAR affinity (Mathisen, Skjelbred, Skoglund, & Oye, 1995; Oye, Paulsen, & Maurset, 1992). This means that s-ketamine is four to five times more psychotomimetic than r-ketamine (Andrade, 2017; Peltoniemi, Hagelberg, Olkkola, & Saari, 2016; Vollenweider, Leenders, Oye, et al., 1997). It is, therefore, important to consider chirality when planning ketamine administration studies and when interpreting and comparing study results.

Psychotomimetic effects of ketamine in studies employing subanesthetic doses of ketamine have robustly been reported in healthy human adults (for an overview, see Corlett et al., 2011a). Psychotomimetic effects have been reported with ketamine plasma concentrations as low as 50ng/ml (Krystal et al., 1994; Pollak et al., 2015). Studies directly comparing different doses of ketamine suggest that psychotomimetic effects of ketamine are higher for higher doses and that some effects may manifest starting at higher doses than others. For example, Pollak and colleagues reported anhedonia for subjects who received racemic ketamine with a target plasma concentration of 150 ng/ml ketamine, but not those who received a lower dose (Pollak et al., 2015).

Ketamine can be administered intravenously, intramuscular, orally or nasally in humans. Oral bioavailability is low and not easy to control, which is why it is a less optimal administration route (Green, Roback, Kennedy, & Krauss, 2011). Intramuscular infusion is safe and predictable, but leads to higher nausea and is more painful than intravenous administration (Green et al., 2011). Nasal administration has the benefit of rapid systemic absorption, as well as easy and painless administration (Huge et al., 2010), but because of the short plasma half-life of ketamine (Javitt et al., 2012; Krystal et al., 1994), it is difficult to ensure a stable plasma concentration using this method (Corlett et al., 2011; Gao, Rejaei, & Liu, 2016). Intravenous administration is the optimal administration route in terms of bioavailability and control of plasma concentration (Gao et al., 2016). Most studies investigating the effects of subanesthetic doses of ketamine in healthy humans employ a bolus-infusion model of administration (Corlett et al., 2011), in which an initial bolus is administered to achieve the target plasma concentration, which is then followed by small maintenance doses to keep the plasma level steady for the duration of the examination (Corlett et al., 2011; Krystal et al., 1994).

Acute ketamine administration is a useful experimental model system, as it has a relatively short plasma half-life and an excellent safety record in clinical and experimental settings (De Simoni et al., 2013; Doyle et al., 2013; Javitt et al., 2012; Krystal et al., 1994; Schmechtig, Lees, Perkins, et al., 2013). All of the three commonly accepted dimensions of psychotic symptoms (positive, negative and cognitive) have been reported during ketamine administration (Krystal et al., 1994; Schmechtig, Lees, Perkins, et al., 2013). Positive symptoms, such as delusions, perceptual distortions and paranoia have been reported during one-off ketamine administration in healthy adults in doses as low as 50 ng/ml ketamine plasma level. Negative symptoms, such as anhedonia, have also been reported under ketamine administration (Krystal et al., 1994; Lahti et al., 2001; Malhotra et al., 1997; Schmechtig, Lees, Perkins, et al., 2013). There is some evidence that negative symptoms, such as anxiety or withdrawal, first appear during somewhat higher doses than positive symptoms, with one study finding negative symptoms at a ketamine

target plasma concentration of 150 ng/ml, but not for lower doses (Pollak et al., 2015). Studies indicate that all symptoms are more pronounced with higher doses (Krystal et al., 1994; Pollak et al., 2015). Cognitive symptoms, such as disorganized speech, have also been reported (Krystal et al., 1994).

In summary, acute ketamine administration constitutes a useful translational model system of psychosis (Chavez-Noriega et al., 2002; Javitt et al., 2012; Krystal et al., 2003; Stone et al., 2011) that can be employed without confounds such as hospitalization, clinical illness and medication.

1.1.4 Schizotypy as a Trait Model of Psychosis

In contrast to pharmacological state models, trait models of psychosis employ time-stable traits, such as high levels of schizotypy, to model psychotic symptoms and syndromes (Barrantes-Vidal et al., 2015). Schizotypy is a multidimensional, time-stable personality trait (Chan et al., 2015; Gross, Silvia, Barrantes-Vidal, & Kwapil, 2015; Venables & Raine, 2015) that consists of positive, negative and disorganized facets. Positive facets include unusual perceptual experiences and ideas of reference. Negative facets include having no close friends and flat affect. Disorganized facets include odd speech and eccentric behavior (Mason, Claridge, & Jackson, 1995; Raine et al., 1994). For the purpose of this thesis, schizotypy will be considered as a construct that can be subdivided into these three facets. These dimensions have been reported independently of sex (Fonseca-Pedrero, Paino, Lemos-giráldez, Sierra-Baigrie, & Muñiz, 2011; Fossati, Raine, Carretta, Leonardi, & Maffei, 2003; Reynolds, Raine, Mellingen, Venables, & Mednick, 2000) cultural background (Chan et al., 2016, 2015; Fonseca-Pedrero et al., 2015; Yu, Bernardo, & Zaroff, 2016), age (Bora & Baysan Arabaci, 2009; Fonseca-Pedrero et al., 2011) and time (Venables & Raine, 2015). It is worth noting, however, that some studies report more than three dimensions (Davidson, Hoffman, & Spaulding, 2016; Gross, Mellin, Silvia, & Kwapil, 2014; Stefanis et al., 2004), while others report only two dimensions of schizotypy facets (Gross et al., 2015; Kwapil, Barrantes-Vidal, & Silvia, 2007).

There is evidence of a considerable overlap between schizotypy and psychosis (Barrantes-Vidal et al., 2015). A similar factor structure underlying psychosis symptoms and schizotypy facets has been proposed (Chan et al., 2016; Rossi & Daneluzzo, 2002). Genetic similarities have been reported (Walter, Fernandez, Snelling, & Barkus, 2016), though there is an ongoing debate whether considerable similarities exist (Stefanis et al., 2007). Similar cognitive impairments have been reported in psychosis and individuals with high levels of schizotypy (Giakoumaki, 2012; Siddi, Petretto, & Preti, 2017), although this overlap seems to be incomplete (Chun, Minor, & Cohen, 2013; Steffens, Meyhöfer, Fassbender, Ettinger, & Kambeitz, 2018). Finally, similar deviations on brain function and brain structure have been reported (Ettinger et al., 2015).

Current research, therefore, suggests that individuals with high levels of schizotypy share many common features with clinical psychosis in an attenuated form, emphasizing the usefulness of schizotypy as a model system of psychosis.

Two competing models aim to describe the distribution of schizotypy in the population (Kwapil & Barrantes-Vidal, 2015; Nelson et al., 2013): The first model, illustrated in figure 2, is based on the research of Eysenck (1967) and Eysenck and Eysenck (1968) and was developed by Claridge & Broks (1984), Claridge (1987, 1972) and Claridge and Beech (1995). This model proposes that schizotypy is a fully dimensional personality trait which, as such, is continuously distributed in the population.

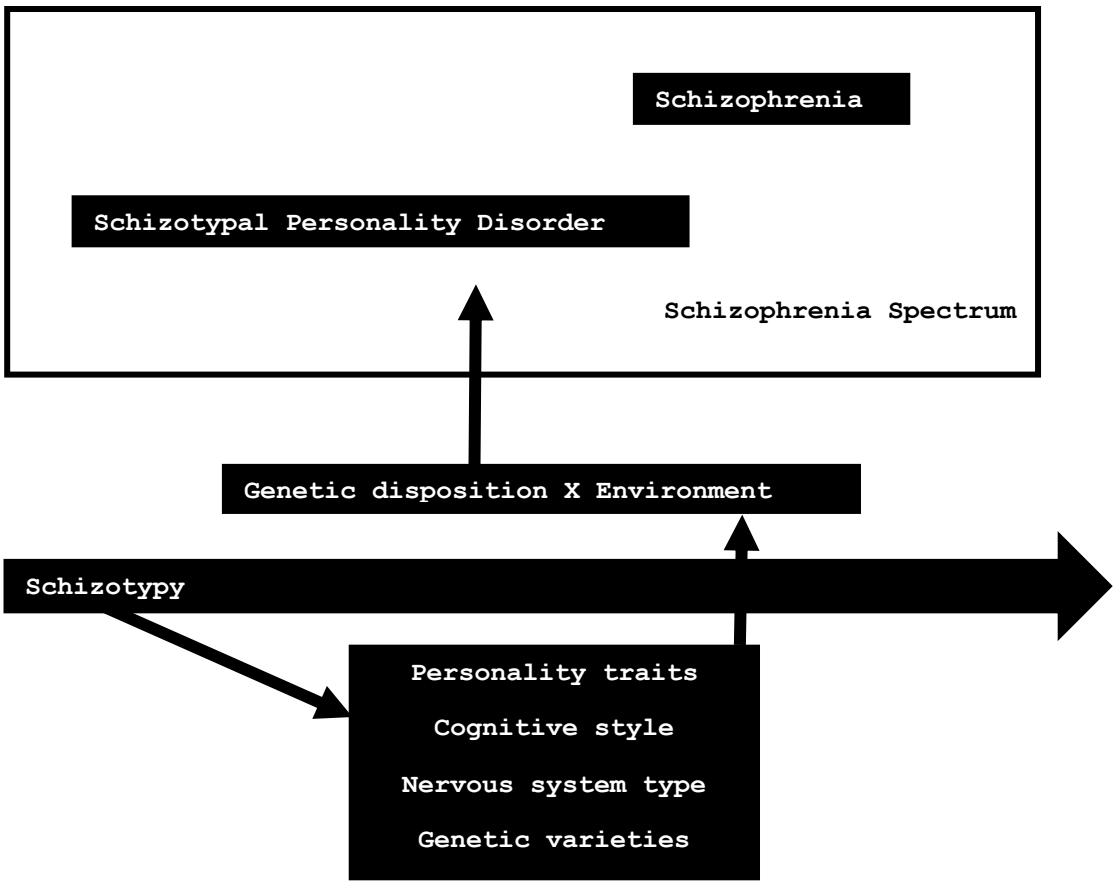

Figure 2. The dimensional model of schizotypy.
Figure based on model described and illustrated by Claridge and Beech (1995).

The second model, illustrated in figure 3, was proposed by Rado (1953) and Meehl (1990, 1989, 1962) and advanced by Lenzenweger (2010, 2006). It assumes that schizotypy is a qualitative latent construct which can either be present or absent. This model argues that a schizogene causes a condition called schizotaxia, which is described as an anomaly of the central nervous system. The model proposes that schizotaxia, then, leads to schizotypal personality in almost all cases. The model predicts that schizotaxia is present in approximately 10% of the population.

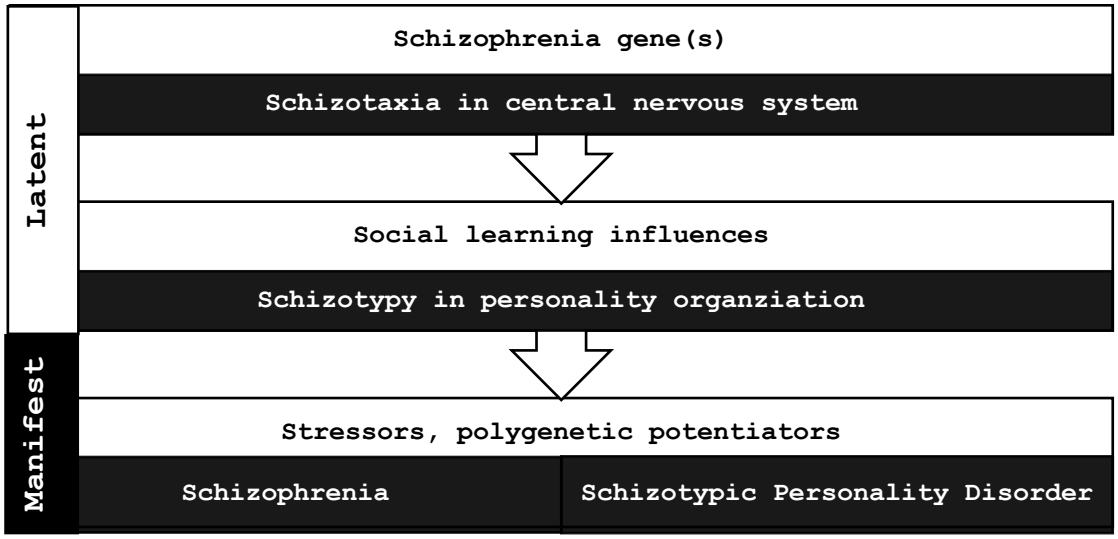

Figure 3. Meehl's Model of Schizotaxia, Schizotypy and Schizophrenia.
Latent Level: Genetic predisposition leads to a schizotaxic brain. An individual with a schizotaxic brain in most social environments develops schizotypy. Manifest Level: Depending on stressors and polygenetic potentiators the individual develops schizophrenia, schizotypy personality disorder or certain endophenotypes of schizotypy (figure adapted from Lenzenweger 2006a).

There is evidence to support each of these models and the question of the distribution of schizotypy in the general population is still unresolved (Lenzenweger, 2015; Mason, 2015). However, recent research suggests that the fully dimensional model is better suited to explain our current knowledge of schizotypy and psychosis (Grant, Judith Leila Munk, Kuepper, Wielpuetz, & Hennig, 2015; Nelson et al., 2013).

Schizotypy can be assessed via interview and self-report, for an overview of current instruments, please refer to table 2. Importantly, most of the available instruments are substantially correlated (Asai, Sugimori, Bando, & Tanno, 2011; Gross et al., 2014; Rössler et al., 2015; Venables & Raine, 2015). The most widely used measures include: The Schizotypal Personality Questionnaire (Cohen, Matthews, Najolia, & Brown, 2010; Davidson et al., 2016; Raine, 1991; Raine & Benishay, 1995; Wuthrich & Bates, 2005), the Champman Psychosis-Proneness Scales (Chapman, Chapman, & Raulin, 1976, 1978; Eckblad & Chapman, 1983; Winterstein et al., 2011) and the Oxford-Liverpool Inventory of Feelings and Experiences (Grant et al., 2013; Mason & Claridge, 2006; Mason et al., 1995; Mason, Linney, & Claridge, 2005).

Table 2. Overview over selected questionnaires for the assessment of schizotypy. (Taken and abridged from Fonseca-Pedrero et al. 2008)

Questionnaire	Authors	Acronym	Number of Items	Format
Perceptual Aberration Scale	Chapman, Chapman and Raulin, 1987	PAS	35	True / False
Physical Anhedonia Scale	Chapman, Chapman and Raulin, 1976	PhA	61	True / False
Social Anhedonia Scale	Chapman et al., 1976	SA	48	True / False
Revised Social Anhedonia Scale	Eckblad, Chapman, Chapman and Mishlove, 1982	RSAS	40	True / False
Magical Ideation Scale	Eckblad and Chapman, 1983	MIS	30	True / False
The Intense Ambivalence Scale	Raulin, 1984	IAS	45	True / False
Schizotypal Traits Questionnaire	Claridge and Broks, 1984	STA	37	True / False
Schizotypy Scale	Venables, Wilkins, Mitchell, Raine and Bailes, 1990	VSS	30	True / False
Schizotypal Personality Questionnaire	Raine, 1991	SPQ	74	True / False
Kings Schizotypy Questionnaire	Williams, 1993	KSQ	63	Yes / No
Junior Schizotypy Scales	Rawlinga and MacFarlane, 1994	JSS	74	Yes / No
Schizotypal Personality Questionnaire Brief	Raine and Benishay, 1995	SPQ-B	22	Yes / No
Oxford-Liverpool Inventory of Feeling and Experiences	Mason, Claridge and Jackson, 1995	O-LIFE	195	True / False

Questionnaire	Authors	Acronym	Number of Items	Format
The Schizophrenia Proneness Scale of the MMPI-2	Bolinskey, Gottesman, Nicholls and Shapiro, 2003; Bolinskey et al, 2001	SzP	32	Likert (4)
Eppenford Schizophrenia Inventory	Mass, 2000; Mass et al, 2007	ESI	39	True / False
Schizotypal Ambivalence Sale	Kwapil, Mann and Raulin, 2002	SAS	19	Yes / No
Peters Delusions Inventory	Peters, Joseph, Day and Garety 2004; Peters, Joseph and Garety, 1999	PDI	21	Likert (5)
Thinking and Perceptual Style Questionnaire	Linscott and Knight, 2004	TPSQ	99	Likert (5)
Schizotypy Traits Questionnaires for Children	Chylarova and Claridge, 2005	STA	37	Yes / No
Schizotypic Syndrome Questionnaire	Ven Kampen, 2006	SSQ	108	Likert (4)

It is important to note that schizotypy is not simply an artefact of prodromal patients who have not yet converted to psychosis (Koychev et al., 2011). This is evidenced by long-term studies which show low psychosis conversion rates for highly schizotypal individuals (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Gooding, Tallent, & Matts, 2005). On this basis, considering the overlap between schizotypy and schizophrenia, schizotypy is a promising trait-model system for psychosis. Schizotypy varies in the general population (Nelson et al., 2013), can be assessed using cheap, reliable and easy to administer instruments (Kwapil & Barrantes-Vidal, 2015; Mason, 2015). Therefore, schizotypy is a useful model of psychosis which allows for studies without confounds such as hospitalization, clinical illness and medication (Lenzenweger, 2010).

1.2 Executive Functions

Executive functions involve the domain-independent representation and maintenance of task goals (Miyake & Friedman, 2012). They enable us to flexibly adapt information processing and behavior to a changing environment and are an important core-component of self-control and self-regulation (Miyake & Friedman, 2012), which have broad significance in our everyday life (Mischel et al., 2011; Moffitt et al., 2011) and can predict clinically and societally important behaviors (Friedman et al., 2007; Friedman, Miyake, Robinson, & Hewitt, 2011; Miyake & Friedman, 2012). Clearly defining executive functions, and especially their distinct subfacets, is difficult (Jurado & Rosselli, 2007). Different methods have been employed to study and define executive functions: Studying patients suffering from localized lesions in different parts of the frontal lobe (Gläscher et al., 2012; Stuss & Alexander, 2007), recording brain activity during performance of tasks which measure executive functions (Gläscher et al., 2012) and employing a latent-variable approach (Miyake & Friedman, 2012; Miyake et al., 2000; Young et al., 2009). One main problem when researching executive functions is the task impurity problem: All tasks which measure executive function necessarily also include systematic variance that is not attributable to executive functions. This systematic variance, combined with random measurement error, is substantial enough to make tasks measuring executive functions "impure" (Miyake & Friedman, 2012).

One of the most influential and well-supported models of executive functions (Eysenck & Keane, 2013) is the model reported by Miyake et al. (2000) and expanded upon in Miyake & Friedman (2012), which was derived by a latent-variable approach. Here, data from tasks with as little systematic non-executive function variance as possible were used to statistically extract common factors across said tasks. The model proposes three developmentally stable (Friedman et al., 2011) main executive functions, namely Shifting, Updating and Inhibition. Shifting is defined as the ability to flexibly switch attention between mental sets or tasks. Updating is defined as the ability to flexibly update and monitor information in working memory. Inhibition is defined as the ability to withhold a prepotent or dominant, but non-desirable response (Eysenck & Keane, 2013; Miyake & Friedman, 2012; Miyake et al., 2000). These three subfacets of executive function seem to share a common function which is one's ability to actively maintain task-goals and use them to influence lower-level processing. In addition to this shared one, they also have diverse, specific functions such as flexibility in the case of Shifting (Friedman et al., 2006, 2011; Rose, Feldman, & Jankowski, 2011; Vaughan & Giovanello, 2010). The Inhibition function shows the highest correlation with common executive function (Miyake & Friedman, 2012; Munakata et al., 2011). Inhibition, Shifting and Updating, as well as the underlying common executive function, show substantial hereditability (Friedman et al., 2008).

Inhibition, Shifting and Updating can be measured using a wide variety of tasks, table 3 gives an overview over commonly used ones.

Executive functions have been associated with the dorsolateral prefrontal cortex (dlPFC) and the anterior cingulate cortex (ACC), as well as other parts of the prefrontal cortex. It has been suggested that these brain regions form a rostro-caudally organized hierarchy for planning and behavioral control (Badre & D'Esposito, 2009; Bechara & Van Der Linden, 2005; Gläscher et al., 2012; Koechlin, Ody, & Kouneiher, 2003).

Table 3. Examples for tasks measuring the executive functions Shifting, Inhibition and Updating.

Shifting
Wisconsin Card Sorting Test (Berg, 1948)
Intra-Extra Dimensional Shift Task ("CANTAB® [Cognitive assessment software]," 2017)
Object Alternation Task (Pribram & Mishkin, 1956)
Trail Making Test (Bowie & Harvey, 2006)
Inhibition
Antisaccade Task (Hallett, 1978)
Eriksen Flanker Task (Eriksen & Eriksen, 1974)
Stroop Task (Stroop, 1935)
Go/NoGo Task (Kiehl, Liddle, & Hopfinger, 2000)
Stop Signal Task (Logan, 1994)
Updating
n-back Task (Kirchner, 1958)
Digit Span Task (Wechsler, 2008)
Spatial Span Task (Corsi, 1972)
Delayed Discrimination Task (Blough, 1959)

1.2.1 Executive Functions in Psychosis

Schizophrenia has a fairly global effect on cognitive function, with impairments across a wide range of cognitive domains (Dickinson, Ramsey, & Gold, 2007; Heinrichs & Zakzanis, 1998; Reichenberg & Harvey, 2007; Schaefer, Giangrande, Weinberger, & Dickinson, 2013). These impairments seem to be relatively stable over patients' life span and every clinical state (Albus et al., 2002; Hill, Schuepbach, Herbener, Keshavan, & Sweeney, 2004; Hughes et al., 2003; Hyde et al., 1994) and are only moderately correlated with overall symptom severity (de Gracia Dominguez, Viechtbauer, Simons, van Os, & Krabbendam, 2009; Hughes et al., 2003; Rund et al., 2004; Schaefer et al., 2013; Ventura, Thames, Wood, Guzik, & Hellemann, 2010). Among the

impaired cognitive dimensions is executive functioning (Green et al., 2004; Reichenberg & Harvey, 2007; Schaefer et al., 2013). Global cognitive impairments are associated with everyday functional capacity (Barch et al., 2013; Heckers et al., 2013). Moreover, measuring executive function has proven to be important for the advancement of our understanding of psychosis symptoms, the underlying psychopathology (Morris & Cuthbert, 2012) and the development of pharmacological treatment (Carter & Barch, 2007; Lesh, Niendam, Minzenberg, & Carter, 2011).

There are numerous studies which have researched impairments of executive functions in schizophrenia. The first meta-analysis (Heinrichs & Zakzanis, 1998), which aggregated studies of cognitive impairments in schizophrenia, reported global impairments in executive functions. Data from 204 studies, comprising 7420 schizophrenia patients and 5865 healthy controls, were included in the analyses. When comparing executive functioning in patients and controls, patients performed more poorly than healthy controls in all three functions as proposed by Miyake et al. (2000) and Miyake & Friedman (2012). The mean difference was highest for Inhibition, measured by the Stroop test, with a mean effect size difference of Cohen's *d*=1.11. The difference for the Shifting function, as measured by the Wisconsin Card Sorting Test (WCST) was Cohen's *d*=.88. However, it should be noted that some of the outcome measures of the WCST used in the included studies may be a better measure for global executive function than for Shifting. Mean effect size difference for the Updating function as measured by the Digit Span task, was *d*=0.61 (Heinrichs & Zakzanis, 1998).

More recently, a meta-analysis by Dickinson et al.(2007) reported similar global impairments in executive function in schizophrenia. This meta-analysis included 40 studies, comprising 1961 schizophrenia patients and 1444 healthy control subjects. The mean effect sizes for the difference between patients and controls which are related to executive functions as defined by Miyake et al. (2000) and Miyake & Friedman (2012) were: WCST (global executive function, especially Shifting): Hedges' *g*=0.26, Trail Making Test B (Shifting): Hedges' *g*= 0.54, Digit Span (Updating) Hedges' *g*=0.23 (Dickinson et al., 2007). Expanding on this work, a more recent meta-analysis that was somewhat wider in scope analyzed data from 100 studies, comprising 9048 patients with schizophrenia and 9914 healthy control subjects. They report similar, but more pronounced, impairment of executive functions. The mean effect sizes for the difference between patients and controls were: Hedges' *g* =0.94 for global executive functioning and of Hedges' *g*=0.89 for working memory (Updating) (Schaefer et al., 2013).

Executive functions in non-schizophrenia psychotic disorders are less studied than in schizophrenia (Bora, Yucel, & Pantelis, 2009). One meta-analysis of available data comparing schizoaffective disorder, affective psychosis, schizophrenia and healthy controls reported that

cognitive deficits in all psychotic disorders were similar, though there was evidence for a subgroup of schizophrenia patients with more severe cognitive symptoms, who also showed more severe negative symptoms (Bora et al., 2009).

1.2.2 Executive Functions in Model Systems of Psychosis

Ketamine

There is abundant evidence that ketamine administration leads to Updating (working memory) deficits. These have been shown at doses as low as 0.1mg/kg racemic ketamine in studies on healthy participants (Adler, Goldberg, Malhotra, Pickar, & Breier, 1998; Ahn et al., 2003; Anticevic et al., 2012; Carter, Kleykamp, Griffiths, & Mintzer, 2013; D'Souza et al., 2012; Driesen et al., 2013; Gunduz-Bruce et al., 2012; Honey et al., 2003; Khalili-Mahani, Martini, Olofsen, Dahan, & Niesters, 2015; Krystal et al., 2005; Lofwall, Griffiths, & Mintzer, 2006; Morgan, Mofeez, Brandner, Bromley, & Curran, 2004b; Murray et al., 2014; Ranganathan et al., 2017; Roberts, Seymour, Schmidt, Williams, & Castner, 2010), as well as in ketamine abusers (Morgan, Monaghan, & Curran, 2004; Morgan, Muetzelfeldt, & Curran, 2009; Zeng, Su, Jiang, Zhu, & Ye, 2016). For review, see Giorgetti, Marcotulli, Tagliabracci, & Schifano (2015) and Morgan & Curran (2006). However, some studies have shown Updating to be unimpaired by ketamine administration in healthy volunteers (Honey et al., 2004; Rowland, Astur, et al., 2005; Scheidegger et al., 2012) and one study reported unimpaired Updating function in ketamine abusers (Liang et al., 2013).

Fewer studies have researched the impact of ketamine administration and ketamine abuse on Inhibition. Two studies employing a distractibility task and one study employing a Stroop task report reduced Inhibition function during ketamine administration in healthy volunteers (D'Souza et al., 2012; Krystal et al., 1999, 1998). One study found that ketamine users show impaired Stroop task performance and poorer performance on the stop-signal task (Zeng et al., 2016). On the other hand, one study found unaltered Stroop task performance during ketamine administration in healthy participants (Rowland, Bustillo, et al., 2005), one showed unimpaired stop-signal task and Stroop task performance in ketamine users (Morgan, Huddy, Lipton, Curran, & Joyce, 2009) and another study showed unimpaired antisaccade performance in ketamine users (Liang et al., 2013).

The literature on the effect of ketamine on Shifting is also not as abundant as the literature on Updating. Ketamine has been shown to lead to impaired Shifting function. Studies in healthy volunteers show that ketamine administration leads to more WCST preservative errors (worse Shifting performance) (Krystal et al., 2000, 1999, 1998, 1994) and impaired Continuous Performance Task (CPT) Shifting performance (Heekeren et al., 2008; Umbricht et al., 2003).

However, one study found unimpaired Trail Making Test (TMT) interference performance (Harborne, Watson, Healy, & Groves, 1996) and WCST Shifting performance was unimpaired in one study on ketamine users (Liang et al., 2013).

Schizotypy

Studies researching the effect of schizotypy on executive function either employ a categorical or a correlational design. Categorical studies allocate individuals to discrete groups, based on their quantitative level of schizotypy. Correlational studies make full use of the variance of schizotypy and do not allocate subjects to discrete groups.

Most studies employ psychometric questionnaires, such as the SPQ or the O-LIFE, to assess schizotypy (Aguirre, Sergi, & Levy, 2008; Beech & Claridge, 1987; Cimino & Haywood, 2008; Delawalla et al., 2006; Holahan & O'Driscoll, 2005; Larrison, Ferrante, Briand, & Sereno, 2000). Though some studies employ structured interviews, such as the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2002; Rosen, Woods, Miller, & McGlashan, 2002), to quantify schizotypy (Chen et al., 1998; Hazlett et al., 2014; Peeters et al., 2015).

Some studies report an overall score of schizotypy (aggregating levels on all three factors of schizotypy) (Bedwell, Kamath, & Baksh, 2006; Schmechtig, Lees, Grayson, et al., 2013; Spitznagel & Suhr, 2002), while others report one or more of the three schizotypy factors (positive, negative, disorganized) (Aichert, Williams, Möller, Kumari, & Ettinger, 2012; Ettinger et al., 2005; Mass, Bardong, Kindl, & Dahme, 2001).

There is evidence of fairly widespread, but subtle cognitive alterations in individuals with high levels of schizotypy (Ettinger et al., 2005, 2015; Gooding, 1999; Gooding, Kwapil, & Tallent, 1999; Karagiannopoulou et al., 2016; Koychev, El-Deredy, Haenschel, & Deakin, 2010; Matheson & Langdon, 2008; Mohr & Claridge, 2015; O'Driscoll, Lenzenweger, & Holzman, 1998; Park & Mctigue, 1997; Raine, Sheard, Reynolds, & Lencz, 1992), though results are somewhat diverse (Chun et al., 2013). When looking at the impact of schizotypy on Inhibition, some studies report a negative association between the level of schizotypy and the performance on tasks measuring Inhibition, meaning that the higher the schizotypy score is, the worse the performance on Inhibition tasks. This has been reported for overall schizotypy (Koychev et al., 2016; Völter et al., 2012; Zou et al., 2014), positive schizotypy (Beech & Claridge, 1987; Ferraro & Okerlund, 1996; O'Driscoll et al., 1998), negative schizotypy (Ettinger et al., 2005; Gooding et al., 1999; Gooding, Matts, & Rollmann, 2006; Völter et al., 2012) and disorganized schizotypy (Ettinger et al., 2005; Smyrnis et al., 2003; Völter et al., 2012). In contrast, some studies find no or only weak association between schizotypy level and Inhibition, again this has been reported for overall

schizotypy (Bedwell et al., 2006; Bergida & Lenzenweger, 2006; García-Montes, Noguera, Alvarez, Ruiz, & Cimadevilla Redondo, 2014), positive schizotypy (Cochrane, Petch, & Pickering, 2012; Kerns, 2006; Lenzenweger, 2001), negative schizotypy (Bergida & Lenzenweger, 2006; Kane et al., 2016; Smyrnis et al., 2003) and disorganized schizotypy (Bedwell, Kamath, & Compton, 2009; Bergida & Lenzenweger, 2006; Mass et al., 2001). Finally, few studies even show a positive association between schizotypy level and Inhibition, results which have been reported for overall schizotypy (Wilson, Christensen, King, Li, & Zelazo, 2008), positive schizotypy (Moritz & Mass, 1997; Watson & Tipper, 1997), negative schizotypy (Delawalla et al., 2006; Zouraraki, Karamaouna, Karagiannopoulou, & Giakoumaki, 2017) and disorganized schizotypy (Zouraraki et al., 2017).

When looking at the impact of schizotypy on Shifting, some studies report a negative association between the level of schizotypy and the performance on tasks measuring Shifting, meaning that the higher the schizotypy score is, the worse the performance on Shifting tasks. This has been reported for overall schizotypy (Cimino & Haywood, 2008; Daneluzzo, Bustini, Stratta, Casacchia, & Rossi, 1998; Koychev et al., 2010), positive schizotypy (Gooding et al., 1999; Gooding, Tallent, & Hegyi, 2001; Suhr, 1997; Tallent & Gooding, 1999; Zouraraki et al., 2017), and negative schizotypy (Gooding et al., 1999, 2001; Louise et al., 2015; Tallent & Gooding, 1999). In contrast, some studies find no or only weak association between schizotypy level and Shifting, this has been reported for overall schizotypy (Chan, Wang, et al., 2011; Hori, Matsuo, et al., 2012; Jahshan & Sergi, 2007), positive schizotypy (Delawalla et al., 2006; Dinn, Harris, Aycicegi, Greene, & Andover, 2002; Matheson & Langdon, 2008), negative schizotypy (Cappe, Herzog, Herzig, Brand, & Mohr, 2012; Chan, Yan, et al., 2011; Mass et al., 2001) and disorganized schizotypy (Hori, Teraishi, et al., 2012; Mass et al., 2001; Zouraraki et al., 2017). Finally, few studies even show a positive association between schizotypy level and Shifting, results which have been reported for overall schizotypy (Wilson et al., 2008), positive schizotypy (Freeman et al., 2012) and negative schizotypy (Matheson & Langdon, 2008).

When looking at the impact of schizotypy on Updating, some studies report a negative association between the level of schizotypy and the performance on tasks measuring Updating, meaning that the higher the schizotypy score is, the worse the performance on Updating tasks. This has been reported for overall schizotypy (Cohen, Iglesias, & Minor, 2009; MacAulay & Cohen, 2013; Marsh, Vachon, & Sörqvist, 2017), positive schizotypy (Kane et al., 2016; Schmidt-Hansen, Killcross, & Honey, 2009; Tallent & Gooding, 1999) and negative schizotypy (Gooding & Tallent, 2003; Kane et al., 2016; Tallent & Gooding, 1999). In contrast, some studies find no or only weak associations between schizotypy level and Updating, again this has been reported for overall schizotypy (Daly, Afroz, & Walder, 2012; Freeman et al., 2012; Wang et al., 2008),

positive schizotypy (Delawalla et al., 2006; Hori, Teraishi, et al., 2012; Noguchi, Hori, & Kunugi, 2008), negative schizotypy (Delawalla et al., 2006; Hori, Teraishi, et al., 2012; Matheson & Langdon, 2008) and disorganized schizotypy (Daly et al., 2012; Freeman et al., 2012; Matheson & Langdon, 2008) . Finally, few studies even show a positive association between schizotypy level and Updating, results which have been reported for overall schizotypy (Park & Mctigue, 1997), positive schizotypy (Avons, Nunn, Chan, & Armstrong, 2003) and negative schizotypy (Park & Mctigue, 1997).

1.3 Oculomotor Control

Studying eye movements provides information about brain functions and can be a useful diagnostic tool (Leigh & Zee, 2015). Humans depend on vision and focused attention to make prompt and correct responses to our environment. Eye movements reflect the central role that vision plays in our survival (Leigh & Zee, 2015). Eye movements are easier to interpret than other types of movements, which makes them especially useful in research: They are easier to interpret for several reasons: Eye movements are, due to the nature of the eye, essentially restricted to rotational movements, while linear displacements are negligible (Leigh & Zee, 2015).The relationship between motor neuron discharge and eye movements is relatively simple (Anderson, Lepora, Porrill, & Dean, 2010; Fuchs & Luschei, 1970). Different classes of eye movements can be distinguished on the basis of their visual function, physiological properties and anatomical substrates (Leigh & Zee, 2015). Abnormalities of eye movements are distinctive and often easy to attribute to specific pathophysiology. Eye movements are readily accessible, even in clinical settings with severely impaired patients (Leigh & Zee, 2015).

Eye movements have helped to further our understanding of a wide range of disorders (Hebert, Daniel, & McLoon, 2013; Jones & Klin, 2013; Kennard, Leigh, & Imperial College, 2008; Knight & Fuchs, 2007; Leigh & Zee, 2015) and eye movement research has provided insight into a wide variety of cognitive functions (Adam et al., 2013; Hikosaka & Isoda, 2010; Leigh & Zee, 2015; Meyhöfer, Kasparbauer, Steffens, & Ettinger, 2019; Nachev, Rees, Parton, Kennard, & Husain, 2005).

Eye movements can be divided into different classes with different main functions, see table 4 for an overview. It would be beyond the scope of this thesis to examine all classes of eye movements in regards to psychosis and model systems of psychosis. This chapter will focus on SPEM, because SPEM performance deficits in psychosis, especially in schizophrenia patients, is a frequently and widely replicated finding (Franco, de Pablo, Gaviria, Sepúlveda, & Vilella, 2014; Hong et al., 2008; Hutton & Kennard, 1998; Lencer et al., 2004; Levy, Holzman, Matthysse, & Mendell, 1993, 1994; Levy, Sereno, Gooding, & O'Driscoll, 2010; Tandon, 1999; Thaker et al.,

2000). It should be noted that the executive function Inhibition, as discussed in chapter 1.2, which can be measured using manumotor tasks such as the computerized Stroop task (Miyake et al., 2000), can also be measured using saccadic eye movements (Hutton, 2008; Hutton & Ettinger, 2006). Eye movements as a means to investigate Inhibition will be discussed further in section 2.2.3.

Table 4. Functional classes of eye movements.
Abridged from Leigh & Zee (2015)

Eye Movement Class	Main Function
Smooth Pursuit Eye Movements	Holding the image of a small moving target on the fovea
Saccades	Bringing images of objects of interest onto the fovea
Visual Fixation	Holding the image of a stationary object on the fovea
Vergence	Moving the eyes in opposite directions to hold the image of one object on the fovea of each eye simultaneously
Nystagmus quick phases	Resetting the eyes during prolonged rotation and direct gaze toward the oncoming visual scene
Optokinetic Eye Movements	Holding images of the visual world steady on the retina during sustained head motion (rotation, translation)
Vestibular Eye Movements	Holding images of the visual world steady on the retina during brief head movement (rotation, translation)

Smooth Pursuit Eye Movements

SPEM hold the image of a small moving target on the fovea (Leigh & Zee, 2015). Generating SPEM follows two phases: The open-loop and the closed-loop phase (Lisberger, Morris, & Tychsen, 1987). About 100 ms after the stimulus begins its movement, SPEM are initialized (Robinson, 1965). The first approximately 100 ms of SPEM is the open-loop phase, in which SPEM are primarily guided by the perception of target motion across the retina (Lisberger & Westbrook, 1985). After these first 100 ms, the closed-loop phase of SPEM begins. Here, retinal slip velocity is used as a feedback control for eye movements (Lisberger et al., 1987). In closed-loop SPEM, retinal slip velocity and extra-retinal input (prediction, anticipation) is used to

perform SPEM. The closed-loop phase of SPEM can best be measured using a triangular or sinusoidal target movement (Barnes, 2008).

SPEM can be disrupted by saccadic eye movements. These can either be compensatory or intrusive in nature (Levy et al., 2010). Compensatory saccades, namely catch-up or back-up saccades, during SPEM reduce the position error by quickly repositioning the eyes onto the target. Intrusive saccades, namely anticipatory saccades, leading saccades or square wave jerks during SPEM increase the position error of the eye (Leigh & Zee, 2006; Levy et al., 2010).

Lencer and Trillenberg (2008) give an overview of the neuronal substrates of SPEM. SPEM are primarily realized in early visual areas, the motion perception area V5 (Dukelow et al., 2001; Mukherjee, Battifarano, Simoncini, & Osborne, 2015), the frontal eye fields (Fukushima et al., 2002; Gagnon, Paus, Grosbras, Pike, & O'Driscoll, 2006; Rosano et al., 2002; Tanaka & Lisberger, 2001), the supplementary eye fields (Gagnon et al., 2006; Lencer, Nagel, Sprenger, Heide, & Binkofski, 2005; Missal & Heinen, 2004; Schmid, Rees, Frith, & Barnes, 2001) and the parietal eye fields (Lencer et al., 2005; Nagel, Sprenger, Hohagen, Binkofski, & Lencer, 2008; Nagel et al., 2006; Schmid et al., 2001). Figure 4 shows an overview of brain activation measured with fMRI during SPEM.

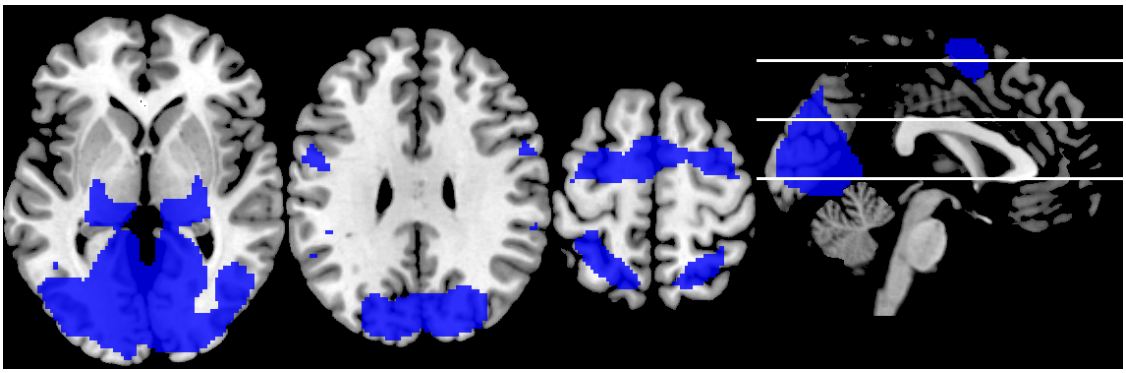

Figure 4. SPEM Network of task related activity > baseline activity (fixation).

A number of dependent variables can be employed when measuring SPEM performance: Smyrnis (2008) give an overview of all variables. In general, variables are classified as either global measures or specific measures. Global measures include SPEM as well as the saccadic eye-movements disrupting SPEM. The most commonly used global measure is the root mean square error (RMSE), the global error of eye compared to target position. RMSE has been used as a helpful diagnostic tool to quantify SPEM deficits in clinical populations, including psychosis patients (Clementz, Iacono, & Grove, 1996), but they do not allow for specific interpretations of the underlying mechanism of these deficits. If SPEM RMSE is reduced, this can be due to either impairments which disturb following the target or disturb the sufficient suppression of the

saccadic system (Abel & Ziegler, 1988). In contrast, specific measures specifically quantify either the ability to follow the target using SPEM or how well the saccadic system is suppressed during SPEM: The most widely used measure to quantify how well SPEM follow the target is the velocity gain, which is a measure of how well the eye velocity during SPEM matches the velocity of the target (Smyrnis, 2008). The most widely used measure of how well the saccadic system is suppressed during SPEM is the number of saccadic intrusions per second (Smyrnis, 2008).

1.3.1 Oculomotor Control in Psychosis

SPEM deficits in psychosis patients has been shown as early as 1908 (Diefendorf & Dodge, 1908), results which, many years later, were replicated using more modern techniques of measuring SPEM (Holzman, Proctor, & Hughes, 1973). Since then, SPEM performance deficits in psychosis, especially in schizophrenia patients, have been replicated many times (Franco et al., 2014; Hong et al., 2008; Hutton & Kennard, 1998; Lencer et al., 2004; Levy et al., 1993, 1994, 2010; Tandon, 1999; Thaker et al., 2000) and a comprehensive meta-analysis of 57 studies found high effect sizes for deficits in global SPEM variables (Cohen's *d*=0.70-1.55), velocity gain (Cohen's *d*=0.87) and frequency of leading saccades (Cohen's *d*=1.31) (O'Driscoll & Callahan, 2008). Interestingly, SPEM deficits in schizophrenia remain stable over time (Benson et al., 2012), are mostly independent from clinical symptoms of schizophrenia (Lencer et al., 2015) and are hardly influenced by current antipsychotic medication (Lencer et al., 2015). Importantly, SPEM impairments in schizophrenia patients have been reported as associated with reduced social and occupational functioning (Beiser et al., 1994).

Globally, SPEM deficits have been described in schizophrenia patients as reduced SPEM quality (Amador et al., 1991; Y Chen et al., 1999), higher signal to noise ratio (Allen, 1997; Benson et al., 2012; Kelly et al., 1990) and increased global position error (Benson et al., 2012; Lee, Williams, Loughland, Davidson, & Gordon, 2001; Sponheim, Iacono, Thuras, Nugent, & Beiser, 2003; Sweeney et al., 1994). Low velocity gain is the most frequently reported SPEM deficit in schizophrenia patients (Bagary et al., 2004; Boudet et al., 2005; Fabisch et al., 2009; Haraldsson et al., 2008; Ivleva et al., 2014; Kathmann, Hochrein, Uwer, & Bondy, 2003; Lencer et al., 2015, 2004; Louchart-De La Chapelle et al., 2005; Morita et al., 2017; Nagel et al., 2007; Irene Nkam et al., 2010; Sprenger, Trillenberg, Nagel, Sweeney, & Lencer, 2013; Trillenberg et al., 2017). Schizophrenia patients also show more saccadic intrusions during SPEM (Allen, 1997; Campion et al., 1992; Haraldsson et al., 2009, 2008; Mather, Neufeld, Merskey, & Russell, 1992). The higher number of saccadic intrusion are caused by higher rates of catch-up saccades, anticipatory saccades (Friedman, Jesberger, Abel, & Meltzer, 1992; Ross, Olincy, Harris, Sullivan, & Radant, 2000; Spengler et al., 2006; Sweeney et al., 1993) and leading saccades (Martin et al., 2007; Ross et al., 2002; Ross, Olincy, & Radant, 1999; Ross et al., 2000). In contrast, square

wave jerks and back-up saccades have generally been shown to be no more frequent in schizophrenia patients than in healthy controls (Campion et al., 1992; Clementz, Sweeney, Hirt, & Haas, 1990; Flechtner, Steinacher, Sauer, & Mackert, 2018; Litman, Hommer, Radant, Clem, & Pickar, 1994; Nkam et al., 2001; Radant & Hommer, 1992; Sweeney et al., 1993).

SPEM deficits have been reported not only for schizophrenia patients, but other phenotypes of psychosis. Namely, in schizoaffective patients (Martin et al., 2007) and affective psychosis patients (Kathmann et al., 2003; Lencer et al., 2010; Lencer, Trillenberg-Krecker, Schwinger, & Arolt, 2003), though deficits in schizophrenia have generally been more severe (Amador et al., 1991; Lencer et al., 2015, 2004). In contrast, SPEM have been found intact in patients with non-psychotic affective disorders (Abel, Friedman, Jesberger, Malki, & Meltzer, 1991; Fabisch et al., 2009; Friedman et al., 1995) and many other psychiatric conditions, such as substance use disorders (Kathmann, Wagner, Rendtorff, Schöchlin, & Engel, 1995; Radant & Hommer, 1992), ADHD (Ross et al., 2000), and OCD (Jaafari et al., 2011).

Cognitive processes that are important for the execution of SPEM are attention, motion processing, predicting and anticipating movement (Leigh & Zee, 2015; Lencer et al., 2015; Trillenberg et al., 2017). There is evidence that motion processing is impaired in schizophrenia patients (Lencer et al., 2010, 2015; Trillenberg et al., 2017). Schizophrenia patients also demonstrate deficits in predicting and anticipating movement (Avila, Hong, Moates, Turano, & Thaker, 2006; Spering, Dias, Sanchez, Schütz, & Javitt, 2013), though one study found that schizophrenia patients demonstrated unimpaired movement anticipation and prediction, but impaired visuomotor transformation during visually guided pursuit (Trillenberg et al., 2017). The dysconnectivity hypothesis, proposed by Friston and colleagues (Friston et al., 2016) suggests that movement prediction may be impaired because of an imbalance between the precision which is afforded sensory prediction errors and that which is afforded higher order prediction errors (Friston et al., 2016). On a neuronal level, SPEM impairments in schizophrenia are associated with lower brain activation in the V5 (Hong et al., 2005; Lencer et al., 2005; Nagel, Sprenger, Steinlechner, Binkofski, & Lencer, 2012) as well as the frontal and supplementary eye fields (Hong et al., 2005; Keedy, Ebens, Keshavan, & Sweeney, 2006; Tregellas et al., 2004).

1.3.2 Oculomotor Control in Model Systems of Psychosis

Ketamine

Literature on the impact of ketamine on SPEM performance is somewhat sparse. SPEM performance deficits have been reported in healthy volunteers during acute ketamine administration: On a specific level, velocity gain was shown to be reduced, and saccadic frequency was increased (Avila, Weiler, Lahti, Tamminga, & Thaker, 2002; Radant, Bowdle,

Cowley, Kharasch, & Roy-Byrne, 1998; Schmechtig, Lees, Perkins, et al., 2013; Weiler, Thaker, Lahti, & Tamminga, 2000). These deficits have been shown to be dose-dependent (Radant et al., 1998), with higher doses causing more pronounced deficits, and they have been reported for doses as low as 50ng/ml racemic ketamine plasma concentration and as high as 200ng/ml racemic ketamine plasma concentration (Avila et al., 2002; Radant et al., 1998; Schmechtig, Lees, Perkins, et al., 2013; Weiler et al., 2000). Ketamine users, however, do not show deficits in SPEM performance (Morgan, Huddy, et al., 2009). The neural mechanisms mediating SPEM deficits under ketamine are as of yet unknown. Understanding these underlying neuronal mechanisms is important for the evaluation of ketamine administration as a psychosis model and to further elucidate the role of the NMDA receptors for oculomotor control.

Schizotypy

SPEM performance deficits have been reported for high levels of overall schizotypy (Koychev et al., 2016; Schmechtig, Lees, Grayson, et al., 2013; van Kampen, Deijen, Kampen, & Deijen, 2009), positive, negative and disorganized schizotypy (Gooding, Miller, & Kwapil, 2000; Holahan & O'Driscoll, 2005; Kattoulas et al., 2011; Lenzenweger et al., 2006; Smyrnis et al., 2007). SPEM deficits in individuals with high levels of schizotypy have been reported for categorical studies comparing high and low schizotypal individuals as well as high and medium schizotypal individuals (Gooding et al., 2000; Holahan & O'Driscoll, 2005; Kattoulas et al., 2011; Koychev et al., 2016; Simons & Katkin, 1985; Smyrnis et al., 2007; van Kampen et al., 2009). SPEM deficits have also been reported in correlative studies (Kattoulas et al., 2011; Kelly, Bakan, Kelley, & Bakan, 1999; Lenzenweger et al., 2006; Smyrnis et al., 2007). However, it is worth noting that some studies found intact SPEM performance in individuals with high levels of schizotypy (Blackwood et al., 1994; Schmechtig, Lees, Grayson, et al., 2013; Thaker, Cassady, Adami, Moran, & Ross, 1996).

SPEM deficits in individuals with high levels of schizotypy have been reported using global SPEM measures, specifically overall lower quality of SPEM (Holahan & O'Driscoll, 2005; O'Driscoll et al., 1998; Simons & Katkin, 1985) and a higher RMSE (Gooding et al., 2000; Smyrnis et al., 2007; van Kampen et al., 2009). SPEM deficits have also been quantified using specific SPEM measures, namely lower velocity gain (Gooding et al., 2000; Holahan & O'Driscoll, 2005; Kattoulas et al., 2011; Koychev et al., 2016) and a higher frequency of saccade rate (Lenzenweger et al., 2006; Smyrnis et al., 2007). There is some evidence that higher saccadic frequency during SPEM in individuals with high levels of schizotypy is based on higher catch-up saccade rates (Lenzenweger et al., 2006), but not higher anticipatory saccade rates (Gooding et al., 2000).

There is very little literature on the neuronal correlates of SPEM deficits in individuals with high levels of schizotypy. One study demonstrated lower BOLD activation in early sensory regions of the occipital lobe, as well as in motion perception region V3A and regions associated with attentional processing (middle occipital gyrus and fusiform gyrus), but no altered BOLD in frontal motor areas (frontal eye fields) during SPEM (Meyhöfer et al., 2015).

1.4 Memory

Human declarative memory relies heavily on hippocampus function. The function of the hippocampus first became clear when patient HM, who was suffering from epilepsy, had a bilateral resection of the medial temporal lobe and developed full anterograde amnesia (Milner, 1972; Scoville & Milner, 2000). This case complemented findings in animal studies which demonstrated the important role of the hippocampus and its surrounding medial temporal cortex structures in memory (Málková, Bachevalier, Mishkin, & Saunders, 2001; Squire, Stark, & Clark, 2004). The hippocampal formation (figure 5) is thought to be the neurological basis of declarative memory, but not other kinds of memory (Gabrieli, 1998; Scoville & Milner, 2000; Squire, 1992). The hippocampus contains pyramidal cell layers which are densely packed with glutamatergic excitatory neurons with a low firing threshold, which gives the hippocampal formation a high capacity for plasticity (Tamminga, Stan, & Wagner, 2010).

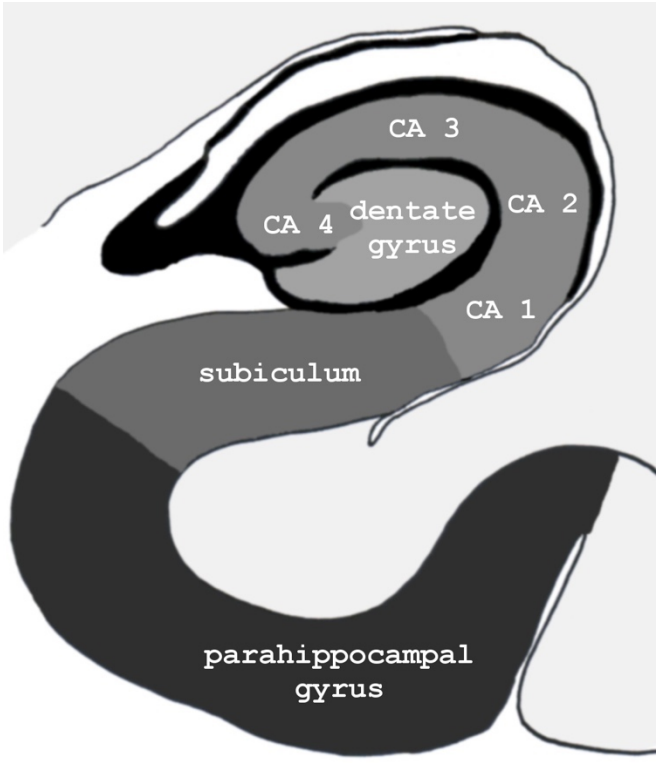

Figure 5. Schematic illustration of the hippocampal formation.

The hippocampus formation binds input from multiple neocortical regions into an integrated, flexibly addressable memory trace. In this regard, the hippocampal formation is where uni- and multimodal neocortical inputs converge (McClelland, McNaughton, & O'Reilly, 1995; Norman & O'Reilly, 2003). This process of conjunctive encoding makes pattern completion during the retrieval process possible: At retrieval, a memory can be retrieved from partial input (Lavenex & Amaral, 2000; Tamminga et al., 2010). Memory function in the hippocampus is realized via the mostly unidirectional trisynaptic pathway, a excitatory projection from entorhinal cortex to the dentate gyrus to the cornu ammonis 3 to the cornu ammonis 1 (Witter, Wouterlood, Naber, & Van Haeften, 2006).

The dentate gyrus and the cornu ammonis 3 play an important role in pattern separation, meaning events which are novel, but similar to past events, are encoded as unique (Leutgeb & Leutgeb, 2007; O'Reilly & McClelland, 1994). Declarative memory, episodic memory in particular, requires one-shot learning. This seems to be realized mainly via the widespread collateral connections within the cornu ammonis 3. Here, co-occurring inputs from an event are rapidly bound into one memory trace. This makes for a powerful auto-associative learning mechanism (Nakazawa et al., 2002, 2003; Rajji, Chapman, Eichenbaum, & Greene, 2006; Tamminga et al., 2010). The pyramidal layers of the hippocampus are densely packed with glutamatergic excitatory neurons. These project within the hippocampus and have a low firing threshold, which gives the structure great capacity for plasticity. NMDAR are the primary receptors involved in these projections (Greene, 2001; Tamminga et al., 2010). Therefore glutamatergic projections in the hippocampus play an essential role in the formation of declarative memory (Tamminga et al., 2010).

Human fMRI studies show evidence that the hippocampus and its surrounding perirhinal, parahippocampal and entrorhinal cortex are activated in response to novel stimuli. If participants have to later discriminate between novel and previously encountered stimuli, the discrimination ability depends to no small extent on the strength of the encoded memory. This encoding strength seems to be influenced by subjective perception of stimulus familiarity (Brown & Aggleton, 2001; Davachi, Mitchell, & Wagner, 2003; Kirwan & Stark, 2004; Mayes, Montaldi, & Migo, 2007; Ranganath et al., 2004; Rugg & Yonelinas, 2003; Tamminga et al., 2010).

Consistent with these findings on the role of glutamate signaling and particularly NMDAR function in declarative memory, NMDAR antagonists have been shown to disrupt memory performance (Ghoneim, Hinrichs, Mewaldt, & Petersen, 1985; Harris, Biersner, Edwards, & Bailey, 1975; Hartvig et al., 1995; Hetem, Danion, Diemunsch, & Brandt, 2000; Krystal et al.,

1994; Malhotra et al., 1996; Newcomer, Farber, et al., 1999b; Pfenninger, Durieux, & Himmelseher, 2002; Puma, Baudoin, & Bizot, 1998). This effect is especially pronounced for the acquisition of novel information (Newcomer, Farber, & Olney, 2000).

1.4.1 Memory in Psychosis

Declarative memory is one of the most consistently impaired functions in schizophrenia (Keefe et al., 1997; Nuechterlein et al., 2004; Ragland et al., 2009; Ranganath, Minzenberg, & Ragland, 2008; Saykin et al., 1991; Stone, Gabrieli, Stebbins, & Sullivan, 1998; Tamminga et al., 2010). The association between hippocampus dysfunction and illness manifestation have been replicated many times (Barch, 2005; Goghari, Sponheim, MacDonald, & III, 2010; Heckers, 2001; Lisman et al., 2008; Lodge & Grace, 2008; Olincy et al., 2006; Preston, Shohamy, Tamminga, & Wagner, 2005; Ranganath et al., 2008). Conjunctive representation has been found to be impaired in schizophrenia, including impairments of inferential use of knowledge, recall relative to item recognition, memory for source or context of an experience relative to item memory and recognition based on the recollection of event details relative to its perceived familiarity (Aleman, Hijman, de Haan, & Kahn, 1999; Danion, Rizzo, & Bruant, 1999; McCarley et al., 1993; Modinos, Ormel, & Aleman, 2010; Shohamy et al., 2010; Tamminga et al., 2010; Titone, Ditman, Holzman, Eichenbaum, & Levy, 2004; Weiss et al., 2006, 2004). Memory deficits in schizophrenia occur early in the course of the illness, they are largely unaffected by antipsychotic treatment and quantitatively large compared to other cognitive deficits in schizophrenia (Cannon et al., 1994; Gruzelier, Seymour, Wilson, Jolley, & Hirsch, 1988; Newcomer, Craft, et al., 1999; Saykin et al., 1991, 1994). It is worth noting that unaffected first-degree relatives of schizophrenia patients also show impaired performance on various memory tests (Whyte, McIntosh, Johnstone, & Lawrie, 2005).

Psychosis is associated with several hippocampal alterations: Anatomically, the size of hippocampus is reduced bilaterally in schizophrenia (Becker et al., 1996; Bilder et al., 1995; Bogerts et al., 1990; Suddath et al., 1989), with reductions usually found to be larger in hippocampus than anywhere else in the brain (Honea, Crow, Passingham, & Mackay, 2005; Steen, Mull, McClure, Hamer, & Lieberman, 2006). Reduced hippocampus volume has also been reported for non-affected first-degree relatives of schizophrenia patients (Tepest, Wang, Miller, Falkai, & Csernansky, 2003), schizophrenia high risk individuals (Lawrie et al., 2001; van Erp et al., 2004) and patients suffering from psychotic bipolar disorder (Strasser et al., 2005). Hippocampus volume reductions have been reported as early as first episode schizophrenia (Narr et al., 2004; Szeszko et al., 2003) and seems to be independent from antipsychotic drugs (Panenka et al., 2007).

On a brain functional level, BOLD activation has been shown to be reduced in the hippocampal formation during performance in a variety of different declarative memory task in schizophrenia patients (Achim et al., 2007; Eyler Zorrilla, Jeste, Paulus, & Brown, 2003; Heckers et al., 1998; Heckers, Zalesak, Weiss, Ditman, & Titone, 2004; Holt et al., 2005; Jessen et al., 2003; Leube et al., 2003; Ongür et al., 2006; Thermenos et al., 2007; Weiss et al., 2004, 2003). At a network level, the medial temporal lobe and prefrontal cortex connectivity has been found to be reduced in schizophrenia (Fletcher, 1998; Meyer-Lindenberg et al., 2005; Molina, Sanz, Sarramea, Benito, & Palomo, 2005).

On the cellular and neurochemical level, though it seems that there is no singular molecular pathology of glutamate in schizophrenia (Reif et al., 2006; Steffek, Haroutunian, & Meador-Woodruff, 2006), glutamate transmission has been shown to be regionally altered in the medial temporal lobe (Crook, Tomaskovic-Crook, Copolov, & Dean, 2000; Steffek et al., 2006). Specifically, the neurogenesis in the dentate gyrus seems to be reduced, which may lead to an imbalance between pattern separation and pattern completion (Clelland et al., 2009). The number of synapses from the dentate gyrus to cornu ammonis 3 neurons has been shown to be reduced in schizophrenia (Kolomeets, Orlovskaya, Rachmanova, & Uranova, 2005; Kolomeets, Orlovskaya, & Uranova, 2007). Additionally, a subunit of the NMDAR is selectively reduced in the dentate gyrus in schizophrenia (Eastwood et al., 1995; Gao et al., 2000; Law & Deakin, 2001; Porter, Eastwood, & Harrison, 1997). Seeing as the dentate gyrus is the gateway of the trisynaptic pathway, it makes sense to assume that these neurochemical and cellular alterations would lead to memory impairment (Tamminga et al., 2010). Therefore, while the dopamine model of psychosis does not account well for hippocampal dysfunction, it is in line with the NMDAR dysfunction hypothesis of psychosis (Javitt et al., 2012; Tamminga et al., 2010).

Emotional information has been shown to reliably enhance memory when compared to neutral information (Dolcos, LaBar, & Cabeza, 2004; LaBar & Cabeza, 2006). Neuroimaging studies indicate that there is a high overlap between NMDAR-rich regions and emotional memory networks, with successful encoding associated with increased activity in hippocampal, fusiform and prefrontal regions and the emotional enhancement relative to neutral information depending on hippocampal formation and the amygdala (Hermans et al., 2014; Kim, 2011; Murty, Ritchey, Adcock, & LaBar, 2010). Higher-order emotional processing has been shown to be impaired in schizophrenia (Marwick & Hall, 2008; McCleery et al., 2015), while immediate emotional experience has been found to be intact (André Aleman & Kahn, 2005; Kring & Moran, 2008). Findings on specific impairments of the emotional memory effect in schizophrenia are inconsistent, with effects ranging from unspecific impairments (Hall, Harris, McKirdy, Johnstone,

& Lawrie, 2007; Lakis et al., 2011) to highly selective impairments for positive information only (Herbener, Rosen, Khine, & Sweeney, 2007).

1.4.2 Memory in Model Systems of Psychosis

Ketamine

NMDAR antagonists disrupt memory performance (Ghoneim et al., 1985; Harris et al., 1975; Hartvig et al., 1995; Hetem et al., 2000; Krystal et al., 1994; Malhotra et al., 1996; Newcomer, Farber, et al., 1999a; Pfenninger et al., 2002; Puma et al., 1998), particularly prominently in the acquisition of novel information (Newcomer et al., 2000). One study found robust, dose-dependent impairments of verbal memory, non-verbal memory and declarative memory under ketamine administration at 13.5ng/ml, 45ng/ml and 150ng/ml ketamine plasma level. At the lowest dose, participants did not exhibit schizophrenia-like symptoms, but already showed memory impairments (Newcomer, Craft, et al., 1999). One study demonstrated that impairments in immediate and delayed memory recall tasks under ketamine administration were mainly a result of interference with the retrieval process (Ghoneim et al., 1985). A study with ketamine dependent patients found that patients addicted to ketamine, who exhibited persistent psychosis symptoms, showed impaired declarative verbal memory similar to the deficits exhibited by schizophrenia patients, while those without persistent psychosis symptoms did not (Cheng et al., 2018).

On a brain functional level, ketamine administration in humans interferes with memory-related neural circuity (Grimm et al., 2015; Honey et al., 2005; Wong, O'Daly, Mehta, Young, & Stone, 2016). Ketamine has also been shown to impair emotional memory and on a brain functional level, namely to alter amygdala and prefrontal functioning during the performance of emotional memory tasks (Abel et al., 2003; Ebert, Haussleiter, Juckel, Brüne, & Roser, 2012; Schmidt, Kometer, Bachmann, Seifritz, & Vollenweider, 2013). Ketamine administration has been linked to stronger fear conditioning (Corlett et al., 2013). However, so far, literature on the effect of ketamine administration on emotional memory is sparse.

Schizotypy

There is relatively little literature on the impact of high levels of schizotypy on emotional memory and most studies focus on trauma—like memory phenomena, such as intrusive emotional memories (Hoshi, Scoales, Mason, & Kamboj, 2011). Some studies have examined emotional memory in individuals with high levels of schizotypy by measuring the memory for narrative elements of emotional studies presented as a video or a narrated slide-show (J. Brown, Brignell, Dhiman, Curran, & Kamboj, 2010). This approach leads to measurable increase

in arousal and allows for the examination of complex memory phenomena (Hoshi et al., 2011). One study found an association of trait dissociation with an increased rate of commission errors in an emotional story task (Candel, Merckelbach, & Kuijpers, 2003). While not direct evidence of a correlation between high schizotypy levels and impaired emotional memory, the results of this study are an indicator of a possible association, because trait dissociation strongly correlates with high levels of positive schizotypy (Merckelbach, Rassin, & Muris, 2000). Trait dissociation and high levels of positive schizotypy are also associated with greater levels of traumatic intrusions after watching a traumatic video (Holmes & Steel, 2004). This effect may represent a higher level of perceptually-based, sensory-driven memory over conceptually-based memory under high levels of emotional arousal (Holmes & Steel, 2004). This shift towards more perceptually-driven memory and higher rates of traumatic intrusions in individuals with high levels of schizotypy may be an expression of aberrant salience (Hoshi et al., 2011; Nelson, Whitford, Lavoie, & Sass, 2014).

One study, which included 28 high positive schizotypals (measured via the unusual experiences scale of the O-LIFE) and 39 non-highly schizotypals, found that participants with low levels of positive schizotypy demonstrated better performance of recall memory and recognition memory for emotional elements compared to non-emotional elements of a story. In contrast, high positive schizotypes did not show an enhancement of recall memory for emotional elements of the story. There was no difference in the recognition memory performance for emotional story elements between high and low positive schizotypes. This suggests, that the difference in emotional memory between high and low positive schizotypes is most prominent for strategic, effortful memory processes. Interestingly, there was no difference in emotional memory between high negative schizotypes (measured via the introvertive anhedonia scale of the O-LIFE) and low negative schizotypes (Hoshi et al., 2011). The study also did not find increased intrusive memories after the emotional narrative task, as was reported in earlier research (Holmes & Steel, 2004). The authors explain this with the significantly less distressing stimuli of the paradigm used in their study (Hoshi et al., 2011).

1.5 Open Questions and Goals of This Thesis

Much about the mechanisms behind psychotic symptoms and syndromes is yet unknown (Javitt et al., 2012). Studying the development of psychotic disorders remains difficult, because of confounding factors such as treatment side effects, effects of hospitalization and that most patients are seen in later stages of illness (Barrantes-Vidal et al., 2015; Mason, 2015). Model systems of psychosis lack the confounds of patient research, such as medication and hospitalization (Lenzenweger, 2010) and can help to further our understanding of the

pathophysiology of psychotic disorders (Stone, 2011; Stone et al., 2010). In addition, currently available antipsychotic compounds have proven to be ineffective in treating cognitive symptoms (Chou et al., 2012; Hill et al., 2010; Keefe et al., 2013; Köster et al., 2014; Nielsen et al., 2015; Remington et al., 2016). This is concerning because cognitive symptoms are linked to global functioning of patients (Chang et al., 2016; Green, 2016; Rabinowitz et al., 2012). It is, therefore, vital to develop new treatments that are able to target this symptom domain. Translational model systems of psychosis, such as acute ketamine administration and individuals with high levels of schizotypy, are a well-established method to inform the development of improved treatments (Chavez-Noriega et al., 2002; Javitt et al., 2018, 2012; Krystal et al., 2003; Stone, 2011; Stone et al., 2010).

Acute ketamine infusion in healthy humans is an established state-model of psychosis (Javitt, 2010). Seeing as cognitive symptoms are linked to global function and currently difficult to treat, they are an important target in model system research. Among the cognitive symptoms of interest are executive functions, which have been reliably demonstrated to be impaired in psychosis patients (Bora et al., 2009; Dickinson et al., 2007; Green et al., 2004; Reichenberg & Harvey, 2007; Schaefer et al., 2013) and promising biomarkers of psychosis, chiefly SPEM (Levy et al., 2000, 2010). SPEM, as a measure of oculomotor control, have been reliably shown to be impaired in psychosis (Franco et al., 2014; Hong et al., 2008; Hutton & Kennard, 1998; Kathmann et al., 2003; Lencer et al., 2010, 2003, 2004; Levy et al., 1993; Martin et al., 2007). To better understand ketamine administration as a state model of psychosis, research must focus on the effect of ketamine administration on biomarkers such as impaired SPEM and cognitive symptoms such as impairments in executive functions and possible changes in neuronal activity during their execution (**publication 1, publication 2**).

Declarative memory is another cognitive function domain which has been shown to be impaired in psychosis (Javitt et al., 2012; Tamminga et al., 2010). As NMDAR dysfunction in the hippocampal formation has been functionally linked to memory impairments in psychosis (Tamminga et al., 2010), acute ketamine administration presents as a useful model system to further our understanding of impairments in this domain. Emotional facilitation of memory is a reliable effect in human declarative memory (Dolcos et al., 2004; LaBar & Cabeza, 2006). This effect has been shown to be impaired in psychosis (Hall et al., 2007; Herbener et al., 2007; Lakis et al., 2011). Seeing as neuroimaging studies indicate high overlap between NMDAR-rich regions and emotional memory networks (Hermans et al., 2014; Kim, 2011; Murty et al., 2010), acute ketamine administration presents as a promising model to further our understanding of this effect and its role in the symptomology of psychosis. To this end, emotional memory facilitation under ketamine administration needs to be investigated with a focus on neuronal

activity during the encoding phase, which is influenced most strongly by NMDAR function (publication 3).

High levels of schizotypy are a promising trait model of psychosis. Seeing as cognitive symptoms are important in the current development of new and more effective treatments, it is unfortunate that the schizotypy literature is inconsistent when it comes to executive functions and possible impairments in this cognitive domain. Sometimes, effects are marginal or unclear (see detailed literature review in chapter 1.2.2). Therefore, it is important to quantitatively assess all literature and include potential moderating variables to explain inconsistencies and shape a clearer view of the current state of research in this domain (publication 4).

To investigate these research goals, the work I report in this dissertation combines the methods of functional resonance imaging, eye-movement recording, computerized cognitive tasks and meta-analysis.

2 Methods

"Knowing that you're crazy doesn't make the crazy things stop happening."

- Mark Vonnegut

2.1 Pharmacological Functional Magnetic Resonance Imaging

2.1.1 Functional Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) was developed in the 1980s. Functional MRI (fMRI), which allows the measuring of hemodynamic changes after enhanced neuronal activity through magnetization differences in different types of tissues (Huettel, Song, & McCarthy, 2014; Logothetis, 2002), was then discovered in the early 1990s (Bandettini, 2012). fMRI has several important advantages: It is noninvasive, provides relatively high spatiotemporal resolution and can measure entire brain networks engaged in a particular task. However, fMRI measures a surrogate signal, not the actual brain activation, and this surrogate signal reflects neuronal mass activity, something that has to be considered when interpreting data from fMRI studies (Logothetis, 2008). Spatial specificity of fMRI increases with increasing magnetic field strength of the fMRI scanner (Logothetis, 2008).

The basis of the fMRI method is that many nuclei, among them those of the hydrogen atoms (i.e. in water), possess a quantum mechanical property called spin. Spins are randomly oriented, but when an external magnetic field is applied, they orient according to the external magnetic field, as this orientation is energetically more favorable. For this, the externally applied magnetic field has to be quite strong (commonly 1.5 to 3 Tesla in human studies). The number of parallel oriented spins to antiparallel oriented spins increases with the field strength of the magnetic field that is applied (Logothetis, 2008).

When a radiofrequency field is then applied, which rotates synchronously with the spins, the magnetization vector rotates away from the initial position along the z-axis by 90 degrees into the transverse. The transverse magnetization can be detected using a radio frequency receiver coil placed around the head of the subject. Additionally, to the reorientation, the introduction of the radio frequency field also causes phase coherence among the spins. This phase

coherence is short-lived as it decreases quickly as soon as the magnetic movements move out of phase due to the spins interacting among themselves. This means that the transverse magnetization decays exponentially. The processes causing this decay of the transverse magnetization are called relaxation. Different types of relaxation have been described, each reflecting a different interaction of the spins with each other and or their environment. Each of these relaxation processes are specified by their time constant (inverse of the relaxation rate). Relaxation rates differ depending on properties of the tissue, which is the basis of the MRI image contrast. The time between two radio frequency pulses is called repetition time (TR) (Logothetis, 2008).

The time-constant T1 describes the time it takes for 63% of the recovery of magnetization along the z-axis. Anatomical images (structural MR images) are usually generated using T1-weighted images, meaning that they are generated using the T1 time constant differences of gray and white brain matter. The time constant T2 describes the time it takes for 37% of the recovery of magnetization on the xy plane (transversal magnetization) caused by molecular interactions. In contrast to T2, which can be described as the "true" T2 constant, T2* is the "observed" T2 constant, which reflects the T2 constant as well as inhomogeneities in the magnetic field. Functional contrasts are often generated using T2*-weighted images, meaning that they are generated using the T2 time constant differences brought about by differences in blood oxygenation between test and control time windows. So, in short, changes over time in one or more relaxation rate at a single site can be used to measure changes in the physical-chemical state at that location (Logothetis, 2008).

Spatial localization is then achieved using smaller magnetic field gradients that are superimposed on the homogenous magnetic field of the scanner. Since the positions of protons within a location at different positions along the gradient field can be inferred by their difference in resonance. The decay signal is conventionally not measured immediately after the radiofrequency pulse but recovered using additional radiofrequency pulses. The time between the recovered signal and the (first) radiofrequency excitation pulse is called echo time (TE). The TR and the TE are used to determine the influence of the time-constants on the image contrast. All studies presented in this thesis use the gradient-echo echo-planar imaging (EPI) sequences method, which is very fast and efficient in tracking hemodynamic response (Logothetis, 2008).

fMRI is most commonly employed using the blood-oxygen-level-dependent (BOLD) contrast, which depicts differences in blood oxygenation. Discovered by Seiji Ogawa (Ogawa & Lee, 1990), this technique relies on the hemoglobin in blood. Hemoglobin in red blood cells is inhomogeneously distributed in the tissue. It is diamagnetic when oxygenated and

paramagnetic when reduced (Pauling & Coryell, 1936). The magnetic susceptibility of fully oxygenated arterial blood is as much as 20% lower than that of deoxygenated blood. This difference is the basis of the BOLD effect which is used to measure neuronal activity, as due to the architecture of blood vessels in the brain, an increase in neural activity in an area will lead to oxygenation changes in all blood vessels in this area (with the potential confound of downstream oxygenation in larger vessels) (Ances et al., 2008).

BOLD signal follows a specific temporal profile. It is important to note that BOLD signal does not correlate perfectly with the neuron firing rate. But there is a strong link between BOLD signal and pre-synaptic activity and action potentials in a region (Logothetis, 2008; Logothetis & Wandell, 2004). Additionally to the activity (firing) of neurons due to task execution, the BOLD signal is also influenced by an interplay between excitatory and inhibitory neuronal communication (Logothetis, 2008). Keeping this in mind, BOLD signal is nevertheless a very useful tool for measuring neuronal correlates of cognitive processes (Cabeza & Nyberg, 2000).

BOLD signal occurs with a latency of three to six seconds after the onset of neural activity. But this latency varies depending on the executed task and the involved brain region (Heeger & Ress, 2002). This delay is the reason why, in contrast to the good spatial resolution, fMRI has relatively poor temporal resolution (i.e. compared the electroencephalography). The BOLD response to a stimulus follows a specific temporal profile. The latency between activation onset and oxygenation can be described as an initial dip in BOLD signal. The response reaches its peak four to six seconds later. The signal returns to baseline after about 30 seconds. This temporal profile of the BOLD response has to be considered when designing fMRI tasks (Logothetis, 2008).

2.1.2 Pharmacological Functional Magnetic Resonance Imaging

To measure the modulation of regional brain activation by drugs, fMRI can be employed while administering a pharmacological compound (Stein, 2001; Wise & Tracey, 2006). BOLD signal does not directly reflect the molecular impact of the administered drug but can be used to draw conclusions on the effects of the compound on transmitter receptor systems and potential behavioral correlates of these changes (Honey & Bullmore, 2004; Wise & Tracey, 2006).

To observe effects of the pharmacological compound as free from confounding effects as possible, it is advisable to employ a double-blind placebo-controlled design. For this, a suitable placebo (compound without the agency of the drug) has to be found. In studies with ketamine for example, saline is a suitable placebo, as the ketamine intravenously injected in most studies is in solution in saline as well (Krystal et al., 1994). Some placebo compounds may purposely mimic certain undesired side effects of the drug (for example itching of nicotine patch in

nicotine studies) (Kasparbauer et al., 2016). Double-blind study designs ensure that neither the investigator nor the subject know which substance (drug or placebo) was administered. Usually, for this, a third person prepares the compound before examination. This minimizes potentially confounding effects of anticipation from both the investigator and the subject (Schmechtig, Lees, Perkins, et al., 2013).

A study can employ a within-subjects design, in which the drug is administered to all participants in one assessment session, and placebo is administered to all participants in the other assessment session (de Winter & Dodou, 2017). The administration should be counter-balanced, meaning half of the participants receive placebo first, half of the participants receive the drug first, to control for administration order effects. Alternatively, a study can employ a between-subjects design, which means half of the participants receive the drug, the other half of the participants receive placebo. This can minimize anticipation effects and repeated measure effects but comes with the drawback of between-subjects variance (de Winter & Dodou, 2017).

2.2 Recording and Analysis of Eye Movements

2.2.1 Video-Based Combined Pupil and Corneal Reflection Recording

Video-based combined pupil and corneal reflection (VCPCR) is one method of recording eye movements. It is one method among others (such as electro-oculography, a scleral lens/search coil and other video based oculography (Duchowski, 2017; Young & Sheena, 1975).

VCPCR is non-invasive, easily accessible and allows for a certain amount of head motion. Here, eye position is measured in relation to its orientation in space (measuring the point of regard) (Duchowski, 2017). The point of regard is inferred by the relative position of two reference points in the eye. The first is the pupil center, the second is the corneal reflection (usually first Purkinje image, which is the reflection of light on the outer part of the cornea). Both are located using infrared light which shines on the eye and a camera which captures the reflections of the infrared light on the eye. While the pupil shows minimal reflection, the corneal reflection is bright. When the eyes move and the head is kept stable, the corneal reflection remains stable but the pupil moves (Duchowski, 2017). This means that the relative positions of pupil center and corneal reflection indicate the point of regard. The sampling frequency (in Hz) of the eye tracker determines how many images per second are taken (Holmqvist et al., 2011).

Employing feature-based algorithms or model-based algorithms, the pupil and the corneal reflection are then segmented and geometric computations are used to map the position of the eye to the stimulus. For this, a spatial calibration procedure is used. During the calibration,

stimuli are presented on different positions of the computer screen. The participant is asked to look directly at the stimuli as they are presented. The relative location of the corneal reflection and the pupil are measured. These data then become the basis for the calculation of the estimated gaze position (Holmqvist et al., 2011).

Raw recorded eye movement data typically result in x and y coordinates in pixels (gaze position on the computer screen) and are often converted to degrees of visual angle. Events of interest, such as saccades and blinks, are then detected in the data using suitable criteria for the gaze position, the velocity of the eye movements and the acceleration of the eye (Holmqvist et al., 2011). Based on these events of interest, dependent variables of interest can be computed.

2.2.2 Dependent Eye Movement Measures: SPEM

The dependent measures for SPEM tasks employed in the research reported in this thesis are among the most widely used measures (Holmqvist et al., 2011):

Root Mean Square Error (RMSE): The deviation of eye position from target position in segments of pursuit and saccade execution. It is computed using the sum of the squared differences between eye and target position for each measured point in the segment. The square root of this sum is then divided by the number of measurement points to give the RMSE value (Holmqvist et al., 2011).

Velocity Gain (in %): The ratio between eye and target velocity including only segments of SPEM (usually time-weighted). Velocity gain is computed by dividing eye velocity by target velocity and multiplying the result by 100 (Holmqvist et al., 2011).

Saccade Frequency: The number of saccades interrupting SPEM. Saccadic frequency is usually a measure of all types of saccades occurring during SPEM, but different types of saccades can also be identified and measures can be calculated for each type of saccade (i.e. leading saccades). For this, saccades are commonly divided into intrusive saccades (which generally disrupt SPEM performance) and compensatory saccades (which help with SPEM performance). Saccadic frequency is commonly computed as the number of saccade per second of SPEM (Holmqvist et al., 2011).

2.2.3 Dependent Eye Movement Measures: Pro- and Antisaccades

The dependent measures for pro- and antisaccade tasks employed in the research reported in this thesis are among the most widely used measures (Holmqvist et al., 2011):

Direction Errors (in %): The rate of incorrect initial saccades after the presentation onset of a peripheral stimulus. For prosaccades, saccades away from the stimulus are counted as incorrect, for antisaccades, saccades towards the stimulus are counted as incorrect. Usually

computed by dividing the number of errors by the number of correct responses and errors (included saccades total) and then multiplying by 100 (Holmqvist et al., 2011).

Latency (in ms): The time elapsed between the onset of a peripheral stimulus and the onset of the saccade. Commonly measured for correct trials (Holmqvist et al., 2011).

2.3 Meta-Analysis

Because science is a cumulative process (Shoemaker, Tankard Jr, & Lasorsa, 2003), it can be useful to aggregate studies with the same basic research question. This can be achieved by using a meta-analytic approach (Olkin, 1995), which is a systematic review of the literature supported by statistical methods. The goals of a meta-analysis is to aggregate findings from several similar, related studies (Glass, 1976). In a meta-analysis, relevant results from all of these studies are quantified in a way that they can be aggregated. It is also possible to aggregate estimates of the strength of the relationship between two measures (for example given in a standardized mean difference or as correlation coefficients) (Borenstein, 2009; Fleiss & Berlin, 2009).

2.3.1 Study Selection and Data Collection

For a meta-analysis to be successful, studies must be selected which can be aggregated both from a methodological and a theoretical standpoint. For this, the conceptualization of relevant constructs, such as schizotypy or executive functions, needs to be defined and all studies that are included in the meta-analysis need to conceptualize the constructs according to these definitions (Viechtbauer, 2010). This prevents the aggregation of studies which examine similar, but not the same concepts and should therefore not be aggregated (Viechtbauer, 2010). Following the study selection, all relevant data, such as the primary effect and moderator variables, are then extracted from all studies. If not all of the necessary data are provided in a publication, the authors can be contacted for further information. Data from all studies must be brought into comparable measures. This includes effect directions, scales and effect size measures. For example, all primary study effects may be converted to Hedges' *g* for aggregation. Documentation of the study selection, data extraction and data aggregation process is crucial, especially when many studies are aggregated (Cooper, Hedges, & Valentine, 2009).

Because reporting of meta-analyses had proven suboptimal in too many publications, an international group of researchers developed a guideline for the reporting of meta-analyses, called QUORUM (Quality of Reporting of Meta-Analyses) (Moher et al., 1999). These guidelines were revised in 2009. This revision was termed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (David Moher, Liberati, Tetzlaff, & Altman, 2009).The

PRISMA guidelines constitute of a 27-item checklist to follow when reporting a meta-analysis. Items include guidelines for the title, abstract, introduction, methods, results, discussion and funding section of publications (for the complete list of all 27 items, see Moher et al. (2009)).

2.3.2 Data Aggregation and Reporting

Random/mixed effects models are the most commonly used approach for meta-analysis. In a random effects model, the heterogeneity between the studies is treated as purely random. The true effects are assumed to be normally distributed and the goal is to estimate the true effects and the amount of heterogeneity. In mixed effects models, one or more moderators are introduced into the model. These are variables on the study level, which may account for part of the heterogeneity in the true effects. The goal is to estimate the true effects, the influence of the moderators and the residual heterogeneity (which cannot be accounted for by the moderators) (Viechtbauer, 2010).

Meta-analytic models are special cases of the general linear (mixed effects) model with heteroscedastic sampling variances that are assumed to be known. The random/mixed effects models are fitted using the two-step approach (Raudenbush, 2009): The amount of (residual) heterogeneity is estimated using an estimator such as the Hedges' estimator (Hedges & Olkin, 1985; Raudenbush, 2009), the maximum likelihood or restricted maximum-likelihood estimator (Raudenbush, 2009; Viechtbauer, 2005). Then, the average true effect is estimated using weighted least squares. Confidence intervals for the estimated average true effect can then be computed (under the assumption of normality) (Viechtbauer, 2010). The between-study heterogeneity is most commonly evaluated using the Q-test (Cochran, 1954).

Since there is a publication bias favoring publications with positive effects, this bias has to be accounted for in meta-analysis. There are several bias correcting methods. The three-parameter selection model (3PSM) has been reported to outperform other correcting methods (Carter, Schönbrodt, Gervais, & Hilgard, 2017). The 3PSM was introduced by Hedges (1984) and extended by Iyengar and Greenhouse (1988) and Hedges and Vevea (1996). It models the process of published versus file-drawered results. This model considers the heterogeneity of the random effect sizes, the population average effect size and the probability that a nonsignificant effect is published. The joint likelihood function of these parameters is maximized given observed data (Carter et al., 2017). One common way of implementing the 3PSM is the weight-function model by Vevea and Hedges (1995) and Vevea and Woods (2005).

3 Experimental Studies

Table 5. Overview of studies included in the current thesis.

Relevant publications for the present thesis	
1	**Steffens M.**, Becker B., Neumann C., Kasparbauer A.M., Meyhöfer I., Weber B., Mehta M.A., Hurlemann R., Ettinger U. (2016) Effects of ketamine on brain function during smooth pursuit eye movements. Hum Brain Mapp. 37(11), 4047-4060. doi: 10.1002/hbm.23294
2	**Steffens, M.**, Neumann, C., Kasparbauer, A.-M., Becker, B., Weber, B., Mehta, M.A., Hurlemann, R., Ettinger, U., 2018. Effects of ketamine on brain function during response inhibition. Psychopharmacology (Berl). 235, 3559–3571. https://doi.org/10.1007/s00213-018-5081-7.
3	Becker B., **Steffens M.**, Zhao Z., Kendrick K.M., Neumann C., Weber B., Schultz J., Mehta M.A., Ettinger U., Hurlemann R. (2017) General and emotion-specific neural effects of ketamine during emotional memory formation. Neuroimage. 15:150, 308-317. doi: 10.1016/j.neuroimage.2017.02.049
4	**Steffens M**., Meyhöfer I., Fassbender K., Ettinger U., Kambeitz J. (2018) Association of Schizotypy With Dimensions of Cognitive Control: A Meta-Analysis. Schizophr Bull. 15. doi: 10.1093/schbul/sby030.
Further relevant publications	
5	Ettinger, U., Meyhöfer, I., **Steffens, M.**, Wagner, M., & Koutsouleris, N. (2014). Genetics, cognition and neurobiology of schizotypal personality: A review of the overlap with schizophrenia. Frontiers in Psychiatry, 5(18), 1–16. http://doi.org/10.3389/fpsyt.2014.00018
6	Meyhöfer I., **Steffens M.**, Faiola E., Kasparbauer AM., Kumari V., Ettinger U. (2017) Combining two model systems of psychosis: The effects of schizotypy and sleep deprivation on oculomotor control and psychotomimetic states. Psychophysiology, 54(11), 1755-1769. doi: 10.1111/psyp.12917
7	Meyhöfer I., **Steffens M.**, Kasparbauer A., Grant P., Weber B., Ettinger U. (2015) Neural mechanisms of smooth pursuit eye movements in schizotypy. Hum Brain Mapp. 36(1), 340-53. doi: 10.1002/hbm.22632.
8	Kasparbauer, A.-M., Meyhöfer, I., **Steffens, M.**, Weber, B., Aydin, M., Kumari, V., Hurlemann, R., Ettinger, U., 2016. Neural effects of methylphenidate and nicotine during smooth pursuit eye movements. Neuroimage 141. doi: 10.1016/j.neuroimage.2016.07.012
9	Faiola, E., Meyhöfer, I., **Steffens, M.**, Kasparbauer, A.-M., Kumari, V., Ettinger, U., 2018. Combining trait and state model systems of psychosis: The effect of sleep deprivation on cognitive functions in schizotypal individuals. Psychiatry Res. 270, 639–648. https://doi.org/10.1016/j.psychres.2018.10.033

10	Meyhöfer, I., Kasparbauer, A.-M., **Steffens, M.**, Ettinger, U., 2019. Effects of nicotine on smooth pursuit eye movements in healthy non-smokers. Psychopharmacology. https://doi.org/10.1007/s00213-019-05223-1
11	Talanow, T., Kasparbauer, A.-M., **Steffens, M.**, Meyhöfer, I., Weber, B., Smyrnis, N., Ettinger, U., 2016. Facing competition: Neural mechanisms underlying parallel programming of antisaccades and prosaccades. Brain Cogn. 107, 37–47. https://doi.org/10.1016/j.bandc.2016.05.006
12	Herweg, N.A., Weber, B., Kasparbauer, A., Meyhöfer, I., **Steffens, M.**, Smyrnis, N., Ettinger, U., 2014. Functional magnetic resonance imaging of sensorimotor transformations in saccades and antisaccades. Neuroimage 102 Pt 2, 848–60. https://doi.org/10.1016/j.neuroimage.2014.08.033

Notes. The studies are sorted according to their relevance in the main text.

3.1 Publication 1. Effects of Ketamine on Brain Function During Smooth Pursuit Eye Movements

Steffens M., Becker B., Neumann C., Kasparbauer A.M., Meyhöfer I., Weber B., Mehta M.A., Hurlemann R., Ettinger U. (2016) Effects of ketamine on brain function during smooth pursuit eye movements. *Hum Brain Mapp*. 37(11), 4047-4060. doi: 10.1002/hbm.23294. (Steffens et al., 2016)

SPEM performance deficits are a well-established biomarker of psychosis (Hutton & Kennard, 1998; Levy et al., 1993; O'Driscoll & Callahan, 2008). A few studies have found that similar SPEM deficits can be found during acute ketamine administration in healthy volunteers (Avila et al., 2002; Radant et al., 1998; Schmechtig, Lees, Perkins, et al., 2013; Weiler et al., 2000). This deficit is modeled by acute NMDAR blockage via ketamine infusion in healthy volunteers. However, the neural mechanisms mediating SPEM impairments during NMDAR blockage are virtually unknown. Ketamine has been shown to induce psychosis-like symptoms across all three symptoms domains (Krystal et al., 1994) and to affect functional connectivity in the brain (Driesen et al., 2014; Frohlich & Van Horn, 2014).

The first aim of this study was to replicate findings that ketamine leads to SPEM dysfunction in healthy volunteers, more specifically reduced velocity gain, increased saccadic frequency and increased RMSE. Our second aim was to replicate psychomimetic effects of ketamine. Our third aim was to investigate, for the first time, the neural correlates of ketamine-induced SPEM deficits. Our final study aim was to investigate whether ketamine administration would lead to dysconnecticity in the SPEM task network during SPEM performance.

In this study, we employed a counter-balanced, placebo-controlled, double-blind, within-subjects design. Twenty-seven healthy male participants received intravenous racemic ketamine, with a 100ng/ml target plasma concentration, on one of two assessment days. On the other day, participants received intravenous saline as a placebo. Participants received the same volume of placebo and ketamine solution. Volume depended on body weight and height to ensure target plasma concentration of ketamine was reached. Participants performed a block-design SPEM task during fMRI at 3 Tesla field strength. Participants also completed the Psychotomimetic States Inventory (PSI) before, during and after ketamine/placebo infusion. To investigate the impact of ketamine administration on functional connectivity during the SPEM task, we used the V5, which is an important node region for motion processing, and the Frontal Eye Fields (FEFs), which are an important node for prediction during SPEM, as origins of connectivity (Lencer & Trillenberg, 2008).

As expected, ketamine induced SPEM deficits, namely reduced maintenance gain, increased saccadic frequency and increased RMSE. Ketamine also induced psychotomimetic symptoms on the PSI subscales cognitive disorganization, delusional thinking, perceptual distortion and mania. This means that ketamine induced positive and cognitive, but not negative, psychosis-like symptoms. On the brain-functional level, ketamine reduced BOLD signal in the SPEM network, including the primary visual cortex, the area V5 and the right FEF. However, ketamine did not alter functional connectivity during SPEM performance.

In summary, ketamine led to psychosis-like subjective symptoms, SPEM performance deficits and altered BOLD response to SPEM performance. All of these were similar to effects reported for psychosis patients. Our results support theories that postulate the glutamate system, and the NDMAR in particular, plays an important role in the etiology and the development of symptoms in psychosis. Our results also strengthen the notion that ketamine administration is a useful state-model of psychosis, especially when combined with SPEM as a biomarker of psychosis.

3.2 Publication 2. Effects of Ketamine on Brain Function During Response Inhibition

Steffens, M., Neumann, C., Kasparbauer, A.-M., Becker, B., Weber, B., Mehta, M.A., Hurlemann, R., Ettinger, U. (2018). Effects of ketamine on brain function during response inhibition. *Psychopharmacology*. 235, 3559–3571. doi: 10.1007/s00213-018-5081-7. (Steffens, Neumann, et al., 2018)

Inhibitory deficits in the schizophrenia spectrum have been reliably reported (Reilly, Lencer, Bishop, Keedy, & Sweeney, 2008; Schaefer et al., 2013). The antisaccade task is one task which measures response Inhibition (Herweg et al., 2014; Hutton & Ettinger, 2006; Talanow et al., 2016), and it is a well-established biomarker of psychosis (Gooding & Basso, 2008; Koychev et al., 2011). Antisaccade performance, but not prosaccade performance, is impaired in psychosis (Hutton & Ettinger, 2006). Ketamine has also been shown to induce psychosis-like symptoms across all three symptoms domains (Krystal et al., 1994) and has therefore been proposed as a model system of psychosis (Kantrowitz & Javitt, 2010; Krystal et al., 2003; Poels et al., 2014). Interestingly, however, although antisaccade deficits similar to those reported in psychosis have been reported in non-human primates (Condy, Wattiez, Rivaud-Péchoux, & Gaymard, 2005; Ma, Skoblenick, Seamans, & Everling, 2015; Skoblenick & Everling, 2012, 2014) and in recreational ketamine users (Morgan, Huddy, et al., 2009), ketamine-induced deficits have not yet been observed in healthy human volunteers during ketamine administration (Radant et al., 1998; Schmechtig, Lees, Perkins, et al., 2013). Neural compensatory mechanisms on the brain functional level may be an explanation for this discrepancy.

The first aim of this study was to replicate psychomimetic effects of ketamine in healthy volunteers. Our second aim was to investigate whether antisaccade performance deficits, such as have been reported in psychosis, can be seen in healthy volunteers during ketamine administration. And lastly, our third aim was to investigate whether changes in BOLD activation patterns during antisaccade task performance during ketamine infusion are similar to those observed in psychosis.

In this study, we employed a counter-balanced, placebo-controlled, double-blind, within-subjects design. Twenty-seven healthy male participants received intravenous racemic ketamine, with a 100ng/ml target plasma concentration, on one of two assessment days. On the other day, participants received intravenous saline as a placebo. Participants received the same volume of placebo and ketamine solution. Volume depended on body weight and height to ensure target plasma concentration of ketamine was reached. Participants performed a mixed design prosaccade and antisaccade task during fMRI at 3 Tesla field strength. Participants also completed the PSI before, during and after ketamine/placebo infusion. Due to technical difficulties of in-MRI scanner eye tracking, the results are based on a subset of fifteen participants.

Ketamine induced psychotomimetic symptoms on the PSI subscales delusional thinking and perceptual distortion but did not induce antisaccade performance deficits. On the neuronal level, we observed an interaction between substance treatment and task condition in the

somatosensory cortex, which may suggest recruitment of additional neural resources during NMDAR blockage in the antisaccade condition.

In conclusion, given the robust evidence of antisaccade deficits in psychosis, our results suggest that ketamine is an incomplete model system of psychosis. These results underline the importance of detailed research to understand effects of acute NMDAR hypofunction and its direct results, as well as the potential long term ("secondary") effects of chronic NMDAR hypofunction.

3.3 Publication 3. General and Emotion-Specific Neural Effects of Ketamine During Emotional Memory Formation

Becker B., **Steffens M.**, Zhao Z., Kendrick K.M., Neumann C., Weber B., Schultz J., Mehta M.A., Ettinger U., Hurlemann R. (2017) General and emotion-specific neural effects of ketamine during emotional memory formation. *Neuroimage*. 15:150, 308-317. doi: 10.1016/j.neuroimage.2017.02.049. (Becker et al., 2017)

NMDAR dependent signaling in limbic and prefrontal regions has been demonstrated to be critically involved in both declarative memory (Tamminga et al., 2010) and emotional functions (Abel et al., 2003; Ebert et al., 2012; Schmidt et al., 2013). Ketamine-induced transient NMDAR hypofunction has been associated with deficient performance in the domains of memory (Ghoneim et al., 1985; Harris et al., 1975; Hartvig et al., 1995; Hetem et al., 2000; Krystal et al., 1994; Malhotra et al., 1996; Newcomer, Farber, et al., 1999a; Pfenninger et al., 2002; Puma et al., 1998), especially for the acquisition of novel information (Newcomer et al., 2000) and higher-order emotional functioning. Ketamine has also been demonstrated to impair emotional memory on a brain functional level (Abel et al., 2003; Ebert et al., 2012; Schmidt et al., 2013).

The first aim of this study was to replicate findings that acute ketamine administration in healthy humans disrupts the emotion-cognition interaction during emotional memory formation. The second aim of this study was to examine if acute ketamine administration produces a pattern of general and emotion-specific neural effects.

In this study, we employed a counter-balanced, placebo-controlled, double-blind, within-subjects design. Twenty-seven healthy male participants received intravenous racemic ketamine, with a 100ng/ml target plasma concentration, on one of two assessment days. On the other day, participants received intravenous saline as a placebo. Participants received the same volume of placebo and ketamine solution. Volume depended on body weight and height to ensure target plasma concentration of ketamine was reached. Participants viewed neutral, positive and negative pictures (encoding), which they were asked to memorize during fMRI at 3

Tesla field strength. Participants also completed the PSI before, during and after ketamine/placebo infusion. Five days after each of the two fMRI assessments, participants completed a recall task of the images they viewed during encoding. Twenty-one participants completed all four study sessions; therefore, the results are based on this subset of participants.

On the behavioral level, ketamine led to decreased memory performance and it abolished the emotional enhancement effect on memory. On the neuronal level, ketamine suppressed parahippocampal and medial prefrontal activity during encoding, irrespective of emotion (positive / neutral / negative). Interestingly, ketamine increased activity in amygdala and orbitofrontal regions during successful encoding of negative stimuli, but not neutral or positive stimuli. Ketamine also increased medial prefrontal-parahippocampal coupling while decreasing amygdala-orbitofrontal coupling during encoding of negative, but not neutral or positive, stimuli.

In conclusion, our findings suggest that ketamine leads to general and emotional valence-specific effects during the formation of memories. In parts, these effects overlap with alterations which have been reported in psychosis.

3.4 Publication 4. Association of Schizotypy With Dimensions of Cognitive Control: A Meta-Analysis

Steffens M., Meyhöfer I., Fassbender K., Ettinger U., Kambeitz J. (2018) Association of Schizotypy With Dimensions of Cognitive Control: A Meta-Analysis. *Schizophr Bull*. 15. doi: 10.1093/schbul/sby030. (Steffens, Meyhöfer, et al., 2018)

Schizotypy is a time-stable, multidimensional personality trait that consists of positive, negative and disorganized facets (Mason et al., 1995; Raine, 2006; Raine et al., 1994). Schizotypy can also be quantified as an overall score derived from combining the three subfacets (“mixed schizotypy”) (Chan et al., 2008). Schizotypy is a model system of psychosis and there is considerable overlap between psychosis and high levels of schizotypy (Ettinger, Meyhöfer, Steffens, Wagner, & Koutsouleris, 2014). High schizotypy is associated with subtle, but widespread cognitive alterations, including poorer performance in tasks measuring cognitive control (Ettinger et al., 2015; Mohr & Claridge, 2015). Similar impairments of cognitive control have been reported in psychosis, with the deficits generally being more pronounced than they have been reported in high schizotypy (Green et al., 2004; Reichenberg & Harvey, 2007; Schaefer et al., 2013).

The aim of this collection of meta-analyses was to provide a quantitative estimation of the effect of schizotypy levels on the cognitive control dimensions Updating, Shifting, and Inhibition. We also aimed to investigate potential moderating effects of the year of publication, the study design (categorical design, correlational design) and the sample type (community sample, college sample) on this relationship.

We conducted meta-analyses of studies including healthy adults from both the general population and college samples, which used either categorical or correlative designs. Separate analyses were conducted for the negative, the positive and the disorganized facets, as well as a combined general schizotypy score ("mixed schizotypy", including more than one facet). We conducted separate analyses for each of the three main factors of cognitive control, namely Inhibition, Updating and Shifting. Due to a limited number of studies, we could not conduct a meta-analysis for the relationship between Updating and disorganized schizotypy and for Shifting and disorganized schizotypy. We conducted ten meta-analyses in total, namely regarding the relationship between Updating and positive, negative and mixed schizotypy respectively; Shifting and positive, negative and mixed schizotypy respectively; as well as Inhibition and positive, negative, mixed and disorganized schizotypy respectively. In each meta-analysis, we included the variables year of publication, study design (categorical design, correlational design) and sample type (community sample, college sample) as moderators.

Negative schizotypy was associated with poorer performance on Shifting (Hedges' g=0.32) and Updating (Hedges' g=0.11). Positive schizotypy was associated with poorer performance on Shifting (Hedges' g=0.18). There were no associations between schizotypy and Inhibition. As for the moderators included in the meta-analysis, publication year had a moderating influence on the relationship between mixed schizotypy and Updating. Study design had a moderating influence on the association between negative schizotypy and Shifting. If only categorical studies were included in the analysis, the effect increased to Hedges' g=0.44 and if only correlative studies were included, the effect decreased to Hedges' g=0.18.

Our divergent results for positive, negative and disorganized schizotypy emphasize the importance of examining the relationship between cognition and these subfacets of schizotypy, rather than using a mixed schizotypy score. Our findings also underline the importance of more detailed research to further defined the complex personality construct of schizotypy. This is especially important in regards to schizotypy as a model system of psychosis.

4 General Discussion

„Remember that all models are wrong; the practical question is how wrong do they have to be to not be useful.“

- (Box & Draper, 1987)

The current thesis is a summary of four studies that examined how oculomotor control (publication 1) executive function (publication 2) and emotional memory (publication 3) are impacted by acute ketamine administration as a state-model of psychosis and a meta-analysis which examined executive function in schizotypy (publication 4) as a trait-model of psychosis.

4.1 Integration

Much about the mechanisms behind psychotic symptoms and syndromes is yet unknown and studying the development of psychotic disorders remains difficult, because of confounding factors such as treatment side effects, effects of hospitalization and that most patients are seen in later stages of illness chapters 1.1.1 and 1.1.2. What is more, currently available treatments have predominantly proven ineffective in treating cognitive symptoms (chapters 1.1.1 and 1.1.2), which is concerning given that cognitive symptoms have been linked to global functioning of psychotic patients (chapters 1.1.1 and 1.1.2). Model systems of psychosis, among them acute ketamine administration (chapter 1.1.3) and high schizotypy (chapter 1.1.4) lack the confounds of patient research, such as medication and hospitalization and can help to further our understanding of the pathophysiology of psychotic disorders (chapters 1.1.2, 1.1.3 and 1.1.4).

The current work provides four publications which examine important cognitive functions in two promising model systems of psychosis: Publications 1-3 examine cognition, oculomotor control and brain function in acute ketamine administration as a state-model of psychosis. Publication 4 examines cognition in schizotypy as a trait model of psychosis.

4.1.1 Acute Ketamine Administration

Acute ketamine infusion is a well-established state-model of psychosis (chapter 1.1.3). Cognitive symptoms have been linked to global functioning of psychotic patients (chapters 1.1.1 and

1.1.2) and currently available treatments have proven less effective in treating cognitive symptoms compared to positive symptoms of psychosis (chapter 1.1.2). Therefore, cognitive symptoms are one important focus in the development of new treatments, they are an important target in model system research. Among the cognitive symptoms of interest are executive functions, which have reliably been demonstrated to be impaired in psychosis patients (Bora et al., 2009; Dickinson et al., 2007; Green et al., 2004; Reichenberg & Harvey, 2007; Schaefer et al., 2013) (chapter 1.2) and promising biomarkers of psychosis, chiefly SPEM impairments (Levy et al., 2000, 2010) (chapter 1.3). We conducted a pharmacological fMRI study to further our understanding of ketamine as a model system of psychosis and to elucidate the role of NMDAR dysfunction in psychosis. In this study, healthy male participants received racemic ketamine (target plasma level of 100ng/ml) on one assessment day and placebo on the other. Administration of ketamine and placebo was pseudo-randomized and double-blind, ensuring that half of the participants received ketamine first. Participants completed the PSI and a sustained attention test before, during and after infusion to examine potential psychotomimetic effects. Blood samples were drawn before, during and after infusion to ensure that randomization was executed as planned and that the ketamine target plasma level of ketamine was met. Participants completed a SPEM task, a pro- and antisaccade task and an emotional memory task during fMRI. For the SPEM and pro- and antisaccade tasks, participants' eye movements were recorded using VCPCR eye tracking.

Publications 1-3 report that ketamine led to subjective psychosis-like symptoms, namely delusional thinking, perceptual distortion and cognitive disorganization. These correspond to positive and disorganized symptoms of psychosis and are similar to psychotomimetic effects described previously (Krystal et al., 1994; Lahti et al., 2001; Schmechtig, Lees, Perkins, et al., 2013). While negative symptoms, such as anxiety and withdrawal, have previously been reported under ketamine (Krystal et al., 1994; Lahti et al., 2001; Malhotra et al., 1997; Schmechtig, Lees, Perkins, et al., 2013), we did not observe them. Possible explanations for this may be that negative symptoms have been reported to be dose-dependent, with one study finding anhedonia symptoms in a concentration of 150ng/ml ketamine target plasma level but not in lower doses (Pollak et al., 2015). Ketamine did not alter sustained attention, which, importantly, indicates that performance deficits cannot be solely explained by sedative effects as sustained attention didn't differ between ketamine and placebo conditions. Blood samples indicate that the randomization was carried out as planned and that the ketamine target plasma level of 100ng/ml was met with a variance similar to those reported by other groups (Driesen et al., 2014; Krystal et al., 2005).

Publication 1 reports the effects of ketamine administration on performance and brain function during SPEM. SPEM are a promising biomarker of psychosis and have been reliably shown to be impaired in psychosis and the psychosis spectrum (chapter 1.3). Only few studies have, as of yet, examined the impact of acute ketamine administration on SPEM in healthy humans and no studies have examined the neuronal activity during a SPEM task under the influence of ketamine. We therefore measured eye movements and brain function during a SPEM task while participants received ketamine on one assessment day and placebo on the other assessment day.

In summary, our results indicate that ketamine caused severe performance deficits in SPEM and altered BOLD response in the SPEM task network. Both the performance deficits and the altered BOLD response are similar to those reported in psychosis patients (Ettinger et al., 2004; Gooding et al., 2000; Lencer et al., 2003; Lenzenweger et al., 2006; Levy et al., 2010; Meyhöfer et al., 2015). Our effects were large but not as high as those reported in psychosis (G. A. O'Driscoll & Callahan, 2008). SPEM performance deficits similar to ours have previously been reported during ketamine infusion (Avila et al., 2002; Radant et al., 1998; Schmechtig, Lees, Perkins, et al., 2013). On the brain functional level, the SPEM network during placebo looked similar to that reported in earlier research by others (Culham, He, Dukelow, & Verstraten, 2001; Meyhöfer et al., 2015; Nagel et al., 2008). Ketamine led to reduced activity in the SPEM network, this dampening effect of ketamine has previously been reported at rest (De Simoni et al., 2013). Regional specific decreases similar to those we observed in our study, have been reported during SPEM in schizophrenia, suggesting we successfully induced psychosis-like alterations on the neuronal level (Hong et al., 2005; Keedy et al., 2006; Lencer et al., 2005; Nagel et al., 2012; Tregellas et al., 2004). Specifically, we found lower activation of areas V3a and V5, as well as the right FEF during ketamine administration compared to placebo. The area V5 is sensitive to speed, acceleration and direction of moving stimuli (Lencer & Trillenberg, 2008), area V3a also plays a role in motion perception (Tootell et al., 1997). The FEF generate oculomotor commands for SPEM and contribute to velocity, initiation and prediction in SPEM (Lencer & Trillenberg, 2008). While some studies report reduced FEF activity during SPEM similar to our results in schizophrenia patients (Hong et al., 2005; Keedy et al., 2006) and healthy relatives of schizophrenia patients with impaired velocity gain (O'Driscoll et al., 1999), some studies do not find decreased FEF activity in schizophrenia patients during SPEM (Lencer et al., 2011; Nagel et al., 2007). In fact, in a SPEM blanking task, schizophrenia patients demonstrated higher FEF activity than controls, which has been interpreted as a compensatory mechanism, with patients relying more heavily on the FEFs for SPEM performance (Nagel et al., 2007).

The changes in FEF and V5 activation we observed did not correlate with behavioral changes in SPEM performance. Possibly because the FEFs and the V5 are only part of the SPEM network and other areas may well contribute important changes in SPEM performance. It is also possible that there is a non-linear association between the decrease in brain activity in these areas and SPEM performance. We also did not find alterations in functional connectivity between area V5, FEFs and other regions. This does not necessarily contrast with the global dysconnectivity reported for ketamine and in psychosis in resting state (Frohlich & Van Horn, 2014; Grimm et al., 2015; Joules et al., 2015; Nejad, Ebdrup, Glenthøj, & Siebner, 2012) as we did not test global alteration of functional connectivity. Connectivity differences have been reported for a working memory task (Driesen et al., 2013), but, so far, have not been found during performance of a SPEM task.

In addition to these neuronal changes, ketamine also led to reduced activity in the cerebellum and primary visual processing areas during SPEM. This is in line with the proposition that frontal-thalamic-cerebellar network alterations may underlie oculomotor control deficits in psychosis (Ross et al., 1998) and that the SPEM deficits induced by ketamine may be mediated by changes in cerebellar circuitry (Avila et al., 2002), especially seeing as ketamine has been shown to alter cerebellar connectivity (Joules et al., 2015). We also found that ketamine reduced activity in regions of primary visual processing, which has been reported in psychosis spectrum (Butler & Javitt, 2005; Yue Chen, Levy, Sheremata, & Holzman, 2004; Meyhöfer et al., 2015; Nagel et al., 2012; Tregellas et al., 2004). This is in line with the proposition that SPEM deficits in schizophrenia are linked both to deficient motion detection and impaired visual perception (Nagel et al., 2012). And, importantly, it underlines NMDA models which discuss early visual and auditory processing deficits as possible underlying causes for many of the higher order cognitive deficits seen in psychosis (Javitt et al., 2012).

We did not observe altered neuronal activity in the SEFs and the putamen, which has generally been reported in psychosis (Keedy et al., 2006; Nagel et al., 2012), though putamen activation changes were not found in all psychosis studies during SPEM (Tregellas et al., 2004). These deviations may suggest that alterations in SPEM activation in psychosis is in part, but not completely, associated with acute NMDAR dysfunction.

Taken together, the results reported in publication 1 strengthen the notion that ketamine administration is a useful state-model of psychosis, especially when combined with SPEM as a biomarker of psychosis. Our results also illustrate the importance of NMDAR function for oculomotor control.

Publication 2 reports the effects of ketamine administration on performance and brain function during a mixed pro- and antisaccade task, which is a measure of response Inhibition. Executive functions have been shown to be impaired in psychosis and the psychosis spectrum. Among those functions is an impairment of response Inhibition (chapter 1.2). Only few studies have, as of yet, examined the impact of acute ketamine administration on response inhibition in healthy humans and no studies have recorded the neuronal activity during antisaccade performance under the influence of ketamine. We therefore measured eye movements and brain function during a mixed anti- and prosaccade task while participants received ketamine on one assessment day and placebo on the other assessment day.

In summary, in line with previous literature, prosaccade latency was shorter than antisaccade latency (Schmechtig, Lees, Perkins, et al., 2013). Our results indicate that ketamine did not impair antisaccade performance, which has been reported in earlier studies on healthy human volunteers (Radant et al., 2010; Schmechtig, Lees, Perkins, et al., 2013) and contrasts with the consistently reported impairments in schizophrenia patients (Hutton & Ettinger, 2006). One possible explanation for this dissociation is that antisaccade deficits in schizophrenia patients have been linked to cognitive dysfunction rather than the dysfunction of the magnocellular pathway, which is influenced by ketamine (Javitt, 2009; Leonard et al., 2013). Our findings also contrast with studies on non-human primates, in which ketamine has been linked to antisaccade performance deficits (Condy et al., 2005; Ma et al., 2015; Skoblenick & Everling, 2012, 2014). This discrepancy may be explained by methodological differences: Non-human primate studies often employ intramuscular injection of ketamine and titration studies to determine individual-specific concentrations of ketamine (Skoblenick & Everling, 2012), while human studies generally use one-off intravenous application of ketamine (Radant et al., 2010; Schmechtig, Lees, Perkins, et al., 2013). Given the heterogeneity of Inhibition as a construct (Wöstmann et al., 2013) it is worth noting that one study showed response Inhibition deficits on the Hayling task during ketamine administration (Morgan, Mofeez, Brandner, Bromley, & Curran, 2004a). Further research will be necessary to describe the effect of ketamine on response inhibition in more detail.

On the neuronal level, we observed increased BOLD response in the saccadic task network as described in previous studies (Leigh & Zee, 2006; McDowell, Dyckman, Austin, & Clementz, 2008; Raemaekers et al., 2002). The network includes regions associated with primary visual, motion and somatosensory processing, as well as oculomotor control and executive function. Ketamine led to task-dependent change in the BOLD response in a bilateral cluster located in the postcentral gyrus which was not located in the task network. Here, BOLD response was higher for prosaccade execution in the placebo condition, but higher for antisaccade execution

in the ketamine condition. This effect was unexpected. One possible explanation is the recruitment of additional neuronal resources in the ketamine condition for antisaccade performance, especially because of the decreased activity during antisaccade performance in the placebo condition (Benjamin Becker et al., 2013; Grady, 2012). Another possible explanation for this unexpected effect is that it may be linked to the pronounced perceptual distortions induced by ketamine (Krystal et al., 1994; Schmechtig, Lees, Perkins, et al., 2013; Stone et al., 2008, 2015). The task-dependence, then, may be linked to the perceptual differences between pro- an antisaccade performance, which may have an effect on proprioception (Balslev, Odoj, & Karnath, 2013; Balslev, Albert, & Miall, 2011).

Taken together, the results reported in publication 2 indicate that acute ketamine administration is an incomplete model of psychosis, as antisaccade performance deficits are a robust and well-validated key finding in psychosis (Calkins, Iacono, & Curtis, 2003; Hutton & Ettinger, 2006; McDowell et al., 2002) and we did not observe any such deficits as a result of acute ketamine administration. Our results pinpoint an important limitation of the ketamine model of psychosis.

Publication 3 reports the effects of ketamine administration on the performance and brain function during an emotional memory task. Declarative memory is another cognitive function domain which has been shown to be impaired in psychosis (chapter 1.4.1). Emotional facilitation of memory is a reliable effect in human declarative memory which has been shown to be impaired in psychosis (chapter 1.4.1). Although seeing as studies indicate that NMDAR dysfunction plays an important role in the emotional memory dysfunction in psychosis (chapters 1.4), so far only few studies have examined the impact of acute ketamine administration on emotional facilitation of declarative memory. We therefore measured neuronal activity and emotional reaction during the encoding phase of an emotional memory task (neutral, positive and negative stimuli). The recall phase of the memory task was then completed five days after each fMRI assessment outside of the MRI scanner and without drug infusion. Our results indicate that ketamine decreased memory performance, which is in line with previous behavioral studies (Hetem et al., 2000; Krystal et al., 1994; Newcomer, Craft, et al., 1999). While ketamine administration did not lead to strong altered emotional experiences, exploratory analysis hinted at less severe memory impairments and intact emotional enhancement for negative stimuli. Overall, the impairments in memory performance following ketamine administration follow the pattern observed in schizophrenia (Herbener, 2008; Horan, Brown, & Blanchard, 2007), with emotional memory enhancement being intact for negative, but not positive stimuli (Calev & Edelist, 1993; Herbener et al., 2007).

On the neuronal level, ketamine suppressed parahippocampal and medial prefrontal activity during emotional encoding independently of the emotional valence of the stimuli (both for negative and positive stimuli). This is in line with findings that the hippocampal formation and the parahippocampal gyrus are fundamental for successful memory encoding (Kim, 2011; Köhler et al., 1998; Schon, 2004). Decreased parahippocampal activity during memory encoding has been associated with memory impairments in psychosis spectrum (Di Giorgio et al., 2013; Rasetti et al., 2014; Thermenos et al., 2007). The medial prefrontal cortex (mPFC) plays an important role in emotional processing and emotion regulation via regulation of limbic regions, especially the amygdala (Buhle et al., 2014; Etkin, Egner, & Kalisch, 2011; Kober et al., 2008). Our results are in line with findings that schizophrenia patients show impairments in functions relying on mPFC function (O'Driscoll, Laing, & Mason, 2014; Savla, Vella, Armstrong, Penn, & Twamley, 2013). We found that ketamine increased the coupling between mPFC and the hippocampus. Seeing as the hippocampus strongly interacts with the amygdala during emotion processing (Fusar-Poli et al., 2009; Kim, 2011; Murty et al., 2010), it is possible that NMDAR hypofunction increases emotional processing and increases the role of the hippocampus in this process, which may disrupt successful memory formation. An alternative explanation might be that, seeing as the hippocampus and mPFC interaction is crucial for integrating new information into existing knowledge (Preston & Eichenbaum, 2013; van Kesteren, Ruiter, Fernández, & Henson, 2012), the increased coupling we observed may be an unsuccessful attempt at compensating for suppressed parahippocampal activation during memory formation by increasing mPFC hippocampal coupling and engaging existing knowledge in the memory process.

Ketamine increased activity in the amygdala and the orbitofrontal regions during successful encoding of negative, but not neutral or positive stimuli. Increased activity for negative stimuli has been reported previously (Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Fusar-Poli et al., 2009), which has been linked to enhanced long-term recognition memory (Hamann, Ely, Grafton, & Kilts, 1999; Herbener et al., 2007). Increased amygdala activity has also been reported in schizophrenia patients (Marwick & Hall, 2008; Pankow et al., 2013). The increased activation we observed was accompanied by decreased amygdala-orbitofrontal coupling during the encoding of negative, but not neutral or positive stimuli. Similar hypoconnectivity has been linked to reduced emotion regulation (Hahn et al., 2011) and the connectivity between the amygdala, the orbitofrontal cortex and their reciprocal connections with the hippocampal formation have been fundamentally linked to the impact of emotional salience on learning (Cavada, 2000).

An exploratory post hoc analysis revealed that ketamine may have increased the perceived arousal for positive stimuli during encoding, an effect which was linked to higher reactivity of the left amygdala. The link between amygdala activity and emotional arousal has been demonstrated for negative and positive stimuli (Bonnet et al., 2015; Costa, Lang, Sabatinelli, Versace, & Bradley, 2010; Garavan, Pendergrass, Ross, Stein, & Risinger, 2001; Phan et al., 2003).

Taken together, the results reported in **publication 3** indicate that acute ketamine administration leads to similar deficits in emotional memory facilitation (intact for negative, but not positive or neutral stimuli) than have been reported in psychosis patients. This underlines the importance of the NMDAR in memory formation and emotional facilitation in long term memory.

The results reported in **publications 1-3** underline the importance of detailed research to understand the effects of acute NMDAR hypofunction and its direct results, as well as the potential "secondary" effects of chronic NMDAR hypofunction. Some, but not all cognitive symptoms commonly found in psychosis were mimicked by acute ketamine administration. The findings reported are in line with glutamate theories of psychosis which generally predict that some psychosis symptoms are directly caused by NMDAR hypofunction, while other symptoms are less direct downstream consequences of altered NMDAR function (Javitt, 2009; Javitt et al., 2012; Nelson et al., 2014; Pynn & DeSouza, 2013). On the basis of this assumption, a one-off administration of ketamine should, then, mimic primary effects of NMDAR hypofunction, such as deficits in SPEM (Meyhöfer et al., 2015; O'Driscoll & Callahan, 2008) and mismatch negativity (Heekeren et al., 2008; Umbricht & Krljes, 2005), but not the downstream consequences of these alterations, such as impaired top-down attentional control and facial recognition (Javitt, 2009). This is in line with findings that long-term ketamine users exhibit an increased antisaccade error rate similar to that found in psychosis patients (Morgan, Huddy, et al., 2009), while antisaccade performance is virtually intact during one-off ketamine administration (Radant et al., 2010; Schmechtig, Lees, Perkins, et al., 2013). It is also in line with the findings that symptoms such as hallucinations and delusions, which have been proposed as long-term consequences of NMDAR dysfunction (Freeman et al., 2009; Javitt, 2009; Nelson et al., 2014), and which have typically not been reported in one-off ketamine administration, are found in long-term ketamine users (Javitt et al., 2012; Krystal et al., 1994; Morgan, Muetzelfeldt, et al., 2009; Muetzelfeldt et al., 2008).

4.1.2 Schizotypy

High levels of schizotypy are a promising trait model of psychosis (chapter 1.1.4). Seeing as cognitive symptoms are important in the current development of new and more effective treatments, it is unfortunate that the schizotypy literature is inconsistent when it comes to executive functions and possible impairments in this cognitive domain. Sometimes, effects are marginal or unclear. So far, the only meta-analysis examining executive functions in schizotypy was somewhat limited in scope. **Publication 4** reports the results of ten meta-analyses we conducted with the goal to include all relevant research to date and included potential moderating variables which may help explain inconsistencies and shape a clearer view of the current state of research in this domain. The meta-analyses conducted were namely regarding the relationship between Updating and positive, negative and mixed schizotypy respectively; Shifting and positive, negative and mixed schizotypy respectively; as well as Inhibition and positive, negative, mixed and disorganized schizotypy respectively. In each meta-analysis, we included the variables year of publication, study design (categorical design, correlational design) and sample type (community sample, college sample) as moderators. In summary, negative schizotypy was associated with poorer performance on Shifting (Hedges' g=0.32) and Updating (g=0.11). Positive schizotypy was associated with poorer performance on Shifting (Hedges' g=0.18). There were no associations between schizotypy and Inhibition. As for the moderators included in the meta-analysis, publication year had a moderating influence on the relationship between mixed schizotypy and Updating. Study design had a moderating influence on the association between negative schizotypy and Shifting. If only categorical studies were included in the analysis, the effect increased to Hedges' g=0.44 and if only correlative studies were included, the effect decreased to Hedges' g=0.18. Our divergent results for positive, negative and disorganized schizotypy emphasize the importance of examining the relationship between cognition and these subfacets of schizotypy, rather than using a mixed schizotypy score. Our findings also underline the importance of more detailed research to further define the complex personality construct of schizotypy. This is especially important in regards to schizotypy as a model system of psychosis.

Our results are in line with a previous meta-analysis by Chun and colleagues (Chun et al., 2013) and extend those findings to a more comprehensive assessment of the impact of schizotypy on cognitive control. Our finding that cognitive control deficits were most pronounced in negative schizotypy is in line with literature discussing the negative dimension as the primary feature of schizotypy (Horan et al., 2007), with it being the most heritable dimension and the one most strongly associated with poorer well-being, poorer quality of life and higher levels of perceived

stress (Grant, 2015; Horan et al., 2007; Mohr & Claridge, 2015). Our results follow a pattern similarly reported in schizophrenia, albeit to a lesser extent (Ettinger et al., 2014).

Taken together, the results reported in **publication 4** underline the usefulness of schizotypy as a model system of psychosis and the importance of more detailed research to understand and define schizotypy. This, in turn, will be of importance when using schizotypy as a model system of psychosis, in which etiological mechanisms and possible protective factors may be identified without confounds like hospitalization and medication (Barrantes-Vidal et al., 2015; Lenzenweger, 2010).

4.1.3 Model Systems of Psychosis

Taken together, the results of **publications 1-4** suggest that both ketamine and schizotypy are incomplete model systems of psychosis. While acute ketamine administration led to impairments and neuronal alterations in SPEM and some of the impairments and neuronal alterations in emotional memory that have been reported in psychosis, it did not impair antisaccade performance as reported in psychosis and did not lead to the neuronal changes during antisaccade performance that have been reported in psychosis. The meta-analysis of schizotypy and executive functions indicates that schizotypy mimics Inhibition and Updating deficits which are also consistently reported in psychosis, but they do not lead to alterations in Shifting function, which is generally reported in psychosis.

Research into human model systems is promising in advancing our understanding of the etiology and pathophysiology of psychosis, as well as informing the development of novel or improved antipsychotic treatments (Pratt, Winchester, Dawson, & Morris, 2012). This is especially true for cognitive symptoms of psychosis, as modelling cognitive impairments in the commonly applied rat and mice animal models is difficult and only possible to a certain degree (Burrows & Hannan, 2016).

No psychosis model system has as yet been able to mimic all features of psychosis (Carhart-Harris et al., 2013). But given the complex nature of psychotic disorders it may be too much to ask of any single model system to mimic all key aspects (van Os & Kapur, 2009). Our results suggest that, instead, ketamine and schizotypy can be viewed as parts in a puzzle that may help to further our understanding of the etiology and pathophysiology of psychosis. If model systems are to be used in the development of new treatments and to further our understanding of psychotic disorders, we must learn more about them, their scope and limitations, to use their advantages while being conscious of their limitations.

4.2 Limitations and Methodological Concerns

4.2.1 Ketamine as a Model System of Psychosis

A key difference between the ketamine state model of psychosis and the development of psychosis symptoms throughout a patient's life is that during ketamine administration, participants are in a safe environment, monitored by physicians and psychologists (Steeds et al., 2015). They know what is causing their symptoms and that there is a definite end point to them. So although the psychological effects of ketamine resemble early onset psychosis, they are obviously attributable to the injected ketamine (Corlett et al., 2011). This is of importance especially because the interpretation and the appraisal of early perceptual dysfunctions have been discussed as a key factor in the development of psychosis (Corlett, Honey, & Fletcher, 2007; Nelson et al., 2014).

Hallucinations are a key symptom of psychosis (Corlett et al., 2011; Krystal et al., 1994). While ketamine has shown to induce perceptual illusions (altering how present stimuli are experienced), it is as of yet debated if it can induce hallucinations (experiences that are not based on present stimuli). Some studies have reported auditory or visual hallucinations (Bowdle et al., 1998; Malhotra et al., 1996; Vollenweider, Leenders, Oye, et al., 1997; Vollenweider, Leenders, Scharfetter, et al., 1997), others have not (Avila et al., 2002; Honey et al., 2004; Krystal et al., 1994; Radant et al., 1998; Schmechtig et al., 2010). The current state of research suggests that ketamine does not induce hallucinations to the degree seen in psychosis (Corlett et al., 2011; Javitt et al., 2012; Krystal et al., 1994). However, it must be noted that auditory illusions in patients with schizophrenia in early stages of illness have been described as precursors to later hallucinations (Bowers, 1968; Bowers & Freedman, 1966; Chapman, 1966; Freedman, 1974). It is, therefore, possible that hallucinations may develop if the neurochemical alteration were to persist (Corlett et al., 2011). This is in line with findings that chronic ketamine abuse has been linked to hallucinations (Morgan, Huddy, et al., 2009) and that chronic administration, but not single-dose administration, of PCP has been shown to evoke hallucinations in monkeys (Linn, O'Keeffe, Lifshitz, Schroeder, & Javitt, 2007).

Like hallucinations, delusions are a key symptom of psychosis that is not fully modeled by ketamine administrations. Some studies, usually under low ketamine doses, do not report any delusional thoughts in participants (Freeman et al., 2009) and studies employing higher doses more reliably report delusional ideas (Corlett et al., 2011). Delusional ideas found in higher dose studies are often reported by participants with less conviction and in more relative terms than in psychosis, though there have been reports of subjects who described delusional beliefs with a high degree of certainty (Pomarol-Clotet et al., 2006). As with hallucinations, this may model

the early stages of psychosis, in which delusional beliefs are commonly described with less certainty and in more relative terms than in later stages (Corlett, D'Souza, & Krystal, 2010; Corlett et al., 2007; Gross & Huber, 1972).

While it may be a concern that negative symptoms, such as apathy, anesthesia, anhedonia and alogia, which have been reported under acute ketamine administration, are nonspecific sedative effects (Pomarol-Clotet et al., 2006), research suggests that the predictive associations across cognitive domains between ketamine administration and negative symptoms as described by neuropsychiatry in psychosis is strong and argues against simple non-specific sedative effects (Honey et al., 2008).

It is probable that the symptoms mimicked by acute ketamine administration reflect a very early stage of psychosis. It is, then, possible that ketamine administration can be used as a model system to further our understanding of this early prodromal phase (Corlett et al., 2007; Corlett, Taylor, Wang, Fletcher, & Krystal, 2010), but will be less helpful as a tool to understand later stages of psychotic disorders.

While ketamine is one of the most selective NMDAR antagonists available for human studies (Driesen et al., 2013), it has secondary sites of action, including dopaminergic D2 receptor sites, muscarinergic and opioid receptors (Kohrs & Durieux, 1998), although the latter may only show relevant effects at higher doses (Hirota & Lambert, 1996). Importantly, however, the effects of ketamine have been shown to be similar to those of more selective NMDAR antagonists used in animal studies (Anis, Berry, Burton, & Lodge, 1983; Moghaddam, Adams, Verma, & Daly, 1997; Wood, Kim, & Moghaddam, 2012). It must also be noted that while negative symptoms have been related to the NMDAR blocking effects of ketamine, positive symptoms have also been linked to non-NMDA sites (Stone et al., 2008), possibly mediated by postsynaptic AMPA receptors (Jackson, Homayoun, & Moghaddam, 2004; Moghaddam et al., 1997).

Ketamine increases the heart rate, which may affect the BOLD response. Although exploratory analyses did no show a strong effect of heart rate changes on BOLD response, we cannot completely rule out confounding cardiovascular effects on the results presented in this work. Ketamine effects are dose-dependent, as discussed in chapter 4, therefore a limitation of the research presented in this thesis is that only one specific ketamine target plasma dose (100 ng/ml) was used and therefore dose-dependency of the effects reported could not be considered. Another limitation of the work presented is that the neurological and behavioral changes under ketamine administration were not directly compared to those in psychosis patients.

4.2.2 Schizotypy as a Model System of Psychosis

Schizotypy is a somewhat heterogeneous construct, as discussed in chapter 1.1.4. This makes comparison of studies and interpretation of research challenging. When aggregating research, it must be considered whether to not include different measures of schizotypy and risk systematic loss of data, or to include different measures and risk analysis bias due to heterogeneity.

It must be considered that while the research presented here indicated overlapping impairments in psychosis and high levels of schizotypy, this is not proof of similar etiological factors. The alternative hypothesis, that psychosis and schizotypy are two unrelated phenomena that, independently, lead to similar impairments via different molecular and cellular mechanisms, must also be considered.

4.2.3 Further Methodological Concerns

The research presented in **publications 1 and 2** relied on eye movement recording during fMRI. Technical challenges of MRI eye-tracking led to loss of data. Therefore, behavioral measures of oculomotor control could only be acquired for a subsample of participants, which is a methodological limitation that has to be taken into account.

The research presented in **publication 4** suggests moderate to high heterogeneity between the studies which examined the executive function of Inhibition. This is in line with findings that tasks measuring Inhibition function do not highly correlate (Aichert, Wöstmann, et al., 2012), which makes the association between this heterogeneous construct and models of psychosis, such as schizotypy, challenging.

Another important methodological concern regarding the results reported in **publication 4** is that when interpreting meta-analysis data, it is always important to note that it is impossible to completely prevent the garbage-in, garbage-out problem associated with any meta-analytic technique. Any meta-analysis can only ever be as good as the research that goes into it. While the methods of study selection and data-extraction used and reported in this work are measures to limit this effect, the dependence on study and publication quality has to be taken in consideration and is not always easy to determine.

4.3 Future Research

Concerning ketamine and schizotypy as model systems of psychosis, future research will profit from direct comparisons of brain function and behavioral correlates of oculomotor control and executive function in these model systems to those in psychosis patients. Future research may want to expand on the data reported in this work by comparing the effects of different doses of ketamine to examine possible dose-dependent effects on oculomotor control and executive

function. Considering previous research and the research presented here, a comparison of 100ng/ml and a higher dose, such as 150ng/ml target ketamine plasma level may prove to be especially insightful.

In terms of schizotypy as a model system of psychosis, streamlining the definition and measurement of schizotypy as a construct would make the aggregation and interpretation of research easier. This would also aid in making it easier to identify subfacets of schizotypy and their link to dysfunction of oculomotor control and executive function.

Building on the literature reviewed and the research presented in this work, a promising goal for future research is the combination of the ketamine and the schizotypy model systems of psychosis, as has already been done with other model systems (Faiola et al., 2018; Meyhöfer et al., 2017). This combination may prove especially useful as both model systems provide different strengths: While ketamine administration as a state model can be considered as a model of very early onset psychosis, schizotypy as a trait model can be considered a model of later stages of psychosis.

4.4 Conclusions

Acute ketamine administration in healthy human volunteers has been proposed as a state model of psychosis, while high levels of schizotypy have been proposed as a trait model of psychosis. At present, both models should be considered useful but incomplete. The research presented in this body of work illustrates the strengths and limitations of both models. Psychosis is still difficult to treat and much about the mechanisms behind psychotic symptoms and syndromes are yet unknown. Considering the side effects of medication and other treatments and that most patients are seen in later stages of illness, studying the development of psychotic disorders remains difficult. Here, model systems can be useful and provide much needed understanding of underlying causes and mechanisms.

When employing model systems in research, it is important to describe both the strengths and the limitations of the models. This is important, because it helps to define which conclusions can be drawn from data and which aspects of psychosis can be examined with which specific model system. The research presented in this thesis provides further insight into the strengths and the limitations of two frequently used model systems of psychosis – acute ketamine administration and high levels of schizotypy. The ketamine model especially can be considered a useful tool to investigate the early phase of psychotic illness, which is otherwise difficult to investigate. This may make it possible to understand the development of delusions and hallucinations. Combining different model systems in future research could build on the research presented here and further our understanding of psychosis.

Cognitive symptoms of psychosis are as yet very difficult to treat and lead to considerable loss of quality of life and severe impairments in everyday life of patients. Therefore, understanding the mechanisms underlying these symptoms is an important research goal. The research presented in this thesis employs model systems of psychosis to further our understanding of the development and the mechanisms behind cognitive symptoms of psychosis. The combination of model systems of psychosis and cognitive tasks will remain an important tool in psychosis research. Oculomotor control can be considered a biomarker for psychosis. Combining biomarkers such as SPEM deficits with model systems of psychosis can further our understanding of underlying causes, the development and possible treatment of psychotic disorders.

Overall, model systems of psychosis can redefine our understanding of the psychology, neurobiology and development of psychotic disorders, and help further psychological and pharmacological treatments more tailored to specific symptoms and targeting underlying causes more directly.

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6 Appendix A [List of Figures and Tables]

6.1 Figures

6.2 Tables

7 Appendix B [List of Abbreviations]

GWAS	Genome Wide Association Studies
SNP	Single Nucleotide Polymorphism
CNV	Copy Number Variant
SPEM	Smooth Pursuit Eye Movements
NMDAR	N-Methyl-D-Aspartate Receptor
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
PCP	Phencyclidine
dlPFC	Dorsolateral prefrontal cortex
ACC	Anterior cingulate cortex
WCST	Wisconsin Card Sorting Test
SIPS	Structured interview for prodromal syndromes
CPT	Continuous Performance Task
TMT	Trail Making Test
RMSE	Root Mean Square Error
MRI	Magnetic resonance imaging
fMRI	Functional magnetic resonance imaging
TR	Repetition time / time to repeat
TE	Echo time
EPI	Echo planar imaging
BOLD	Blood oxygen dependent
VCPCR	Video-based combined pupil and corneal reflection
RMSE	Root Mean Square Error
3PSM	Three-parameter selection model
PSI	Psychotomimetic States Inventory
FEF	Frontal Eye Field
mPFC	Medial prefrontal cortex

8 Appendix C [Publications Included in the Thesis]

The present thesis is based on four original publications. To avoid violations of copyright, the articles were removed from the appendix section. The articles can be found online using the following references or in hardcopies of the present thesis at the Universitäts- und Landesbibliothek Bonn.

Steffens M., Becker B., Neumann C., Kasparbauer A.M., Meyhöfer I., Weber B., Mehta M.A., Hurlemann R., Ettinger U. (2016) Effects of ketamine on brain function during smooth pursuit eye movements. *Hum Brain Mapp.* 37(11), 4047-4060. doi: 10.1002/hbm.23294

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9 Appendix D [Further Relevant Publications]

Ettinger, U., Meyhöfer, I., **Steffens, M.**, Wagner, M., & Koutsouleris, N. (2014). Genetics, cognition and neurobiology of schizotypal personality: A review of the overlap with schizophrenia. Frontiers in Psychiatry, 5(18), 1–16. http://doi.org/10.3389/fpsyt.2014.00018.

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