Eye movements and schizophrenia risk genes

Associations of the putative schizophrenia risk genes *COMT* and *NRG-1* with smooth pursuit and antisaccade eye movement endophenotypes in schizophrenia patients and healthy controls drawn from the homogenous Icelandic population

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ÁGRIP

Markmið: Meginmarkmið þessa verkefnis var að rannsaka tengsl innri svipgerða smooth pursuit (SPEM) og antisaccade augnhreyfinga við áhættuarfgerðir catechol-*O*-methyltransferasa (*COMT*) og neuregulin-1 (*NRG-1*) gena í hópi íslenskra sjúklinga með geðklofa og í heilbrigðum samanburðarhópi. Breytileiki (val^{158}met) í *COMT* geni kann að tengjast áhættu fyrir geðklofa vegna mismunandi áhrifa á niðurbrot dópamíns í framheila. Breytileikar í *NRG-1* geni kunna að auka hættu á geðklofa vegna þess að NRG-1 gegnir margþættu hlutverki í þroskun taugakerfisins, en vísbendingar eru um að truflanir í taugaþroska eigi þátt í orsökum sjúkdómsins. Áhrif þessara gena á vitræna starfsemi heilans eru lítt þekkt. Finnist tengsl á milli frávika í augnhreyfingum og áhættuarfgerða geðklofa kunna þau að auka skilning á þætti erfðabreytileika í truflunum á vitrænni starfsemi heilans í geðklofa.

Önnur markmið voru að rannsaka innra samræmi augnhreyfimælinga og breytileika í frammistöðu innan hverrar mælingar ásamt því að kanna tengsl alvarleika geðklofaeinkenna og tegund geðrofslyfja við frammistöðu á augnhreyfiprófum. Auk þess var rannsakað hvort fylgni væri á milli frammistöðu á SPEM og antisaccade prófum.

Aðferðir: Prosaccade, antisaccade, fixation og SPEM augnhreyfingar voru mældar með innrauðri ljóstækni í 118 einstaklingum með geðklofa og 109 þátttakendum í samanburðarhópi. Allir þátttakandur voru arfgerðargreindir með tilliti til *COMT* val^{158}met/rs4680 breytileika og tveggja áhættuarfgerða *NRG-1* (SNP8NRG222662/rs4623364 og SNP8NRG243177/rs6994992). Frammistaða á augnhreyfiprófum var greind með sérhönnuðum hálfsjálfvirkum tölvuforritum.

Niðurstöður: Einstaklingar með geðklofa höfðu marktækt afbrigðilegar SPEM og antisaccade augnhreyfingar samanborið við heilbrigða. Þátttakendur með geðklofa höfðu einnig marktækt meiri frávik á prosaccade og fixation prófum en heilbrigðir. Breytileiki val^{158}met í *COMT* geni tengdist hvorki geðklofagreiningu né einkennum geðklofa. Ekki voru marktæk tengsl á milli *COMT* val^{158}met og frammistöðu á SPEM prófi. *COMT* val^{158} tengdist betri frammistöðu á antisaccade prófi en ekki voru marktæk víxlhrif á milli sjúklinga og heilbrigðra. Áhættuarfgerðir *NRG-1* sýndu hvorki marktæk tengsl við frammistöðu á augnhreyfiprófum né við einkenni geðklofa. Þó var frammistaða þeirra sem höfðu *NRG-1* áhættuarfgerð lítilega verri á

flestum SPEM og antisaccade mælingum en hjá þeim sem ekki höfðu *NRG-1* áhættuarfgerð (d= 0.1-0.3).

Innra samræmi var hátt fyrir nánast allar augnhreyfibreytur (Cronbach's α >0.85) og breytileiki í frammistöðu innan hverrar mælingar var svipaður hjá þátttakendum með geðklofa og heilbrigðum. Aldur við greiningu geðklofa, tímalengd veikinda, tegund geðrofslyfja og alvarleiki sjúkdómseinkenna sýndu almennt ekki fylgni við frammistöðu á augnhreyfiprófum. Fylgni á milli frammistöðu á SPEM og antisaccade prófum var lítil og ekki sambærileg hjá sjúklingum og heilbrigðum.

Ályktanir: Rannsóknin staðfestir að frávik á SPEM og antisaccade augnhreyfiprófum eru til staðar í stóru íslensku þýði einstaklinga með geðklofa. *COMT* val^{158}met breytileiki tengist ekki frammistöðu á SPEM prófi. Tengsl *COMT* val^{158} við niðurstöður á antisaccade prófi bendir til þess að hraðara niðurbrot dópamíns í framheila bæti frammistöðu á prófinu og að áhrifin tengist ekki geðklofa. Þó að útiloka megi sterk áhrif *NRG-1* áhættuarfgerða á frammistöðu á SPEM og antisaccade prófum er mögulegt að rannsóknina skorti tölfræðilegt afl til þess að greina væg áhrif áhættuarfgerða.

Hátt innra samræmi og sambærilegur breytileiki í frammistöðu innan hverrar mælingar hjá sjúklingum og samanburðarhópi ásamt því að alvarleiki sjúkdómseinkenna og tegund geðrofslyfja tengist lítið frammistöðu á prófunum styður gildi þessara augnhreyfifrávika sem innri svipgerða. Veik fylgni á milli frammistöðu í SPEM og antisaccade prófum bendir til þess að prófin endurspegli ekki sömu erfðafræðilegu áhættuþætti sjúkdómsins.

Lykilorð: Geðklofi, innri svipgerðir, áhættuarfgerðir, smooth pursuit, antisaccade

ABSTRACT

Aims: The main objective of this thesis was to investigate the association of smooth pursuit (SPEM) and antisaccade eye movement endophenotypes with polymorphisms in the putative schizophrenia risk genes, catechol-*O*-methyltransferase (*COMT*) and neuregulin-1 (*NRG-1*), in schizophrenia patients and controls drawn from a homogenous Icelandic sample. A functional polymorphism (val^{158}met) in the *COMT* gene may increase risk for schizophrenia through its effects on dopamine turnover in the frontal brain and *NRG-1* may be associated with schizophrenia due to its involvement in several neurodevelopmental processes implicated in the pathogenesis of schizophrenia. However, the effects of these genes on neurocognitive functions are not well characterized. Associations between putative schizophrenia risk genes and eye movement endophenotypes may provide information on neural mechanisms by which these genes increase risk for schizophrenia or modulate the expression of the disorder.

Secondary aims were to investigate internal consistency and intra-session performance variability of eye movement performance, to assess the association of schizophrenia symptom levels, illness duration and type of antipsychotic medication with eye movements and to examine the relationship between SPEM and antisaccade performance measures.

Methods: Eye movements were measured in 118 schizophrenia patients and 109 healthy controls using infrared oculography. Each participant performed prosaccade, antisaccade, visual fixation and SPEM tasks and was genotyped for *COMT* val^{158}met (rs4680) and two putative risk variants of *NRG-1* (SNP8NRG222662/rs4623364 and SNP8NRG243177/rs6994992). Eye movement recordings were analyzed using semi-automated computer programs.

Results: Schizophrenia patients performed worse on SPEM and antisaccade tasks than healthy controls. Patients also performed worse than controls on the prosaccade and visual fixation tasks. Allele frequencies of *COMT* val^{158}met were neither associated with diagnosis of schizophrenia nor with symptoms of schizophrenia. *COMT* val^{158}met was not associated with SPEM performance. The *COMT* val^{158} allele was significantly associated with better performance on the antisaccade task, but there were no diagnosis-by-genotype interactions. The *NRG-1* genotypes were

neither significantly associated with eye movement task performance nor with clinical measures of schizophrenia. However, *NRG-1* risk carriers had numerically worse performance on most eye movement measures (d= 0.1-0.3).

Internal consistency was high for most eye movement variables (Cronbach's α >0.85) and systematic intra-session performance changes were similar in patients and controls. Age of illness onset, duration of illness, type of antipsychotic medication and schizophrenia symptom scores were generally not associated with eye movement task performance. Relationships between SPEM and antisaccade performance measures were weak and inconsistent between patients and controls.

Conclusions: The study confirms the presence of SPEM and antisaccade deficits in schizophrenia in a homogenous Icelandic sample. *COMT* val^{158}met was not associated with SPEM performance. The association of *COMT* val^{158} with antisaccade performance indicates that more efficient dopamine degradation in the frontal cortex improves the task performance irrespective of diagnosis of schizophrenia. *NRG-1* risk variants were not significantly associated with eye movement performance. However, while large *NRG-1* genotype effects on SPEM and antisaccade eye movements can be excluded it is possible that the study lacks power to examine weak effects.

High internal consistency, similar intra-session performance changes and limited associations between clinical measures and eye movement task performance support the use of these eye movement task deficits as endophenotypes. Weak relationships between SPEM and antisaccade performance indicate that deficits on the two tasks probably reflect separate sources of genetic risk.

Key words: Schizophrenia, endophenotypes, risk genes, smooth pursuit, antisaccade

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LIST OF ORIGINAL PAPERS

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I. Haraldsson, H.M., Ettinger, U., Magnusdottir, B.B., Sigmundsson, T., Sigurdsson, E., Petursson, H. (2008). Eye movement deficits in schizophrenia: Investigation of a genetically homogenous Icelandic sample. *European Archives of Psychiatry and Clinical Neuroscience,* 258, 373-383.

II. Haraldsson, H.M., Ettinger, U., Magnusdottir, B.B., Sigmundsson, T., Sigurdsson, E., Ingason, A., Petursson, H. (2009). COMT val^{158}met genotype and smooth pursuit eye movements in schizophrenia. *Psychiatry Research,* 169 (2): 173-175.

III. Haraldsson, H.M., Ettinger, U., Magnusdottir, B.B., Sigmundsson, T., Sigurdsson, E., Ingason, A., Petursson, H. (2010). Catechol-*O*-Methyltransferase Val^{158}Met polymorphism and antisaccade eye movements in schizophrenia. *Schizophrenia Bulletin*, 36(1):157-64.

IV. Haraldsson, H.M., Ettinger, U., Magnusdottir, B.B., Ingason, A., Hutton, S.B., Sigmundsson, T., Sigurdsson, E., Petursson, H. (2010) Neuregulin-1 genotypes and eye movements in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience.* 260(1):77-85.

DECLARATION OF CONTRIBUTION

Paper I

Magnús Haraldsson (MH) and Ulrich Ettinger (UE) were equally responsible for designing the study. MH recruited and screened all participants in the study. MH collected all eye movement data. MH collected and analyzed all clinical data. All eye movement data was analyzed by MH under the supervision of UE. The first draft of the manuscript was written by MH. Subsequent versions were edited by MH, UE, Engilbert Sigurðsson (ES) and Hannes Pétursson (HP). The final version was approved by all authors.

Paper II

MH and UE designed the study together. Participants were recruited and screened by MH. MH collected and analyzed all eye movement data. MH collected and analyzed all clinical data. Hreinn Stefánsson (HS) and his staff at Decode Genetics performed Genotyping. Eye movement-genotype associations were analyzed by MH under the supervision of UE. MH wrote the first draft of the manuscript and MH, UE, HP and ES edited subsequent versions. All authors were responsible for its editing and approving the final version of the manuscript.

Paper III

The study was designed by MH and UE. Subjects were recruited by MH and eye movement data was collected and analyzed by MH under the supervision of UE. MH collected and analyzed all clinical data. HS and his colleges at Decode Genetics performed Genotyping. Eye movement-genotype associations were analyzed by MH under the supervision of UE. MH wrote the first draft of the manuscript and MH, UE, ES and HP edited subsequent manuscripts.

Paper IV

The study was designed by MH and UE. Subjects were recruited by MH and eye movement data was collected and analyzed by MH under the supervision of UE. MH collected and analyzed all clinical data. Genotyping was performed by HS and his staff at Decode Genetics. Eye movement-genotype associations were analyzed by

MH. MH wrote the first draft of the manuscript. All authors were responsible for its editing and all approved the final version of the manuscript.

LIST OF ABBREVIATIONS

5-HT	5 Hydroxytryptamine
ACC	Anterior Cingulate Cortex
ADHD	Attention Deficit Hyperactivity Disorder
ANOVA	Analysis of Variance
BOLD	Blood Oxygen Level Dependent
CGH	Comparative Genomic Hybridization
CHIP	Chromatin Immunoprecipitation
CNV	Copy Number Variation
COMT	Catechol-*O*-methyltransferase
CPT	Continuous Performance Test
CT	Computed Tomography
d	Cohen's d
DAO	D-amino Acid Oxidase
DAOA	D-amino Acide Oxidase Activator
DAT	Dopamine Transporter
DISC1	Disrupted in Schizophrenia 1
DLPFC	Dorsolateral Prefrontal Cortex
DNA	Deoxyribonucleic Acid
DRD2	D2 Dopamine Receptor
DRD3	D3 Dopamine Receptor
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Version IV
DTI	Diffusion Tensor Imaging
DTNBP-1	Dystrobrevin-binding Protein 1
DZ	Dizygotic
EEG	Electroencephalography
EOG	Electrooculography
FEF	Frontal Eye Fields
FISH	Fluorescent In Situ Hybridization
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-aminobutyric Acid
Gly	Glycine

GWAS	Genome Wide Association Study
HLA	Human Leucocyte Antigen
Hz	Hertz
ICD-10	International Classification of Diseases, Version 10
IQ	Intelligence Quotient
IRO	Infrared Oculography
LLC	Least-likely Carrier
ln	Natural Logarithm
M.I.N.I.	Mini International Neuropsychiatric Interview
MEG	Magnetoencephalography
MET	Methionine
MHC	Major Histocompatibility Complex
MLC	Most-likely Carrier
MRI	Magnetic Resonance Imaging
Ms	Millisecond
MZ	Monozygotic
NMDA	N-methyl D-aspartate
NRG-1	Neuregulin-1
NRGN	Neurogranin
º/s	Degrees per second
OCD	Obsessive Compulsive Disorder
PANSS	Positive and Negative Syndrome Scale
PCP	Phencyclidine
PCR	Polymerace Chain Reaction
PET	Positron Emission Tomography
PPI	Prepulse Inhibition
rCBF	Regional Cerebral Blood Flow
RDC	Research Diagnostic Criteria
RELN	Reelin
RGS4	Regulator of G Protein Signaling 4
RMSE	Root Mean Square Error
S/N	Signal-to-Noise Ratio
SADS	Schedule for Affective Disorders and Schizophrenia

SANS	Schedule of Assessment for Negative Symptoms
SD	Standard Deviation
SEF	Supplementary Eye Fields
Ser	Serine
SNP	Single Nucleotide Polymorphism
SPECT	Single Photon Emission Computed Tomography
SPEM	Smooth Pursuit Eye Movements
TCF4	Transcription Factor 4
TMT	Trail Making Test
Val	Valine
WCST	Wisconsin Card Sorting Test
ZDHHC8	Zink Finger and DHHC Domain-containing Protein 8
ZNF804A	Zink Finger Protein 804A

INTRODUCTION

Chapter summary

In this chapter several important aspects of schizophrenia research will be reviewed. First, symptoms and diagnostic criteria of schizophrenia are described followed by an overview of epidemiology, risk factors, treatment and outcome of schizophrenia. Next, key findings from neuropathological, brain imaging, neurochemical and neuropsychological studies of schizophrenia are reviewed. Then, the rapidly growing area of schizophrenia genetics will be introduced with special emphasis on two putative schizophrenia risk genes that are subjects to investigation in the present thesis. These are the neuregulin-1 (*NRG-1*) and catechol-*O*-methyltransferase (*COMT*) genes. Recent genome-wide association studies (GWAS) of schizophrenia and studies on copy number variations (CNVs) associated with risk for psychosis are reviewed. This is followed by a discussion on endophenotypes and the main roles they have in genetic studies of schizophrenia, which are to facilitate the discovery of novel schizophrenia genes and to characterize the neurobiological effects of putative schizophrenia risk genes. The validity of eye movement tasks as endophenotypes in schizophrenia research is then evaluated. Each task applied in this thesis is described separately. These are smooth pursuit eye movements (SPEM), visual fixation, antisaccade, and prosaccade eye movements. Several important methodological aspects of measuring and analyzing these eye movements are discussed and studies investigating the qualification of eye movement deficits as schizophrenia endophenotypes are reviewed. Finally, previous studies of neurological, cognitive and molecular genetic correlates of eye movements are summarized.

Definition and diagnosis of schizophrenia

Schizophrenia is a disabling syndrome characterized by symptoms of hallucinations, delusions, disorganized thoughts and behavior, abnormal affect, poverty of speech and loss of motivation. Most schizophrenia patients also have cognitive deficits such as problems with attention, working memory and executive function (Green, 2001). The diagnosis of schizophrenia is based on an examination of the clinical presentation. No diagnostic biological markers exist. The development of standardized diagnostic criteria has helped increasing the reliability of diagnosis. The

most widely used criteria are presented in the International Classification of Diseases (ICD-10) of the World Health Organization (WHO, 1992) and the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association (APA, 1994).

The ICD-10 requires a minimum of one "very clear-cut symptom" or at least two symptoms if "less clear-cut" belonging to symptom groups a) – d) or symptoms from at least two of the groups e) – h) listed in Table 1. The symptoms should have been present for most of the time during a one-month period or more. Schizophrenia should not be diagnosed in the presence of depressive or manic symptoms unless the schizophrenia symptoms preceded the mood symptoms. The illness onset can often be difficult to time and prodromal symptoms such as inactivity and loss of interest may precede the onset of psychotic symptoms by weeks or months. Schizophrenia should not be diagnosed in the presence of organic brain disorders or during drug intoxication or withdrawal.

Table 1

ICD-10 symptom groups

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a) Thought echo, thought insertion or withdrawal, and thought broadcasting;
b) Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations; delusional perception;
c) Hallucinatory voices giving a running commentary on the patient's behavior, or discussing the patient among themselves, or other types of hallucinatory voices coming form some part of the body;
d) Persistent delusions of other kinds that are culturally inappropriate and completely impossible, such as religious or political identity, or superhuman powers and abilities (e.g. being able to control the weather, or being in communication with aliens from another world);
e) Persistent hallucinations in any modality, when accompanied either by fleeting or half-formed delusions without clear affective content, or by persistent overvalued ideas, or when occurring every day for weeks or months on end;
f) Breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologism;

g) Catatonic behavior, such as excitement, posturing, or waxy flexibility, negativism, mutism, and stupor;
h) "Negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses, usually resulting in that these are not due to depression or neuroleptic medication;
i) A significant and consistent change in the overall quality of some aspects of personal behavior, manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal.

The DSM system was developed as a psychiatric classification system for the United States, but is currently used in many other countries, especially for research. It is now in its fourth edition and the fifth edition is expected in May 2012. Most DSM-IV criteria for schizophrenia are the same as those in the ICD-10. The main difference from ICD-10 is that DSM-IV uses operational criteria for clinical work as well as research. The DSM-IV diagnostic criteria for schizophrenia are listed in Table 2.

Table 2

DSM-IV diagnostic criteria for schizophrenia

A. *Characteristic symptoms:* Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):
   (1) Delusions
   (2) Hallucinations
   (3) Disorganized speech (e.g., frequent derailment or incoherence)
   (4) Grossly disorganized or catatonic behavior
   (5) Negative symptoms, e.g. affective flattening, alogia, or avolition

   Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices are conversing with each other.

B. *Social/occupational dysfunction:* For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. *Duration:* Continuous signs of the disturbance persist for at least six months. This six month period must include at least one month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A are present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. *Schizoaffective and mood disorder exclusion:* Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms their total duration has been brief relative to the duration of the active and residual periods.

E. *Substance/general medical condition exclusion:* The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. *Relationship to a pervasive developmental disorder:* If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

In the 1970s the Research Diagnostic Criteria (RDC) were developed in response to the low reliability of psychiatric diagnosis and they have since been commonly used in research (Feighner et al., 1972). Table 3 lists the RDC criteria for schizophrenia. A structured interview, Schedule for Affective Disorders and

Schizophrenia (SADS), was developed for obtaining information relevant to RDC criteria. A lifetime version (SADS-L) covers past and present episodes of the illness and is the diagnostic interview used in the present thesis.

Table 3

RDC diagnostic criteria for schizophrenia

A. During an active phase of the illness (may or may not now be present) at least two of the following are required for definite and one for probable diagnosis:
    1) Thought broadcasting, insertion, or withdrawal.
    2) Delusions of being controlled (or influenced), other bizarre delusions, or multiple delusions.
    3) Somatic, grandiose, religious, nihilistic, or other delusions, without persecutory or jealous content lasting at least one week.
    4) Delusions of any type if accompanied by hallucinations of any type for at least one week.
    5) Auditory hallucinations in which either a voice keeps up a running commentary on the subject's behaviors or thoughts as they occur or two or more voices converse with each other.
    6) Non-affective verbal hallucinations spoken to the subject.
    7) Hallucinations of any type through the day for several days or intermittently for at least one month.
    8) Definite instances of marked formal thought disorder accompanied by either blunted or inappropriate affect, delusions or hallucinations of any type, or grossly disorganized behavior.

B. Signs of the illness have lasted at least two weeks from the onset of a noticeable change in the subject’s usual condition.

C. At no time during the active period (delusions, hallucinations, marked formal thought disorder, bizarre behavior, etc) of illness being considered did the subject meet the full criteria for either probable or definite manic or depressive syndrome to such a degree that it was a prominent part of the illness.

Symptoms of schizophrenia

The symptoms of schizophrenia vary broadly between individuals and they often change significantly with time. There are no pathognomonic symptoms for schizophrenia and every single symptom or sign of the disorder can occur in multiple psychiatric and neurological disorders. The most common features of schizophrenia are hallucinations, delusions, formal thought disorder, disorganized behavior, motor abnormalities and negative symptoms such as flat affect and lack of interest. The term psychosis most often refers to the symptoms of hallucinations and delusions but it is also used in relation to other symptoms such as disorganized speech and behavior.

Hallucinations are perceptions without real external stimuli and they can occur in any sensory modality. In schizophrenia the most common hallucinations are auditory but patients can also experience visual, tactile, olfactory and gustatory hallucinations. Auditory hallucinations range from simple noises to clear voices, which often repeat the patient's thoughts or comment on his/her actions. These comments are often critical and demeaning. Sometimes two or more voices discuss the patient in third person.

Delusions are false beliefs, which are inconsistent with the patient's cultural background and are not affected by rational evidence to the contrary. There are several types of delusions and the most common types are; persecutory delusions (the patient believes he/she is being followed or spied on by other people or agencies); delusions of reference (the sufferer believes that objects, events or other people's behaviors refer to him/her) and delusions of control (other people or some external forces are believed to control one's thoughts, feelings or behaviors).

Formal thought disorder is characterized by illogical or incoherent speech patterns. The patient has disordered thought processes, moves from one topic to another during conversation (loosened associations), may have sudden interruption of speech (thought blocking), sometimes makes up idiosyncratic words (neologism) and may even have completely incomprehensible speech (word salad).

Disorganized behavior. Patients with schizophrenia may appear entirely normal but some appear awkward or odd in social situations, others are withdrawn and seem to be preoccupied with their own thoughts, some are restless or may show sudden and unexpected behaviors and others may show inappropriate or silly behavior such as laughing out load for no obvious reason.

Negative symptoms include diminished volition (lack of drive and initiation), lack of interest, poverty of speech, diminished social contact and flattening of affect. Symptoms of delusions and hallucinations are often referred to as *positive symptoms.*

Cognitive symptoms: Concentration and attention are often impaired. Neuropsychological tests often reveal impairments in high-level cognitive functions such as working memory and executive function.

Motor abnormalities may include catatonic stupor (immobility and lack of awareness of the environment), catatonic excitement (excessive movement), catalepsy (maintenance of the same position for long periods of time), stereotypic movements (repeated movements that are not goal-directed) and mannerism (repeated movements that appear to be goal-directed).

Cognitive symptoms and motor abnormalities are not assessed as part of the present DSM and ICD diagnostic criteria.

Epidemiology and risk factors of schizophrenia

Although schizophrenia has a rather low incidence of 15/100.000/year (Saha et al., 2005) the life time prevalence is fairly high (7/1000) (Saha et al., 2005) because it is usually a chronic disabling disorder that most often starts in adolescence or early adult life. Recent systematic reviews have found the disorder to be slightly more common in males; risk ratio 1.4:1 (Saha et al., 2005). Men also have an earlier age of onset than women and they tend to have a more severe illness course with more negative symptoms and are less likely to recover (Jablensky, 2000). Epidemiological studies have identified several risk factors for developing schizophrenia. The etiology of schizophrenia is unknown but the identification of risk factors is important because they may cast a light on the pathogenesis of the disorder.

Family history: The strongest risk factor is family history of schizophrenia. The risk is 6.5 % in first degree relatives (Kendler et al., 1993) about 10% in dizygotic (DZ) twins and just over 40% in monozygotic (MZ) twins (Cardno et al., 1999). The genetic aspects that may underlie these familial factors are discussed in more detail below.

Obstetric complications: Several population-based studies have found premature delivery (Hultman et al., 1999, Jones et al., 1998), perinatal brain injury (Cannon et al., 2000, Jones et al., 1998) and low birth weight (Cannon et al., 2000, Ichiki et al., 2000, Jones et al., 1998) to be associated with subsequent schizophrenia.

However, negative findings have also been reported (Byrne et al., 2000, Kendell et al., 2000) and it is possible that the obstetric complications either interact with or are consequences of other environmental or genetic predisposing factors for schizophrenia (Mittal et al., 2008).

Viral infections: Maternal viral infections during the second trimester of pregnancy have been implicated as risk factor for schizophrenia in the offspring (Brown et al., 2000, Mednick et al., 1988) but many negative findings have been reported and no specific type of virus infection has been consistently associated with schizophrenia.

Social status: Lower social class has been linked with increased risk of schizophrenia (Bruce et al., 1991). Two hypotheses have been proposed to account for this association. The first suggests that the increase in schizophrenia risk is caused by increased stress imposed on those who are poor (Corcoran et al., 2003) and the second that schizophrenia reduces social and occupational functioning and therefore causes a downward social drift (Fox, 1990).

Geographic location: People born in urban areas have a higher risk of schizophrenia than those who grow up in rural areas (Peen & Dekker, 1997). This is seen across different ethnic groups (Jablensky, 2000) but an increased rate has been seen in certain ethnic minority populations such as first and second generation Afro-Caribbean people in the UK (Coid et al., 2008). This may be associated with the stressful effects of the urban environment and difficulties with adjusting to a new and much different culture.

Substance abuse: Intermittent and chronic consumption of stimulants such as amphetamine and cocaine can induce psychotic symptoms in healthy individuals and lead to relapse in individuals with schizophrenia (Curran et al., 2004). Regular cannabis use at a young age increases the future risk of schizophrenia and this effect is moderately strong even after controlling for the effects of self medication (Henquet et al., 2005).

Treatment of schizophrenia

Antipsychotic medications are the keystone of schizophrenia treatment (Stahl, 2008). Until the late 1980s the conventional or typical antipsychotics were the primary medications for schizophrenia. These medications are effective in treating hallucinations and delusions. All typical antipsychotic medications block dopamine

D_2 receptors in the brain. This action accounts for the therapeutic effects on positive symptoms but can also produce troublesome neurological side effects such as extrapyramidal symptoms (e.g. muscle rigidity and tremor), dystonia, akathisia and tardive dyskinesia. These medications also block noradrenergic and cholinergic receptors, which is associated with many of their side effects such as postural hypotension, sexual dysfunction, dry mouth, blurred vision and urinary retention.

Clozapine was the only atypical antipsychotic medication available until the 1980s. It is the most potent antipsychotic medication for treating positive and negative symptoms (Wahlbeck et al., 1999). A meta-analysis has shown that clozapine is the most effective drug for treatment resistant schizophrenia patients (Chakos et al., 2001). Clozapine is a weak dopamine D_2 antagonist and binds more strongly to dopamine D_4 receptors. It also binds to serotonin, histamine, alpha-adrenergic and muscarinic acetylcholine receptors. It does not cause extrapyramidal side effects. A major disadvantage of clozapine is that it can cause a sudden drop in white blood cell count that can cause serious, even fatal infections if not detected early.

Since 1990 several atypical antipsychotic medications have emerged. These include risperidone, olanzapine, quetiapine and ziprazidone. They are equally effective as typical antispsychotics in treating positive psychotic symptoms but they also have some effects on negative symptoms and cognitive function when compared to typical antipsychotics (Harvey & Keefe, 2001). The atypical antipsychotics block dopamine D_2 receptors reducing positive symptoms and they also block serotonin receptors, which may improve cognitive and affective symptoms. The atypicals cause far less neurological side effects because they block primarily dopamine receptors in the mesolimbic and mesocortical dopamine tracts and have very low affinity for striatal dopamine receptors. However, they have other side effects which may, in the long term, be just as debilitating such as sedation, weight gain, glucose intolerance and hyperprolactinemia. The novel antispsychotic aripiprazole is a partial agonist at dopamine D_2 and serotonin 1A receptors and an antagonist at serotonin 2A receptors. It may stabilize dopamine output in certain areas of the brain causing improvements in positive, negative and cognitive symptoms of schizophrenia (Hirose & Kikuchi, 2005).

Several psychological treatments can improve symptoms and prevent relapse in schizophrenia. Unfortunately only a minority of patients has access to these

treatments mainly due to lack of trained therapists. Cognitive behavioral therapy has been shown to reduce symptoms and improve insight (Tai & Turkington, 2009). Psychoeducation for patients and families can reduce relapse and readmission rate (Rummel-Kluge & Kissling, 2008). Other promising psychological treatments for schizophrenia include social skills training and cognitive remediation therapy (Kern et al., 2009).

Course and outcome of schizophrenia

The onset of schizophrenia is typically between the ages of 16 and 30 years and onset after the age of 45 is rare (Almeida et al., 1995). The emergence of psychotic symptoms is often preceded by a prodromal phase characterized by negative and depressive symptoms, which are commonly associated with increasing cognitive, emotional and social impairment (Hafner et al., 2003). The course of the illness varies between individuals but is often chronic and relapsing. Some patients have an acute onset with symptoms of delusions, hallucinations and thought disorder. Others may have a long insidious onset of cognitive and negative symptoms with few if any positive symptoms (APA, 1994). The majority of people who develop schizophrenia experience severe suffering and life-long disability. Modern treatments can improve symptoms and reduce suffering but about 70% of people with schizophrenia are unable to return to work or school and require assistance from the public health and social security systems within a few years causing an enormous burden on their families and society (Knapp et al., 2004). Schizophrenia patients are 12 times more likely to die from suicide than the general population (Saha et al., 2007). The social development attained at the onset of psychosis is an important predictor of illness course. Older and more socially developed individuals fare better than those who become ill at a young age. Prominent negative symptoms, long prodromal phase, poor premorbid adjustment, co-morbid substance abuse and male gender are associated with worse outcome, while good premorbid adjustment, an acute onset of symptoms, few negative symptoms and female gender are associated with better prognosis (Murray & Van Os, 1998).

Neuropathology of schizophrenia

Neuropathological studies have not found any clear evidence of neurodegenerative features such as reactive gliosis, cytopathological inclusions or neuronal loss in

schizophrenia (Arnold et al., 1998). The absence of degenerative brain changes has lead investigators to concentrate more on possible alterations in the morphology and arrangement of neurons, which may suggest that neurodevelopmental abnormalities contribute to the etiology of schizophrenia. Most of these studies have focused on the prefrontal cortex and the hippocampal formation. Some subtle cytoarchitectural abnormalities have been found in the entorhinal cortex (Arnold, 1999, Falkai et al., 2000) and researchers have seen abnormal neuronal morphology in temporal and parahippocampal regions (Arnold et al., 2005) and also in white matter underlying the prefrontal cortex (Akbarian et al., 1996). The finding of reduced volume of cortical neurophil (axon terminals and dentritic spines) without equivalent neuronal loss also supports the role of abnormal neurodevelopment in schizophrenia (Selemon & Goldman-Rakic, 1999). Cytoarchitectural abnormalities were not found in monkeys who received antipsychotic medications at therapeutic blood levels for up to 12 months (Selemon et al., 1999) suggesting that these changes are not influenced by antipsychotics. Furthermore, the reduction in dendritic spine density appears to be specific to schizophrenia because it was not seen in a control group of patients with other psychiatric disorders who had been treated with antipsychotic medications (Glantz & Lewis, 2000).

There is evidence supporting the notion that schizophrenia is associated with reduced synaptic connectivity of the dorsolateral prefrontal cortex (DLPFC) (Glantz & Lewis, 2000). Studies in rodents have found that dysfunctions in the DLPFC may appear postpubertally when there have been perinatal lesions in the hippocampus (Daenen et al., 2003, Flores et al., 2005). These dysfunctions may therefore be associated with age-related development of hippocampal-frontal pathways. These early lesions to the hippocampus are associated with schizophrenia-like behaviors in rats such as increased response to stress and impaired prepulse inhibition, which only emerge after the animals have reached puberty (Daenen et al., 2003). Postpubertal hippocampal lesions do not lead to similar abnormalities. The neuro-developmental theory of schizophrenia is also supported by evidence of motor abnormalities, cognitive deficits and behavioral abnormalities in children who later develop schizophrenia (Cornblatt et al., 1999, Olin et al., 1998).

Neurochemistry of schizophrenia

A large body of evidence implicates alterations in certain neurotransmitter systems in the pathophysiology of schizophrenia. Most attention has been paid to the dopamine and glutamate systems but other neurotransmitter systems such as gamma-amino butyric acid (GABA), serotonergic and cholinergic systems have also been implicated. The "classical dopamine hypothesis" suggested that positive symptoms of schizophrenia (e.g. hallucinations and delusions) are associated with hyperactive dopamine transmission (Carlsson & Lindqvist, 1963). This hypothesis is supported by evidence that clinically effective doses of antipsychotic medications are related to their potency to block subcortical dopamine D_2 receptors (Seeman & Lee, 1975) and that drugs enhancing dopamine release such as amphetamine can induce psychotic symptoms, which are virtually indistinguishable from positive symptoms of schizophrenia (Lieberman et al., 1990). However, negative symptoms and abnormal cognitive functions such as working memory deficits, which are prominent symptoms of schizophrenia, respond poorly to most antipsychotic medications (Keefe et al., 1999).

Studies in primates have found that decreased dopamine receptor stimulation in the prefrontal cortex is associated with cognitive impairments similar to those found in patients with schizophrenia (Goldman-Rakic et al., 2000). Functional brain imaging studies indicate that negative and cognitive symptoms may be associated with abnormal prefrontal brain function (Weinberger et al., 2001). This evidence lead to the presentation of the "revised dopamine hypothesis", which suggests that schizophrenia may be associated with dopaminergic imbalance involving excessive dopamine activity in subcortical mesolimbic projections and hypoactive mesocortical dopamine projections to the prefrontal cortex (Tzschentke, 2001). Recent neuro-receptor brain imaging studies support this hypothesis. These studies found evidence of increased striatal dopamine activity and indirect evidence of an up-regulation of D_1 receptors in the prefrontal cortex in schizophrenia patients compared to healthy controls (Abi-Dargham, 2004, Gur et al., 2007). Up-regulation of D_1 receptors may reflect a compensatory response associated with dopamine deficiency in the prefrontal cortex. The dopamine dysregulation in schizophrenia may therefore be associated with a cortical-subcortical dysconnectivity. This is supported by studies showing that there is a reciprocal and opposite regulation between cortical and subcortical dopamine systems. Stimulation of prefrontal dopamine activity leads to

inhibition in the subcortical dopamine system (Kolachana et al., 1995). Hence, a deficiency in cortical dopamine function in schizophrenia may lead to disinhibition of subcortical mesolimbic dopamine activity.

Alterations in glutamate transmission, especially hypoactivity in N-methyl-D-aspartate (NMDA) glutamate receptors has been associated with schizophrenia (Olney & Farber, 1995). The glutamate hypofunction hypothesis stems from observations, that the NMDA receptor antagonist phencyclidine (PCP) can cause psychotic symptoms identical to symptoms of schizophrenia in healthy individuals and an exacerbation of pre-existing symptoms in chronic stabilized schizophrenia patients (Javitt & Zukin, 1991). In a model presented by Carlsson et al. (1999) the prefrontal cortex modulates the activity of midbrain dopamine neurons by both inhibitory and activating pathways. The activation is mediated by direct and indirect glutamatergic projections from the prefrontal cortex onto midbrain dopaminergic cells and the inhibiting pathway consists of cortical glutamatergic efferents to inhibitory GABAergic interneurons in the midbrain (Carlsson et al., 1999). This model is supported by studies showing that administration of the NMDA glutamate receptor antagonist ketamine more than doubles the increase in amphetamine induced subcortical dopamine release in humans (Kegeles et al., 2000). These data suggest that there may be a link between the dopamine hypothesis and glutamate hypofunction hypothesis of schizophrenia (Jentsch & Roth, 1999).

An alternative explanation for the impaired cortical control of subcortical dopamine release may originate from a deficit in GABAergic inhibitory function in the prefrontal cortex, which may lead to disinhibition of subcortical dopamine activity. This theory is supported by postmortem studies showing signs of reduction in GABAergic function in the prefrontal cortex in schizophrenia patients. However, these findings have been hard to replicate and are not specific to schizophrenia (Benes & Berretta, 2001).

A series of postmortem and pharmacological studies suggest that a deficit in cortical 5-Hydroxytryptamine/serotonin (5HT) receptor function is involved in schizophrenia (Abi-Dargham et al., 1997). There is also evidence that 5-HT_2 receptor antagonism may be a factor in the efficacy of atypical neuroleptic medications possibly by stimulation of dopamine release in the prefrontal cortex, while having no significant effects on striatal dopamine activity (Andersson et al., 1995).

Alteration in cholinergic neurotransmission at both muscarinic and nicotinic receptors has been implicated in schizophrenia (Sarter & Bruno, 1998). Of special interest are studies showing an association between a variation in the α7 nicotinic receptor gene and deficits in auditory sensory gating in schizophrenia (Leonard et al., 2002).

In summary, there is growing evidence suggesting that schizophrenia may be associated with interactions between abnormalities of dopamine and glutamate transmission. It has been proposed that glutamate hypoactivity in the prefrontal cortex and its connections may lead to dysregulation of dopamine pathways which subsequently causes further interruptions in glutamate mediated connectivity (Laruelle et al., 2003). However, other neurotransmitter systems may also be involved such as serotonin, GABA and cholinergic systems.

Brain imaging research in schizophrenia

Structural imaging

Before the advent of *in vivo* structural brain imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), researchers had long suspected that abnormal brain structure might be associated with schizophrenia. Johnstone et al. (1976) conducted a pioneering CT study in which the ventricular volume was found to be significantly larger in schizophrenia patients compared to healthy controls. Since then a large number of structural imaging studies using mainly MRI have replicated this finding and most studies have shown small volumetric changes in various brain structures in schizophrenia. Literature reviews and meta-analyses have documented about 3% reduction in whole-brain volume, especially grey matter volume, and a concurrent increase in cerebrospinal fluid (Gur et al., 2007). The most significant volume reductions have been observed in temporal brain areas. There is evidence that structures in the medial temporal lobe, particularly the hippocampus, parahippocampal gyrus, amygdala and superior temporal gyrus are reduced by a proportionately larger amount than the whole brain (Lawrie & Abukmeil, 1998, Shenton et al., 2001). Volume reductions have also been found in frontal brain areas, particularly prefrontal and orbitofrontal cortices (Lawrie & Abukmeil, 1998) and in sub-cortical structures such as thalamus (Konick &

Friedman, 2001), cerebellum (Levitt et al., 1999) and corpus callosum (Woodruff et al.,1995).

Although the specific relevance of these structural changes to symptoms of schizophrenia is not well understood there is evidence that memory impairments and positive psychotic symptoms are associated with reduced volumes of the hippocampus and superior temporal gyrus and that abnormal prefrontal cortex volume is associated with impaired executive function and negative symptoms (Gur et al., 2007).

The findings of structural brain abnormalities in schizophrenia raise important questions such as whether these changes are present at illness onset or appear only after the emergence of clinical symptoms and whether the changes are static or progress during the course of the disease. Studies of first episode psychosis patients have provided evidence that structural brain changes are indeed present early in the disease course (Copolov et al., 2000, Ettinger et al., 2001, Sumich et al., 2002). In a recent meta-analysis of 68 MRI studies, including almost 2000 first episode schizophrenia patients, whole brain and hippocampal brain volumes were found to be reduced and ventricular volume increased in patients compared to healthy controls (Steen et al., 2006). Regarding the effects of illness duration on these structural changes some longitudinal studies have demonstrated progressive gray matter volume loss and ventricular enlargement over periods of several years, which may suggest that neurodegeneration may be involved (Lieberman, 1999). However, the basis for a neurodegenerative explanation is rather weak because many of these studies have serious methodological problems and the structural abnormalities may be confounded by factors such as the effects of antipsychotics and substance abuse (Steen et al., 2006). Also, earlier, neuro-pathological studies have not found evidence of degenerative processes such as reactive gliosis, cytopathological inclusions or neuronal loss in schizophrenia (Arnold et al., 1998).

Typical antipsychotics have consistently been associated with increased volume of basal ganglia structures and decreased gray matter volume especially in frontal gray matter. These changes were detected as early as after 12 weeks of treatment (Scherk & Falkai, 2006). Atypical antipsychotics do not seem to increase basal ganglia volume and may actually normalize the volume increase after switching from typical to atypical antipsychotics. Some recent studies have associated atypical antipsychotics with increased gray matter volume but these

findings have not been consistently replicated (Brandt & Bonelli, 2008, Scherk & Falkai, 2006).

The question of whether structural brain abnormalities are a vulnerability or trait marker of schizophrenia can be addressed by studying the patients' relatives and individuals at high risk for developing schizophrenia. A recent systematic review and meta-analysis of studies of relatives found significant hippocampal reduction in relatives compared to healthy controls (Boos et al., 2007). Two studies, the Edinburgh High-Risk Study and a study conducted in Melbourne Australia, have examined structural brain changes over 10 years in large groups of individuals with high risk of schizophrenia (Johnstone et al., 2005, Pantelis et al., 2003). Both research groups have reported progressive volume reductions in parahippocampal gyri, fusiform gyri and cerebellar gray matter over a period of one to two years prior to the development of psychotic symptoms. These findings suggest that a temporal lobe volume reduction may be a vulnerability marker of schizophrenia.

Diffusion tensor imaging (DTI) is a recent technique for investigating brain white matter integrity. It measures the directionality of axonal flow of water molecules, which is called anisotropy and is an index of white matter integrity. Several DTI studies have found white matter abnormalities in schizophrenia patients, especially in the frontal and temporal lobes (Kanaan et al., 2005). These findings correspond with observations of functional deficits in fronto-temporal connectivity and support several proposals of schizophrenia being primarily a disorder of neuronal connectivity (Friston & Frith, 1995, Tononi & Edelman, 2000).

Functional imaging

Brain activity can be examined with techniques such as single photon emission computed tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). SPECT is a tomographic imaging technique using gamma rays, PET measures variations in regional blood flow or glucose metabolism using radioactive tracers and fMRI measures the hemodynamic response to neuronal activity. SPECT and PET are also used to study neuroreceptor availability using radiolabeled compounds or drugs that bind selectively to certain types of receptors.

In schizophrenia these techniques have been used to study brain activity both in relation to specific symptoms such as negative symptoms and with various

neurobehavioral activation tasks in order to elucidate the relevant underlying brain circuitry. Negative symptoms have been associated with decreased prefrontal brain activity (Liddle et al., 1992) and auditory hallucinations with increased activity in the auditory association cortex (Shergill et al., 2000, Silbersweig et al., 1995). The activation tasks have probed cognitive functions such as attention, working memory, abstraction and sensorimotor and emotion processing. The performance deficits of schizophrenia patients on these cognitive tasks have repeatedly been associated with reduced prefrontal, temporal and basal ganglia activity (Shenton et al., 2001, Vink et al., 2006, Weinberger et al., 2001) adding support to the notion that schizophrenia is a disorder of distributed neural circuits.

Some fMRIstudies have found equal (Honey et al., 2002) or increased activity (Manoach et al., 2000) of the DLPFC in schizophrenia patients performing working memory tasks. Several factors may affect hypo-/hyperfrontality in schizophrenia (Manoach, 2003). Group averaging of imaging data may obscure functional heterogeneity of the prefrontal cortex. This is supported by fMRI data showing that a group of schizophrenia patients activated fewer voxels in common than healthy subjects during a working memory task, but the total activation was not less in the patients (Manoach et al., 2000). Another factor that may affect patterns of brain activation is the choice of cognitive tasks. Schizophrenia patients may have selective impairments on certain domains of a task, which may lead to contradictory findings in functional imaging studies (Wexler et al., 1998). Hypofrontality may also be related to factors such as poor motivation, use of an inappropriate strategy for solving the task or the task may simply be too difficult. Findings of hyperfrontality in schizophrenia patients have also been interpreted as a sign of neural inefficiency associated with patients having to put increased strain on the neural circuitry in order to perform adequately (Weinberger et al., 2001).

Several functional imaging studies have investigated the effects of antipsychotics on brain function in schizophrenia. A review of these studies suggests that atypical antipsychotic medications in contrast to typical antipsychotics can have normalizing effects when hypoactivations are observed (Davis et al., 2005). However, these findings need to be interpreted cautiously because the studies are fraught with methodological problems such as variability in imaging techniques, research design, subject characteristics and statistical methods.

Cognitive deficits in schizophrenia

Although the existence of cognitive impairments in schizophrenia were well recognized by Emil Kraepelin who, over a century ago, coined the term Dementia Praecox for what today is called schizophrenia, it was not until late last century that substantial attention was paid to cognition in schizophrenia. Most patients with schizophrenia have cognitive deficits, which account for much of the functional decline associated with the disorder (Green, 2001). Functional outcomes such as independent living and work performance have been shown to have a stronger association with cognitive function than with positive and negative symptoms of schizophrenia (Harvey et al., 1998).

In a large meta-analysis of cognitive studies in schizophrenia more than 70% of patients performed on average 1.5-2 standard deviations (SD) below the mean of healthy subjects on multiple cognitive domains. The deficits were most prominent on domains of verbal and working memory, processing speed and word fluency (Heinrichs & Zakzanis, 1998). Although studies show that approximately 20% of schizophrenia patients fall within the limits of normal cognitive function it is likely that many of these patients are actually performing below their premorbid potential. This notion is difficult to prove but has been supported by the finding that most schizophrenia patients perform below expectations based on maternal educational level, which is shown to be a reliable predictive factor (Keefe et al., 2005). Also among MZ twins discordant for schizophrenia the affected twin consistently performs worse than the unaffected twin even if his/her performance is within the normal range (Goldberg et al., 1990).

When cognitive performance in schizophrenia patients is compared with the performance of healthy controls one has to keep in mind that severely ill patients are often too difficult to test or unable to provide informed consent and are therefore often excluded. Therefore it is possible that studies underestimate cognitive deficits in schizophrenia.

In many schizophrenic individuals intellectual impairments are present years prior to the onset of psychotic symptoms. Retrospective case-control, prospective follow-up and population-based cohort studies have found that children who later develop schizophrenia often have cognitive impairments when compared to healthy children (Lewis, 2004). In a study on Swedish male army conscripts a low IQ at age 18 was associated with increased risk for developing schizophrenia later in life

(David et al., 1997). There is also some evidence that children who later develop schizophrenia show a progressive cognitive decline and deteriorating scholastic performance between early childhood and late adolescence (Fuller et al., 2002). This data suggests that individuals who develop schizophrenia have worse cognitive performance than their healthy peers at a young age and these deficits tend to worsen until psychotic symptoms emerge.

Studies have found schizophrenia patients to be more cognitively impaired than patients with bipolar disorder (Goldberg, 1999). Cognitive deficits in schizophrenia have been shown to be uncorrelated with psychotic symptoms (Hughes et al., 2003) but there is evidence that cognitive deficits in bipolar disorder are associated with symptom severity (Goldberg, 1999), suggesting these may be traits in schizophrenia but state markers in bipolar disorder.

The question whether cognitive deficits in schizophrenia are stable or progressive over the illness course remains unresolved. However, most studies suggest that after the illness onset the cognitive impairments remain relatively stable. In a study following both schizophrenia and bipolar patients from the time when they had a psychotic episode until eight months after the psychotic symptoms had remitted schizophrenia patients had the same level of cognitive impairment while bipolar patients had significantly improved their cognitive performance (Harvey et al., 1990). A review of 15 longitudinal studies testing schizophrenia patients at various stages of their illness did not find cognitive impairments to be progressive (Rund, 1998). In first-episode studies cognitive performance of schizophrenia patients can be assessed without the possible confounding effects of psychotropic medications and disease chronicity. When a group of first-episode patients was followed for 5 years their cognitive function did not deteriorate and some patients even showed some improvement (Gold et al., 1999).

Despite strong evidence that cognitive deficits are relatively static premorbid core features of schizophrenia and essentially independent of clinical symptoms they are not part of the current diagnostic criteria for the disorder. Some researchers have suggested that if found to be sufficiently reliable and specific in future studies cognitive deficits should be added to the diagnostic criteria for schizophrenia (Keefe & Fenton, 2007, Lewis, 2004). Also, since cognitive impairments are often detectable long before psychotic symptoms appear it is possible that a focused cognitive assessment could become a useful screening tool in high-risk populations.

Genetics of schizophrenia

In this section the genetic aspects of schizophrenia will be discussed. First, behavioral genetic studies will be reviewed. Then the rapidly progressing area of molecular genetic research in schizophrenia will be outlined with special emphasis on variations in two putative schizophrenia risk genes, whose effects are subject to investigation in the present thesis. These are the neuregulin-1 (*NRG-1*) and catechol-*O*-methyltransferase (*COMT*) genes. Finally, recent genome wide association studies (GWAS) and investigations of DNA copy number variations (CNVs) in schizophrenia will be addressed.

Behavioral genetics

Since the first systematic family study showing that schizophrenia is more common in siblings of probands than in the general population was published in 1916 (Rudin, 1916) multiple family studies have consistently found higher risk in the patients' relatives than the general population. Studies using operational diagnostic criteria and meticulously collected control samples have found that first degree relatives have 3-15% risk of developing schizophrenia while relatives of healthy controls have 0.5-1% risk (Shih et al., 2004). Second and third degree relatives of schizophrenia patients are also at an increased (1.5-3%) risk (Maier et al., 2002). Patients with early onset schizophrenia are more likely to have a family history of schizophrenia than patients who develop the disorder after the age of 25 (Waddington & Youssef, 1996).

First degree relatives of schizophrenia patients are not only at increased risk of developing schizophrenia but also of several other related disorders such as schizotypal personality disorder, schizoaffective disorder and delusional disorder, that have been referred to as schizophrenia spectrum disorders (Lenzenweger, 1994).

Family studies do not provide evidence of how much of the risk is explained by shared genes and how much is explained by shared environmental factors. In twin and adoption studies it is possible to investigate the relative contributions of genetic and environmental factors.

In twin studies the concordance rate for schizophrenia is compared between MZ and DZ twins. Twins are concordant for a disorder when both individuals are affected and discordant when only one individual is affected. All twin studies have found a higher concordance rate for schizophrenia among MZ twins than DZ twins.

In studies using operational diagnostic criteria the concordance rate is 45-75% among MZ twin pairs but 4-15% among DZ pairs, which is similar to what is seen in first degree relatives (Lichtermann et al. , 2000). This difference in concordance rate between MZ and DZ twins shows that genetic factors are strongly associated with schizophrenia. From twin studies heritability, which is the proportion of phenotypic variation that is attributed to genetic variation, can be assessed. A meta-analysis of 12 schizophrenia twin studies found the estimate of heritability in liability to schizophrenia to be 81% (Sullivan et al., 2003). This is higher than the heritability of most complex diseases with a well established genetic risk such as type II diabetes and breast cancer (Kirov et al., 2005).

Twin studies have been criticized for assuming that environmental factors are shared in an equal way among MZ and DZ twins. It has been pointed out that environmental factors are more likely to be similar among MZ than DZ twin pairs and this may account for an increased concordance rate for schizophrenia among MZ twins (Riley, 2003). However, when twin studies are reviewed the concordance rate among MZ twin pairs reared apart is found to be similar to the concordance rate among MZ pairs who were reared together (Gottesman, 1982).

Adoption studies provide a method for evaluating the role of genetic factors in schizophrenia independent of influences from the family environment. Studies show that the lifetime prevalence of schizophrenia is about ten times higher among individuals who are adopted away from schizophrenic parents than among individuals who are adopted away from healthy parents. Also, schizophrenia and schizotypal personality disorder are much more common among biological relatives of adoptees diagnosed with schizophrenia than among adoptees who do not develop schizophrenia (Ingraham & Kety, 2000). One study did not find an increased rate of schizophrenia among individuals who were adopted by parents who later developed schizophrenia compared to individuals who were adopted by healthy parents (Wender et al., 1974).

It is of particular interest that the risk for schizophrenia in relatives of individuals with schizophrenia is similar in family and adoption studies (Kendler & Gardner, 1997). This suggests that the effects of environmental factors are similar in adopted and non-adopted individuals with schizophrenia.

Family, twin and adoption studies provide robust evidence for the role of genetic factors in the etiology of schizophrenia. However, the mode of genetic

transmission in schizophrenia has not been defined. The genetics of this heterogeneous syndrome are most likely very complicated and a simple Mendelian mode or a single gene model is exceedingly unlikely. In recent years it has been postulated that schizophrenia may be associated with combined effects of multiple genes each having a relatively small effect on the risk (Gogos & Gerber, 2006). Schizophrenia may also be associated with interactions between risk genes (epistasis) as well as interactions between genes and various unidentified environmental factors (van Os et al., 2008). Furthermore, there is growing evidence that epigenetic mechanisms and *de novo* chromosomal mutations may be involved in the etiology of the disorder (Mill et al., 2008, Stefansson et al., 2008).

Molecular genetics

Identification of genes responsible for the high heritability of schizophrenia is essential for understanding the etiology and pathophysiology of the disorder. Finding schizophrenia genes may also lead to new developments in pharmacological treatment. Modern molecular genetic research started in the early 1980s with the introduction of new technologies using DNA markers and polymerase chain reaction (PCR), which allowed researchers to investigate pieces of DNA in more detail than before. In PCR a DNA polymerase is used to amplify a DNA fragment of interest by *in vitro* enzymatic replication.

The two main methods for identifying disease genes are linkage and association studies. In linkage analysis families with two or more affected individuals are studied to identify the co-transmission of genomic regions with the disease. Statistical analysis is employed to determine whether two pieces of the genome are transmitted together to an offspring more often than would be expected by chance. This approach can be applied genome-wide by using a few hundred equally spaced genetic markers to screen the whole genome for possible disease genes. However, linkage studies are difficult to conduct because they involve the participation of multiply affected families, which are generally hard to collect. The linkage approach is a powerful tool for locating DNA markers or genes of major effect, without any previous knowledge of disease etiology, but it is a weak strategy for identifying genes of small effect. A linkage signal does not identify a specific liability gene but a particular region of the genome, which can be quite large and include a large number of genes.

In association studies the frequencies of previously identified candidate susceptibility genes are compared between unrelated samples of affected individuals and healthy controls drawn from the same population. Unlike the linkage approach association studies are able to identify genes of small effect. Until recently it was not possible to apply the association approach genome-wide. The methods of newly developed genome-wide association studies (GWAS) are described below.

Early genome-wide linkage studies in schizophrenia implicated multiple chromosomal areas but very few of those fulfilled criteria for statistical significance and subsequent studies were consistently unable to replicate positive findings (Jurewicz et al., 2001). The inability to find replicable positive linkage in schizophrenia was explained by inadequate sample sizes and small effects of individual risk genes. However, at the end of the 20th century when over 20 genome-wide linkage studies had been completed several chromosomal areas had shown linkage in two or more samples. In two meta-analyses of schizophrenia linkage studies evidence of linkage was found for regions on chromosomes 1q, 2q, 3p, 6p, 8p, 11q, 13q, 14p, 20q and 22q (Badner & Gershon, 2002, Lewis et al., 2003). However, only 8p and 22q were supported by both meta-analyses. These linkage studies supported the notion that schizophrenia is associated with multiple genes that each account for a small increase in risk and that a locus of large effect is very unlikely to exist.

Early association studies were focused on genes, which were selected on the basis of their functionality, or on previous linkage findings. The limited number of functional candidate genes and the lack of replicated linkage findings were major problems in association studies for many years and no clear cut evidence of association was found. Stratification and multiple testing did also pose significant problems in these studies. A stratification effect may appear when a certain marker and a specific disorder are common in a part of the population but there is in fact no true causal relationship. An example of a stratification effect is the association between the *HLA-A1* genotype and the ability to eat with chopsticks among people in the San Francisco Bay area (Lander & Schork, 1994). The *HLA-A1* marker is more common among people of Chinese origin than Caucasians. A multiple testing effect refers to the risk of false positive findings due to chance when many markers are investigated in the same study.

Many association studies have looked at functional genes involved in dopamine and serotonin transmission (Jurewicz et al., 2001). Meta-analyses of these studies have demonstrated significant associations of polymorphisms in the dopamine D_2 receptor gene (DRD2) and tryptophan hydroxylase (TPHI) gene with schizophrenia (Williams et al., 2009). TPH1 is the rate-limiting enzyme in the synthesis of serotonin.

Recent advances in genome analysis technology and the application of linkage disequilibrium mapping have made it possible for researchers to identify candidate genes within linkage regions. Linkage disequilibrium refers to the non-random association of alleles at two or more loci either on the same or different chromosomes. An allele is one member of a pair or series of genes that occupy a specific position on a chromosome. This has led to testing of specific allele variants, which can be any kind of genetic marker such as a SNP (single nucleotide polymorphism), microsatellite or a CNV. SNPs are transformations of one DNA nucleotide into another, for example C to T or A to G that are inherited across generations. Microsatellites are short tandem repeats of variable length and CNVs are deletions or duplications of large or small DNA segments. Alleles are said to be in linkage disequilibrium because they do not travel randomly but together as a contiguous sequence across generations. Finding a suspected disease variant more frequently in patients than healthy controls constitutes evidence of genetic association. If such an association is not an artifact caused by for example multiple testing, genotyping errors or population stratification the variant is either a causative marker or it is in linkage disequilibrium with a nearby sequence variant that is causative.

When several SNPs are in linkage disequilibrium with each other, univariate association analyses of individual SNPs may lead to a biased estimation of the genetic effect. This problem can be circumvented with haplotype analyses in which sets of several SNPs (haplotypes) are investigated together. Haplotype analysis can help increasing the power of association analysis by differentiating the true effects of a SNP from what is due to its linkage disequilibrium with another SNP. Haplotypes also increase the power of association analyses because fewer SNPs need to be typed. This is because some of the SNPs are so-called tag SNPs, which can represent the whole set of polymorphisms belonging to the haplotype. Therefore it is possible

to identify genetic traits involving multiple SNPs by detecting only one or a few SNPs from a haplotype.

Since the year 2002 a series of studies employing various methods of fine mapping of linkage regions have identified several putative risk genes for schizophrenia. There is an enormous and constantly growing schizophrenia candidate-gene literature including both positive and negative findings. However, for many of the positive studies evidence for association with schizophrenia is weak and replications are lacking. None of the candidate genes can be declared a clear cause of schizophrenia. The strongest evidence is for the genes dystrobrevin-binding protein 1 (*DTNBP1* or dysbindin) (Straub et al., 2002) and neuregulin 1 (*NRG-1*) (Stefansson et al., 2002). The *NRG-1* gene will be discussed later in this section. Data for several other genes such as D-amino acid oxidase (*DAO*) (Schumacher et al., 2004), D-amino acid oxidase activator (*DAOA*) (Chumakov et al., 2002), regulator of G protein signaling 4 (*RGS4*) (Chowdari et al., 2002) and *COMT* (Shifman et al., 2002) have also been considered promising but less compelling (Norton et al., 2006).

DTNBP1

The *DTNBPI* gene maps to chromosome 6p22.3, which is one of the most consistently replicated linkage regions for schizophrenia. Positive association of *DTNBP1* with schizophrenia has now been shown in more than 10 samples (Norton et al., 2006). In these studies haplotype analysis has generally yielded more significant association than single SNPs alone suggesting that a true susceptibility marker is yet to be found. Postmortem studies have found reduced *DTNBP1* mRNA expression in frontal brain areas of schizophrenia patients. Cultured neurons with reduced *DTNBP1* expression show reduction in glutamate release. This suggests that variations in *DTNBP1* may confer risk of schizophrenia by altering glutamate function (Kirov et al., 2005).

DAO and DAOA

The *DAO* and *DAOA* genes have both been associated with schizophrenia (Norton et al., 2006). At least five studies have replicated the association for *DAOA* and one study found evidence for statistical interactions between the two genes and risk for schizophrenia. DAO oxidizes D-serine, which is a potent activator of the NMDA glutamate receptor and DAOA is an activator of DAO. At least four studies have

found associations between *DAOA* and bipolar disorder and in one of these studies analysis across diagnostic categories found no association with psychosis but a strong association with history of major depression (Chen et al., 2004c, Hattori et al., 2003, Schumacher et al., 2004, Williams et al., 2006). It is therefore possible that variations in *DAOA* confer risk for major depression across diagnostic boundaries rather than being a specific risk gene for schizophrenia.

RGS4

Attention was drawn to the *RGS4* gene after a postmortem study showed decreased expression of the protein in brains of schizophrenia patients (Mirnics et al., 2001). There is evidence that *RGS4* modulates the activity of glutamatergic receptors and that its own activity is regulated by dopaminergic neurotransmission (Saugstad et al., 1998, Taymans et al., 2004). The gene maps to a putative linkage region on chromosome 1q22. There is modest evidence of positive association with schizophrenia but the pattern of markers being associated differs among samples (Chowdari et al., 2002, Morris et al., 2004, Zhang et al., 2005). Negative findings have also been reported (Cordeiro et al., 2005, Sobell et al., 2005).

COMT

COMT is an enzyme that catabolizes catecholamines. The *COMT* gene has been extensively studied in schizophrenia because of the key role it plays in metabolic inactivation of dopamine, a neurotransmitter known to be involved in prefrontal cortex function (Sawaguchi & Goldman-Rakic, 1991) and the pathophysiology of schizophrenia (Laviolette, 2007). It has also attracted attention because it maps to chromosome 22q11, which has been identified as a susceptibility locus for schizophrenia in several linkage studies (Chen et al., 2004b, Liu et al., 2002) and it is a region affected in a hemi-deletion syndrome called velocardiofacial syndrome. This syndrome is associated with a high (25%) incidence of psychotic symptoms indistinguishable from schizophrenia (Murphy et al., 1999).

Since 1996 over 250 peer-reviewed papers have been published on *COMT* and schizophrenia and the *COMT* gene is currently the most extensively studied gene in psychiatry. Most studies have focused on a co-dominant functional SNP (rs4680) in the *COMT* gene. This mutation causes a substitution of the amino acid methionine (met) for valine (val) at codon 158 of the membrane-bound isoform of the enzyme.

The met^{158} variant is three to four times less active than the val^{158} variant. Therefore, met^{158} homozygotes have less efficient dopamine degradation than val^{158} homozygotes and heterozygotes have intermediate enzyme activity (Lachman et al., 1996)

Investigations of humans have shown association between the *COMT* val^{158}met polymorphism and neuropsychological measures of prefrontal cortex function (Egan et al., 2001, Goldberg et al., 2003, Malhotra et al., 2002, Rosa et al., 2004). This is relevant to schizophrenia because abnormal prefrontal cortex function is an important feature and proposed trait marker of schizophrenia. Egan et al (2001) found val^{158} carrier status among schizophrenia patients, relatives of schizophrenia patients and healthy controls to be associated with worse performance on the Wisconsin Card Sorting Test (WCST). The WCST is a commonly used test for assessing frontal lobe functions such as executive function and modulation of impulsive responses. Goldberg et al (2003) showed that working memory performance measured with the N-back test was associated with *COMT* val^{158}met in schizophrenia patients, their siblings and healthy controls. Val^{158} homozygotes performed worse than met^{158} homozygotes and the heterozygotes showed intermediate performance. On the other hand, there is also data suggesting that the val^{158} allele is associated with better performance on tasks requiring cognitive flexibility (Nolan et al., 2004) and it has been suggested that whether a *COMT* genotype is beneficial or detrimental for cognitive function may not only depend on the dopaminergic state of the frontal cortex but also on the nature of the task being performed (Tunbridge et al., 2006).

Studies of *COMT* val^{158}met associations with schizophrenia have been inconsistent. Although some have found the val^{158} allele to be a risk factor for schizophrenia (Chen et al., 2004b, Egan et al., 2001, Kremer et al., 2003) others have not (Daniels et al. 1996, Karayiorgou et al., 1998) and recent meta-analyses did not find support for significant association (Fan et al., 2005, Glatt et al., 2003, Munafo et al., 2005, Okochi et al., 2009) indicating that it is unlikely that a potential relationship between *COMT* and schizophrenia is limited to a main effect of the single locus val^{158}met polymorphism on the risk for schizophrenia. Therefore, investigators have studied the possibility that *COMT* val^{158}met interacts with other potential genetic and environmental risk factors for schizophrenia. Interestingly, a recent study found that val^{158} carriers had an increased risk of developing

schizophrenia if they used cannabis, while cannabis use did not increase the risk in individuals who where met^{158} homozygotes (Caspi et al., 2005). *COMT* may therefore modulate the effects of cannabis on risk for psychosis. Another study observed an association between several SNPs in the *COMT* gene (including val^{158}met) and SNPs in other potential schizophrenia risk genes such as *RGS4, DAOA* (Nicodemus et al., 2007). Finally, several studies have reported associations of various other *COMT* SNPs and haplotypes with schizophrenia (Williams et al., 2007). These findings, and the role of *COMT* in dopamine regulation in the brain, suggest that the *COMT* gene might exert a minor effect on the genetic risk for schizophrenia. At the time of planning of the present thesis in 2004 the *COMT* gene was considered a better candidate schizophrenia risk gene than it is now.

NRG-1

The *NRG-1* gene is located on chromosome 8p21-p12, which is one of the most replicated linkage loci for schizophrenia (Tosato et al., 2005). Neuregulins are a family of growth factors that share an epidermal growth factor-like domain and are encoded by four genes (*NRG 1-4*), of which *NRG-1* is the best characterized. *NRG-1* is a large and complex gene producing six protein types and more than 30 isoforms involved in growth and development of multiple tissues, including the central nervous system (Mei & Xiong, 2008). NRG-1 is involved in neuronal migration and differentiation, glial development, synapse formation and it regulates the activity of NMDA glutamatergic receptors. This is relevant to schizophrenia because, as described earlier, there is evidence that schizophrenia may be a neurodevelopmental disorder and that glutamatergic hypoactivity may be associated with schizophrenia (Olney & Farber, 1995). NRG-1 also regulates expression of $GABA_A$ and nicotinic acetylcholine receptor subunits but both of these receptors have been implicated in pathophysiology of schizophrenia (Liu et al., 2001).

The *NRG-1* gene was first associated with schizophrenia in an Icelandic sample by Stefansson et al (2002). They first discovered evidence of linkage between a locus on chromosome 8p and schizophrenia in a genome scan of 33 Icelandic pedigrees including 105 schizophrenia probands. Extensive fine mapping with SNPs and microsatellites using haplotype analysis of 478 patients and 394 controls identified three haplotypes mapping to the *NRG-1* gene. The three haplotypes shared a core haplotype consisting of five SNPs (SNP8NRG221132, SNP8NRG221533,

SNP8NRG241930, SNP8NRG243177 and SNP8NRG433E1006) and two microsatellites (478B14-848 and 420M91395). The core haplotype was present in 15.4% of the schizophrenia patients and 7.5% of controls yielding a relative risk of 2.2. Stefansson et al (2002) also examined mutant mice that were heterozygous for either *NRG-1* or its receptor *ErbB4*. They found that the mutant mice showed hyperactivity in the novel open-field test and impaired prepulse inhibition (PPI). The novel open-field test is a behavioural mouse model for schizophrenia and PPI is a measure of sensory gating. Studies have shown that schizophrenia patients have impaired PPI (Braff & Geyer, 1990). Stefansson et al (2002) demonstrated that the two behavioural phenotypes were partially reversible with the antipsychotic medication clozapine. Furthermore, the *NRG-1* hypomorphs had fewer functional NMDA glutamate receptors than the wild-type mice.

The association of *NRG-1* with risk for schizophrenia was soon replicated in a Scottish sample where the core haplotype was associated with a similar, although slightly lower, relative risk (Stefansson et al., 2003). These findings were followed by studies in several ethnic populations that reported an association between schizophrenia and genetic markers either within the original core haplotype or related markers (Bakker et al., 2004; Benzel et al., 2007; Corvin et al., 2004; Fukui et al., 2006; Georgieva et al., 2008; Hall et al., 2004; Kim et al., 2006; Li et al., 2004; Petryshen et al., 2005; Tang et al., 2004; Williams et al., 2003; Yang et al., 2003; Zhao et al., 2004). However, several negative findings have also been reported (Duan et al., 2005, Ingason et al., 2006, Iwata et al., 2004, Rosa et al., 2007, Thiselton et al., 2004) and while one meta-analysis found strong association of the original core haplotype with schizophrenia (Li et al., 2006) another meta-analysis reported a non-significant association of SNP8NRG221533 with the disorder (Munafo et al., 2008). The between study heterogeneity may possibly be explained by different operation of this SNP in distinct populations.

The mechanisms by which *NRG-1* variants may contribute to the pathogenesis of schizophrenia have not been identified. The *NRG-1* risk variants are all located on non-coding and promoter regions of the gene. They may therefore operate by altering gene expression and splicing rather than affecting protein structure. This notion is supported by recent findings of altered NRG-1 isoform expression associated with some *NRG-1* risk markers. In a post-mortem study SNP8NRG221132 was associated with increased expression of NRG-1 type I

isoform in the hippocampus of schizophrenia patients (Law et al., 2006). The same researchers found SNP8NRG243177, which is located on a promoter area, to be associated with increased expression of the brain-specific type IV isoform in frontal brain areas of both healthy and schizophrenia subjects (Law et al., 2006).

Recent studies have found associations between the SNP8NRG243177 marker and alterations in several measures of brain function. Hall et al (2006) found this allele to be linked with decreased fronto-temporal brain activation and decreased IQ in individuals with high risk of developing schizophrenia (Hall et al., 2006). Furthermore, this risk allele correlated with decreased white matter density and neuronal connectivity of the internal capsule in healthy subjects (McIntosh et al., 2008), increased lateral ventricular volume in first episode schizophrenia (Mata et al., 2009), increased unusual thoughts in schizophrenia patients in situations of high expressed emotions (Keri et al., 2009), reduced spatial working memory (Stefanis et al., 2007) and higher neuroticism in healthy subjects (Krug et al., 2008) and with lowered expression of α7 nicotinic acetylcholine receptors in the DLPFC of schizophrenia patients and healthy controls (Mathew et al., 2007). The last finding is interesting in light of a recent study that found axonal expression of α7 nicotinic acetylcholine receptors on sensory neurons to be regulated by NRG-1 (Hancock et al., 2008) and there is evidence that decreased nicotinic receptor expression may contribute to working memory impairments in schizophrenia (Green et al., 2005).

In summary, recent association studies suggest that *NRG-1* is a promising candidate risk gene for schizophrenia but the relationship is not conclusive and more studies with large case and control samples are needed. Some *NRG-1* risk markers, such as SNP8NRG243177, are associated with altered gene expression in post-mortem studies and they are also found to correlate with several structural and functional brain abnormalities.

Genome wide association studies

Until recently the use of association studies to detect common genetic variants was hampered by the requirement to use hundreds of thousands of markers in each study. This approach was therefore limited to investigations of functional candidate genes. Technical advances in the past few years have made it possible to conduct GWAS on thousands of subjects to detect variations of small effect based on a positional design and without requirements of functional knowledge. These studies employ so called

microarrays or chips which allow rapid scanning of each individual for 300.000 – 900.000 SNPs across complete sets of DNA to find markers associated with a particular disease. Each GWAS may therefore involve over a billion genotypes. This methodology is currently being used to search for genetic variations that contribute to many common, complex diseases such as asthma, cancer, diabetes and psychiatric illnesses. These studies have already provided strong evidence for multiple previously unidentified candidate genes.

In recently published GWAS of schizophrenia no associations with any of the previously identified candidate risk genes were detected (Owen et al., 2009). However, these studies have identified a number of other interesting candidate genes and several large studies are currently ongoing which may have more power to detect additional markers. In a GWAS of 479 cases and 2937 controls with follow up of loci reaching a significance threshold in 6829 cases and 9897 controls O'Donovan et al (2008) found support for a locus in the vicinity of a putative transcription regulator called zinc finger protein 804A or *ZNF804A*. A GWAS by Shifman et al (2008) found evidence in two samples of a female-specific association between reelin (*RELN*) and schizophrenia. Reelin is involved in corticogenesis and therefore this finding supports the notion of schizophrenia being a neurodevelopmental disorder. Recently, Stefansson et al (2009) combined SNP data from several large GWAS and followed up the most significant association signals. They found significant association with five markers spanning the major histocompatibility complex (MHC) region on chromosome *6p21.3-22.1,* one SNP located upstream from the neurogranin gene (*NRGN*) on chromosome *11q24.2* and one SNP in the transcription factor 4 gene (*TCF4*) on chromosome *18q21.2*. *NRGN* encodes a postsynaptic protein kinase and is widely expressed in brain regions important for cognitive function and *TCF4* is involved in brain development. Two other independent research groups also found associations of SNPs within the MHC region on chromosome *6p* with schizophrenia (Purcell et al., 2009, Shi et al., 2009). These findings suggest that immune components may be involved in the pathophysiology of schizophrenia.

Chromosomal abnormalities in schizophrenia

There are multiple reports of schizophrenia being associated with chromosomal abnormalities (Blackwood et al., 2008). Two chromosomal abnormalities have been extensively investigated in recent years and both have provided evidence for location

of schizophrenia susceptibility genes within them. Individuals with deletions on chromosome 22q11 have a high risk for schizophrenia (Murphy et al., 1999). Several genes mapping to this region have been studied such as *COMT*, and zinc finger- and DHHC domain-containing protein 8 (*ZDHHC8*). The other significant chromosomal abnormality associated with schizophrenia is a balanced 1:11 translocation disrupting a gene on chromosome 1 called disrupted in schizophrenia 1 (*DISC1*) (Blackwood et al., 2001). There is evidence for association of schizophrenia with several haplotypes and SNPs within the *DISC1* gene but the markers are different between studies, which may indicate that there is allelic heterogeneity at this locus (Norton et al., 2006). Polymorphisms in the *DISC1* gene have also been associated with bipolar disorder (Palo et al., 2007).

A recent study examined the association of a duplicated portion and two base pair deletion/inversion of the α_7 nicotinic acetylcholine receptor subunit gene on chromosome 15q13-14 with antisaccade performance in healthy subjects (Petrovsky et al., 2009a). This genotype is called *CHRFAM7A* and there is evidence that it is associated with cognitive deficits (Dempster et al., 2006) and psychosis (Flomen et al., 2006). The study did not observe significant association of the *CHRFAM7A* with antisaccade performance.

Copy number variations and schizophrenia

Identifying the true causative genetic factors in schizophrenia constitutes a challenging task. Recent studies employing traditional methods of linkage and association analysis have implicated several putative risk markers and genomic regions of interest but no causative schizophrenia genes have yet been found. Furthermore, these positive findings have proved notoriously difficult to replicate and several recent GWAS have not identified the alleged candidate genes. Several researchers have recently proposed that CNVs may be involved in the genetic etiology of schizophrenia (Singh et al., 2009). This is supported by the well-known association of the chromosome 22q11 deletion syndrome (velocardiofacial syndrome) with schizophrenia described above.

A CNV is a DNA segment in which deletions or duplications have occurred. Inversions and translocations of DNA segments are also types of CNVs but they are much less frequent than deletions and duplications. CNV segments may vary in size and they can either be inherited from parent to offspring or caused by *de novo*

mutations. These mutations may therefore be unique to a family or even unique to an individual. Different *de novo* CNV profiles have been observed in MZ twins who otherwise have identical genomes (Fraga et al., 2005). Following the completion of the Human Genome Project in 2003 it was discovered that CNVs are common and widespread among humans.

CNVs can be detected by various methods including FISH (fluorescent in situ hybridization), CGH (comparative genomic hybridization) and by analyzing dosage data from SNP/CHIP arrays similar to those used in GWAS. The vast amount of data already generated through genotyping samples using the SNP/CHIP arrays has uncovered thousands of rare CNVs throughout the genome. Genes that are altered by CNVs are good candidates for research of disease susceptibility. Proving causality can though be difficult as many of the CNVs are rare and strong association may not be detected unless the CNV variants/events are recurrent.

Several recent studies suggest that multiple rare *de novo* CNVs as well as some inherited CNVs contribute to a proportion of the genetic susceptibility to several neuropsychiatric disorders including autistic spectrum disorders and schizophrenia (Cook & Scherer, 2008, Guilmatre et al., 2009). CNVs may provide a partial explanation for the discordance rate of schizophrenia (approximately 50%) in MZ twins. This is supported by studies showing that MZ twins attain genetic and epigenetic differences during their lifetime (Fraga et al., 2005) and that both phenotypically concordant and discordant MZ twin pairs have different CNV profiles (Bruder et al., 2008). Studies have found more individually rare CNVs in schizophrenia patients than controls. In a case-control study novel and rare CNVs were found in 15% of patients with adult onset schizophrenia, 20% of patients with childhood onset schizophrenia and 5% of healthy controls (Walsh et al., 2008). In the patients the mutations disproportionately disrupted genes involved in controlling neurodevelopmental processes such as *NRG* and genes in the glutamate pathway. Another study found an association of *de novo* CNVs with sporadic cases of schizophrenia but not with familial cases (Xu et al., 2008). Two independent research groups found rare recurrent *de novo* deletions on chromosomes *1q21.1* and *15q13.3* to have strong effects on risk for schizophrenia, with odds ratios of 6.6 and 17.9, respectively (International schizophrenia consortium, 2008, Stefansson et al., 2008). Based on these recent findings it has been suggested that multiple rare and individually different CNVs, disrupting the function of genes involved in

neurodevelopment, may contribute to the causes of schizophrenia. The affected genes may vary significantly between patients depending on the number and extent of CNVs making it difficult to investigate the association of CNVs with few specific candidate disease genes.

The rapidly growing knowledge of CNVs is helping researchers developing new strategies for investigating the genetic causes of complex disorders such as schizophrenia. In the near future new developments in whole-genomic sequencing technology and new types of microarrays will further increase our understanding of how common and rare CNVs and SNPs are involved in schizophrenia.

The endophenotype concept

Endophenotypes are measurable biological or behavioral features thought to be more direct expressions of disease related genes than a clinical phenotype (Gottesman & Gould, 2003). They cannot be seen by the unaided eye, but can be measured by e.g. neurophysiological, biochemical, endocrinological, neuroanatomical or neuro-psychological methods. Endophenotypes are trait markers that reflect the actions of genes predisposing an individual to a disease, even in the absence of any noticeable pathology. Therefore, they can be measured not only in patients but also in groups of individuals with high risk for developing the disease such as close relatives of patients. Endophenotypes may represent the action of fewer genes than the clinical phenotype and therefore simplify and increase the power of genetic studies of complex disorders. The endophenotype concept was originally introduced to psychiatry by Gottesman and Shields (1973) who suggested that risk genes are more likely to be detected through their effects on a more penetrant endophenotype than their effects on a less penetrating disease phenotype.

Researchers have identified several criteria that a behavioral or biological deficit should fulfill in order to qualify as a promising endophenotype (Egan et al., 2003, Gottesman & Gould, 2003).

1. It should be associated with the illness. Therefore it should be frequently found in patients and have a low base rate in the general population.
2. It should have significant heritability, which means that its intra- and interfamilial variance should be associated with shared genetic

rather than environmental factors. This can be investigated in twin and adoption studies.

3. Test-retest reliability and stability over time should be high. The deficit should be a trait marker and not state dependent. This means that it should be independent of variations in clinical symptoms and the effects of environmental factors such as changes in medications and the use of alcohol and tobacco. The deficit should also be unaffected by the secondary effects of disease chronicity such as long-term pharmacological treatment and institutionalization.
4. An endophenotype should have good discriminating power across a range of individual differences
5. It should co-segregate with the illness in families and should also be present at a higher rate in unaffected relatives of patients and other high-risk individuals than in the general population.
6. An endophenotype should represent a distinct and well-characterized neurobiological mechanism that is informative of the pathophysiology of the disorder.

The fact that a trait marker is not specific to one particular psychiatric illness does not disqualify it as an endophenotype in genetic studies. There is high co-morbidity and significant diagnostic overlap among many psychiatric disorders and there is cumulating evidence for genetic overlap between illnesses. For example, some of the recently identified schizophrenia candidate genes such as *DAOA, DISC-1* and *NRG-1* have also been found to increase the risk for bipolar disorder (Serretti & Mandelli, 2008). Therefore, endophenotypes that are present across diagnostic boundaries may represent genes that increase the risk for more than one psychiatric illness.

Several candidate endophenotypes have been proposed for schizophrenia. These include various electrophysiological markers, neuroimaging phenotypes and cognitive deficits (Egan et al., 2003). Abnormalities in certain eye movements are among the most promising and extensively studied candidate endophenotypes in schizophrenia. These eye movement deficits include decreased accuracy of smooth pursuit eye movements (SPEM) (O'Driscoll & Callahan, 2008) and increased error rate on the antisaccade task (Hutton & Ettinger, 2006). Support for the validity of

SPEM and antisaccade eye movements as endophenotypes comes from studies showing that healthy relatives of schizophrenia patients perform worse than individuals without family history of psychotic illnesses (Calkins et al., 2008). Twin studies indicate that the performance on these eye movement tasks has a considerable heritable component (Katsanis et al., 2000, Malone & Iacono, 2002). Furthermore, the performance on these tasks is stable over time and relatively unaffected by disease status (Calkins et al., 2003, Ettinger et al., 2003a, Flechtner et al., 2002, Gooding et al., 2004).

Endophenotypes have mainly been used in two ways in studies of psychiatric disorders. First, as originally proposed, to facilitate the discovery of disease causing genes, and second, to investigate neurobiological or functional consequences of putative risk genes.

Endophenotypes have been helpful for finding disease genes in some complex medical disorders. For example, when serum iron level was used as a biological indicator of intrinsic disease liability in haemochromatosis it led to the discovery of a linkage with the HLA-A locus (Lalouel et al., 1985) and when investigators concentrated on families with the highest blood glucose levels a genetic deficit associated with type II diabetes was uncovered (Mahtani et al., 1996).

Some studies have provided evidence of association between proposed schizophrenia endophenotypes and specific genotypes. Leonard et al (2002) found deficits in inhibition of the P50 waveform of the auditory evoked response to be linked with markers on the alpha-7 nicotinic acid receptor gene and as previously described Egan et al (2001) found evidence of an association between measures of prefrontal brain function and the high activity val allele of the *COMT* gene.

Originally there were hopes that the endophenotype approach would lead to dissection of schizophrenia into a number of single gene deficits. This has not yet been the result and most investigators agree that it is an unlikely outcome (Walters & Owen, 2007). Although the proposed schizophrenia endophenotypes may be more genetically complicated than originally assumed most commentators still believe that their genetic architecture is likely to be simpler than that of the disease phenotype (Walters & Owen, 2007). However, this notion has recently been questioned based on meta-analytical examination of genetic association studies employing endophenotypes (Flint & Munafo, 2007).

An important caveat is the fact that it is difficult to provide direct evidence that endophenotypes lie on a causal pathway between genes and disorders and to exclude the possibility that they reflect pleitropic effects of risk genes (Walters & Owen, 2007). Pleiotropy means that a single gene can influence multiple distinct phenotypic traits.

The use of endophenotypes for investigating neurobiological effects of putative risk genes of psychiatric disorders has increased in recent years following the identification of multiple candidate risk genes. Very little is known about the mechanisms by which these genes may confer the risk of disorders such as schizophrenia (Sullivan, 2008). By investigating relationships between risk alleles and endophenotypes such as neurocognitive and structural brain deficits, researchers try to characterize the neural mechanisms that are affected by risk gene variants in schizophrenia (Meyer-Lindenberg & Weinberger, 2006). This is the approach used in the present thesis, where associations of the putative schizophrenia risk genes *COMT* and *NRG-1* with performance on SPEM and antisaccade eye movement tasks are investigated. Both *COMT* and *NRG-1* have been associated with frontal brain cognitive function (Egan et al., 2003, Goldberg et al., 2003, Hall et al., 2006, Stefanis et al., 2007) and several lesion and imaging studies have provided evidence that deficits on SPEM and antisaccade tasks in schizophrenia patients are associated with impaired prefrontal brain functions (Lencer & Trillenberg, 2008, McDowell et al., 2008). Finding relationships between putative risk variants of *COMT* and *NRG-1* and deficits on SPEM and antisaccade tasks may therefore suggest that these genes influence neural mechanisms that are affected in schizophrenia. The following sections of the introduction provide a review of eye movement research in schizophrenia with special focus on studies testing the validity of eye movement deficits as endophenotypes in schizophrenia.

Eye movements in schizophrenia

There are three main purposes for investigating eye movements in schizophrenia. The majority of studies have focused on deficits in SPEM and antisaccade eye movements as endophenotypes in schizophrenia. This research is based on the hypothesis that these eye movement deficits are associated with specific genes involved in the pathogenesis of schizophrenia (Calkins et al., 2008). Eye movements are also used for investigating the cognitive and neurological processes involved in

the pathophysiology of schizophrenia. Neuropsychological, brain lesion and imaging studies have provided information on the cognitive, neuro-anatomical and neuro-physiological components involved in specific eye movement measures. By comparing the performance of patients and healthy controls on a range of oculomotor tasks specific brain areas and neural processes involved in schizophrenia may be identified. Finally, it is possible that eye movement deficits will function as markers for evaluating treatment response in schizophrenia and aid in the development of new treatment strategies.

In this section eye movement research in schizophrenia will be reviewed. Following a description of methods for measuring eye movements each of the eye movement tasks used in this thesis will be introduced separately. These are SPEM, visual fixation, antisaccade, and prosaccade eye movements. SPEM and antisaccade tasks have been extensively investigated in schizophrenia and are among the most promising endophenotypes for genetic studies of schizophrenia. The methods of analyzing these eye movements will be described. Then, findings of eye movement studies in schizophrenia patients are reviewed. An overview of studies examining the qualification of eye movement deficits as endophenotypes will be provided. These include studies of disease specificity, temporal stability and reliability of eye movement measures, family and twin studies and investigations of the effects of medications on eye movements. Then neurological and cognitive correlates of eye movements will be outlined and finally, molecular genetic studies of eye movements in schizophrenia are reviewed.

Methods for measuring eye movements

A variety of methods have been used to measure eye movements (Leigh & Zee, 1999). In the first eye movement study of schizophrenia patients, which was conducted 100 years ago, Diefendorf and Dodge (1908) used a photographic method. The Dodge Photochronograph (Figure 1) was equipped with a moving photographic plate that captured the corneal reflections of filtered electronic light rays. This technique provided remarkable accurate recordings of eye movements, even when compared to some of the later electronic eye trackers.

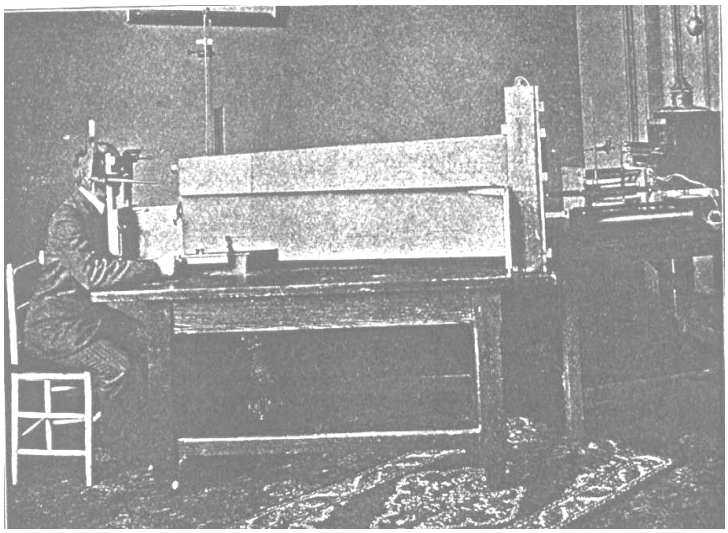

Figure 1
The Dodge Photochronograph

Eye movement research in schizophrenia was very limited until the 1970s. Most of the early studies used electrooculography (EOG). This method employs skin electrodes that are placed around the eye (Leigh & Zee, 1999, Shaunak et al., 1995). The electrodes measure changes in corneo-retinal potential induced by eye movements. Horizontal eye movements can be measured with two electrodes that are placed over the outer canthi of both eyes. This is an inexpensive, reliable and accurate technique that can measure lateral displacements of the eyes up to +/- 60° with an accuracy of 1.5-2.0º. The main disadvantages of EOG are its sensitivity to bioelectric noise and variations in skin resistance and that it is prone to artifacts from movements of facial muscles and blinks.

The presently most widely used method for studying eye movements is infrared oculography (IRO) with either limbus or combined corneal and pupil reflection trackers. In the present thesis an infrared limbus tracking device is used. Infrared light is projected onto the eye and its reflections from the limbus (border of sclera and iris) are detected by infrared light detectors (Reulen et al., 1988). Usually both the infrared light emitting and detecting diodes are incorporated into plastic frames or goggles that are worn by the subject. The precision of this technique is higher than for EOG. It also has the advantages over EOG of not contacting the eyelids and not being affected by muscle artifacts and bioelectric noise. Furthermore, IRO has good linearity for horizontal eye movements up to ±30º. The main disadvantages are that the infrared detectors are sensitive to ambient light, the subject can not were eye glasses during testing, long exposure to infrared light can cause

dryness and irritation in the eyes and large eye displacements can not be measured because of limited recording range (Leigh & Zee, 1999, Reulen et al., 1988). However, these disadvantages are rarely problematic because the ambient light can be adjusted, most tasks do not involve large eye movements and testing sessions are usually brief enough to prevent significant eye discomfort.

Eye movements can also be measured with video cameras. Most of these systems use complex pattern algorithms to detect the pupil or the iris. Recently miniature video cameras that are incorporated into goggles have been manufactured. These systems can also use table-mounted cameras that can both measure eye movements and head movements and thus provide measurements of gaze (Smyrnis, 2008).

Smooth pursuit eye movements (SPEM)

SPEM are voluntary tracking eye movements that allow us to keep the retinal image of a moving target within the foveal area. The fovea is the retinal area providing the highest visual resolution due to its combination of high cone receptor density and small receptor fields. Visual acuity decreases whenever the retinal image moves out of the foveal area, either because of visual object motion or head movements. SPEM compensate for such retinal image dislocations.

The first known report of abnormal SPEM in schizophrenia was published a century ago by Diefendorf and Dodge (1908). They found that schizophrenia patients have an excessive number of fast jerky eye movements, which are called saccades, during a task requiring a SPEM response. Their finding did not receive much attention for many decades or until Holzman et al. (1973, 1974) observed abnormal SPEM in schizophrenia patients and also in their first-degree relatives. In the past 35 years more than 200 peer reviewed papers have been published on SPEM and schizophrenia, focusing on issues such as specificity, frequency, heritability, effects of medications and finding the neural and genetic correlates of abnormal pursuit.

SPEM – Stimulus properties

The SPEM task involves following a moving target that is displayed using, for example, a cathode ray oscilloscope, light emitting diode arrays, laser spots or computer monitors. Nowadays computer monitors are the most commonly used

method of presenting the target. With computer monitors target characteristics such as shape, size and color can easily be adjusted, which provides possibilities for investigating the function of various cognitive processes during eye movements. The target is typically a small dot or square that is first presented in the center of the monitor and then starts moving horizontally to one side until it reverses and continues moving from side to side throughout the task. The monitor is usually placed at eye level approximately 40-60 cm away from the subject, which is a comfortable reading distance for most people. Subjects are instructed to follow the target with their eyes wherever it moves as accurately as they possible can. To reduce the effects of movement artifacts subjects are asked to sit still during the task and head movements are usually minimized with the use of a chin rest (Clementz & McDowell, 1994, Ettinger et al., 2003a).

Studies have both used sinusoidal and constant velocity target waveforms. In the sinusoidal waveform the target moves like a pendulum and therefore its velocity varies continuously reaching maximum speed in the center and slowing down towards the peripheral target locations. This stimulus type is useful for establishing the acceleration saturation of SPEM (Leigh & Zee, 1999) and for rating overall pursuit performance using global or qualitative measures. Two types of constant speed waveforms have been used. In the triangular waveform the target moves with a constant speed and makes abrupt turnarounds without stopping. In the trapezoid waveform the target moves at a constant speed but stops at the left and right peripheral locations for approximately one - two seconds and then starts moving again in the opposite direction. Both sinusoidal (Flechtner et al., 2002, Nkam et al., 2001, Ross et al., 1997) and constant velocity (Ettinger et al., 2004b, Hutton et al., 2000, Lencer et al., 2003) target waveforms have been used in schizophrenia research. Studies have shown abnormal SPEM in schizophrenia spectrum disorders irrespective of the target waveform being used.

Another stimulus characteristic that varies between SPEM studies of schizophrenia is the target velocity. Since velocity varies continuously for the sinusoidal target waveform it is usually presented as the frequency (Hz) of target motion or peak velocity (º/s). Some studies report the average velocity based on the frequency and amplitude (º) of target motion. The velocity of triangular and trapezoid target waveforms is simply presented as º/s. The human pursuit system is well adapted to follow targets moving at velocities up to 40º/s. Most studies have

used target velocities between 10º/s and 30º/s. All SPEM performance parameters are affected by target velocity and generally performance deteriorates with increasing target speed (Ettinger et al., 2003a, Hong et al., 2005, Hutton et al., 2001).

Two other parameters that differ between SPEM studies in schizophrenia are the horizontal amplitude, in degrees, covered by the moving target and the total duration or number of cycles of each task session. One cycle represents the motion from one peripheral location to the other peripheral location and back to the original location. In most studies the amplitude ranges between ±10º and ±30º from the central fixation location (Smyrnis, 2008). This range is suitable for IRO recording and poses minimal strain on the eyes. The number of cycles ranges between 5 and 50 in most schizophrenia studies (Smyrnis, 2008). Short testing sessions provide fewer available measurements, which may limit the reliability of the measured eye movement parameters. Long testing sessions increase the number of measurements, which can possible increase reliability but on the other hand may be susceptible to task duration effects such as learning (improvement) and fatigue (deterioration).

Some studies have used other types of tasks for measuring specific features of SPEM. Two of these tasks are the step ramp task (Avila et al., 2002, Ross et al., 1996a) and the predictive pursuit task (Hong et al., 2003, Thaker et al., 1998). In the step ramp task (Rashbass, 1961) the stimulus appears in the central location, then steps suddenly to a peripheral location and moves at a constant velocity in the opposite direction. This task is useful for studying so called open loop pursuit, which is the average acceleration during the first 100-200ms when the eye is catching up with the target following the step and perceptual feedback about pursuit performance is not yet available (Leigh & Zee 1999). During this period the pursuit system cannot be updated about its performance and the eye movement is therefore only controlled by retinal sensory input. Open loop pursuit is followed by closed loop pursuit when perceptual feedback is utilized to direct the pursuit. In the predictive pursuit task the target occasionally disappears for a few hundred milliseconds (ms) and then reappears during constant velocity pursuit. This allows the study of predictive pursuit, which is entirely based on extra retinal cues.

SPEM - Performance measures

Early studies of eye movements in psychiatry used qualitative scoring of SPEM data. This was done by visually inspecting how the SPEM tracking corresponded with the

target waveform and then rate the eye movements either as normal or abnormal (Holzman et al., 1973) or by using an analog scale ranging from poor to excellent (Shagass et al., 1974). These studies provided many important findings that have later been confirmed in studies using global and specific quantitative measures such as the presence of SPEM deficits in relatives of schizophrenia patients (Holzman et al., 1974).

A major problem with global qualitative scoring is that it is entirely based on subjective assessment. This problem was resolved with the introduction of global quantitative measures of SPEM such as root-mean square error (RMSE) (Iacono & Lykken, 1979) and the natural logarithm of signal to noise ratio (lnS/N) (Lindsey et al., 1978), which replaced the qualitative scoring procedures. These are mathematical measures that quantify the overall difference between target and eye positions during the SPEM task. Both measures are objective and relatively easy to score and their validity has been well established (Campion et al., 1992, Gooding et al., 1994, Grawe & Levander, 1995). However, a significant disadvantage of these measures is their inability to discriminate between specific oculomotor system components contributing to the overall pursuit performance. It is known that normal SPEM is based on integrated functions of both the pursuit and the saccadic system (Leigh & Zee, 1999). The pursuit system is involved in generating continuous eye movements for tracking moving objects such as a bird flying in front of a cliff. The saccadic system generates fast eye movements that enable us to direct our gaze to a specific object. Global deficits in SPEM may therefore both be caused by an inability of the pursuit system to keep up the correct eye movement speed and an inability to inhibit the saccadic system resulting in occurrence of intrusive saccades during pursuit. This indistinctiveness was demonstrated in a study using computer simulated pursuit records of poor ln(S/N) (Abel & Ziegler, 1988). It was found that even if different SPEM records had identical ln(S/N) scores they differed significantly in the frequency of various saccadic eye movements. This shows that ln(S/N) scores do not distinguish between SPEM deficits generated by different oculomotor systems. Researchers still debate about whether global quantitative measures should be used. In studies comparing schizophrenia patients and healthy controls global measures have generally provided larger effect sizes than specific measures (O'Driscoll & Callahan, 2008). However, specific SPEM measures are better targets for investigating the underlying neurophysiological and neuroanatomical correlates of

the smooth pursuit system in structural and functional imaging studies. Many laboratories still use global measures such as RMSE (Kallimani et al., 2009, Sporn et al., 2005).

The majority of recent SPEM studies in schizophrenia have employed specific measures of SPEM performance and the most widely used measures are smooth pursuit gain and frequency of saccades.

Smooth pursuit gain: Smooth pursuit gain is defined as the ratio of eye velocity to target velocity. If eye velocity matches target velocity this ratio is 1 or 100 (if multiplied by 100) but when the eye is not able to sustain target velocity the ratio falls below 1. If eye velocity exceeds target velocity the gain becomes higher than 1. Pursuit gain has been used in many studies of schizophrenia patients (Clementz et al., 1990, Ettinger et al., 2004b, Hutton et al., 2000, Lencer et al., 2003). Pursuit gain can easily be measured using constant velocity targets. After removing saccadic eye movements and artifacts such as eye blinks the eye velocity is calculated for each saccade free segment by dividing the distance traveled by time. Then eye velocity is divided by target velocity and the mean of gain values for all the segments provides the mean pursuit gain. In some studies the gain values for each segment are multiplied by the corresponding time and then summed. The sum is divided by the total time duration of all the segments to yield a time weighted pursuit gain. This method is employed in the present thesis. For sinusoidal target waveforms this becomes more complicated and the definitions and methods of calculating pursuit gain vary considerably between studies. Therefore it is more difficult to compare pursuit gain results between studies using sinusoidal waveforms.

Pursuit gain is most often calculated for segments of the cycle when pursuit is at a steady state, such as the mid 50% of a cycle for constant velocity target waveforms and segments during peak target velocity for sinusoidal target waveforms.

Saccadic frequency: Another commonly used measure of SPEM integrity is the frequency of saccadic eye movements during pursuit. Usually this measure is presented as number of saccades per unit of time such as N/s. The two main categories of saccades that occur during SPEM are corrective saccades and intrusive saccades (Leigh & Zee 1999). Corrective saccades correct for SPEM deficiencies and consist of catch up saccades and back up saccades. Catch up saccades take the eye in the same direction as the target motion and bring the eye closer to the target

when pursuit gain is low. They can either bring the eye to a position slightly behind or slightly ahead of the target. Back up saccades bring the eyes from a position ahead of the target to a position close to the target.

Intrusive saccades are caused by intrusions of the saccadic eye movement system into pursuit eye movements. They consist of anticipatory saccades and square wave jerks. Anticipatory saccades are movements in the direction of eye motion that bring the eyes ahead of the target. They are followed by an episode during which the eyes are nearly stationary or they make a corrective back up saccade to the target. Square wave jerks are another type of intrusive saccades. These are pairs of small saccades (1º-3º) that are separated by a period (50-500 ms) of uninterrupted smooth pursuit. The first saccade usually moves the eye ahead of the target and the second brings it back towards the target.

In many studies of SPEM in schizophrenia the total number of saccades is counted without classifying saccades according to their putative role (Levy et al., 1993). This approach has been criticized because it does not provide information about the nature of the saccades; specifically whether the saccades reflect compensation by the saccadic system for a dysfunctional pursuit system (corrective saccades), disinhibition of the saccadic system (intrusive saccades) or deficits in both systems (Abel & Ziegler, 1988, Levy et al., 1993). Therefore many recent studies have focused more on the specific subtypes of saccades. Although some studies find evidence that saccadic measures such as the frequency of catch-up saccades and anticipatory saccades are more specific to schizophrenia (Rosenberg et al., 1997b, Ross et al., 1999b, Sweeney et al., 1994) other studies have not (Abel et al., 1991, Clementz et al., 1990, Radant & Hommer, 1992, Sweeney et al., 1992). These mixed results may to some extent be related to the fact that many of these studies use different criteria for defining the saccadic subtypes. For example, researchers have used at least six different criteria for defining catch-up saccades (Smyrnis, 2008). Some researchers have added quantitative criteria for catch-up saccades such as how close the eye should get to the target (Radant & Hommer, 1992) others have added criteria of maximal saccade amplitude (Calkins et al., 2001) and some investigators have even defined catch-up saccades as all saccades that are not square wave jerks (Roy-Byrne et al., 1995). Ross et al. (2001) showed that different criteria for catch-up saccades lead to very different estimates of their frequency. Definitions of anticipatory saccades and square wave jerks are also quite heterogeneous in studies

of schizophrenia (Smyrnis, 2008). Future research of SPEM in schizophrenia would clearly benefit from standardization of saccade criteria. In the present thesis the total frequency of saccades during SPEM was measured and no subtyping was performed.

SPEM in schizophrenia

Abnormal SPEM is one of the most reproducible finding in schizophrenia research (Levy et al., 1993). Studies using various recording and analysis techniques have found that schizophrenia patients have decreased pursuit gain when compared to healthy individuals e.g. (Abel et al., 1991, Clementz et al., 1992, Friedman et al., 1991, Friedman et al., 1992, Hutton et al., 2004, Levin et al., 1988, Litman et al., 1989, Louchart-de la Chapelle et al., 2005, Radant & Hommer, 1992, Schmid-Burgk et al., 1982, Yee et al., 1987). Many studies have found increased saccadic frequency in patients with schizophrenia and the increase is most often a result of an increase in catch-up saccades (Friedman et al., 1991, Hutton et al., 1998, Radant & Hommer, 1992). In some studies an increase in anticipatory saccades has been observed in schizophrenia patients (Friedman, 1992, Ross et al., 1999b, Ross et al., 2001), but not in others (Clementz et al., 1990, Hutton et al., 2000, Radant & Hommer, 1992). Schizophrenia patients have generally not been distinguished from healthy individuals by the frequency of square wave jerks (Clementz et al., 1990, Friedman, 1992, Lencer et al., 1999, Radant & Hommer, 1992) and back-up saccades (Lencer et al., 1999).

In a recent meta-analytic review of SPEM studies in schizophrenia since 1993 (O'Driscoll & Callahan, 2008), the difference in performance between patients and controls was found to be high for all global measures with effect sizes (Cohen's d) ranging between 0.70-1.55. The effect size was also high for maintenance gain; d= 0.87 and frequency of anticipatory saccades larger than 1° (also called leading saccades); d= 1.31. The confidence interval was narrowest for maintenance pursuit, which was ascribed to the large number of studies including this measure (n= 42). For catch-up saccades a medium effect size (d= 0.47) was observed and square wave jerks and back-up saccades failed to discriminate patients from controls (d< 0.2).

Studies employing different target velocities have shown that SPEM performance deteriorates with increasing target velocity (Abel et al., 1991, Hutton et al., 2001). At faster target velocities it becomes more difficult to correct retinal mismatch between target velocity and eye velocity. Schizophrenia patients and their

relatives have impaired motion perception, which has been shown to correlate with SPEM performance (Chen et al., 1999b). One study found that pursuit gain deteriorated significantly more with increasing target velocity in chronic schizophrenia patients than in first episode patients and healthy controls, when they were tested at four target velocities ranging from 10-36°/s (Hutton et al., 2001). However, in a recent meta-analysis of SPEM studies in schizophrenia no significant moderating effects of target speed were found on SPEM performance differences between schizophrenia patients and controls (O'Driscoll & Callahan, 2008).

One study compared SPEM performance in schizophrenia patients who had first and second degree relatives affected by the illness and patients with sporadic schizophrenia (Malaspina et al., 1998). The sporadic patients had significantly worse SPEM performance indicating that the pathophysiology may differ in sporadic and familial schizophrenia. The study therefore does not provide support for the co-familialty endophenotype criterion for SPEM deficits in schizophrenia. If replicated this finding may suggest that some non-familial factors cause additional worsening of SPEM on top of inherited factors. The study employed qualitative measures for analyzing SPEM and therefore it is possible that quantitative methods would have provided a different result.

SPEM performance deteriorates with increasing age (Ross et al., 1999a) but the differences between patients and controls remain stable (Muir et al., 1992, O'Driscoll & Callahan, 2008, Ross et al., 1999a). Gender does not affect SPEM performance or differences between schizophrenia patients and controls (Iacono et al., 1992, Karoumi et al., 2001).

Specificity of SPEM deficits to schizophrenia

There is evidence that SPEM deficits are not specific to schizophrenia. Abnormal SPEM have been observed in multiple neurological and psychiatric disorders such as Parkinson's disease (Ladda et al., 2008, Marino et al., 2007), Alzheimer's disease (Garbutt et al., 2008) and obsessive-compulsive disorder (OCD) (Clementz et al., 1996, Sweeney et al., 1992). Investigating SPEM in patients with affective disorders is particularly pertinent to schizophrenia research because there is growing evidence that these disorders are genetically related (Craddock et al., 2009). Studies of SPEM in patients with affective disorders have provided mixed results. While some studies have found worse SPEM performance in schizophrenia patients than patients with

affective disorder (Diefendorf & Dodge, 1908, Holzman et al., 1974, Iacono et al., 1992, Tien et al., 1996) others have found similar SPEM deficits in groups of schizophrenia patients and patients with affective disorders (Amador et al., 1991, Amador et al., 1995, Friedman et al., 1992, Iacono et al., 1992, Sweeney et al., 1999). There is some evidence that SPEM deficits in patients with affective disorder may be related to clinical state and the effects of medications (Malaspina et al., 1994). Lithium treatment was associated with SPEM impairments in a few studies (Holzman et al., 1991, Iacono, 1982, Levy et al., 1985) but a meticulously performed study by Gooding et al (1993) did not find any lithium effects on SPEM.

A powerful method for studying the specificity of a disease marker is to investigate unaffected relatives. Finding SPEM deficits in relatives of schizophrenia patients but not in relatives of bipolar patients would indicate specificity to schizophrenia. Early studies, using global measures, failed to find SPEM deficits in relatives of patients with affective disorders (Holzman et al., 1984, Levy et al., 1983). However, more recent studies have observed impaired SPEM performance in relatives of patients with affective disorders (Blackwood et al., 1996, Kathmann et al., 2003, Rosenberg et al., 1997b) suggesting that that SPEM deficits are present across the schizophrenia-bipolar spectrum.

Temporal stability of SPEM

Several studies have investigated temporal stability of SPEM performance measures. These studies have found that SPEM performance is fairly stable both in healthy individuals and schizophrenia patients over time periods of one week to two years (Calkins et al., 2003, Campion et al., 1992, Ettinger et al., 2003a, Flechtner et al., 2002, Gooding et al., 1994, Holzman et al., 1991, Iacono & Lykken, 1981, Kaufman & Abel, 1986, Roy-Byrne et al., 1995). Correlation coefficients for most SPEM variables, including both global and specific measures, range between 0.5 and 0.9. This is comparable to what has been found for some other psycho-physiological measures used in schizophrenia research such as PPI (Cadenhead et al., 1999) and P300 amplitude (Mathalon et al., 2000). The lack of significant improvements on most SPEM performance measures in follow up assessments suggests that there is not a significant practice effect (Calkins et al., 2003, Campion et al., 1992, Ettinger et al., 2003a, Gooding et al., 1994).

Internal consistency of SPEM

Internal consistency is a reliability marker that provides a measure of stability of task performance within one session. Internal consistency can be measured using Cronbach's coefficient alpha, which is an index of the average correlation among all items of a psychometric instrument (Cronbach & Warrington, 1951). Internal consistency of SPEM performance has been systematically addressed in only two previous studies finding high internal consistency in groups of healthy (Ettinger et al., 2003a) and schizophrenic subjects (Cegalis & Sweeney, 1979). Internal consistency of SPEM performance measures is a subject of investigation in the present thesis.

Task duration effects on SPEM

Similarly to internal consistency relatively few neuro-cognitive and psycho-physiological studies have investigated systematic within-session performance changes in schizophrenia. By only reporting the mean performance of a testing session involving a series of trials it is possible that some important characteristic related to within-session performance changes are missed. The importance of studying intra-individual performance variability in psychiatric populations has been demonstrated in recent neuro-psychological studies, where variability measures provided considerably larger group effects sizes (Klein et al., 2006) and were better able to distinguish clinical groups (Antoniades et al., 2007). One study on healthy subjects found a linear decrease in catch up saccade frequency at target velocities of 12º/s and 36º/s and a linear increase in anticipatory saccade frequency at 36º/s (Ettinger et al., 2003a). Such performance changes may be ascribed to factors such as practice (improvement) and fatigue or boredom (deterioration). Effects of task duration on eye movement performance in schizophrenia patients and healthy controls are investigated in the present thesis.

Heritability of SPEM performance

Several studies of healthy twins have assessed heritability of SPEM performance. Intra-class correlation of global SPEM performance has been reported to range from 0.49 to 0.68 in MZ twins and from 0.14 to 0.35 in DZ twins (Iacono & Lykken, 1979, Iacono, 1982, Katsanis et al., 2000).

One study has investigated specific SPEM measures in both MZ and DZ twins (Katsanis et al., 2000). Correlations for pursuit gain, generic saccade rate and frequency of square wave jerks, catch-up saccades and anticipatory saccades were higher for MZ than DZ twins with heritability estimates ranging between 0.50 and 0.70. These findings suggest that SPEM performance is under strong genetic influences but environmental factors must also be involved.

Family and twin studies of SPEM in schizophrenia

Since the first observation of SPEM deficits in first-degree relatives of schizophrenia patients 35 years ago (Holzman et al., 1974) multiple studies have documented subtle SPEM abnormalities in first-degree relatives using global qualitative (Holzman et al., 1976, Holzman et al., 1984), global quantitative (Iacono et al., 1992, Ross et al., 1996b) and specific measures (Clementz et al., 1990, Ettinger et al., 2004b, Thaker et al., 1998). Among SPEM deficits found in first-degree relatives are reduced maintenance pursuit gain (Clementz et al., 1990, Ettinger et al., 2004b, Kathmann et al., 2003, Lencer et al., 1999), reduced predictive pursuit gain (Thaker et al., 1999) and increased frequency of saccades (Clementz et al., 1990, Lencer et al., 1999, Ross et al., 1998). These studies provide support for the validity of SPEM deficits as schizophrenia endophenotypes. Generally, SPEM performance of relatives falls between the performance of their patient relatives and healthy controls. However, a few studies have not found significant SPEM performance deficits in first-degree relatives of schizophrenia patients (Hong et al., 2006, Thaker et al., 1998). A recent meta-analysis of SPEM studies comparing relatives of schizophrenia patients and controls showed that both global qualitative and global quantitative methods differentiate patient relatives from healthy controls and this was also found for pursuit gain (Calkins et al., 2008). However, relatives had only moderately more frequent anticipatory saccades (d= 0.36) and catch-up saccade rate did not reliably separate the patient relatives from controls.

Several studies show that SPEM performance correlates between patients and their relatives (Ettinger et al., 2004b, Hong et al., 2006, Iacono et al., 1992). This suggests that relatives of patients with poor SPEM perform worse than relatives of patients with mild SPEM deficits.

The few studies that have examined familial specificity of SPEM deficits to relatives of schizophrenia patients have provided inconsistent findings. These studies compare relatives of schizophrenia patients with relatives of patients with bipolar disorder and other psychosis spectrum disorders. Levy et al (1983) found significantly less SPEM deficits in relatives of patients with unipolar and bipolar affective disorder than relatives of schizophrenia patients and Holzman et al (1984) reported significantly more SPEM deficits in parents of schizophrenia patients than parents of bipolar patients. On the other hand Rosenberg et al (1997b) observed similar global SPEM deficits in offspring of schizophrenia and depressed probands and Kathmann et al (2003) found no difference in pursuit gain between relatives of schizophrenia patients and relatives of affective disorder patients.

Important information on the contribution of genetic factors to eye movement deficits in schizophrenia can be obtained by examining concordance of deficits in twins that are discordant for schizophrenia. Only three studies have investigated SPEM in discordant MZ and DZ twins. In the first study, Holzman et al (1977) investigated 11 MZ pairs and 15 DZ pairs. Seven of the MZ pairs were discordant for schizophrenia and all of them were concordant for global qualitative deficits. The frequency of velocity arrests was also measured in this study. A velocity arrest occurs when pursuit velocity reaches zero. The correlation for this measure was 0.77 for the MZ twins and 0.49 for the DZ twins. These results provide evidence that genetic factors are involved in SPEM deficits in schizophrenia.

Holzman et al (1980) replicated their 1977 findings in a different sample of 10 MZ pairs and 15 DZ pairs using both qualitative and global quantitative (ln(S/N) measures for scoring SPEM data. Six of the MZ pairs and all of the DZ pairs were discordant for psychotic disorders. The MZ twins had higher concordance of abnormal SPEM and the correlation for ln(S/N) was 0.80 and 0.39 for the MZ and DZ pairs, respectively.

The third and most recent study, by Litman et al. (1997), did not replicate the findings by Holzman et al (1977,1980). They investigated 12 pairs of MZ twins discordant for schizophrenia and 12 pairs of normal MZ twins. The SPEM data were scored using specific quantitative measures of pursuit gain and also numbers, amplitude and subtypes of saccades. The affected twins had significantly decreased pursuit gain and significant increases in frequency of intrusive saccades. However, the unaffected co-twins did not perform significantly worse than the control twins.

These findings suggest that SPEM deficits are associated with a schizophrenia phenotype but not a genotype.

All three studies can be criticized for having small sample sizes and they all used different scoring methods, which makes between study data comparison difficult. More twin studies using larger samples and well defined SPEM performance measures are needed to elucidate whether SPEM deficits are concordant in twins discordant for schizophrenia.

Symptom correlates of SPEM in schizophrenia

Most studies that have considered clinical correlates of SPEM deficits in schizophrenia have investigated the correlations of negative symptoms with SPEM performance. These studies have provided inconsistent results. While some studies found association between SPEM dysfunction and negative symptoms (Ciuffreda et al., 1994, Katsanis & Iacono, 1991, Matsue et al., 1993, Roitman et al., 1997, Slaghuis et al., 2005, Sweeney et al., 1994) others did not (Flechtner et al., 2002, Karoumi et al., 2001, Kelly et al., 1990, Lee et al., 2001, Lieberman et al., 1993, Litman et al., 1997, Sweeney et al., 1999). Ross et al (1996a) stated that the lack of consistency may be related to the use of inappropriate measures of negative symptoms. Many of the studies assessing negative symptoms and SPEM used the Schedule of Assessment for Negative Symptoms (SANS) (Andreasen, 1984), which measures both state-dependent and trait-dependent negative symptoms. Assessments performed with SANS may therefore be confounded by variations in clinical state and medication effects. Trait-dependent negative symptoms are also referred to as the deficit syndrome, which is defined with specific criteria (Carpenter et al., 1988). Ross et al (1996a) found an association between specific SPEM measures and the deficit syndrome in schizophrenia patients. Only three other studies have examined SPEM and the deficit syndrome. Malaspina et al (2002) and Hong et al (2003) found worse SPEM performance in deficit patients than non-deficit patients but Nkam et al. (2001) did not find a significant association between abnormal SPEM and deficit syndrome.

A few studies have found that SPEM deficits correlate with symptoms of formal thought disorder (Keefe et al., 1989, Lee et al., 2001, Solomon et al., 1987).

Heterogeneous small patient samples and treatment with antipsychotic medications may contribute to the inconsistent findings in studies of SPEM and schizophrenia symptoms. Larger studies with carefully defined subject samples may help clarifying the relationship of schizophrenia symptoms with SPEM deficits.

There is evidence that SPEM deficits are stable despite significant improvement in measures of schizophrenia psychopathology (Flechtner et al., 2002, Kallimani et al., 2009). This supports that SPEM deficits are trait markers of schizophrenia rather than state dependent phenomena associated with symptom severity. Most studies have not found a significant association between SPEM performance and age of illness onset, duration of illness or number of hospitalizations (Flechtner et al., 2002, Katsanis & Iacono, 1991, Schlenker et al., 1994). It should, however, be stressed that most of these studies were not specifically designed to investigate these factors.

Pharmacological effects on SPEM

It is well known that many psychotropic medications can have effects on human motor and cognitive function. Therefore, investigating the effects of medications on neuro-psychological and neuro-physiological markers, such as eye movements, is highly relevant. Although a large number of studies have examined the effects of psychotropics on eye movements in schizophrenia patients many of these studies compare groups of patients that were not randomized to receive a particular medication regimen or medication dose and often the patient groups were taking multiple different medications. Therefore, these studies provide indirect information on medication effects. Also, few studies have examined the effects of medications on eye movements over time by following patients longitudinally from treatment initiation. Studies of never medicated patients and healthy individuals receiving medications are important for differentiating disease effects and medication effects on eye movement control (Reilly et al., 2008b).

Healthy individuals: For obvious reasons studies of pharmacological effects on eye movements in healthy individuals are limited to one time or short-term drug administration. Studies of the typical antipsychotic medications chlorpromazine and haloperidol have provided inconsistent findings. In a randomized placebo controlled cross-over study haloperidol did not have an adverse effect on SPEM (Lynch et al., 1997) and in another study no effect of chlorpromazine was found (Holzman et al.,

1975). This is in contrast with two other studies showing adverse effects of these medications on SPEM (King, 1994, Malaspina et al., 1994). The effects of atypical antipsychotics on SPEM have not been studied in healthy volunteers.

Benzodiazepines, which are commonly prescribed anxiolytic medications, have consistently been shown to decrease SPEM velocity in healthy individuals (Green et al., 2000, Jansen et al., 1988, Masson et al., 2000, Roy-Byrne et al., 1993). This probably reflects the general sedating effects of these medications on central nervous system function. Furthermore, SPEM velocity was found to correlate with serum concentrations of benzodiazepines, which suggests that SPEM velocity may be a reliable pharmacodynamic measure for these medications.

Regarding other medications there is some evidence that serotonin enhancing medications may improve performance on both SPEM and saccadic eye movement tasks (Friedman et al., 1994). Stimulants (Malaspina et al., 1994, Tedeschi et al., 1983) and lithium (Flechtner et al., 1992) were not found to affect SPEM performance in healthy individuals. Studies of the anticonvulsant carbamazepine are contradictory, with some reporting impaired SPEM (Bittencourt et al., 1980) while others find no adverse effects (Noachtar et al., 1998, Pieters et al., 2003). Finally, administration of ketamine, which can induce schizophrenia-like symptoms, was associated with impaired SPEM in healthy individuals (Avila et al., 2002, Weiler et al., 2000).

Schizophrenia patients: Studies comparing antipsychotic-naïve schizophrenia patients or medication withdrawn patients with patients taking mostly typical antipsychotics have generally not found significant differences in SPEM deficits (Campion et al., 1992, Friedman et al., 1992, Spohn et al., 1988, Sweeney et al., 1999, Thaker et al., 1999). In longitudinal studies, following SPEM performance in medicated patients over time, no association with medication dose was observed (Flechtner et al., 2002, Levy et al., 1983, Saletu et al. , 1986, Schlenker et al., 1994). These findings support the role of SPEM deficits as trait markers or endophenotypes in schizophrenia. There are, however, several studies showing that patients with past or present history of treatment with typical antipsychotics have worse SPEM performance than untreated patients (Bartfai et al., 1985, Kufferle et al., 1990) and one study found that long term treatment (mean > 10 years) but not short term treatment (< 12 weeks) was associated with reduced pursuit gain (Hutton et al., 2001). It is, however, possible that the effects of past and long term treatment may be

confounded by the effects of disease chronicity. In a study on first episode psychosis patients by Hutton et al (1998) smooth pursuit velocity gain was lower in drug-naïve patients than in healthy controls but patients taking antipsychotics did not differ from controls. This finding indicates that antipsychotic medications may improve SPEM deficits in first episode patients.

Few studies have examined the effects of atypical antipsychotic medications on SPEM in schizophrenia patients. Clozapine was associated with reduced pursuit gain and increased catch-up saccade frequency in two studies (Friedman et al., 1991, Litman et al., 1994). The adverse sedating and anticholinergic effects of clozapine on cognition may possibly explain these findings. In a recent study examining the effects atypical antipsychotic medications on SPEM in antipsychotic-naïve schizophrenia patients, pursuit gain was found to decrease when the target moved in an unpredictable way but not when it made predictable oscillations (Lencer et al., 2008). This suggests that atypical antipsychotics may selectively impair sensorimotor control of pursuit but does not affect prediction and rule-based learning required in pursuit of predictable moving targets. Follow-up examinations showed that these medication effects were still present after six months of treatment but partly disappeared after one year.

In summary, benzodiazepines cause slowing of SPEM. Most studies show that SPEM deficits in schizophrenia patients are unaffected by typical antipsychotic medications but the deficits may worsen with long-term treatment. There is some evidence that atypical antipsychotics may affect SPEM but this needs to be further investigated.

Effects of nicotine on SPEM

Nicotine is an acetylcholine receptor agonist. Human and animal studies have shown that nicotine can have beneficial effects on cognitive functions such as sustained attention and psychomotor speed (Picciotto et al., 2000). It has been proposed that deficits in the brain cholinergic system are involved in pathophysiology of schizophrenia. This is supported by postmortem findings of altered acetylcholine receptors in brains of schizophrenia patients (Freedman et al., 1995), observations that nicotine can improve sensory motor gating deficits in schizophrenia (Adler et al., 1993) and evidence that variations in the acetylcholine α-7 subunit gene may be associated with schizophrenia (Leonard et al., 2002).

Studies of the effects of smoking on SPEM have provided evidence that nicotine may improve SPEM performance in schizophrenia patients. Domino et al (1997) reported increased smooth pursuit velocity after inhalation of nicotine in healthy smokers and non-smokers. Olincy et al (1998) found that smoking led to an improvement of SPEM deficits in schizophrenia patients but had no effects on SPEM in healthy subjects. Sherr et al (2002) observed improved eye acceleration during smooth pursuit initiation following nicotine administration to schizophrenia patients but it had no effects on SPEM in healthy controls. Two studies showed that nicotine decreased the number of small leading saccades during SPEM in schizophrenia patients (Avila et al., 2003, Olincy et al., 2003). Finally, Ettinger et al (2003b) investigated the effect of distorted cholinergic activity on SPEM by administrating the anticholinergic drug procyclidine to schizophrenia patients. This led to a non-significant decrease in smooth pursuit gain and increase in frequency of anticipatory saccades.

Neurological basis of SPEM

Based on evidence from primate neurophysiological studies and human lesion and functional imaging studies a model for SPEM control in humans has been suggested (Leigh & Zee, 1999). Information is projected from the retina to the primary visual cortex (V_1) via the lateral geniculate nucleus of the thalamus. From V_1 information is projected to extrastriatal area V_5 (lateral occipitotemporal cortex), which is a primary area of motion perception and processes information on target velocity, acceleration and direction. From V_5 signals are transmitted to the frontal eye field (FEF) and several other frontal brain areas. In the FEF an oculomotor response is generated. Signals from V_5 are also sent to the posterior parietal cortex, which along with the supplementary eye field (SEF) and dorsolateral prefrontal cortex (DLPFC) are involved in attentive response selection and monitoring features of SPEM (Lencer et al., 2004, Nagel et al., 2006). From the extrastriatal and frontal visual areas descending projections reach the pontine nuclei and from there signals are sent to several areas within the cerebellum, including the flocculus, paraflocculus and vermis. These cerebellar structures are involved in both initiation and maintenance of SPEM. From the cerebellum information is projected to brainstem oculomotor nuclei. There are also reciprocal projections from the cerebellum to cortical areas.

Functional imaging studies in healthy humans have generally shown that the brain areas in the above model are involved in SPEM (Berman et al., 1999, Lencer et al., 2004, Lencer & Trillenberg, 2008, Petit et al., 1999). By varying the attentional load of SPEM tasks additional activations have been observed in the intraparietal sulcus, superior parietal lobe, precuneus and precentral sulcus (Culham et al., 2001).

Studies focusing on properties of V_5 have shown that the area has three distinct sub-regions that are activated differently depending on the nature of the motion signal. There is evidence for a specific type of neurons within V_5, which are activated during anticipatory eye movements and when a visual stimulus is absent (Dukelow et al., 2001). Multiple other brain areas are involved in generating SPEM when a visible target is not present. An fMRI study of predictive pursuit, demonstrated extraretinal activations in FEF, supramarginal gyrus and also in SEF, pre-SEF, DLPFC and flocculus of the cerebellum (Lencer et al., 2004). This suggests that these brain areas process an internal representation or efference copy of smooth pursuit and are involved in cognitive functions important for predictive pursuit such as prediction, visuo-spatial attention, sequence learning and working memory (Lencer et al., 2004).

The neurological basis of SPEM deficits in schizophrenia has been investigated in several structural and functional brain imaging studies. Early structural studies using CT (Bartfai et al., 1985) and MRI (Blackwood et al., 1991) found worse SPEM performance to correlate with increased lateral ventricle volume but others did not observe such an association (Jacobsen et al., 1996, Katsanis & Iacono, 1991, Siever et al., 1986). An early PET study demonstrated lowered glucose metabolism in the frontal cortex during SPEM in schizophrenia patients and the hypofrontality correlated with negative symptoms (Volkow et al., 1987). A PET study of schizophrenia relatives showed that slower pursuit was associated with failure to activate the FEF (O'Driscoll et al., 1999).

In the first fMRI study of SPEM in schizophrenia a whole brain analysis demonstrated higher activity in the posterior hippocampus bilaterally and the right fusiform gyrus in patients compared to controls (Tregellas et al., 2004). When brain areas, that are known to be involved in SPEM in healthy individuals, were examined with a region-of-interest analysis the patients had lower activity in the right FEF, cingulate gyrus and occipital regions. The authors suggest that these findings are

related to fronto-temporal impairment and decreased hippocampal inhibitory function in schizophrenia.

Evidence for fronto-temporal dysfunction in schizophrenia was also found in an fMRI study by Hong et al (2006). The patients had decreased activation in FEFs, SEFs, medial superior temporal cortex and anterior cingulate cortex during sustained SPEM compared to controls. The patients showed increased activity in the medial occipitotemporal cortex. The authors suggest that due to impaired extraretinal motion processing the patients had to rely more on immediate retinal information and therefore they showed elevated occiptotemporal activity.

Support for prefrontal cortex abnormalities being associated with SPEM deficits in schizophrenia was obtained in a structural MRI study showing that lower smooth pursuit gain was associated with decreased gray matter integrity in the right prefrontal cortex in schizophrenia patients but there were no correlations with brain volume (Bagary et al., 2004).

In an fMRI study by Keedy et al (2006) medication naïve first episode schizophrenia patients had reduced activation in the FEFs, SEFs and areas of the parietal and cingulate cortex during sustained SPEM compared to controls. These findings indicate that SPEM deficits in schizophrenia are associated with widespread dysfunction in sensorimotor cortical areas that is already present early in the disease course.

Lencer et al (2005) found that reduced smooth pursuit velocity correlated with decreased blood oxygen level dependent (BOLD) signal in the V_5 area in schizophrenia patients, suggesting that dysfunction in the V_5 motion perception area is associated with SPEM deficits in schizophrenia. Newsome et al (1985) had previously shown that lesions to this area result in decreased accuracy of SPEM but a PET study did not associate SPEM impairments in relatives of schizophrenia patients with abnormal V_5 activation (O'Driscoll et al., 1999).

Neural activity related to retinal and extra-retinal processing of SPEM in schizophrenia was investigated in an fMRI study examining both traditional maintenance pursuit and predictive pursuit in groups of schizophrenia patients and controls (Nagel et al., 2007). During maintenance pursuit decreased gain in patients was associated with reduced activity in the right ventral premotor cortex, the right thalamus and an area of the left cerebellar hemisphere. In the predictive pursuit task patients had decreased activity in a right cerebellar area but increased activity in right

anterior cingulate cortex, the right superior temporal cortex and bilateral FEFs compared to controls. The authors' interpretation of these findings is that schizophrenia patients are forced to use different strategies while performing SPEM tasks. They speculate that healthy individuals activate cerebellar processes during predictive pursuit while schizophrenia patients have to rely more on cortical mechanisms.

In conclusion, imaging studies of SPEM in schizophrenia have demonstrated abnormalities in frontotemporal brain areas particularily hypoactivity of sensorymotor areas such as FEF, SEF and cingulate gyrus. Due to impaired extraretinal processing of SPEM schizophrenia patients may have to engage different brain mechanisms than healthy individuals, which may explain observations of increased activity in areas such as the hippocampus in patients.

Cognitive control of SPEM

The cognitive processes that are thought to be involved in SPEM deficits in schizophrenia include motion perception, attention and executive functions. Studies examining executive functions in relation to SPEM deficits have provided inconsistent results and some functional imaging studies do not support that SPEM and executive deficits share the same neural processes (Berman et al., 1999, Petit & Haxby, 1999).

Motion perception: Studies have shown that schizophrenia patients have impaired motion perception (Chen et al., 1999a). Stuve et al (1997) investigated the relationship between motion perception threshold and smooth pursuit gain in schizophrenia patients and controls. The motion perception threshold was measured by having the participants detecting the direction of motion of dots within a large constellation of stationary dots. Lower pursuit gain was associated with higher motion perception threshold in the patient group and this relationship was not secondary to attention deficits. This indicates that SPEM deficits are related to impaired motion perception rather than attention. Chen et al (1999b) found that sensitivity to perception of velocity was associated with measures of both open loop and quantitative measures of closed-loop pursuit gain but not with saccade frequency or qualitative ratings of gain in schizophrenia patients. These findings suggest that impaired functioning of motion sensitive areas of the brain may by causally related to SPEM deficits in schizophrenia and as discussed in the previous section SPEM

deficits have been associated with lesions (Newsome et al., 1985) and decreased activity (Lencer et al., 2005) of the motion perception area V_5.

Clementz et al (2007) called attention to the fact that stimuli used in motion perception studies (patterns of dots and gratings) differ from the visual stimuli used in SPEM studies. This may confound studies of correlations between SPEM and tests of motion perception. Clementz et al (2007) measured speed discrimination threshold using stimuli and conditions similar to those used in SPEM studies. Schizophrenia patients had significantly higher speed discrimination threshold compared to healthy subjects. The authors argue that this finding provides evidence for a direct link between SPEM and motion perception deficits.

Hong et al (2009) argued that speed discrimination, per se, is not impaired in schizophrenia patients. They hypothesize that impaired processing of feedback information from eye movements causes the observed motion perception abnormalities in schizophrenia. Therefore, the motion perception problem in schizophrenia may be a consequence rather than the cause of SPEM deficits. They investigated the interaction between SPEM and motion perception in schizophrenia patients and controls in two speed discrimination experiments. In experiment 1, the target stimulus was presented for only 150 ms so it had disappeared before the initiation of SPEM, limiting the effects of feedback from eye movement during motion perception. In experiment 2, the target was presented for 300 ms, which allowed enough time for SPEM initiation and generation of a motor command that could be integrated into the motion perception. They found that patients had similar speed discrimination as healthy subjects in experiment 1 but performed worse than controls in experiment 2. This finding supports their hypothesis and suggests that schizophrenia patients have intact motion perception but it can be affected by feedback from eye movements.

Attention: It has been suggested that abnormal SPEM performance in schizophrenia may, to some extent, be related to attention deficits (Schwartz et al., 2001). Several studies have demonstrated that attention-enhancing manipulations of the visual target improve SPEM performance in schizophrenia patients, their relatives and controls (Clementz et al., 1990, Rosenberg et al., 1997b, Schlenker et al., 1994, Yee et al., 1998). These manipulations include, for example, the use of changing letters (Clementz et al., 1990) and symbols that change in color (Yee et al., 1998) as visual targets. The improved SPEM performance has been explained by an

increased attentiveness and corrective feedback about the eye position from the additional stimulus features. In a study by Yee et al (1998) an attention enhancing manipulation improved SPEM performance more in patients with recent-onset schizophrenia than normal controls.

The relationship between attention and SPEM performance has also been investigated by introducing secondary tasks that either direct the attention toward or away from the visual-tracking target (Schlenker et al., 1994). Schlenker et al (1994) added a secondary reaction time task to a SPEM task in groups of schizophrenia patients and controls. Distraction from the target resulted in significant worsening of SPEM performance in all participants but more so in patients. Attention-enhancement improved, but did not normalize, patients' performance.

The probable contribution of attention deficits to SPEM impairments has also been investigated by examining correlations of SPEM measures with scores on the Continuous Performance Test (CPT), which is a test of sustained attention. In the CPT series of brief visual stimuli (e.g. letters or numbers) are presented and the participant is required to respond (e.g. with a button click) to the occasional presentation of a rare target stimulus. The results of studies comparing SPEM performance and CPT scores are inconsistent. One study reported a modest association in schizophrenia patients (Roitman et al., 1997), one study found a weak association in patients and controls (van den Bosch, 1984) and three studies did not find significant correlation between the two tasks in patients, controls (Siever et al., 1982, Stuve et al., 1997) or first-degree relatives of schizophrenia patients (Keefe et al., 1997).

A study by Kathmann et al (1999) did not support that SPEM accuracy depends on controlled attention. They found that SPEM performance in healthy subjects did not deteriorate with presentations of additional auditory discrimination tasks of varying difficulty. On the contrary SPEM performance rather improved when the additional task was processed concurrently. The authors argued that SPEM are primarily an automatic process and that limiting the allocation of controlled attention to SPEM may actually improve performance.

Frontal lobe cognitive function: Spatial working memory deficits have been reported in schizophrenia and suggest that impaired DLPFC function is associated with the disorder (Keefe et al., 1995, Park & Holzman, 1993). Correlations between SPEM and spatial working memory have been reported (Park & Holzman, 1993,

Snitz et al., 1999). However, in a large study on first episode schizophrenia patients and healthy controls Hutton et al (2004) did not find a correlation between smooth pursuit gain and spatial working memory.

Some studies have reported correlations between SPEM deficits and performance on the WCST, which measures working memory, executive function and the ability to display flexibility in the face of changing schedules of reinforcement (Grawe & Levander, 1995, Katsanis & Iacono, 1991, Litman et al. , 1991, Rybakowski & Borkowska, 2002, Schlenker et al., 1994). However, other studies have not found significant associations between SPEM and WCST (Friedman et al., 1995, Gambini & Scarone, 1992, Nkam et al., 2001, Radant et al., 1997, Tien et al., 1996).

Other frontal lobe function tests that have been investigated in relation to SPEM include Trail Making Test A (TMT-A), which measures psychomotor speed and coordination and Trail Making Test B (TMT-B), measuring spatial working memory and the ability to shift strategy. The results of these studies are inconsistent with some finding significant associations between SPEM and TMT performance (Bartfai et al., 1985, Grawe & Levander, 1995) while others have not found significant relationships (Litman et al., 1991, Rybakowski & Borkowska, 2002).

Radant et al (1997) observed a significant correlation between performance on WCST and TMT A and B and predictive pursuit but not traditional maintenance pursuit in schizophrenia patients. This finding may suggest that predictive pursuit involves a working memory component and it may be more sensitive to frontal lobe dysfunction than maintenance pursuit.

In summary, a number of studies have associated impaired motion perception and attentional deficits with abnormal SPEM in schizophrenia. Several studies have examined the relationship between SPEM performance and tests of frontal brain cognitive functions. These studies have not provided consistent findings, which may be related to task differences, medication effects and variability in disease severity and chronicity.

Molecular genetic studies of SPEM

The genetic factors involved in SPEM deficits in schizophrenia are not known. Relatively few studies have employed eye movement endophenotypes in molecular genetic studies of schizophrenia. In the first study using SPEM Arolt et al (1996)

carried out a scan of the chromosome 6p21-23 region to test for linkage between chromosomal markers and SPEM deficits as well as schizophrenia. They reported that two markers on chromosome 6p21-23 were linked with poor SPEM performance, but not with schizophrenia, in eight multiple affected families. The markers are located close to a 6p locus that had previously shown linkage to schizophrenia (Moises et al., 1995). Arolt and colleagues replicated their finding in another linkage study using an extended sample from their previous study (Arolt et al., 1999). They detected significant linkage of markers on chromosome 6p21.1 with SPEM deficits but not with schizophrenia. In 2004 another research group analyzed the markers identified in the Arolt studies (1996, 1999) in two large Danish families (Matthysse et al., 2004). They found significant linkage between SPEM deficits and a marker located in 6p21.1 close to the markers identified by Arolt and colleagues.

In a study of 119 schizophrenia patients and 94 controls SPEM impairments were associated with a serine^{9}glycine (ser-gly) polymorphism of the dopamine D_3 receptor (DRD3) gene on chromosome 3q (Rybakowski et al., 2001). Individuals with the ser-ser genotype had significantly worse SPEM than those with ser-gly and participants with gly-gly had the best SPEM performance. Dysfunction in the D3DR has long been implicated in pathogenesis of schizophrenia but studies of ser-gly and other polymorphisms have provided inconsistent findings (Talkowski et al., 2006).

Two studies have examined the association of the *COMT* val^{158}met genotype and SPEM performance (Rybakowski et al., 2002, Thaker et al., 2004). Rybakowski et al (2002) found that met^{158} homozygous male schizophrenia patients had lower mean intensity of saccades during SPEM than male patients carrying at least one val^{158} allele, but no such effect was found in females or healthy individuals. They did not use saccade frequency but instead they classified the intensity of saccade disturbance into four categories using a zero to three scale, ranging from no saccades to high saccade frequency, and compared clinical and genotype groups using non-parametric tests. Thaker et al (2004) did not find *COMT* val^{158}met to be associated with maintenance pursuit gain in 53 healthy subjects and 62 schizophrenia patients. However, they found that met^{158} homozygous healthy individuals had higher predictive pursuit gain than healthy val^{158} homozygotes, whereas met^{158} homozygous patients had non-significantly lower predictive pursuit than patient val^{158} homozygotes. These findings suggest that extra-retinal SPEM processes may be

more sensitive to differences in prefrontal dopamine levels than processes that also receive retinal input and that slow dopamine degradation is beneficial in healthy individuals but not in patients.

In a recent study by Wonodi et al (2009) a tandem repeat variant of the dopamine transporter gene (*DAT1* 10/10) was associated with predictive pursuit performance but it was not associated with schizophrenia. DAT1 controls the duration of extra-cellular dopamine activity and is, along with COMT, a major regulator of dopamine signaling in the brain (Tunbridge et al., 2006). The *DAT1* 10/10 genotype has either been associated with low or high DAT1 expression in the brain (Brookes et al., 2007). Wonodi et al (2009) also performed a gene expression study on 16 schizophrenia patients and 16 controls and found that *DAT1* 10/10 was associated with reduced DAT1 expression in controls but increased expression in patients. *DAT1* 10/10 resulted in better predictive SPEM performance in 73 healthy controls, intermediated performance in 40 relatives of schizophrenia patients and worse performance in 87 schizophrenia patients. This finding is in concert with the 2004 *COMT* val^{158}met study by Thaker et al (2004) suggesting that increased dopamine tone is associated with better predictive pursuit in healthy individuals but not in schizophrenia patients.

Visual fixation

The visual fixation task examines the ability to resist eye movements in order to maintain stable gaze on a stationary target. Visual fixation is often considered a component of the smooth pursuit system because it involves detection and correction of drifts in gaze but there is also evidence that fixation control involves a distinct system (Leigh & Zee, 1999). Visual fixation is not a resting or passive process but a constantly active process involved in maintaining attention and prevention of inappropriate eye movements. Failure to maintain fixation is associated with deficits in inhibitory control.

Visual fixation - Stimulus poperties

Target stimuli are usually small dots or squares similar to the ones used in the SPEM task. The stimulus is presented in a central location (0º) or in one or more peripheral horizontal locations. The use of peripheral locations makes it possible to assess the

stability of both central and eccentric fixation and look for gaze-induced drift (Kissler & Clementz, 1998). The duration of each target location is typically 10 – 30s and the subject is instructed to keep the eyes on the target at all times.

In order to further investigate inhibitory control during visual fixation researchers have developed fixation tasks with distracters. In these tasks peripheral stimuli are displayed briefly during a fixation task. Fixation tasks with and without distracters have been used to investigate fixation stability and inhibitory control in patients with schizophrenia (Curtis et al., 2001b, Hutton et al., 2002).

Visual fixation - Performance measures

Fixation performance has either been scored using qualitative rating scales, similar to those used for SPEM, or by quantitative ratings of intrusive saccades and drift away from the target during a fixation period. In healthy subjects very small saccades (microsaccades) are observed at a rate of approximately 120/min (Martinez-Conde et al., 2009). These are distinct from the larger intrusive saccades that disrupt normal fixation. Most studies of visual fixation in schizophrenia have used frequency of intrusive saccades as a performance measure (Curtis et al., 2001b, Gooding et al., 2000a, Kissler & Clementz, 1998). As for saccades during SPEM researchers have used different minimum amplitude criteria for identifying saccades during fixation.

Visual fixation in schizophrenia

Studies of visual fixation in schizophrenia patients have provided conflicting results. While several studies have found fixation to be normal (Gooding et al., 2000a, Kissler & Clementz, 1998) others have observed increased fixation errors in schizophrenia patients compared to control subjects (Amador et al., 1995, Curtis et al., 2001b, Rybakowski & Borkowska, 2002). These contradictory findings may be attributed to heterogeneity in subject populations and variations in measuring and analyzing methods between studies. Some of the studies showing abnormal fixation in schizophrenia used qualitative ratings and EOG, which is prone to generate bioelectric artifacts. Visual fixation abnormalities have not been found in patients with psychotic bipolar disorder (Amador et al., 1991, Gooding et al., 2000a).

Temporal stability of visual fixation

Two studies have found fixation performance in healthy subjects to be stable over several weeks (Ettinger et al., 2003a, Roy-Byrne et al., 1995). Temporal stability of visual fixation has not been assessed in schizophrenia patients.

Family studies of visual fixation in schizophrenia

Two studies have found impaired fixation stability in first degree relatives of schizophrenia patients (Amador et al., 1995, Rybakowski & Borkowska, 2002) and one study showed increased saccade frequency in relatives performing a fixation task with distracters but not without distracters (Curtis et al., 2001b). In one study saccade frequency during fixation did not differ between schizophrenia patients and their healthy siblings (Ettinger et al., 2004b). Studies of visual fixation in twins discordant for schizophrenia have not been published.

Pharmacological effects on visual fixation

Few studies have examined the effects of psychiatric medications on visual fixation. In one study fixation performance did not correlate with dose of antipsychotic medication (Amador et al., 1995). In a recent study schizophrenia patients were tested with a fixation task with distracters both when they were acutely ill and not medicated and again when they were in remission and taking an antipsychotic medication. No difference in fixation performance was found between the two assessments (Kallimani et al., 2009).

Neurological basis of visual fixation

Non-human primate studies and brain lesion studies have demonstrated that visual fixation recruits a distributed neural network including the prefrontal cortex, posterior parietal cortex, superior colliculus and cerebellum (Leigh & Zee, 1999). Functional imaging studies of healthy humans have shown that several frontal brain areas such as the DLPFC, precentral gyrus, inferior frontal gyrus, intraparietal sulcus and posterior parietal cortex are activated during visual fixation (Anderson et al., 1994, Petit et al., 1995, Petit et al., 1999).

In order to investigate the neural correlates of visual fixation in schizophrenia, groups of neuroleptic free schizophrenia patients and healthy controls

were scanned using SPECT while performing a visual fixation task (Malaspina et al., 1999). Compared to controls the patients had left prefrontal hypoperfusion along with medial temporal lobe hyperperfusion. This finding is consistent with the hypofrontality hypothesis of schizophrenia (Weinberger et al., 2001) and also with the hypothesized impairment in functional connectivity between frontal and temporal brain areas in schizophrenia (Friston & Frith, 1995).

Molecular genetic studies of visual fixation

One research group has found associations between impaired fixation performance in schizophrenia patients and polymorphisms in the *DRD3* gene, *COMT,* and phospholipase A_2 gene (Rybakowski et al., 2001, Rybakowski et al., 2002, Rybakowski et al., 2003). If replicated by other researchers these findings suggest that visual fixation may be used as an endophenotype in genetic studies of schizophrenia.

Antisaccade eye movements

In the antisaccade task a participant is required to refrain from looking at a target appearing unpredictably in a right or left peripheral location, and instead, make a rapid voluntary eye movement (saccade) to the opposite peripheral location. Generation of a reflexive saccade in direction of the peripheral target is considered an error (Hallett, 1978). Antisaccade performance is sensitive to the function of several cognitive processes and the task has become an important research tool for psychologists and psychiatrists for investigating cognitive deficits in psychiatric disorders. The antisaccade task has been proposed as a promising endophenotype in studies of schizophrenia (Hutton & Ettinger, 2006).

Antisaccades - Stimulus properties

The target stimulus in the antisaccade task is most often displayed on a computer monitor, which is placed approximately 50 cm away from the participant's head. Similar to SPEM tasks the target is usually a small symbol, such as a dot or a square. Each antisaccade trial typically starts with the target in a central location (0º) and the participant is required to visually fixate on it. A novel target that appears at a left or right peripheral location then replaces the central stimulus. The participant is then supposed to avoid making a visually guided saccade (prosaccade) to the peripheral

target and direct the gaze to an opposite location. Generally a few practice trials are presented before the actual testing begins in order to familiarize the participant with the task. The task session usually includes 20 to 60 trials (Smyrnis, 2008).

Antisaccade tasks can differ on several spatial and temporal parameters and studies have shown that these parameters can significantly affect performance. Different target eccentricities have been used, ranging from ±5° to ±25°. One study observed that increasing stimulus eccentricity was associated with increased reflexive error rate and decreased latency of correct antisaccades in healthy subjects (Fischer & Weber, 1997). Another study found that larger target eccentricities (±16º) better separated performance of schizophrenia patients and controls than smaller target eccentricities (±8º) (McDowell et al., 1999). In most studies two or more peripheral target locations are presented in each hemi-field.

The duration of target presentation varies between studies. In most studies of schizophrenia patients the central and peripheral targets are displayed for 1000 – 4000 ms. By randomly varying duration of the central fixation target between trials the appearances of peripheral targets become less predictable. Many antisaccade studies of schizophrenia patients have used variable central target duration (Clementz et al., 1994, Ettinger et al., 2006, Karoumi et al., 2001, Nieman et al., 2007, Petrovsky et al., 2009b).

Antisaccade studies have used three ways of shifting from central to peripheral target presentation. In the most commonly used step trial antisaccade task a peripheral target appears simultaneously with the disappearance of the central target. In the gap antisaccade task the central target is extinguished about 200 ms before a peripheral target appears. In healthy individuals response latencies are reduced and reflexive errors are more frequent in the gap task compared to the task using step trials (Fischer & Weber, 1997). Schizophrenia patients have also shown reduced latency in the gap condition in several studies (McDowell & Clementz, 1997, Reilly et al., 2008a). It has been proposed that the gap causes a disengagement of fixation at the time of stimulus onset, which causes a reduction in saccade latency and facilitates an increase in reflexive error rate (Fischer & Weber, 1997). A third version is the overlap task, in which central fixation and peripheral targets overlap. Contrary to the gap task response latencies are increased and reflexive error rates are decreased in the overlap task compared to the step trial task. An overlap effect has been observed in schizophrenia patients (McDowell & Clementz, 1997). Overlap

versions of the antisaccade task have been shown to better separate schizophrenia patients and non-psychiatric controls than the more frequently used step paradigm (McDowell & Clementz, 1997, McDowell et al., 1999). The overlap paradigm increased group separation mainly by decreasing the error rate in the control group.

Finally, an important parameter that can have significant effects on antisaccade task performance is the instructions given to participants. Mosimann et al (2004) examined the effects of different instructions on saccade performance in healthy individuals. In addition to performing the regular antisaccade task participants were instructed make redirected saccades, i.e. to glimpse towards and then immediately opposite to the target. The intersaccadic intervals were longer and the gain was higher for redirected saccades than for corrected erroneous antisaccades (Mosimann et al., 2004). This finding suggests that verbal instructions affect both temporal and spatial parameters of the antisaccade task. A recent study showed that by instructing subjects to delay making a response the latencies to correct antisaccade eye movements increased significantly and the rate of reflexive errors decreased (Taylor & Hutton, 2009). If participants were instructed to make antisaccades as quickly as they could latencies to correct responses decreased and if they were told to focus on spatial accuracy the latencies increased but neither instruction affected error rate. Antisaccade studies rarely describe the instructions to participants word by word and it is quite possible that this factor contributes significantly to the cross-laboratory performance differences that are frequently seen. It is important to consider these effects when antisaccade data are interpreted.

Antisaccade performance measures

The key antisaccade abnormality reported in schizophrenia and a reliable measure of antisaccade performance is the rate of reflexive saccade errors. The finding of an increased error rate in schizophrenia is very robust and has been replicated in over 75 studies regardless of which task paradigm and recording technique was used. A correct antisaccade is performed when the participant generates a saccade in opposite direction to the peripheral target and a reflexive error occurs when the participant makes a saccadic eye movement towards the peripheral target. The error rate simply reflects the percentage of errors over the total number of antisaccade trials. Figure 2 displays antisaccade performance measures for an antisaccade error trial and a correct antisaccade trial.

Researchers have used different criteria for detecting saccades in automatic or semi-automatic computer programs. Usually the criteria are based on minimum saccade velocity (30°/s), minimum saccade amplitude (1-5º), and minimum response latency (70-100 ms). The latency criterion is based on the fact that it takes the brain at least 70-100 ms to generate an eye movement in response to a visual stimulus (Leigh & Zee, 1999).

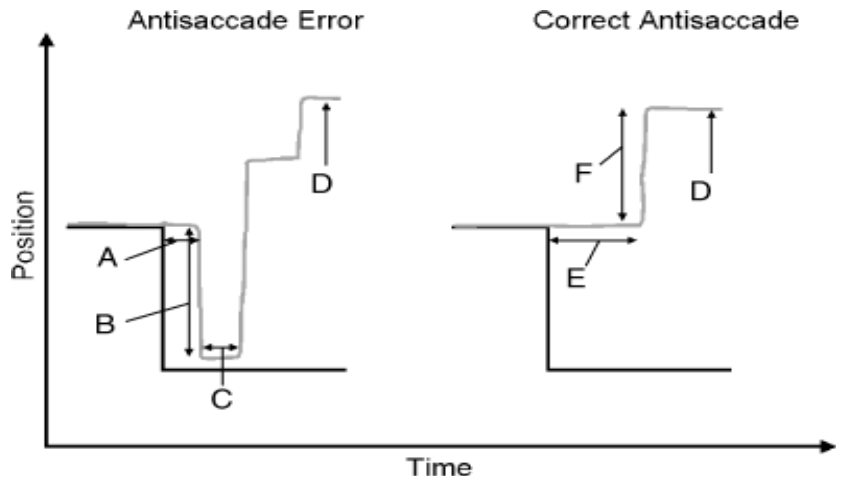

Figure 2
Antisaccade performance measures
A: Error latency, B: Error amplitude, C: Time to correct, D: Final eye position,
E: Correct antisaccade latency, F: Correct antisaccade amplitude
The figure was obtained from Hutton and Ettinger 2006 with kind permission

Some studies have reported the rate of corrected reflexive errors (Clementz et al., 1994, Gooding & Tallent, 2001, Polli et al., 2008). A correction occurs when the subject makes a saccade in the opposite direction right after a reflexive error. Correction rate reflects the percentage of error trials that are corrected. This measure is important, because a high correction rate suggests that the subject understands the task instructions and is motivated to perform the task.

Most studies measure the latency of correct antisaccade response. This is the time between target illumination and saccade initiation in ms. Response latencies of correct antisaccades indicate the processing speed necessary for planning and performing a voluntary act.

Some studies have measured the spatial accuracy of correct antisaccades. Antisaccade amplitude gain is the most commonly used measure of spatial accuracy. The percentage of amplitude gain is calculated by dividing the primary saccade amplitude with the target amplitude and multiplying by 100.

Spatial error is another measure of antisaccade spatial accuracy. It is of importance because it takes into account the effects of hypometric (undershooting) and hypermetric (overshooting) saccades (Ettinger et al., 2003a). Antisaccade amplitude gain can possible provide an underestimation of spatial inaccuracy because hyper- and hypometric saccades compensate each other. For example, a subject that makes approximately equal numbers of antisaccades with amplitude 10% above and antisaccades with amplitude 10% below the target amplitude may end up with a mean gain score of 100%. Antisaccade spatial error (%) is obtained in the following way. First the percentage of residual error is calculated for each saccade. This is done by subtracting the target amplitude from the saccade amplitude and dividing the result by the target amplitude. The absolute value of this term reflects the residual error and is then averaged across all saccades and multiplied by 100. A perfectly accurate saccade thus has a spatial error score of 0% and higher scores indicate greater spatial error (Ettinger et al., 2003a).

Antisaccade eye movements in schizophrenia

Fukushima et al (1988) were the first to report an increased reflexive error rate on the antisaccade task in schizophrenia patients compared to healthy controls. All following studies have replicated this finding and error rates have varied from approximately 25 to 70% in patients and 5 to 25% in healthy individuals (Hutton & Ettinger, 2006). This performance variability is probably related to differences in task parameters. Importantly, antisaccade deficits are observed in patients with first onset schizophrenia (Broerse et al., 2001, de Wilde et al., 2008, Ettinger et al., 2004a, Hutton et al., 1998, Hutton et al., 2002, Nieman et al., 2000) chronic schizophrenia (Boudet et al., 2005, Curtis et al., 2001b, Fukushima et al., 1988) and patients who are in symptomatic remission (Curtis et al., 2001a, Kallimani et al., 2009), indicating that the deficits are independent of illness duration and symptom levels. Impaired antisaccade performance has also been found in antipsychotic naïve patients (Harris et al., 2006), suggesting that the deficits are not merely induced by the effects of medications. Furthermore, there is evidence of increased antisaccade errors in individuals with schizotypal traits (Ettinger et al., 2005a, Gooding, 1999, Gooding et al., 2005, Larrison et al., 2000, O'Driscoll et al., 1998, Smyrnis et al., 2003) and in patients with prodromal symptoms of psychosis (Nieman et al., 2007) indicating that antisaccade deficits precede the appearance of schizophrenia.

By and large schizophrenia patients correct their reflexive errors at a similar rate to healthy subjects (Gooding & Tallent, 2001, Polli et al., 2008) suggesting that they are motivated and understand the task instructions.

Although most investigations find increased latencies to correct antisaccades in schizophrenia patients compared to controls (Fukushima et al., 1990, Karoumi et al., 1998, Maruff et al., 1998, Sereno & Holzman, 1995, Spengler et al. , 2006), some studies have not (Clementz et al., 1994, Ettinger et al., 2004b, Hutton et al., 2002, Nieman et al., 2000).

Several studies have shown reduced spatial accuracy of correct antisaccades in schizophrenia patients (Ettinger et al., 2004a, Ettinger et al., 2004b, Karoumi et al., 1998, McDowell et al., 1999).

Specificity of antisaccade deficits to schizophrenia

Antisaccade deficits are not specific to schizophrenia. Impaired antisaccade performance has been observed in several other psychiatric and neurological disorders. Several studies have observed significantly higher reflexive error rates in bipolar patients than in healthy individuals (Gooding & Tallent, 2001, Katsanis et al., 1997, Martin et al., 2007, Tien et al., 1996), but similar performance in bipolar patients and controls has also been reported (Crawford et al., 1995b). In most studies schizophrenia patients make more reflexive errors than bipolar patients (Crawford et al., 1995b, Gooding & Tallent, 2001, Tien et al., 1996) and the performance of bipolar patients generally falls between those of schizophrenia patients and controls. Gooding et al (2004) reported poor temporal stability of antisaccade performance in bipolar patients suggesting that the deficit is a state rather than a trait marker in bipolar disorder. Studies of patients with major depression have shown that antisaccade performance is state dependent. Patients with mild to moderate symptoms (Fukushima et al., 1990) have error rates similar to healthy subjects but patients with severe or psychotic symptoms have impaired performance (Sweeney et al., 1998).

Several studies have investigated antisaccade performance in OCD, Tourette's syndrome and attention deficit hyperactivity disorder (ADHD). Fronto-striatal dysfunctions have been implicated in all three disorders (Bradshaw & Sheppard, 2000). Two studies using small sample sizes and small numbers of antisaccade trials observed increased reflexive error rates in patients with OCD

compared to healthy controls (Rosenberg et al., 1997a, Tien et al., 1992). A low number of trials may have affected the outcome because of lack of adequate practice and familiarity to the task (Maruff et al., 1999). Three other studies using more trials did not find elevated error rates in OCD patients but the response latencies were significantly longer than in controls (Maruff et al., 1999, McDowell & Clementz, 1997, van der Wee et al., 2006). Elevated reflexive error rates have been reported in several studies of individuals with ADHD (Carr et al., 2006, Feifel et al., 2004, Mostofsky et al., 2001, Nigg et al., 2002) but studies on patients with Tourette's syndrome have provided mixed results (Dursun et al., 2000, Farber et al., 1999, LeVasseur et al., 2001). Antisaccade performance has also been investigated in several other psychiatric and neurological disorders such as Parkinson's disease (Mosimann et al., 2005) and autism (Luna et al., 2007).

Temporal stability of antisaccade performance

Longitudinal studies of antisaccade task performance in schizophrenia patients and healthy controls are relatively few. Most of them have demonstrated moderate to high performance stability, adding support to antisaccade deficits being feasible endophenotypes. Thaker et al (1989) reported high intra-class correlation ranging from 0.75 to 0.90 for antisaccade error rate and latency in schizophrenia patients and healthy individuals who were tested at intervals up to one year. However, low test-retest reliability was found for antisaccade accuracy and latency in a small group (n = 8) of healthy subjects who were tested four times at intervals of one to two weeks (Roy-Byrne et al., 1995). Ettinger et al (2003a) reported good intra-class correlation of 0.65 for latency and 0.79 for reflexive error rate in 21 healthy subjects who were retested after an average interval of 58 days. Calkins et al (2003) observed high test-retest reliability for reflexive error rate and antisaccade latency in a mixed group of schizophrenia patients and their relatives that were retested after 1.8 years. High test-retest reliability of antisaccade performance was observed in a study of 23 chronic schizophrenia patients and 10 bipolar patients who were retested after an interval of almost three years (Gooding et al., 2004). It is interesting that the performance remained stable despite changes in medications and clinical status. Gooding et al (2005) reported good temporal stability of antisaccade performance in a large group

of young adults with and without high levels of schizotypal traits who were tested at average intervals of 59 months.

Internal consistency of antisaccade performance

High internal consistency (Cronbach's alpha > 0.87) for all antisaccade variables was observed in a study of healthy subjects (Ettinger et al., 2003a). Internal consistency of antisaccade performance has not been reported in schizophrenia.

Task duration effects on antisaccade performance

Two studies on healthy subjects have shown some within-session performance changes of antisaccade performance, which have been related to factors such as learning (improvement) and fatigue or boredom (deterioration) (Ettinger et al., 2003a, Smyrnis et al., 2002). In a large multi-center study of schizophrenia patients and controls Radant et al (2007) compared antisaccade performance in three blocks of 20 trials that were presented with a brief rest between blocks. They found that the intra-class correlation was high between the blocks, ranging from 0.87 to 0.93 at individual study centers and the reflexive error rate decreased significantly from block one to block two but plateaued at the third block in both patients and controls. This suggests similar learning effect in both groups.

Symptom correlates of antisaccade performance in schizophrenia

There are indications that the level of clinical symptoms has limited correlations with antisaccade performance in schizophrenia patients. Antisaccade impairments have been reported in clinically remitted schizophrenia patients (Curtis et al., 2001a). In a three-year follow up study antisaccade performance in schizophrenia patients remained stable despite significant changes in clinical status (Gooding et al., 2004). No difference in antisaccade performance was observed in a group of schizophrenia patients who were first studied when they were unmedicated and acutely ill and again several weeks later when they were in symptomatic remission (Kallimani et al., 2009).

Several studies have found reflexive error rates to be elevated in patients with high levels of negative symptoms (Ettinger et al., 2004a, Ettinger et al., 2006, Nkam et al., 2001, Tien et al., 1996) but no such association has also been reported (Hutton et al., 2004, Rosse et al., 1993). Some investigators have observed associations

between longer response latencies and high levels of negative symptoms (Louchart-de la Chapelle et al., 2005, Nkam et al., 2001). One study found that positive symptoms were associated with fewer reflexive errors (Tien et al., 1996).

Heritability of antisaccade performance

Two studies have examined heritability of antisaccade task performance and both provide evidence that variability in reflexive error rate is under genetic effects. Heritability of antisaccade latency and spatial accuracy has not been investigated. Malone and Iacono (2002) measured reflexive error rates in 207 11 year old and 207 17 year old MZ twin pairs and in 126 11 year old and 102 17 year old DZ twin pairs. They found that, despite a significant age effect on error rate, additive genes accounted for 57% of the variance in error rate in both age groups combined. In a large multi-site family-based heritability study, Greenwood et al (2007) found an estimated heritability of 42% for reflexive error rate in 525 members of schizophrenia pedigrees. These findings of moderate heritability support that reflexive error rate is a promising endophenotype. In addition to these two studies several family studies have shown significant within-family correlations of antisaccade task performance (Brownstein et al., 2003, Crawford et al., 1998, Curtis et al., 2001a).

Family and twin studies of antisaccades in schizophrenia

Studies comparing antisaccade performance in relatives of schizophrenia patients and healthy controls have provided inconsistent results. Over 20 studies have examined reflexive error rates in schizophrenia relatives. Most of them used the standard step paradigm but a few employed gap and overlap paradigms. While several studies report that relatives make significantly more reflexive errors than controls (Clementz et al., 1994, Curtis et al., 2001a, Ettinger et al., 2004b, Karoumi et al., 2001, Katsanis et al., 1997, McDowell & Clementz, 1997, Petrovsky et al., 2009b) other studies do not find significant difference (Boudet et al., 2005, Brownstein et al., 2003, Crawford et al., 1998, Louchart-de la Chapelle et al., 2005, Maccabe et al., 2005, Raemaekers et al., 2006) and some have shown relatives to have higher error rate at a trend level for statistical significance (de Wilde et al., 2008, Price et al., 2006). There is no obvious explanation for the inconsistencies between the studies but it is possible that

methodological differences such as variations in task paradigms and instructions are involved.

A recent meta-analysis of studies comparing relatives of schizophrenia patients with controls showed moderately increased reflexive error rates in relatives vs controls (d = 0.46) (Calkins et al., 2008).

Similar to what has been observed for SPEM deficits, relatives of patients with high reflexive error rate have higher error rate than relatives of patients with low error rate (Crawford et al., 1998, Curtis et al., 2001a).

Effect of genetic loading for schizophrenia on antisaccade performance has been investigated in a few studies. A study using an overlap paradigm showed that two samples of multiplex families had significantly higher reflexive error rate than a sample of simplex families (McDowell et al., 1999). Another study using the traditional step paradigm Maccabe et al (2005) reported no significant difference in error rate between simplex and multiplex families.

Another method of investigating the effects of genetic loading is to compare patient parents with family history of schizophrenia (most-likely gene carrier; MLC) to parents with no family history (least-likely gene carrier; LLC). Ross et al. (1998) found a small group of MLC parents to have higher reflexive error rate than LLC parents on a gap version of the antisaccade task. Petrovsky al. (2009b) observed a linear increase in reflexive errors from controls to LLC to MLC parents. From this it seems that the ability to uncover effects of genetic loading on antisaccade performance depends on which task paradigm is used.

Most studies do not find significant differences in saccade latency between relatives and controls (Boudet et al., 2005, Brownstein et al., 2003, Crawford et al., 1998, Curtis et al., 2001a, de Wilde et al., 2008, Ettinger et al., 2004b, Karoumi et al., 2001, Katsanis et al., 1997, Louchart-de la Chapelle et al., 2005, Maccabe et al., 2005, McDowell & Clementz, 1997). In the only antisaccade study of schizophrenia discordant twins Ettinger et al (2006) found that non-schizophrenic co-twins had significantly longer latencies than the control twins. In two studies Thaker et al. (1996, 2000) reported longer latencies in sub-groups of schizophrenia relatives compared to controls. A recent meta-analysis suggests that relatives have slightly longer latencies to all antisaccade trials (d = 0.34) and to correct antisaccade trials (d = 0.39) but not to error trials (d = -0.16) (Calkins et al., 2008).

Six studies have examined spatial accuracy in relatives of schizophrenia patients by measuring amplitude gain. In three studies patient relatives had significantly reduced gain compared to controls (Ettinger et al., 2004b, Ettinger et al., 2006, Karoumi et al., 2001). In one study the relatives had significantly increased gain (de Wilde et al., 2008) and in two studies they did not differ significantly from the control groups (Crawford et al., 1998, McDowell & Clementz, 1997).

Due to inconsistent results in family studies of antisaccade performance it is probably not appropriate to state with certainty that any antisaccade measure indisputably meets the co-familiality criterion for a valid endophenotype. However, the data on reflexive error rate is promising and future studies should focus on identifying the optimal task paradigms for identifying performance differences. Antisaccade latency and spatial accuracy will have to be investigated more extensively.

Pharmacological effects on antisaccade performance

Studies have shown that several medications affect antisaccade performance in both healthy individuals and patients with schizophrenia (Reilly et al., 2008b). These findings are important because medication effects need to be considered in all antisaccade studies and also because knowledge of pharmacological effects on antisaccade performance can provide researchers with an important tool for investigating and developing new drugs that are targeted at cognitive symptoms of neuropsychiatric disorders.

Healthy individuals: Studies of medication effects on antisaccade performance in healthy individuals provide important information, because complicated effects of a brain disorders do not confound them. Benzodiazepines elevate reflexive errors and response latencies in healthy subjects (Green & King, 1998, Green et al., 2000). The typical antipsychotic chlorpromazine and the atypical medication risperidone were associated with increased reflexive error rates but did not affect latency in one study (Barrett et al., 2004). However, this effect of risperidone was associated with the level of drug-induced akathisia. Another study of chlorpromazine found no effects on error rate or latency (Green & King, 1998). In a placebo controlled cross-over study a single dose of the antidepressant sertraline did not affect antisaccade latency or reflexive error rate (Green et al., 2000). Amphetamine did not affect antisaccade performance in healthy volunteers (Wonodi

et al., 2006a) but two placebo-controlled studies showed that methylphenidate administration resulted in reduced reflexive error rate and shorter latencies in teenagers with ADHD (Klein et al., 2002, O'Driscoll et al., 2005).

Schizophrenia patients: In a study of chronic schizophrenia patients reflexive error rate was not affected by typical antipsychotic medications (Crawford et al., 1995a). A study of mostly first episode schizophrenia patients, who were either started on typical or atypical antipscyhotics, no significant treatment effect was found on reflexive error rate (Muller et al., 1999) and similar findings were obtained in a study of first episode patients by Hutton et al (1998). Burke and Revelely (2002) compared the effects of typical and atypical medications in patients who were either switched from typical antipsychotic medication to the atypical medication risperidone or from risperidone to a typical medication. The switch to risperidone led to a reduction in reflexive error rate but the switch to a typical medication resulted in increased error rate. Interestingly these performance changes were independent of symptomatic change.

Harris et al (2006) conducted a longitudinal study examining 39 antipsychotic naïve first episode schizophrenia patients who were initiated on typical or atypical antipsychotics. Patients' reflexive error rates and response latencies to correct antisaccades progressively decreased throughout a one year follow-up period although they did not reach the performance level of healthy controls. The latency reduction was significantly more in patients taking an atypical medication than in those taking a typical medication.

In a randomized double blind crossover study the effects of the serotonergic antagonist cyproheptadine on antisaccade performance was examined in chronic medicated schizophrenia patients (Chaudhry et al., 2002). Cyproheptadine treatment was associated with a significant reduction in reflexive error rate compared to placebo. The results of this study are particularly interesting in light of the previously mentioned findings of improved antisaccade performance with atypical antipsychotic medications (Burke & Reveley, 2002, Harris et al., 2006), because all atypical antipsychotics are potent serotonin antagonists.

In summary, studies of typical antipsychotic medications have provided mixed results but there are indications that atypical antipsychotics may improve antisaccade performance in schizophrenia patients.

Effects of nicotine on antisaccades

Acute nicotine administration was shown to decrease reflexive error rates in two studies of healthy smokers (Larrison-Faucher et al., 2004, Rycroft et al., 2006) and a study of healthy non-smokers found a single dose of nicotine nasal spray do decrease response latencies over a five hour period but reflexive error rate did not differ from a placebo group (Rycroft et al., 2007). An increase in reflexive errors was observed in a group of healthy smokers who were first tested after regular smoking and then again after an overnight abstinence (Pettiford et al., 2007). Nicotine administration was associated with reduced reflexive error rates in two studies of schizophrenia patients (Depatie et al., 2002, Larrison-Faucher et al., 2004).

Instead of examining the cholinergic enhancing effects of nicotine Ettinger et al. (2003b) showed that administration of the anticholinergic medication procyclidine was associated with increased reflexive errors in schizophrenia patients compared to placebo. However, this effect was only observed when the patients received procyclidine first but not when they received placebo first, probably due to a practice effect (Ettinger et al., 2003b).

In a recent placebo controlled fMRI study Ettinger et al (2009) investigated the neural mechanisms of nicotine effects on antisaccade eye movements in healthy male smokers and non-smokers. They found nicotine administration to be associated with reduced antisaccade response latency in both groups and a reduced BOLD signal in the left frontal eye field of non-smokers. This may suggest that neural efficiency in the left frontal eye field is enhanced by nicotine in non-smokers.

In summary, there is evidence that acute exposure to nicotine improves antisaccade task performance in both schizophrenia patients and healthy individuals.

Neurological basis of antisaccade eye movements

Functional imaging studies using PET and fMRI have shown that antisaccade performance involves a fronto-parieto-subcortical network including FEF, SEF, DLPFC, anterior cingulate cortex (ACC), posterior parietal cortex, thalamus and striatum (Hutton & Ettinger, 2006, McDowell et al., 2008). Human brain lesion studies have shown that FEF lesions are associated with increased antisaccade latency and lesions to the DLPFC and associated areas result in increased reflexive error rates (Pierrot-Deseilligny et al., 2002, Ploner et al., 2005). Elevated error rates

have also been observed after lesions to ACC, superior colliculus (Gaymard et al., 1998) and ventral prefrontal cortex (Walker et al., 1998).

With the introduction of event related fMRI it became possible to temporally dissociate specific neural processes that are involved in different components of the antisaccade task. Some studies have used electro-encephalography (EEG) and magneto-encephalography (MEG), which have higher temporal resolution but worse spatial resolution than fMRI (Clementz et al., 2001, McDowell et al., 2005).

Functional imaging studies consistently show that antisaccade eye movements are associated with increased FEF activity when compared to prosaccade eye movements (Clementz et al., 2001, DeSouza et al., 2003, Ettinger et al., 2008, Ford et al., 2005, McDowell et al., 2005). Several studies have observed that FEF activity is increased prior to saccade initiation (Clementz et al., 2001, DeSouza et al., 2003, Ford et al., 2005, McDowell et al., 2005). Increased activity has also been seen in SEF (Ford et al., 2005, McDowell et al., 2005) and inferior parietal cortex (Ettinger et al., 2008, Matsuda et al., 2004) in relation to antisaccades. It has been suggested that inhibitory input is increased to these brain areas in the preparatory phase of an antisaccade in order to prevent release of a reflexive saccade towards the peripheral target (DeSouza et al., 2003). This hypothesis is supported by a study showing less pre-saccade FEF activation prior to reflexive errors compared to correct antisaccades (Cornelissen et al., 2002).

There are indications that the intraparietal sulcus may be involved in sensorimotor transformation necessary for generating a correct antisaccade (Medendorp et al., 2005, Moon et al., 2007). Evidence for this were obtained in an event-related fMRI study showing increased intraparietal sulcus activity in the hemisphere contra-lateral to a peripheral target but the activity shifted to the other hemisphere when the subject was instructed to generate an antisaccade (Medendorp et al., 2005).

Neurophysiological studies have shown that the DLPFC is associated with brain inhibitory functions and plays important roles in cognitive functions such as attention, planning, spatial orientation and behavioral inhibition (Goldman-Rakic, 1995). Individuals with lesions that are limited to the DLPFC make more reflexive errors on the antisaccade task but prosaccade performance is not affected (Pierrot-Deseilligny et al., 2003). Functional imaging studies have observed that elevated DLPFC activity precedes the generation of correct antisaccades (DeSouza et al.,

2003, Ford et al., 2005, McDowell et al., 2005), which indicates that the DLPFC is involved in the inhibition of reflexive saccades towards a peripheral cue. However, some studies have not found increased DLPFC activity during antisaccades compared to prosaccades (O'Driscoll et al., 1995, Raemaekers et al., 2002, Raemaekers et al., 2006). This discrepancy may be related to differences in eye movement task designs and the use of block vs event-related fMRI protocols.

Several fMRI studies show that the ACC is involved in generation of antisaccades (Gaymard et al., 1998, Pierrot-Deseilligny et al., 2005, Polli et al., 2005). This is not surprising given the assumed role of the ACC in conflict monitoring, inhibitory control and error detection (Braver et al., 2001, Garavan et al., 2002). In a study by Ford et al (2005) ACC activity was higher for correct antisaccades than for error trials in the period prior to peripheral stimulus onset but during the response period the activity was increased for incorrect antisaccades. This indicates that the ACC is both involved in signaling the probability of reflexive errors and monitoring errors during the antisaccade task.

The first functional imaging study of antisaccades in schizophrenia used SPET to compare patients with low reflexive error rates to patients with high error rates (Crawford et al., 1996). Patients with high reflexive error rate demonstrated lower regional cerebral blood flow (rCBF) in the ACC, insula and left striatum. Since then several fMRI studies have been conducted using either block or event-related imaging designs. In a study by McDowell et al (2002) schizophrenia patients failed to show an increase in DLPFC activity that was observed in healthy controls during antisaccade performance. Camchong et al (2008) observed decreased activity in FEF and SEF in schizophrenia patients during antisaccades and both patients and their first-degree relatives had decreased activity in the middle occipital gyrus, insula, cuneus, ACC and the anterior prefrontal cortex. The authors conclude that impaired antisaccade performance in schizophrenia patients and their relatives may be associated with decreased activation in brain regions managing and evaluating early sensory and attention processing.

In an event-related fMRI study schizophrenia patients failed to activate the striatum during inhibition of saccades but no differences were observed between patients and controls in other areas such as FEF and SEF (Raemaekers et al., 2002). The same research group found that siblings of schizophrenia patients also showed an isolated striatal deficit during antisaccade performance although they did not

make more reflexive errors than control subjects (Raemaekers et al., 2006). The authors suggest that antisaccade deficits in schizophrenia are associated with abnormal fronto-striatal connectivity (Raemaekers et al., 2002). Previous imaging studies have implicated fronto-striatal deficits in schizophrenia (Buchsbaum et al., 1998). The reason no functional abnormalities were observed in frontal brain areas in the Raemakers et al. (2002, 2006) studies may be that event-related fMRI is not sensitive to sustained activation, which is best examined with a block design. An fMRI study by Tu et al (2006) provides evidence that fronto-striatal-thalamo-cortical circuit abnormalities are involved in antisaccade deficits in schizophrenia. In this block design study, schizophrenia patients failed to activate lentiform nuclei (striatum), thalamus and the left inferior frontal gyrus.

A recent event related fMRI study by Polli et al (2008) provides evidence that the ACC is involved in antisaccade deficits in schizophrenia. Schizophrenia patients showed decreased activation in relation to reflexive errors in the dorsal ACC, striatum and brainstem, which are components of a reinforcement-learning network. Activation was also decreased in the rostral ACC, insula and amygdala, which are parts of an affective appraisal network. These findings suggest that schizophrenia patients have impaired reinforcement learning and sensitivity to behavioral outcomes (Polli et al., 2008).

Three structural MRI studies have examined structural brain correlates of antisaccade eye movements in schizophrenia. In a study by Ettinger et al (2004a) larger caudate volumes predicted longer latencies and reduced amplitude gain in first-episode psychosis patients and larger premotor cortex volumes predicted fewer reflexive errors in control subjects but not in patients. Another study on first-episode patients found that elevated reflexive errors were associated with decreased right superior medial frontal cortical volume (Bagary et al., 2004). In a study of 70 schizophrenia/schizoaffective patients, 105 unaffected first-degree relatives and 67 controls, smaller prefrontal lobe volume was associated with longer latencies of correct antisaccades in the total subjects sample (Schulze et al., 2006). The authors conclude that lack of between-group differences indicates that this relationship is not influenced by factors involved in the pathophysiology of schizophrenia. These structural imaging studies suggest that structural abnormalities of frontal and striatal brain regions may be associated with antisaccade performance.

Cognitive control of antisaccade eye movements

Despite a large body of studies utilizing the antisaccade task for investigating cognitive impairments in psychiatric and neurological disorders, researchers debate about which cognitive processes are used for performing the task. There is, however, some evidence for the involvement of several cognitive processes in antisaccade performance, including inhibitory processes, attention, working memory, error monitoring and learning (Hutton, 2008).

Inhibitory processes: Response latencies for correct antisaccades are generally approximately 50-100 ms longer than for prosaccades (Evdokimidis et al., 1996). It has been claimed that this is because it takes time to implement inhibitory processes that suppress reflexive saccades towards the visual stimulus and activate a specific voluntary response (Everling & Fischer, 1998). Based on this notion, antisaccade errors in schizophrenia patients are often interpreted as resulting from failures in inhibitory processes (Crawford et al., 2002, Hutton & Kennard, 1998).

Recently a competition model for saccade generation in the antisaccade task has been proposed (Massen, 2004). The model suggests that neural signals for pro- and antisaccades compete with each other. If an internally triggered antisaccade is processed fast enough it wins the race and a reflexive saccade is terminated. On the other hand if an externally triggered prosaccade is processed fast enough, or the antisaccade is too slow, a reflexive error is generated first. This model is supported by two observations. First, task manipulations that result in increased response latencies for correct antisaccades lead to increased reflexive errors, suggesting that slowing down the antisaccade helps a prosaccade "winning the competition" (Massen, 2004). Second, when a reflexive error is corrected the time between the error and a corrective antisaccade is frequently shorter than the time needed for a correct antisaccade to be generated as a response to an error (Tatler & Hutton, 2007). This suggests that antisaccades following reflexive errors are not always corrective responses but are rather processed parallel to faster acting prosaccades.

There is evidence that perservative errors on the WCST, which indicate inhibitory failure, are associated with reflexive error rate in schizophrenia patients (Crawford et al., 1995a, Crawford et al., 1995b, Crawford et al., 1996, Karoumi et al., 1998, Rosse et al., 1993, Tien et al., 1996). On the other hand Levy et al. 2004 did not find significant correlation between antisaccade error rate and WCST performance in schizophrenia patients and non-psychiatric controls. Radant et al

(1997) observed a significant correlation between perservative errors on WCST and antisaccade errors in healthy controls but not in schizophrenia patients.

Attention: The role of attention in antisaccade performance has been investigated in studies using task manipulations. In one study on healthy subjects a cue was presented in the peripheral location opposite the subsequently presented target (Weber et al., 1998). Although the cue signaled the correct location for an antisaccade it did not improve performance. On the contrary, it led to an increase in reflexive errors and latencies to correct antisaccades. The authors suggest that the cue caused a shift in attention leading the subject, who was prepared for making an antisaccade, to generate an erroneous saccade in the direction opposite to the cue.

Kristjánsson et al (2001) added a distracting discrimination task to an antisaccade task in a study on healthy subjects. Depending on the timing of the discrimination task, latencies to correct antisaccades either increased or decreased. When the discrimination event was presented 100 – 300 ms prior to peripheral target appearance the latencies were significantly shorter than when there was no additional task. Kristjánsson et al (2001) suggest that the discrimination task disrupts a reflexive prosaccade allowing the antisaccade to start sooner. This explanation is essentially another example of a saccade competition model.

There is evidence that impaired attention may contribute to antisaccade deficits in schizophrenia. Tendolkar et al (2005) recorded the P100 evoked potential in schizophrenia patients and controls while they performed prosaccade and antisaccade tasks. The amplitude of P100 is enhanced with suppression of irrelevant stimuli during task performance. In this study the healthy controls had a larger P100 for antisaccades than prosaccades but this was not seen in patients. This suggests that the schizophrenia patients were less able to suppress irrelevant stimuli during the antisaccade task. Radant et al (1997) observed an association between antisaccade deficits and measures of sustained attention on the CPT and TMT-A among schizophrenia patients.

Working memory: Several studies have examined the role of working memory in antisaccade performance. Working memory refers to the ability to temporally store and manipulate task relevant information while performing a goal directed task. The antisaccade task clearly has working memory components. It requires ability to retain task instructions, formation of an internal representation of the target and constant monitoring of task performance. Roberts et al (1994)

induced working memory impairment in healthy subjects while they performed antisaccades. When the participants performed a concurrent mental arithmetic task a significant increase in reflexive errors and latencies to correct antisaccades was observed. A similar manipulation of the prosaccade task did not affect performance. Another study demonstrated that antisaccade performance deteriorated with simultaneous performance of an n-back working memory task (Mitchell et al., 2002). The participants were auditorily presented with a series of letters and were required to specify whether each letter matched a letter that was presented n letters earlier. A 2-back task led to increased reflexive errors and latencies to correct antisaccades compared to 0-back and 1-back tasks. Hutton et al (2004) did not find correlations between spatial working memory measures and antisaccade performance in healthy subjects but a significant correlation was seen in schizophrenia patients. Worse spatial working memory was associated with worse antisaccade performance in patients (Hutton et al., 2004).

The WCST has working memory components and most studies examining the relationship between antisaccade and WCST performance in schizophrenia patients have shown that antisaccade deficits are significantly associated with working memory deficits (Karoumi et al., 1998, Rosse et al., 1993).

Error monitoring: The antisaccade task requires constant monitoring of performance in order to detect and correct errors. This suggests that there may be some contingency effects, meaning that the performance in one trial will affect the performance in a subsequent trial. An example of such an effect is post-error slowing. It is commonly seen that subjects performing reaction time tasks respond slower on trials following error trials (Notebaert et al., 2009). This has often been explained by a tendency of subjects to become more cautious after they make an error but cognitive scientists debate about the causes of this effect (Notebaert et al., 2009). Tatler and Hutton (2007) found signs of post-error slowing in a study examining a large number of antisaccade trials but, surprisingly, this slowing did not lead to a reduction in error rate. On the contrary, the likelihood of making an error increased following error trials. These results are in agreement with studies showing that participants are generally unaware of approximately 50% of the reflexive errors they make on an antisaccade task (Mokler & Fischer, 1999, Nieuwenhuis et al., 2001). These un-noticed errors typically have smaller amplitudes and shorter correction times than errors the subject is aware of. It is therefore possible that there

are two types of reflexive errors. One type is made without the subject's awareness, has small amplitude and is rapidly corrected. The other type is characterized by larger amplitudes and is corrected more slowly after the subject becomes aware of it.

Learning: Several studies have shown that antisaccade performance can improve with repeated testing, both over several weeks (Dyckman & McDowell, 2005, Ettinger et al., 2003a) but also within the same session (Ettinger et al., 2003a, Smyrnis et al., 2002). It is important to consider these learning effects in studies involving repeated testing.

Finally, it has been demonstrated that the cognitive control of antisaccade performance can be modulated by incentives. Duka and Lupp (1997) showed that monetary incentives presented prior to target onset reduced error rates in healthy participants. These findings were later replicated in both healthy subjects and patients with anxiety and depression (Hardin et al., 2007).

Molecular genetic studies of antisaccade eye movements

The precise molecular genetic factors underlying antisaccade performance deficits remain unknown. A few studies have investigated the relationship of genetic markers with antisaccade performance. A linkage study of multigenerational families with schizophrenia showed linkage of a composite antisaccade reflexive error rate and P50 evoked potential suppression endophenotype to a locus on chromosome 22q11-q12 (Myles-Worsley et al., 1999). This locus has been identified as a susceptibility locus for schizophrenia in several linkage studies (Chen et al., 2004a, Liu et al., 2002) and it is a region affected in velocardio-facial syndrome, which is associated with a high risk of psychotic symptoms (Murphy et al., 1999).

A study of *COMT* val^{158}met and antisaccades in young healthy males found a linear trend for val^{158} homozygotes having higher reflexive error rate (Stefanis et al., 2004). The same research group recently reported an association of one risk allele in the *RGS4* gene with increased antisaccade error rate (Stefanis et al., 2008). Ettinger et al (2008) did not find association between *COMT* val^{158}met and antisaccade performance in healthy subjects.

In a recent study by Petrovsky et al (2009a) *CHRFAM7A*, which is a copy number variation in the α_7 nicotinic acetylcholine receptor subunit (*CHRNA7*), was

not associated with antisaccade performance in healthy subjects. *CHRFAM7A* has been associated with psychosis (Flomen et al., 2006).

In the present thesis antisaccade eye movements are studied in relation to the putative schizophrenia risk genotypes *COMT* val^{158}met and *NRG-1* in schizophrenia patients and healthy controls.

Prosaccade eye movements

Prosaccades are rapid eye movements towards suddenly appearing visual stimuli. A prosaccade is generated in order to bring an object image onto the fovea. The terms reflexive saccade and refixation saccade are also used for this type of eye movement. The prosaccade task is often considered a control task for the antisaccade task because it involves some overlapping neural processes but different cognitive requirements. Most studies have shown that schizophrenia patients have normal prosaccade task performance.

Prosaccades - Stimulus properties

The visual target is typically a small symbol that is presented on a computer screen. In the most commonly used prosaccade task each trial begins with the target in the central location (0º). After a fixation period the central target disappears and simultaneously a peripheral target appears horizontally from the central location. The peripheral target is presented for approximately 1000 ms before the central target is presented again. Participants are instructed to keep their eyes on the target and follow it as accurately as possible. There are usually 20-60 trials in each session and studies have used target eccentricities ranging between ±5º and ±30º (Crawford et al., 1998, Ettinger et al., 2005b, Petrovsky et al., 2009b, Reilly et al., 2008a, Thaker et al., 2000). Most studies use two or more target locations in each hemifield in order to examine saccades of different amplitudes. In some studies the duration of the central fixation target varies (1000-3000 ms) between trials (Ettinger et al., 2005b, Petrovsky et al., 2009b, Reilly et al., 2008a, Thaker et al., 2000) in order to make the appearance of the peripheral targets temporally unpredictable.

Investigators have studied both gap and overlap versions of the prosaccade task. In the gap paradigm there is an approximately 200 ms gap between disappearance of the central fixation target and appearance of a peripheral target.

Studies have shown that this reduces saccade latency and can induce so-called express saccades with latencies of 80-120 ms (Fischer et al., 1993). In the overlap paradigm the fixation and peripheral targets overlap for periods that can range from small fractions to the entire duration of the peripheral target. Similar to the antisaccade task the overlap paradigm is associated with increased saccade latency (Fischer & Weber, 1997).

Prosaccade performance measures

The most commonly used prosaccade performance measures in studies of schizophrenia patients are amplitude gain, latency and peak velocity. Prosaccade amplitude gain is a measure of the ability to accurately locate the peripheral target. The percentage of prosaccade amplitude gain is calculated by dividing the saccade amplitude by the target amplitude and multiplying by 100. A gain score of 100% indicates a saccade that is exactly on the target. Prosaccade latency is the time between peripheral target appearance and saccade initiation. Some studies have also examined peak and average velocity of saccades (Clementz et al., 1994, Levin et al. , 1981, Levin et al., 1982, Ross et al., 1988, Thaker et al., 2000, Yee et al., 1987). Similar to antisaccade data analysis investigators have used criteria of minimum saccade amplitude (1º-5º), latency (70-100 ms) and velocity (30°/s) (Clementz et al., 1994, Crawford et al., 1998, Ettinger et al., 2005b, Petrovsky et al., 2009b).

Prosaccades in schizophrenia

Most studies have found no significant differences in prosaccade latency (Clementz et al., 1994, Crawford et al., 1995a, Crawford et al., 1995b, Fukushima et al., 1988, Grootens et al., 2008, Karoumi et al., 1998, Krebs et al., 2001, Tendolkar et al., 2005) and spatial accuracy (Clementz et al., 1994, Crawford et al., 1995a, Crawford et al., 1995b, Fukushima et al., 1988, Iacono et al., 1981, Karoumi et al., 1998, Krebs et al., 2001, Sweeney et al., 1997) between schizophrenia patients and controls suggesting that basic saccadic mechanisms are intact in schizophrenia. However, other studies have demonstrated prolonged latency (Evans & Schwartz, 1997, Mackert & Flechtner, 1989) and reduced accuracy (Cegalis et al., 1982, Schwartz et al., 1995) in schizophrenia patients. In general, schizophrenia patients have normal average and peak saccade velocity (Levin et al., 1982, Ross et al., 1988, Yee et al.,

1987) but one study reported slower peak velocity in patients (Cegalis et al., 1982). Prosaccade performance has generally not been associated with symptom levels in schizophrenia patients (Kallimani et al., 2009, Karoumi et al., 2001). The between-study heterogeneity may be associated with variability in eye movement recording techniques and target presentation. It is also possible that some subtle prosaccade deficits may be associated with schizophrenia.

Temporal stability of prosaccades

Studies of healthy individuals have shown that measures of prosaccade accuracy and latency are stable over time intervals of several weeks to approximately two years (Ettinger et al., 2003a, Iacono & Lykken, 1981, Reilly et al., 2005, Wilson et al., 1993)

Family studies of prosaccades

Most studies have shown that first-degree relatives of schizophrenia patients have normal prosaccade latency and accuracy (Crawford et al., 1998, Curtis et al., 2001a, Ettinger et al., 2006, Karoumi et al., 2001, Petrovsky et al., 2009b). However, a few studies have observed less accurate (hypometric) saccades in patient relatives (Calkins et al., 2003, Schreiber et al., 1995). A recent meta-analysis found that relatives of schizophrenia patients did not have different prosaccade latency or accuracy than healthy controls with effect sizes of 0.02 and -0.01, respectively (Calkins et al., 2008).

Pharmacological effects on prosaccades

Multiple psychiatric medications are known to interfere with saccade generation in healthy individuals. Benzodiazepines are associated with a dose dependent slowing in saccade peak velocity (Ball et al., 1991, Roy-Byrne et al., 1993) and saccade hypometria (Ball et al., 1991). Lorazepam caused increased prosaccade latency on gap and overlap paradigms in a study of healthy subjects (Masson et al., 2000). Both typical and atypical antipsychotic medications have been associated with slowing of saccade peak velocity in healthy individuals (Green et al., 1996, Morrens et al., 2007). Saccadic peak velocity is considered to be one of the best biomarkers for

sedative drug effects (de Visser et al., 2003). Nicotine does not seem to affect prosaccade performance (Depatie et al., 2002, Sherr et al., 2002).

Studies of schizophrenia patients have mainly focused on the effects of antipsychotic medications on saccadic eye movements. Typical antipsychotics were associated with reduced prosaccade gain in a study of chronic schizophrenia patients (Crawford et al., 1995a). Slowing of prosaccade peak velocity was observed with administration of both typical and atypical antispsychotics in two studies that included primarily first episode patients (Muller et al., 1999, Straube et al., 1999). Treatment with the atypical antispsychotic medication risperidone has been associated with reduced prosaccade peak velocity, decreased prosaccade gain and prolonged prosaccade latency in schizophrenia patients (Harris et al., 2006, Reilly et al., 2005, Sweeney et al., 1997). On the other hand Burke and Reveley (2002) found no effects of risperidone on prosaccades.

Neurological basis of prosaccades

The saccadic system has been extensively studied in lesion, neurophysiological and neuroimaging studies of humans and non-human primates. Generation of prosaccades involves both cortical structures such as FEF, SEF, primary visual (V_1), extrastriate (V_2/V_3) and parietal cortices as well as subcortical structures such as thalamus, superior colliculus and cerebellum (McDowell et al., 2008). A visual signal is sent from the retina to the lateral geniculate nucleus of the thalamus and from there via the optic radiation to V_1. The extrastriate areas V_2 and V_3 receive information from V_1 and are involved in spatial mapping of the visual stimulus (Dyckman et al., 2007). The visual cortex projects information to saccade generating neurons in the brain stem via the midbrain superior colliculus (Collins et al., 2005). Information is also projected from visual cortex along the magnocellular dorsal stream to areas of the parietal cortex (Greenlee, 2000), mainly the superior parietal lobe and parietal eye fields. The importance of the parietal cortex in generation of prosaccades is supported by studies showing that parietal lesions are associated with increased prosaccade latencies (Gaymard et al., 2003). The parietal areas send direct signals to the superior colliculus and are also reciprocally connected with the FEF and SEF (Ferraina et al., 2002, Pare & Wurtz, 2001). Human neuroimaging studies show increased FEF and SEF activity during prosaccades (Cornelissen et al., 2002, McDowell et al., 2005, Raemaekers et al., 2002) and the level of FEF activity

correlates with prosaccade latency (Connolly et al., 2005). Higher activity in the FEF contralateral to the saccade direction is associated with shorter prosaccade latency.

Frontal and parietal cortical areas have reciprocal connections with several subcortical regions that are involved in saccade generation, including striatum and thalamus but mainly the superiour colliculus and cerebellum (Matsuda et al., 2004, Sweeney et al., 1996). Lesion studies have shown that the cerebellum, specially the vermis and fastigial nucleus, is important for saccade accuracy (Botzel et al., 1993, Vahedi et al., 1995) and two structural MRI studies showed that volume of the vermis was associated with prosaccade accuracy (Ettinger et al., 2002, Ettinger et al., 2005a). Increased activity of the superior colliculus was found to be related to shorter saccade latencies (Neggers et al., 2005).

As previously described, most studies show that schizophrenia patients have normal prosaccade performance suggesting that they have an intact basic saccadic neural circuitry. However, there are occasional findings of impaired prosaccade performance in schizophrenia. It is possible that differences in eye movement recording techniques and differences in the timing and predictability of targets may have an effect. It is also possible that some subtle deficits are associated with the disorder. It has been demonstrated that when the task is made more difficult, for example by adding commanding signals and choice paradigms, the patients perform worse than controls (Done & Frith, 1984). This suggests that higher-order neural processes that are necessary for performing slightly more difficult tasks than the basic prosaccade task are defective in schizophrenia.

Functional imaging studies comparing schizophrenia patients and healthy individuals while performing prosaccades have provided inconsistent results. In an fMRI study by McDowell et al (2002) chronic schizophrenia patients had normal FEF, SEF and posterior parietal cortex activation during prosaccades. Conversely, in an event related fMRI study by Raemakers et al (2002) chronic medicated schizophrenia patients displayed slightly decreased FEF, SEF and parietal eye field activations while performing a prosaccade task. The same research group found healthy siblings of schizophrenia patients to have normal frontal and parietal activation during prosaccades (Raemaekers et al., 2006). Finally, an fMRI study of first episode antipsychotic naïve schizophrenia patients showed decreased activation in FEF, SEF, internal parietal sulcus, precuneus and areas of the cingulate cortex

compared to healthy participants (Keedy et al., 2006). This study indicates that schizophrenia patients have abnormal brain activity during prosaccades and the authors suggest that beneficial effects of atypical antipsychotic medications on the oculomotor system may explain the lack of patient control differences in the McDowell et al study (2002) and the subtle group differences in the Raemakers et al study (2002).

In summary, although most eye movement studies indicate that the neural processes involved in prosaccade generation are generally intact in schizophrenia patients some eye movement studies and recent functional imaging studies suggest that some subtle deficits may be related to schizophrenia.

Relationship between SPEM and antisaccades

Neuropsychological and brain imaging studies suggest that both SPEM and antisaccade eye movement deficits may be based on prefrontal cortex dysfunction (Calkins & Iacono, 2000). However, recent functional imaging studies show that some brain regions are more specific to either SPEM or antisaccades. For example, the DLPFC is activated during antisaccades (DeSouza et al., 2003) and motion perception areas are recruited during SPEM (Lencer et al., 2005). Although both SPEM and antisaccade deficits have been proposed as endophenotypes in schizophrenia it has not been established whether they reflect the same risk genes. Only a few studies have investigated relationships between SPEM and antisaccade task performance and they have provided inconsistent findings. While some have found higher reflexive error rate on the antisaccade task to correlate with worse SPEM performance (Louchart-de la Chapelle et al., 2005, Matsue et al., 1994, Schlenker & Cohen, 1995, Sereno & Holzman, 1995) others have not (Hutton et al., 1998, Nkam et al., 2001, Tien et al., 1996 Zanelli et al., 2005). More research is needed to elucidate the relationship between the two tasks preferably using large subject samples in order to avoid failures to detect small correlations due to low power.

If SPEM and antisaccade deficits are found to correlate in schizophrenia it might be beneficial to combine the two into one composite endophenotype for use in genetic studies. This approach was successfully employed by Myles-Worsley et al (1999) when they combined antisaccade error rate and P50 suppression into one

composite inhibitory endophenotype and demonstrated linkage between this endophenotype and a locus on chromosome 22q11-q12.

AIMS OF THESIS

The research problem

There is substantial evidence for involvement of genetic factors in the etiology of schizophrenia and recent molecular genetic studies using combinations of linkage and association methods have identified several genes that may be associated with the disorder (Riley & Kendler, 2006). However, no allelic variants with clear causative links to schizophrenia have yet been found for any gene. The mode of inheritance of schizophrenia is complicated and the pathogenesis may be based on interactions between multiple genes of small effects, and environmental factors (Gogos & Gerber, 2006). Evidence is also cumulating that epigenetic phenomena (Mill et al., 2008) and CNVs (Stefansson et al., 2008) may increase risk for schizophrenia.

The variable and obscure clinical presentation of schizophrenia complicates studies of how genetic factors are involved in the disorder. Using endophenotypes in genetic studies of schizophrenia may possibly circumvent this problem. Deficits in SPEM and antisaccade eye movements are promising endophenotypes for genetic studies of schizophrenia (Calkins et al., 2008). As outlined in the introduction the validity of SPEM and antisaccade eye movements as endophenotypes in schizophrenia is supported by evidence that schizophrenia patients show deficits irrespective of disease stage (Flechtner et al., 2002, Gooding et al., 2004), unaffected relatives of schizophrenia patients have worse performance than subjects without family history of the illness (Clementz et al., 1990, Clementz & McDowell, 1994, Clementz et al., 1994, Ettinger et al., 2004b, Holzman et al., 1974, Katsanis et al., 1997), twin studies have found significant heritability of SPEM and antisaccade performance (Katsanis et al., 2000, Malone & Iacono, 2002) and high temporal stability of task performance has been reported in patients, relatives and controls (Calkins et al., 2003, Ettinger et al., 2003a). Although not strictly speaking an endophenotype criterion, the value of SPEM and antisaccades in schizophrenia research is also supported by functional imaging studies showing that eye movement deficits in patients and their relatives are associated with frontal brain dysfunctions (Camchong et al., 2008, Keedy et al., 2006, McDowell et al., 2002, O'Driscoll et al.,

1999), compatible with evidence that the pathophysiology of schizophrenia involves impaired frontal brain function (Weinberger et al., 2001).

Studies of humans have shown association between *COMT* val^{158}met (rs4680) polymorphism and neuropsychological measures of prefrontal cortex function such as the WCST (Egan et al., 2001) and N-back test (Goldberg et al., 2003), with val^{158} carriers performing worse than met^{158} carriers. However, there is also data suggesting that the val^{158} allele is associated with better performance on tasks requiring cognitive flexibility (Nolan et al., 2004) and it has been suggested that whether a *COMT* val^{158}met genotype is beneficial or detrimental for cognitive function may not only be associated with the dopaminergic state of the frontal cortex but also on the nature of the task being performed (Tunbridge et al., 2006). The *COMT* gene has been associated with risk for schizophrenia (Chen et al., 2004b, Shifman et al., 2002) but recent meta-analyses suggest that if present the relationship is weak (Fan et al., 2005, Glatt et al., 2003, Munafo et al., 2005, Okochi et al., 2009). The effects of *COMT* val^{158}met on antisaccade eye movements have only been studied in healthy subjects (Ettinger et al., 2008, Stefanis et al., 2004) and the few previous studies of *COMT* val^{158}met effects on SPEM had small subject samples and provided inconsistent results (Rybakowski et al., 2002, Thaker et al., 2004). Based on the putative role of dopaminergic and frontal brain dysfunction in schizophrenia the present thesis aimed to investigate the relationship between *COMT* val^{158}met and performance on eye movement tasks that require frontal brain cognitive function.

There is compelling evidence that the *NRG-1* gene is associated with increased risk for schizophrenia (Harrison, 2007) but several negative findings have also been reported (Duan et al., 2005, Ingason et al., 2006, Iwata et al., 2004, Rosa et al., 2007, Thiselton et al., 2004) and the mechanisms by which *NRG-1* variants may contribute to the pathogenesis of schizophrenia have not been identified. Therefore the relationship between *NRG-1* and schizophrenia remains inconclusive. In the present thesis the associations of two *NRG-1* markers with SPEM and antisaccade eye movements were investigated. These are the SNP8NRG222662 (rs4623364), which has been shown to be a particularly good surrogate marker for the original Icelandic risk haplotype (r^2= 1) (Decode Genetics unpublished data) and the SNP8NRG243177 (rs6994992), which is part of the original Icelandic core haplotype (Stefansson et al., 2002) and has on its own shown strong association with schizophrenia (Stefansson et al., 2003). The SNP8NRG243177 has in recent studies

been associated with several interesting biochemical (Law et al., 2006, Mathew et al., 2007), brain imaging (Hall et al., 2006, McIntosh et al., 2008), cognitive (Hall et al., 2006, Stefanis et al., 2007) and clinical (Hall et al., 2006, Keri et al., 2009, Krug et al., 2008) impairments in schizophrenia and healthy subjects.

Specific aims of present thesis

The first aim of this thesis was to validate the SPEM, antisaccade, prosaccade and fixation tasks in a large Icelandic sample. The intention was to replicate the observation of SPEM and antisaccade performance deficits in schizophrenia patients compared to healthy individuals and to investigate the reliability of eye movement task performance by measuring intra-individual variability, internal consistency and within-session changes of SPEM, antisaccade, prosaccade and fixation performance. Relatively few previous studies have addressed these performance characteristics of SPEM and antisaccades and intra-individual variability on saccadic tasks and systematic within-session changes in SPEM and antisaccade tasks have not been previously studied in schizophrenia.

A second aim was to investigate the effects of target velocity on SPEM performance in schizophrenia. It has been demonstrated that schizophrenia patients have impaired motion perception, which correlates with SPEM performance (Chen et al., 1999b) and recent functional imaging studies have shown reduced activity in motion processing pathways in the brains of schizophrenia patients (Hong et al., 2005, Lencer et al., 2005).

The third goal was to examine the interrelationships between SPEM and antisaccade variables in order to investigate whether these endophenotypes index overlapping or separate genetic factors. Although both tasks have been proposed as endophenotypes in schizophrenia and have been related to frontal brain dysfunctions (Calkins et al., 2008), the relatively few previous studies investigating correlations between SPEM and antisaccade performance have provided inconsistent results (Hutton et al., 2001, Matsue et al., 1994, Nkam et al., 2001, Schlenker & Cohen, 1995, Sereno & Holzman, 1995, Zanelli et al. 2005) suggesting that the genetic contribution to these two tasks differs.

The fourth objective was to examine whether eye movements are affected by symptoms of schizophrenia, age of illness onset, illness duration, nicotine use or type of antipsychotic medication.

The fifth goal of the present thesis was to investigate the associations between *COMT* val^{158}met polymorphism and SPEM and antisaccade performance in schizophrenia patients and healthy controls. This is the first study of the relationship between *COMT* val^{158}met and antisaccade eye movements in schizophrenia patients.

The sixth aim was to explore whether individual differences in SPEM and antisaccade performance can be explained by genetic variations in the *NRG-1* gene. We studied schizophrenia patients and healthy controls because it has been shown that gene-endophenotype associations may depend on disease status (Thaker et al., 2004, Wonodi et al., 2009). This is the first study investigating possible associations between *NRG-1* risk genotypes and eye movement endophenotypes in schizophrenia.

Finally, SPEM and antisaccade eye movement performance in the three patients with CNVs on chromosomes *1q21.1* and *15q13.3* were compared to the performance in patients without these CNVs. All patients in the present thesis were participants in a previous study investigating the association of recurrent CNVs with schizophrenia (Stefansson et al., 2008). Two independent research groups (International schizophrenia consortium, 2008, Stefansson et al., 2008), found that rare recurrent *de novo* deletions on chromosomes *1q21.1* and *15q13.3* increase the risk for schizophrenia.

Below is a summary of the aims accompanied by corresponding hypotheses and research questions:

1) Confirm the well-known observation of SPEM and antisaccade eye movement performance deficits in schizophrenia by investigating a large sample drawn from the genetically homogenous Icelandic population (Paper **I**).

   Hypothesis: Schizophrenia patients will perform worse than healthy subjects on the SPEM and antisaccade tasks.
   Research question: How do schizophrenia patients perform on the prosaccade and fixation tasks compared to healthy controls?
   Research question: What is the internal consistency and within-session performance variability on antisaccade, prosaccade, SPEM and visual fixation tasks in patients and controls?

2) Examine the effects of target velocity on SPEM performance in schizophrenia patients (Paper **I**).

   Research question: How will increasing target velocity affect SPEM performance?

3) Explore the interrelationships between antisaccade and SPEM variables to help identify to which degree these endophenotypes represent overlapping rather than separate genetic factors (Paper **I**).

   Hypothesis: Low to moderate correlations between SPEM and antisaccade task performance are expected.

4) Assess the association of symptoms of schizophrenia, type of antipsychotic medication and nicotine use with SPEM and antisaccade task performance (Paper **I**).

   Research question: How are schizophrenia symptoms, nicotine use and type of antipsychotic medication associated with performance on antisaccade, prosaccade, SPEM and visual fixation tasks?

5) Study the association of the *COMT* val^{158}met polymorphism with SPEM (paper **II**) and antisaccade eye movement performance (Paper **III**) in schizophrenia patients and healthy controls.

   Hypothesis: SPEM and antisaccade performance will be associated with *COMT* val^{158}met genotype. A higher number of val^{158} alleles will be associated with worse performance.

6) To explore whether inter-individual differences in SPEM and antisaccade eye movement performance in schizophrenia patients may be explained by variations in the *NRG-1* gene (Paper **IV**).

Hypothesis: Carriers of the *NRG-1* SNP8NRG222662 and SNP8NRG243177 at risk genotypes will perform worse than non-carriers on the SPEM and antisaccade tasks

7) Examine SPEM and antisaccade performance in schizophrenia patients with CNVs on chromosomes *1q21.1* and *15q13.3*. Associations of eye movements with genetic markers within these loci have not previously been investigated.

   Research question: How will patients with CNVs on chromosomes *1q21.1* and *15q13.3* perform on SPEM and antisaccade tasks compared to other patients?

MATERIAL AND METHODS

In this chapter the methods employed in the investigations of this thesis are described. A detailed description of the relevant methodology is also presented in the four empirical papers (**I-IV)** on which the thesis is based. First the subject recruitment process is outlined and the means of screening patients and controls for exclusion and inclusion criteria are described. Following an account of ethical aspects the methods of eye movement data collection and analysis are explained. Then the genotyping methods are summarized and finally the statistical tests used in this thesis are outlined.

Participants

Schizophrenia patients were selected from a group (N=412) that participated in a previous genetic study where they provided venous blood samples for DNA analysis (Stefansson et al., 2002). The healthy controls (N=150) were selected from a large group of subjects that had been used as an unscreened population control group by Decode Genetics and had participated in some of their earlier genetic studies. From these two groups a list of 459 potential participants was created based on the carrier status of the *NRG-1* SNP; SNP8NRG222662. This SNP is a good surrogate marker (r^2=1.0) for the originally described five SNP Icelandic core haplotype (Decode Genetics, unpublished data). Approximately 50% of the participants on this list were G risk allele carriers and the other half non-G carriers. This was done in order to increase the power of the carrier vs. non-carrier comparison of eye movement task performance as the estimated frequency of the five SNP risk haplotype is only 15.4% in patients and 7.5% in the general population (Stefansson et al., 2002).

Both patients and controls were screened for common psychiatric disorders using the Mini International Neuropsychiatric Interview (M.I.N.I.), edition 5.0.0 (Sheehan et al., 1998). The M.I.N.I. is a structured interview for the major Axis I psychiatric disorders in ICD-10 (WHO, 1992) and DSM-IV (APA, 1994). In this interview each diagnostic module starts with filter question/questions regarding core symptoms. If the subject's answer is "yes" to the filter questions, further questions are asked in that module in order to find out whether diagnostic criteria are reached or not. If the answer is "no" to the filter questions the interviewer goes to the next

module. Individual modules of the M.I.N.I. are listed in Table 4. The M.I.N.I was used to exclude subjects from the control group. Having a current episode of a non-psychotic disorder, a current or past history of a psychotic episode or substance abuse/dependence in the past 12 months were exclusion criteria.

Table 4
Diagnostic modules measured with the Mini International Neuro-psychiatric Interview (M.I.N.I.)

A. Major depressive episode - Current (past two weeks)
A. Major depressive episode - Recurrent
B. Dysthymia – Current (past two weeks)
C. Suicidality – Current (past one month)
C. Suicidality – Suicide risk (low/moderate/high), Current (past one month)
D. Manic episode – Current
D. Manic episode – Lifetime
D. Hypomanic episode – Current
D. Hypomanic episode – Lifetime
E. Panic disorder – Current (past one month)
E. Panic disorder – Lifetime
F. Agoraphobia – Current
G. Social phobia – Current (past one month)
H. Obsessive compulsive disorder – Current (past one month)
I. Posttraumatic stress disorder – Current
J. Alcohol Dependence – Current (past 12 months)
J. Alcohol abuse – Current (past 12 months)
K. Substance dependence other than alcohol – Current (past 12 months)
K. Substance abuse other than alcohol – Current (past 12 months)
L. Psychotic disorders – Lifetime
L. Psychotic disorders – Current
L. Mood disorders with psychotic features – Current
M. Anorexia nervosa – Current (past 3 months)
N. Bulimia nervosa – Current (past 3 months)
O. Generalized anxiety disorder – Current (past six months)

Prior to eye movement testing the examiner performed a brief non-structured screening interview and participants with history of neurological illness (e.g. stroke,

seizures, and Parkinson's disease), ophthalmologic abnormalities (such as amblyopia) or head injury (causing loss of consciousness for 5 minutes or longer) were excluded. Subjects taking medications that are known to impair performance on eye movement tasks, such as benzodiazepines and antihistamines, were also excluded. Because studies have shown that performance on antisaccade and SPEM tasks deteriorates with age participants older than 55 years old were not recruited (Ross et al., 1999a). Because cigarette smoking can affect performance on eye movement tasks (Larrison-Faucher et al., 2004, Olincy et al., 1998) subjects were asked whether they smoke cigarettes daily or not. Participants were asked to abstain from drinking alcohol the night before testing and not to smoke during the hour prior to eye movement testing. All participants were able to understand the study procedures and provide informed consent.

Schizophrenia patients

All patients were recruited in the Department of Psychiatry at the Landspitali-University Hospital in Reykjavik. This is the main psychiatric hospital in Iceland (population of approximately 320.000), treating over 90% of all schizophrenia patients in the country. All the patients had previously been genotyped for *NRG-1* risk genotypes. Their hospital and outpatient clinic charts were reviewed and each treating psychiatrist was then consulted regarding possible participants in the study. The treating psychiatrists provided information whether they thought patients would be able to participate, passed basic information about the study to the patients and obtained permission for the eye movement researcher to contact them. Patients not aged 18-55 years old (N=60) and those who could not be reached (N=37) were excluded. Of 272 patients approached, 78 were excluded because they were severely psychotic, had significant co-morbidity or were taking medications known to impair eye movement task performance such as bensodiazepins and antihistamins. Seventy-four patients declined participation. One patient withdrew consent and one patient was excluded due to being the only subject of non-Icelandic descent. Data were collected from the remaining 118 patients. Figure 3 is a flow chart demonstrating the patient recruitment process.

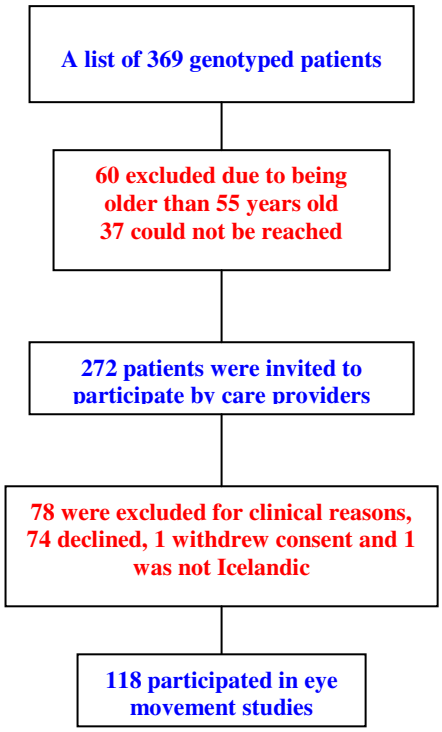

Figure 3
Flow chart demonstrating the patient recruitment process

Diagnosis of schizophrenia was initially made by the treating psychiatrist according to ICD-10 criteria and was then confirmed according to Research Diagnostic Criteria (RDC) (Spitzer et al., 1978), with the use of the lifetime version of the Schedule of Affective Disorders and Schizophrenia (SADS-L) (Spitzer & Endicott, 1977). This is a semi structured diagnostic interview that is used by interviewers with graduate degrees and clinical experience. The interviewer is given a set of standard probes for evaluating symptoms, but must also use clinical skills to determine whether the symptoms described correspond with RDC diagnostic criteria. Information for the SADS-L was obtained from interviews with patients and from hospital and clinical charts. Information on age of illness onset and duration of illness was obtained from the patients´ medical records.

Patients´ current symptom levels were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) on the day of eye movement testing. The PANSS is a 30-item scale based on a semi-structured interview and gives scores of total negative symptoms (seven items), total positive symptoms (seven items), general psychopathology (16 items) and overall symptoms. Each item

consists of a seven point scale varying from one = "not present" to seven = "extremely severe". Total scores range from 30–210. Table 5 lists the PANSS sub-scales and their individual symptom items.

Table 5

PANSS sub-scales and the symptom items belonging to each scale

Scale	Symptom items
Negative	Blunted affect, Emotional withdrawal, Poor rapport, Passive social withdrawal, Difficulty in abstract thinking, Lack of spontaneity
Positive	Delusions, Conceptual disorganization, Hallucinatory behavior, Excitement, Grandiosity, Suspiciousness, Hostility
General psychopathology	Somatic concern, Anxiety, Guilt feelings, Tension, Posturing, Depression, Motor retardation, Uncooperativeness, Unusual thought content, Disorientation, Poor attention, Lack of judgment and insight, Disturbance of volition, Poor impulse control, Preoccupation, Active avoidance

PANSS: Positive and Negative Syndrome Scale

Healthy controls

From the original list of 150 potential healthy controls 113 were willing to participate. They were all recruited from the local community through a study recruitment centre in Reykjavik. During a non-standardized screening interview the controls were asked about history of psychotic illnesses in their first and second-degree relatives. Four individuals were excluded because they had second-degree relatives with schizophrenia leaving 109 control subjects for eye movement testing. No control subject fulfilled any Axis I criteria on the M.I.N.I.

Ethical aspects

Approval for the study was obtained from the Icelandic Scientific Ethics Committee (04-084-S1, 10/2004).

Following a full description of the study to the participants, written informed consent was obtained. Participants received no payment for their participation.

Confidentiality was carefully secured. Each participant was given a unique study number and the key to the system was kept in a locked cabinet. All clinical and diagnostic questionnaires and eye movement data files were only identified with the unique number. According to the Icelandic law on genetic information, genotype data were specially coded and could not be associated with the personal identification data of individual participants.

Equipment for eye movement recording

Eye movements were recorded using an IRIS eye tracker, model 6500 (Skalar Medical BV, Delft, The Netherlands) (Figure 4). A plastic frame containing nine infrared light emitting and nine infrared light detecting photodiodes was attached to a headgear and placed in front of one eye. An infrared filter, to minimize artifacts from ambient light, covered the photodiodes. The frame could be adjusted in three perpendicular directions. Infrared light was projected onto the eyeball and the light detectors monitored the reflection from an area between the white sclera and the darker iris. A phototransistor transformed the reflected infrared light into a voltage. The voltage of nasally positioned phototransistors was subtracted from temporally placed phototransistors and the difference was then demodulated and amplified. The result of this was a signal that was proportional to the angular deviation of the eye. Since all the tasks involved horizontal eye movements only horizontal eye movements were recorded. In order to minimize calibration time and because only conjugate eye movements over a relatively short amplitude range were made only left eye movements were recorded. The eye tracker logged the eye position, which was subsequently converted from analogue to digital by a custom-built analogue-digital (AD) converter card with a sampling frequency of 500 Hz.

The IRIS eye tracking system was chosen because it has been used by many prominent laboratories investigating eye movements in schizophrenia (Crawford et al., 1998, Ettinger et al., 2003a, Lencer et al., 2005, Nkam et al., 2001) and also

because there are plans for future collaboration with other laboratories using this system such as the one at the Institute of Psychiatry in London.

Figure 4
IRIS Skalar infrared eye tracker
Left: Headgear Right: Eye tracker

Eye movement testing

Eye movements were tested in a soundproof room in the laboratory of the Division of Psychiatry at the Landspitali-University Hospital. The examiner was unaware of the subjects' genotype status but aware of patient/control status. The latter was unavoidable because the examiner contacted all patients prior to testing and did the M.I.N.I. interview and PANSS evaluation on every patient subject. Lights were dimmed in order to minimize possible disturbing effects of ambient light on the infrared light detectors. Subjects were seated in a comfortable chair in front of a 16-inch Hewlett Packard computer screen. Head movements were minimized using an adjustable chinrest, which was attached to a small desk (Figure 5). Participants were instructed to rest their arms on the desk to minimize movement artifacts. The distance between the eye and screen centre was 57 cm, which is a comfortable reading distance for most people. The visual stimuli programs for eye movement testing were run on a PC computer (IBM NetVista) and were purpose written in C++ for Windows 98.

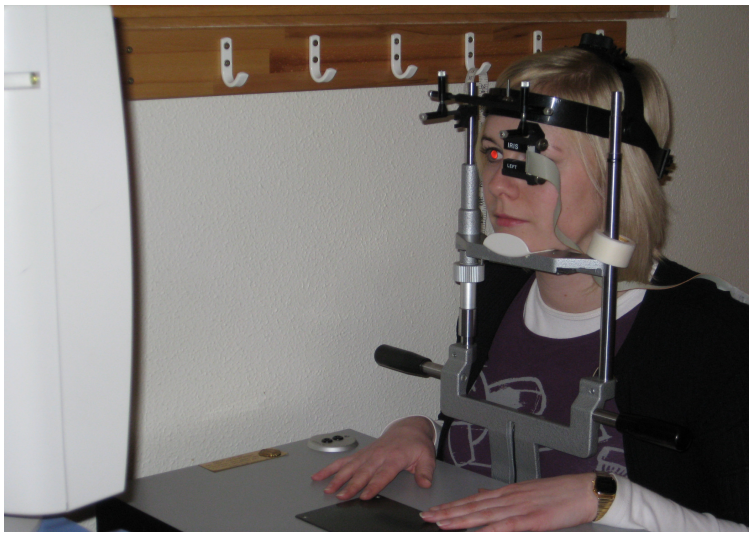

Figure 5
Eye movement testing (The picture is staged)

The visual target was a white circular dot (subtending about 0.3º of visual angle) presented on a black background. Similar stimulus properties have been used in several previous studies (Ettinger et al., 2004b, Ettinger et al., 2006, O'Driscoll et al., 1998). The eye movement test battery consisted of four tasks, which were administered to each subject in the following order: Prosaccade, antisaccade, fixation and SPEM. Each task was preceded by the same three-point calibration trial in which the subjects followed the target between three screen locations; first in the centre (0º) then at -12º and finally at +12º. Each stimulus lasted 1000 ms. The calibration task immediately preceded the fixation and SPEM tasks (no gap) so the subjects were not aware of the transition between calibration and the actual task. In the prosaccade and antisaccade tasks the calibration was followed by a break, which was used for explaining the test requirements and the actual task only began when the examiner pressed the keyboard. This break generally lasted about 30 seconds. If the participant moved during the break the task was rerun starting with the calibration.

Prosaccade task

Each trial began with the target in the central location (0º) for a random duration of 1000-2000 ms. The target then stepped to one of four peripheral locations (±6º, ±12º) where it remained for 1000 ms. Each peripheral location was used 15 times, resulting in a total of 60 trials, which was expected to provide adequate between subjects variance, without challenging the participants´ motivation and alertness. The

sequence of peripheral target presentations was random (sampling without replacement). Four practice trials using each target location were carried out before the experimental trials and could be repeated if necessary. Participants were instructed to keep their eyes on the target and follow it as accurately as possible. The duration of the central fixation task was randomized in order to make the peripheral targets temporally unpredictable.

Antisaccade task

The target movements were identical to those in the prosaccade task and the number of trials was also the same. However, on this occasion the participants were instructed to look at the target while in the central position and redirect their gaze to the exact mirror image location of the target as soon as it moved to the side (Figure 6). Emphasis was thus placed not only on the inhibition of a reflexive saccade to the target but also on the voluntary generation of a spatially accurate antisaccade.

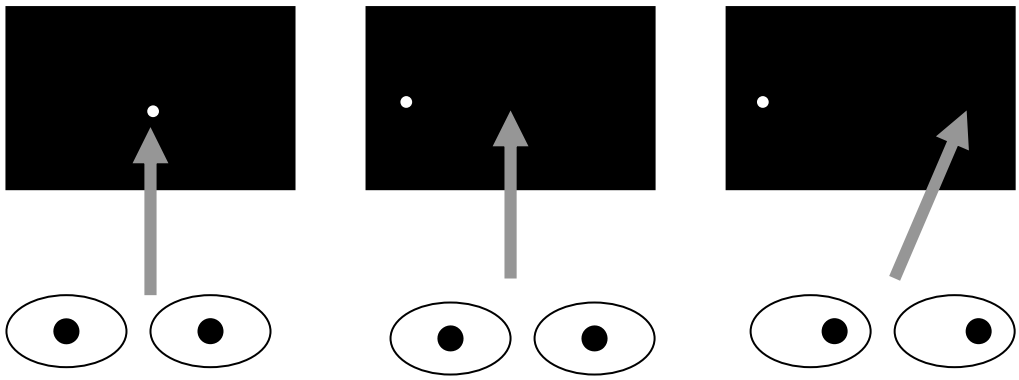

Figure 6
The antisaccade eye movement task

Fixation task

Following a calibration task as described above, the target was presented in three target locations. First the target was presented in a central location for 1000 ms in order to bring the subject's attention to the target and this was not included in the analysis. The target then moved either to the far right or the far left target locations (± 12º). Subsequently the target moved to the central location, followed by the peripheral location not used before and finally back to the central location. The target

duration at each location was 20000 ms, which is similar to what has been used in previous studies (Kissler & Clementz, 1998).

SPEM task

A triangular target waveform was employed three times at 12°, 24° and 36°/s, respectively. In a triangular waveform the target moves horizontally at a constant speed but does not slow down at target turnarounds as in the sinusoidal waveform. The target velocities used in this thesis are within the velocity range used by most previous studies (Ettinger et al., 2003a, Hutton et al., 1998, Hutton et al., 2004). The three target velocities were always presented in the same order and therefore the examination of velocity effects on SPEM performance was confounded by repeated exposure. The target appeared in the central position (0º) and then moved horizontally to ±12°, where it reversed abruptly and moved to the opposite side. The direction of the first ramp was random (right or left). The first ramp (from 0° to ±12°) was considered practice and was not included in the analyses. A total of 16.5 half-cycles were run at each target velocity. Participants were instructed to keep their eyes on the target as closely as possible until the task ended.

Eye Movement Analyses

Prosaccade, antisaccade and fixation eye movement data were analyzed with semi-automated programs in the EYEMAP software package (Version 2.0, AMTech GmbH, Weinheim, Germany). SPEM analyses were carried out using purpose-written routines in LabView 6i (National Instruments, Austin, Texas, USA). In these programs the horizontal target position, horizontal eye position and the overlapping target and eye traces were displayed simultaneously on the computer screen. Before the data files could be opened for analysis in EYEMAP and LabView they had to be formatted in order to include information required by the analyzing software such as data format, output file and number of channels required. When the reformatted data files had been analyzed they were stored in a tab-delimited (*.dat) output file. These files were then opened in Microsoft Excel 2000 and copied into different templates specially designed for each eye movement task. The template files contained several formulas, which provided the final eye movement data for each subject. These average measures were then copied into a SPSS 11.1 (statistical program) spreadsheet for statistical analysis. Two raters individually analyzed eye movement

data from 15 subjects that were chosen randomly (Magnus Haraldsson and Ulrich Ettinger). This yielded high inter-rater reliabilities for all eye movement variables (0.95-0.99). Magnus Haraldsson rated all the data that is actually used in this PhD thesis.

Antisaccade analysis

For saccade analysis the EYEMAP software detected changes in the eye movement trace, which fulfilled predefined criteria. Two vertical cursors were placed over an event and the rater then decided whether to accept it as a saccade or to reject it as an artifact by labeling it. This was done by choosing an appropriate label from a menu by pressing a specific button on the keyboard. In the present research the automatic detection of saccades was based on criteria of minimum target amplitude (1º), minimum target velocity (30º/s) and minimum latency to target movement (100 ms). Currently there is no consensus among eye movement researchers on any single set of criteria. The above criteria were selected based on the present knowledge of eye movement physiology and the fact that similar criteria have been used in many eye movement studies in recent years (Broerse et al., 2001, Crawford et al., 1998, Ettinger et al., 2003a, Nieman et al., 2000, Radant et al., 2007). Antisaccade trials were discarded if the subject failed to make a saccade or if eye blinks occurred immediately before, during or after target presentation. Figure 7 demonstrates an antisaccade eye movement trace in EYEMAP.

The dependent antisaccade variables derived from this analysis, which are relevant for the present thesis, are:

1) *Reflexive error rate* (%), which reflects percentage of error trials over the number of valid trials. A reflexive error was counted when the participant performed a primary saccade towards the peripheral target. Valid trials included saccades that fulfilled the minimum amplitude, velocity and latency criteria described above.

2) *Corrective saccade rate* (%), which is the percentage of saccades in the opposite direction of the target following a reflexive error.

3) *Antisaccade latency* (ms) reflects the time from target appearance to correct antisaccade initiation.

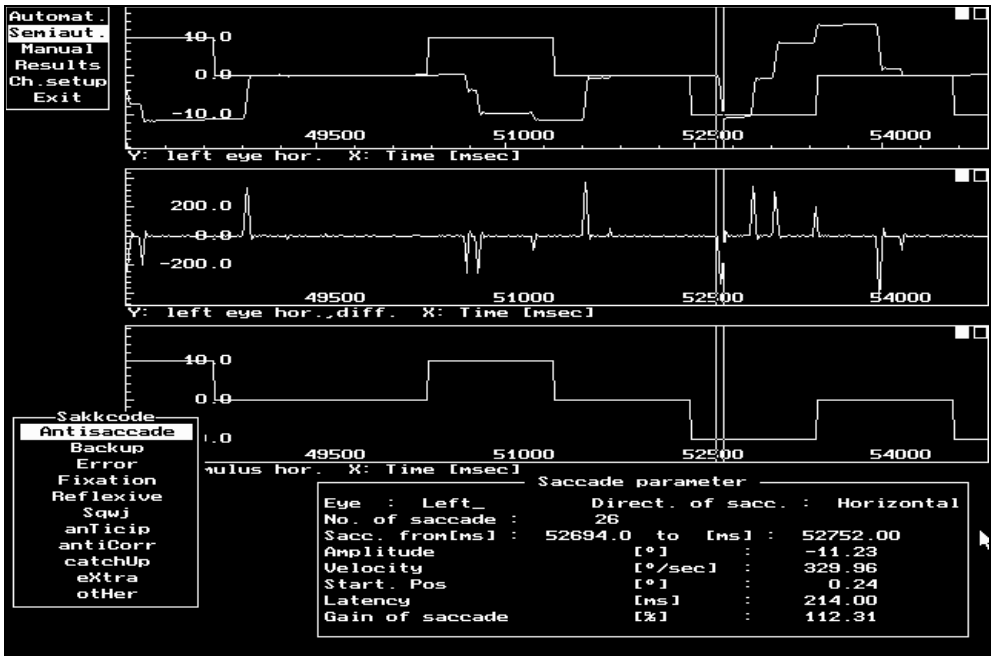

Figure 7
Antisaccade eye movements in EYEMAP**.** In the top trace two vertical cursors identify a reflexive error, which is corrected after a brief moment. The subject makes a correct antisaccade in the previous trial.

4) *Antisaccade latency variability* is the standard deviation (SD) of antisaccade latency.

5) *Antisaccade amplitude gain* (%) was calculated by dividing the saccade amplitude of correct antisaccades by the target amplitude and multiplying the outcome by 100.

6) *Antisaccade amplitude gain variability* is the SD of antisaccade amplitude gain.

7) *Antisaccade spatial error* (%) was obtained by calculating, for each correct antisaccade, the percentage of residual error. This was done by subtracting target amplitude from the saccade amplitude and dividing the result by the target amplitude. The absolute value of this term reflects the residual error and is then averaged across all saccades and multiplied by 100. A perfectly accurate saccade thus has a spatial error score of 0% and higher scores indicate greater spatial error.

8) *Antisaccade spatial error variability* is the SD of antisaccade spatial error.

Prosaccade analysis

Prosaccade error (%), latency (ms), amplitude gain (%) and spatial error (%) were calculated based on the same criteria as were used in the antisaccade task. Incorrect prosaccades were performed when the subject did not follow the target.

SPEM analysis

Smooth pursuit velocity gain (%) and saccade frequency (N/s) were obtained for each of the three target velocities (12º, 24º and 36º/s). The velocity gain was calculated by dividing mean eye velocity by target velocity. Using purpose written LabView programs, cursors were placed at each end of sections of pursuit (excluding saccades and eye blinks), during the central half of each ramp (Figure 8). This was done in order to exclude pursuit initiation and slowing close to target turnarounds during the first and last quarters of each ramp, respectively. The gain value for each segment was multiplied by the corresponding time. All the values were then summed and divided by the total time duration of all the segments to yield a time weighted pursuit gain. Several previous studies have used similar methods of gain analysis (Ettinger et al., 2003a, Gooding et al., 2000b, Hutton et al., 1998, Hutton et al., 2001, O'Driscoll et al., 1999).

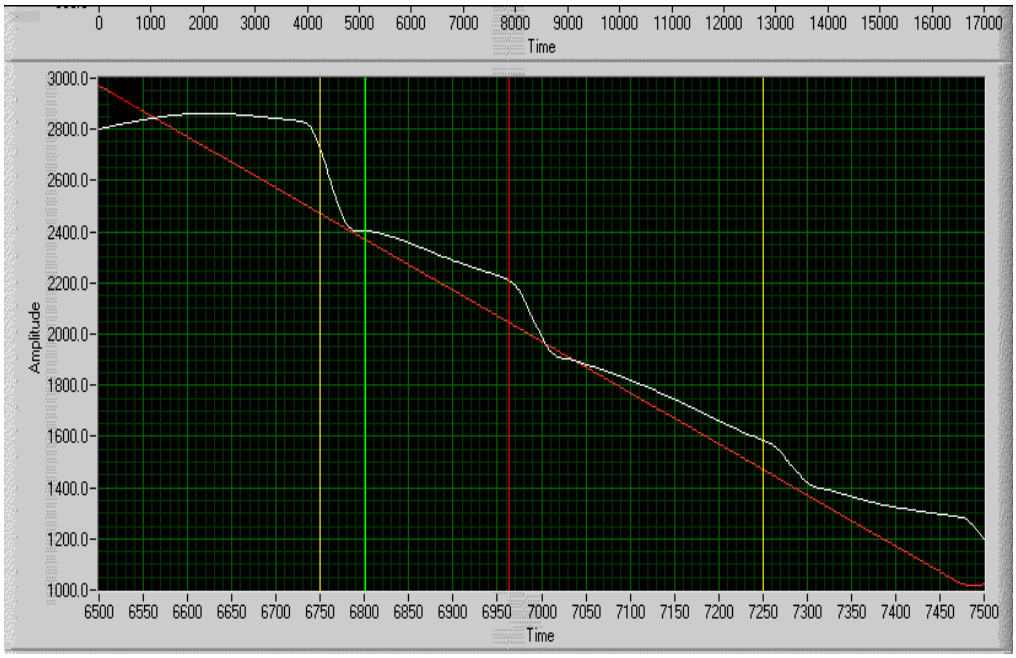

Figure 8
Smooth pursuit gain analysis in LabView. The central half of a ramp lies between the two yellow vertical cursors. The green cursor marks the beginning of a pursuit section and the red cursor marks the end. Saccades are excluded from gain analysis.

The semi-automated LabView software used a velocity based saccade detection algorithm. Saccade onsets were defined as occurring when three consecutive samples exceeded a set threshold. This threshold differed as a function of target speed, and was set so as to maximize saccade detection and minimize false

alarms (Figure 9). The number of saccades was divided by the duration of pursuit at each target velocity to obtain the saccade frequency (N/s).

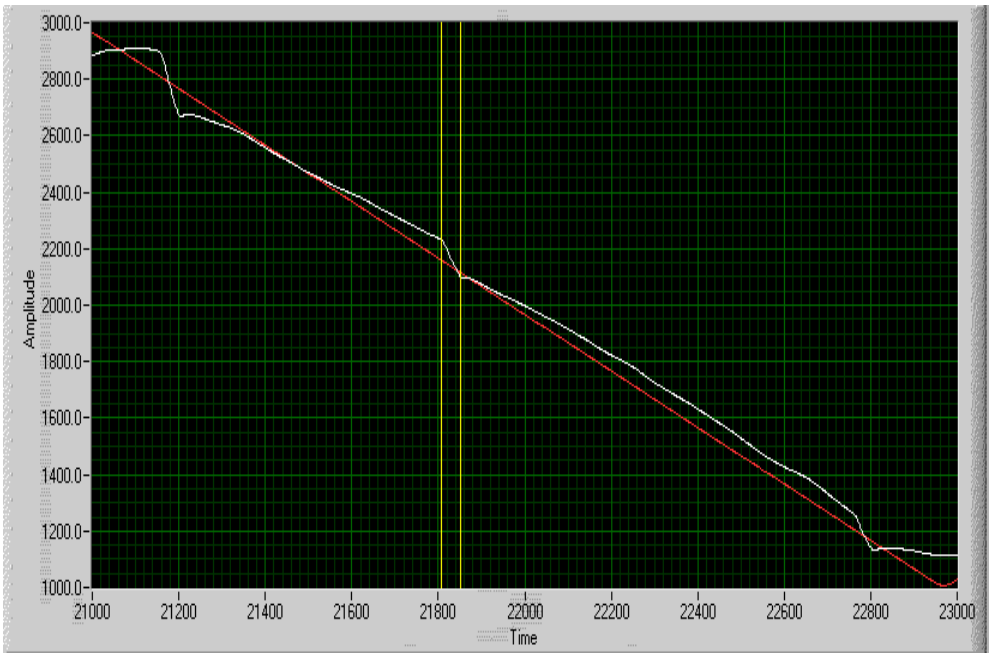

Figure 9
Smooth pursuit saccade analysis in LabView. The two vertical yellow cursors identify a saccade (catch up saccade) that fulfills criteria of a velocity based saccade detection algorithm

Fixation analysis

Frequency of saccadic eye movements was the measure of ability to maintain gaze stability during the fixation task. Saccades were detected in EYEMAP using the same amplitude and velocity criteria as for pro- and antisaccades. The number of saccades was counted and divided by the time of task duration to yield saccade frequency (N/s). The higher the number of saccades the worse is the performance on this task. This measure has been used in previous studies of visual fixation (Curtis et al., 2001b, Ettinger et al., 2003a, Gooding et al., 2000a) and is considered to be a reliable assessment of the fixation system (Leigh & Zee, 1999).

Genotyping

Subjects were selected from a large group of participants in a previous study of the association between *NRG-1* genotypes and schizophrenia (Stefansson et al., 2002). In that study DNA was isolated from whole blood or lymphoblastoid cell lines using an extraction column method (Qiagen Inc, Valencia, CA USA). First a genomewide linkage scan of schizophrenia families in Iceland was performed by using a framework map of 950 microsatellite markers that mapped schizophrenia to chromosome 8p. Then extensive fine-mapping of the 8p locus and haplotype-association analysis were performed, supplemented by a transmission/disequilibrium test that identified *NRG-1* as a candidate gene for schizophrenia (Stefansson et al., 2002). All personal identifiers associated with blood samples, medical history and genealogy database, were encrypted by the Data Protection Commission with a third-party encryption system.

Genotyping of the *COMT* val^{158}met polymorphism and the *NRG-1* SNP8NRG222662 and SNP8NRG243177 SNPs were carried out using the Centaurus platform (Nanogen Inc. San Diego, CA, USA).

Samples were genotyped for copy number variations (CNVs) using the Illumina HumanHap300 or HumanCNV370 chips. The methods for identifying *de novo* deletions and duplications are described in more detail in Stefansson et al (2008).

All genotyping was done in the laboratories of Decode Genetics in Reykjavik, Iceland. Scientists performing the genotyping were blind to all subjects´ clinical and demographic information.

Statistical analyses

Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 11.1 (SPSS Inc. Chicago, Ill). Level of significance was set to $p< 0.05$. Outliers in the eye movement data were identified using box plots and all individual extreme value data points (more than three box lengths from edge of box) were removed. Distributions of eye movement variables were assessed for normality using the skewness index. If positively (>1) or negatively (<1) skewed, variables were transformed using square root or square transformations, respectively.

Univariate analysis of variance (ANOVA) was employed for the following examinations. These analyses are also described in each individual paper belonging to the present thesis:

1) Effects of diagnosis on prosaccade and antisaccade eye movements and on visual fixation, with each eye movement variable as a dependent variable and Diagnosis (patient, control) as independent variable.
2) Effects of the two *NRG-1* risk genotypes on eye movement task performance. This was done by running two separate univariate ANOVAs for each eye movement variable, with Diagnosis (patient vs. control) and Genotype (first SNP8NRG222662 G carrier, non-G carrier and then SNP8NRG243177 T carrier, non-T carrier) as independent variables. In order to obtain sufficiently large groups for statistical analysis risk allele homozygotes and heterozygotes were combined into one group for both SNPs. Univariate ANOVA was chosen because it examines patient-control interactions.
3) Effects of type of antipsychotic medication on eye movements in patients, with Medication (typical, atypical, typical + atypical, none) as independent variable.
4) Effects of smoking on eye movement performance, with Smoking Status (smoker, non-smoker) as independent variable.
5) Associations between age and genotypes. Separate ANOVAs were run, with each Genotype (*COMT* val^{158}met, *NRG-1* SNP8NRG222662 and *NRG-1* SNP8NRG243177) as independent variables.

Repeated measures ANOVAs were used in the following evaluations:

1) Effects of task duration on eye movement performance, with TaskDuration (represented by four equally long sub-segments of each eye movement task) as within-subject factor and Group (patient, control) as between subjects factor.
2) Effects of target velocity and diagnosis on SPEM, with Velocity (12º, 24º and 36º/s) as a within-subject variable and Diagnosis (patient, control) as between subjects variable.

3) Effects of *COMT* val^{158}met genotype on SPEM, with Velocity (12º, 24º and 36º/s) as within-subject variable and Diagnosis (patient, control) and Genotype (val/val, val/met, met/met) and Gender (male, female) as between subjects variables.
4) Effects of the two *NRG-1* genotypes on SPEM in two separate ANOVAs, with Velocity (12º, 24º and 36º/s) as within-subject variable and Diagnosis (patient, control) and Genotype (first SNP8NRG222662 G, non-G carriers and then SNP8NRG243177 T, non-T carriers) as between subjects variables.

For all ANOVAs Mauchly´s test was considered to evaluate assumptions of sphericity. If assumptions of sphericity were violated, Greenhouse-Geisser epsilon corrections of degrees of freedom were used.

Independent samples t test was used for comparing the mean age of patients and controls (age matching).

Multiple linear regression was used for analysing the relationship between *COMT* val^{158}met Genotype (val/val, val/met, met/met) with antisaccade, prosaccade and visual fixation performance. Given previous evidence of the relationship between *COMT* val^{158} allele dosage and neurocognitive function (Egan et al., 2001, Malhotra et al., 2002, Rosa et al., 2004), Genotype was entered as a linear predictor.

Linear regressions were used for assessing the relationship between PANSS scores and *COMT* val^{158}met genotype.

Internal consistency of task performance was measured using Cronbach´s coefficient alpha (Cronbach & Warrington, 1951). Cronbach's coefficient alpha is an index of the average correlation among all the items of a psychometric instrument. The alpha coefficient ranges from zero to one and the higher the score, the more reliable the instrument is. The coefficient was calculated using sub-scores of eye movement recording from four equally long consecutive sub-segments of each eye movement task.

Pearson correlation was employed in the following evaluations:

1) Relationship between SPEM and antisaccade variables. Correlations were first carried out in the combined sample (patients and controls) and then in each group separately.
2) Relationships between eye movement variables and PANSS scores, age of illness onset and illness duration.

Chi-square test was used for examining whether:

1) Diagnostic groups (patients, controls) were matched for gender.
2) The *COMT* val^{158}met allele distribution differed from a distribution expected under Hardy-Weinberg equilibrium.
3) The *COMT* val^{158}met allele distribution differed between patients and controls.
4) The *COMT* val^{158}met allele groups differed by gender.
5) The *NRG-1* risk allele carriers differed from non-risk carriers by gender.

RESULTS

In this chapter the results of studies included in the present thesis are summarised. First, demographic and clinical characteristics of the subject samples are described. Then results of the four eye movement tasks examined in schizophrenia patients and controls: SPEM, visual fixation, antisaccade and prosaccade tasks, are presented. This includes patient-control performance comparisons, measurements of internal consistency and within-session performance changes for each task and the effects of target velocity on SPEM performance. Relationships between eye movements and several clinical variables are then described and correlations between antisaccade and SPEM performance measures are presented. Next, results of analyses of *COMT* and *NRG-1* genotype associations with performance on SPEM antisaccade, prosaccade and fixation tasks are provided. Finally, performance on these eye movement tasks is described in three patients with CNVs.

Demographic and clinical data (I)

Eye movement data were analyzed from 118 patients and 109 healthy controls. The patients´ mean age was 41.2 years (SD= 9.8) and 73.7% were males. The mean age of the healthy controls was 40.8 years (SD= 9.1) and 62.4 % were males. The groups did not differ in sex (χ^2 = 2.61; df = 1; p = 0.11) and age (t = 0.30; df = 221; p = 0.77). Demographic and clinical data are summarized in Table 6.

Ethnicity: All participants were Icelanders.

Age of illness onset and illness duration: The patients´ mean age of illness onset was 22.9 years (range: 14-41; SD= 5.3) and the mean illness duration was 941 weeks (range: 25-1988; SD= 510).

Schizophrenia symptom assessment with PANSS: The patients´ mean PANSS total score was 73.4 (range: 39-141; SD=20.8). For the negative subscale it was 20.5 (range: 7-48; SD=7.3), positive symptoms subscale 15.0 (range: 7-40; SD= 5.7) and general psychopathology subscale 37.9 (range: 21-72; SD=10.7). This data is comparable to PANSS scores obtained from a sample of 240 chronic medicated schizophrenia inpatients participating in studies conducted in order to standardize and test the validity and reliability of PANSS (Kay et al., 1990).

Table 6

Demographic and clinical data

	Patients N=118	Controls N=109
Age (mean [SD] years) *	41.2 [9.8]	40.8 [9.1]
Sex (% males) **	73.7%	62.4%
Ethnicity (% native Icelandic)	100%	100%
Smoking (% smokers)***	73.9%	21.1%
Age of illness onset (mean [SD] years)	22.9 [5.3]	
Illness duration (mean [SD] weeks)	941 (512)	
PANSS negative symptoms score (mean [SD]) †	20.5 [7.3]	
PANSS positive symptoms (mean [SD])	15.0 [5.7]	
PANSS general psychopathology (mean [SD])	37.9 [10.7]	
PANSS total score (mean [SD])	73.4 [20.8]	
Conventional antipsychotic medications (%)	16 (13.9)	
Atypical antipsychotic medications (%)	59 (51.3)	
Conventional and atypical medications (%)	36 (28.7)	
No antipsychotic medications (%)	7 (6.1)	

T test: * t=0.30; df=221; p=0.77

Chi square: ** 2.61; df=1; p=0.11, *** 57.1; df=1; p<0.001

† PANSS = Positive and Negative Syndrome Scale

Antipsychotic medications: Over 90% of the patients were taking antipsychotic medications (14.0% typical, 51.3% atypical, 28.7% both typical and atypical antipsychotics and 6.1% were not on antipsychotics). Approximately a third (28.7%) of the patients was on the atypical medication clozapine.

Smoking: The majority of patients were smokers (73.9%) but less than a quarter of controls (21.1%) smoked daily. The smoking prevalence in the patient group is similar to what has been observed in other schizophrenia populations (Diaz et al., 2008) and the prevalence of smokers in the control group is identical to the general Icelandic population (Njalsson, 2003).

Eye Movements (I)

Descriptive statistics and effect sizes for all eye movement variables are shown in Table 7.

Extreme values (outliers) were removed from the dataset. The following individual data points were removed: SPEM saccade frequency: one patient and four

controls, fixation saccades: ten patients and three controls, antisaccade gain: one patient and one control, antisaccade latency: two patients, antisaccade correction: six patients and three controls, prosaccade latency: one patient and one control, and prosaccade spatial error: two patients.

Table 7
Descriptive statistics and effect sizes of eye movement variables

	Patients	Controls	d
Prosaccade	N=113	N=108	
Mean gain % (SD)	91.8 (11.6)	94.6 (9.7)	-0.26
Mean latency ms (SD)	188.2 (30.2)	177.7 (20.2)	0.41
Mean spatial error % (SD)	17.9 (8.2)	14.5 (5.5)	0.48
Antisaccade	N=108	N=105	
Mean errors % (SD)	60.7 (21.7)	30.9 (20.3)	1.42
Correction % (SD)	90.9 (12.8)	97.8 (5.6)	-0.69
Mean gain % (SD)	92.8 (28.9)	107.4 (28.2)	-0.51
Mean latency ms (SD)	330.7 (77.1)	294.1 (41.6)	0.59
Mean spatial error % (SD)	43.6 (13.2)	40.3 (14.4)	0.24
Fixation	N=115	N=108	
Saccades n/s (SD)	0.09 (0.10)	0.05 (0.07)	0.46
Smooth pursuit	N=116	N=108	
Gain % at 12°/s (SD)	92.4 (10.9)	96.1 (8.2)	-0.38
Gain % at 24°/s (SD)	83.7 (15.2)	93.1 (12.1)	-0.68
Gain % at 36°/s (SD)	66.2 (19.9)	79.8 (16.1)	-0.75
	N=112	N=109	
Saccades n/s at 12°/s (SD)	1.53 (0.57)	1.16 (0.53)	0.67
Saccades n/s at 24°/s (SD)	2.34 (0.79)	1.88 (0.78)	0.58
Saccades n/s at 36°/s (SD)	3.01 (1.01)	2.60 (0.82)	0.45

d: Cohen's d (Cohen, 1992)

The following eye movement variables were skewed (skewness index) (Lehman et al., 2005): SPEM saccade frequency at 36°/s (1.44), fixation saccade frequency (1.92), antisaccade latency standard deviation (SD) (1.49), antisaccade spatial error SD (1.64), antisaccade correction (-3.05), prosaccade spatial error (1.30) and prosaccade spatial error SD (1.24). These variables were transformed and all inferential statistics were done on the transformed data.

SPEM

A repeated measure ANOVA found a significant main effect of Velocity (12°/s, 24º/s and 36°/s) and Diagnosis (patient, control) on SPEM velocity gain and there was a significant Velocity-by-Diagnosis interaction. Table 8 lists the repeated measures ANOVA statistics for SPEM. These findings demonstrate that gain deteriorated with increasing velocity, patients had lower pursuit gain than controls and the difference between patients and controls increased with increasing target velocity.

Table 8
Repeated measure ANOVA for SPEM velocity gain and saccade frequency

SPEM variable	Velocity effect	Diagnosis effect	Velocity-by-Diagnosis interaction
Velocity gain	F[2,444] = 291.3 p < 0.001	F[1,122] = 29.6 p < 0.001	F[2,444] = 14.7 p < 0.001
Saccades	F[2,430] = 422.6 p < 0.001	F[1,220] = 23.8 p < 0.001	F[2,440] = 0.3 p = 0.74

Within subjects variable: Velocity (12º, 24º/ and 36º/s)
Between subjects variable: Diagnosis (patient, control)

Figure 10 shows the mean velocity gain at the three target velocities (12º, 24º and 36º/s) in patients and controls.

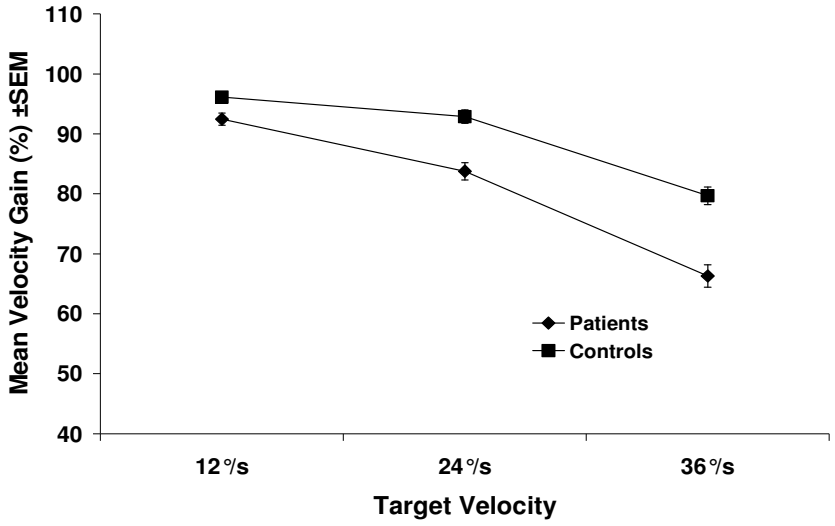

Figure 10
Smooth pursuit velocity gain by diagnosis and target velocity

For SPEM saccade frequency a repeated measures ANOVA demonstrated a significant effect of Velocity and a significant effect of Diagnosis but there was no significant Velocity-by-Diagnosis interaction (Table 8). This shows that saccade frequency increased with target velocity and that patients made more saccades than controls but the difference between patients and controls was not affected by target velocity.

Internal consistency of SPEM

Internal consistency of SPEM performance was high (Cronbach's coefficient alpha > 0.85) for all variables in both patients and controls. Table 9 lists the alpha coefficients for all the SPEM variables separately for each group.

Table 9
Internal Consistency of SPEM Variables

SPEM variable	Cronbach´s alpha	
Velocity gain	Patients	Controls
12º/s	0.85	0.87
24º/s	0.92	0.86
36º/s	0.95	0.93
Saccade frequency		
12º/s	0.88	0.91
24º/s	0.90	0.91
36º/s	0.88	0.86

Task duration effects on SPEM

Table 10 demonstrates the results of repeated measures ANOVAs for evaluating within-session performance changes on SPEM performance with TaskDuration (four time segments of equal length) as within-subject factor and Diagnosis (patient, control) as between subject factor. No significant TaskDuration effect was found on velocity gain at 12º/s but there were significant effects at target velocities 24º/s and 36º/s. The effect at 24º/s was quadratic with velocity gain increasing in the second quarter and then decreasing. At target velocity 36º/s, the TaskDuration effect was mainly cubic with velocity gain increasing in the second quarter, decreasing in the third and finally increasing in controls in the fourth quarter. There was also a significant overall decrease in velocity gain with time. A TaskDuration-by-Diagnosis

interaction was present only at 36º/s. This interaction was both quadratic and linear due to an increase in velocity gain in the second quarter and a decrease in the third and fourth quarters in patients (Figure 11).

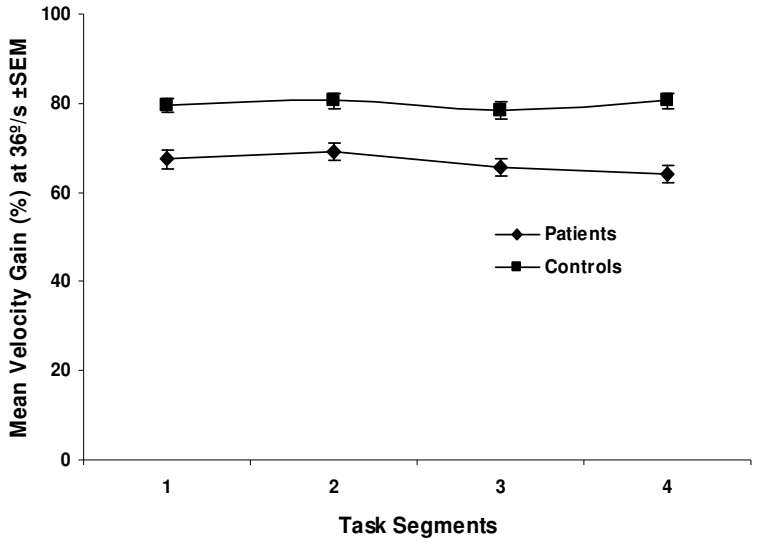

Figure 11
Mean velocity gain at 36º/s by diagnosis and task segment. Each task segment corresponds to 15 consecutive trials

A significant TaskDuration effect was found on saccade frequency during SPEM at all three target velocities (Table 10). The effect was linear for all three velocities with saccade frequency decreasing over the duration of the task. There was also a significant quadratic effect with an increase in saccade frequency in the fourth quarter in controls at 12º/s and 24º/s and a small cubic effect at 12º/s due to an increase in saccade frequency in the third quarter in patients. There were no significant TaskDuration-by-Diagnosis interactions for SPEM saccade frequency.

Table 10
Task duration effects on SPEM performance

	TaskDuration effect	Contrasts	Task Duration-Diagnosis interaction	Contrasts
Velocity gain				
12°/s	F[3.222] = 2.2 p =0.11		F[3,222] = 0.4 p = 0.70	
24°/s	F[3,223] = 3.7 p = 0.015	Quadratic; p = 0.02	F[3,223] = 0.3 p = 0.80	
36°/s	F[3,224] = 5.2 p = 0.002	Cubic; p = 0.001 Linear; p = 0.02	F[3.224] = 3.5 p = 0.02	Quadratic; p = 0.03 Linear; p = 0.04
Saccade frequency				
12°/s	F[3,225] = 20.6 p < 0.001	Linear; p < 0.001 Quadratic; p = 0.002 Cubic; p = 0.03	F[3,225] = 2.3 p = 0.08	
24°/s	F[3,222] = 15.8 p < 0.001	Linear; p < 0.001 Quadratic; p < 0.001	F[3,222] = 0.9 p = 0.45	
36°/s	F[3,223] = 12.9 p < 0.001	Linear; p < 0.001	F[3,223] = 1.6 p = 0.18	

Visual fixation

Patients made significantly more frequent saccades during the visual fixation task than controls ($F[1,209]= 17.72$; $p < 0.001$).

Internal consistency of visual fixations

Internal consistency of fixation performance was high for both patients (alpha= 0.86) and controls (alpha= 0.92).

Task duration effects on visual fixation

No significant TaskDuration effect was found on saccade frequency during fixation ($F[3,225] = 0.45$; $p= 0.66$).

Antisaccade eye movements

There were significant effects of Diagnosis on reflexive error rate, error correction rate, amplitude gain, antisaccade latency and the variability of latency. Table 11

shows the results of univariate ANOVAs for the antisaccade variables. The patients displayed significantly more reflexive errors, fewer error corrections, reduced (i.e. hypometric) amplitude gain and longer and more variable latency than controls. Spatial error and variability of spatial error and amplitude gain did not differ significantly between patients and controls.

Table 11
Univariate ANOVAs for antisaccade variables

Antisaccade variable	Diagnosis effect
Reflexive error rate	$F[1,208] = 106.9;\ p < 0.001$
Error correction rate	$F[[1,208] = 30.4; p < 0.001$
Latency	$F[1,208] = 19.8;\ p < 0.001$
Latency SD	$F[1,208] = 20.5;\ p < 0.001$
Amplitude gain	$F[1,208] = 8.6;\ p = 0.004$
Amplitude gain SD	$F[1,208] = 0.01;\ p = 0.92$
Spatial error	$F[1,208] = 3.6;\ p = 0.06$
Spatial error SD	$F[1,208] = 0.03;\ p = 0.86$

SD = Standard deviation

Internal consistency of antisaccades

Internal consistency was high for all antisaccade variables in both patients (alpha > 0.77) and controls (alpha > 0.80) except for spatial error in patients (alpha $= 0.38$). Table 12 lists the Cronbach's alpha coefficients for antisaccade variables.

Table 12
Internal consistency of antisaccade variables

Antisaccade variable	Cronbach's alpha	
	Patients	Controls
Reflexive error rate	0.89	0.91
Latency	0.81	0.89
Amplitude gain	0.77	0.84
Spatial error	0.38	0.81

Task duration effects on antisaccades

Table 13 shows the results of repeated measures ANOVAs for evaluating within-session performance changes on antisaccade performance with TaskDuration (four

time segments of equal length) as within-subject factor and Diagnosis (patient, control) as between subject factor. There was a significant TaskDuration effect on reflexive error rate but no TaskDuration-by-Diagnosis interaction. The effect on reflexive error rate was quadratic with error rates decreasing in the second quarter and then increasing in the third and fourth quarters. Figure 12 shows the TaskDuration effect on reflexive error rate in patients and controls.

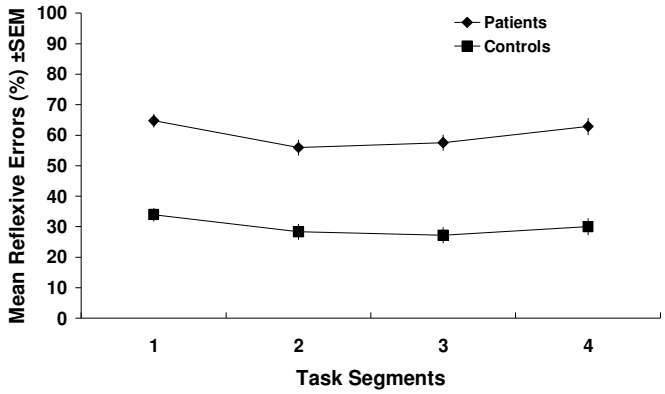

Figure 12
Reflexive error rate by diagnosis and task segment. Each task segment corresponds to 15 consecutive trials

Table 13
Task Duration effects on antisaccade performance

	TaskDuration effect	Contrasts	TaskDuration-Diagnosis	Contrasts
Reflexive error rate	F[3,198]= 12.1 p < 0.001	Quadratic; p< 0.001	F[3,198]= 1.01 p= 0.39	
Latency	F[3,171]= 2.7 p= 0.049	Linear; p= 0.04	F[3,171]= 2.9 p= 0.04	Cubic; p= 0.01
Latency SD	F[3,169] = 0.3 p= 0.79		F[3,169]= 0.2 p= 0.89	
Amplitude gain	F[3,175] = 5.6 p= 0.001	Linear; p= 0.006 Quadratic; p= 0.02	F[3,172]= 1.5 p= 0.22	
Amplitude gain SD	F[3,169] = 1.9 p= 0.14		F[3,169]= 1.2 p= 0.31	
Spatial error	F[3,175] = 1.3 p= 0.27		F[3,175]= 0.8 p= 0.49	
Spatial error SD	F[3,169] = 1.5 p= 0.22		F[3,169]= 1.49 p= 0.22	

SD = Standard deviation

A TaskDuration effect was found on antisaccade latency and there was also a TaskDuration-by-Diagnosis interaction (Table 13). The main effect was linear with antisaccade latency increasing with time. The interaction was due to a cubic effect in patients with latency increasing in the second quarter, decreasing in the third and finally increasing again in the fourth quarter.

A significant TaskDuration effect was found on amplitude gain but there was no TaskDuration-by-Diagnosis interaction. The effect was mainly linear with amplitude gain decreasing with time. There was also a quadratic effect with an increase in amplitude gain in the fourth quarter in patients. There were no significant TaskDuration effects on spatial error or the variability of amplitude gain, latency and spatial error.

Prosaccade eye movements

The average rate of incorrect prosaccades (subject not following target) was only 0.47% (SD= 1.32) for patients and 0.22% (SD= 0.79) for controls and the difference between the two groups was not significant (p= 0.09).

There were significant differences between patients and controls for prosaccade latency and spatial error (Table 14). Patients had significantly longer saccade latency and greater spatial error than controls. There were also significant patient control differences in the intra-individual variability (SD) of prosaccade latency, spatial error and amplitude gain. The patients had larger individual performance variability on these measures. No significant difference was seen between patients and controls for prosaccade amplitude gain.

Table 14

Univariate ANOVAs for prosaccade variables

Prosaccade variable	Diagnosis effect
Latency	$F[1,214] = 9.9$; $p = 0.002$
Latency SD	$F[1,214] = 23.9$; $p < 0.001$
Amplitude gain	$F[1,214] = 1.4$; $p = 0.27$
Amplitude gain SD	$F[1,214] = 11.4$; $p = 0.001$
Spatial error	$F[1,214] = 9.9$; $p = 0.002$
Spatial error SD	$F[1,214] = 12.6$; $p < 0.001$

Internal consistency of prosaccades

Internal consistency of prosaccade performance was high for all variables in both patients and controls (all Cronbach´s alpha > 0.85). Alpha values for prosaccade variables are shown in Table 15.

Table 15
Internal consistency of prosaccade variables

Prosaccade variable	Cronbach's alpha	
	Patients	Controls
Latency	0.95	0.93
Amplitude gain	0.86	0.86
Spatial error	0.89	0.91

Task duration effects on prosaccades

Table 16 describes the effects of task duration on prosaccade performance. There was a TaskDuration effect on prosaccade latency. The effect was quadratic with latency decreasing after the first quarter and then increasing. There was also a cubic effect with latency decreasing again in the last quarter in patients. There was a TaskDuration-by-Diagnosis interaction on prosaccade latency. The interaction was due to a general decrease in latency over time in controls whereas in patients the latency increased in the last quarter.

A significant TaskDuration effect was seen on prosaccade amplitude gain but there was no TaskDuration-by-Diagnosis interaction. The effect was linear with gain scores decreasing (i.e. becoming more hypometric) over the four time segments.

There was a significant TaskDuration effect on prosaccade spatial error but there was no TaskDuration-by-Diagnosis interaction. A linear increase in spatial error in the third and fourth quarters was seen in both patients and controls and there was also a small cubic effect with an initial decrease in the second quarter and then a steep increase.

There were no significant TaskDuration effects on the variability of prosaccade latency, spatial error or amplitude gain.

Table 16

Task duration effects on prosaccade performance

	TaskDuration effect	Contrasts	TaskDuration-Diagnosis interaction	Contrasts
Latency	F[3,191] = 4.9 p = 0.002	Quadratic; p = 0.004 Cubic; p = 0.01	F[3,191] = 2.8 p = 0.04	Linear; p = 0.01
Latency SD	F[3,187] = 1.2 p = 0.30		F[3,187] = 1.9 p = 0.12	
Amplitude gain	F[3,191] = 17.1 p < 0.001	Linear; p < 0.001	F[3,191] = 1.5 p = 0.21	
Amplitude gain SD	F[3,187] = 2.5 p = 0.06		F[3,191] = 0.9 p = 0.43	
Spatial error	F[3,191] = 11.4 p < 0.001	Linear; p < 0.001 Cubic; p = 0.02	F[3,191] = 0.22 p = 0.84	
Spatial error SD	F[3,187] = 1.1 p = 0.37		F[3,187] = 1.1 p = 0.35	

Relationship between eye movements and clinical variables (I)

Schizophrenia symptoms measured with PANSS

The only eye movement variable that correlated significantly with PANSS scores was antisaccade correction rate (negative scale score; r= -0.29, p= 0.005, and total score; r= -0.24, p= 0.02). Patients with higher negative and total PANSS scores had lower antisaccade correction rate (Figure 13).

Age of illness onset

Patients' age at onset of illness did not correlate with any eye movement variable (all p> 0.05).

Duration of illness

While controlling for age, duration of schizophrenia illness correlated with antisaccade correction rate (r= -0.27; p= 0.008), SPEM velocity gain at 24°/s (r= -0.36; p< 0.001) and 36°/s (r= -0.34; p< 0.001) and number of saccades during visual fixation (r= 0.23; p= 0.02). Longer duration of illness was associated with lower

antisaccade correction rate, lower SPEM velocity gain and a larger number of fixation saccades.

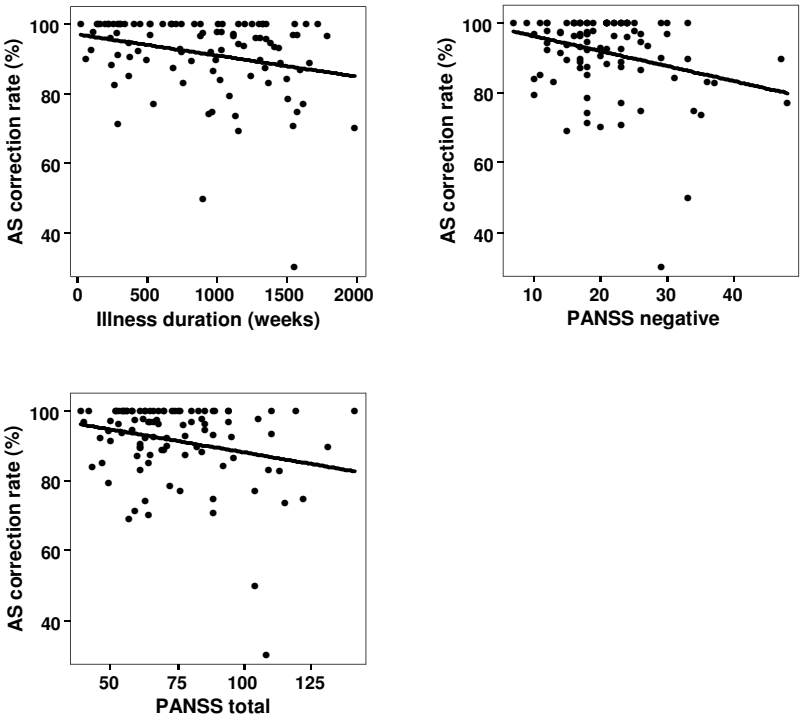

Figure 13
Relationship between antisaccade (AS) correction rate and three clinical variables: Illness duration (r= -0.27; p= 0.008), PANSS negative syndrome scale (r= -0.29; p= 0.005) and PANSS total score (r= -0.24; p = 0.02)

Antipsychotic medication type and nicotine use

Patients' eye movement performance was not associated with type (typical, atypical, both typical and atypical, none) of antipsychotic medication (all p> 0.12). Due to the unique pharmacology of clozapine patients taking that compound were compared to those who were not. No significant effect of clozapine was found (all p> 0.07). Eye movement performance did not differ between smokers and non-smokers and there were no Diagnosis-by-Smoking interactions (all p≥ 0.1).

Relationship between SPEM and antisaccade eye movements (I)

Several moderate but statistically significant correlations between SPEM and antisaccade measures were observed in the combined sample. Higher antisaccade

reflexive error rate was associated with lower SPEM velocity gain at 24º/s (r= -0.27; p< 0.001) and 36º/s (r= -0.34; p< 0.001). The reflexive error rate was also associated with increased SPEM saccade frequency at all three target velocities (12°/s: r= 0.23; p< 0.001, 24°/s: r= 0.25; p< 0.001, 36°/s: r= 0.23; p= 0.001). Increased antisaccade latency was associated with decreased SPEM velocity gain at all target velocities (12°/s: r= -0.24; p< 0.001, 24°/s: r= -0.35; p< 0.001, 36°/s: r= -0.37; p< 0.001) and higher SPEM saccade frequency at 12º/s (r= -0.26; p< 0.001) and 24º/s (r= -0.13; p = 0.03). Antisaccade spatial error correlated weakly with SPEM velocity gain at 36º/s (r= -0.15; p= 0.04) and saccade frequency at 12º/s (r= 0.15; p= 0.03). There were no significant correlations between antisaccade amplitude gain and SPEM variables. These findings indicate that less accurate antisaccade performance is moderately associated with lower velocity gain and saccade frequency during SPEM in the combined patient and control sample.

In the patient group, longer antisaccade latency was associated with decreased SPEM velocity gain at all target velocities (12°/s: r= -0.22; p= 0.03, 24°/s: r= -0.29; p= 0.003, 36°/s: r= -0.27; p= 0.005). No other correlations were significant.

In controls, increased antisaccade error rate was associated with lower SPEM velocity gain at 36º/s (r= -0.22; p= 0.028) and with higher saccade frequency at 24º/s (r= 0.20; p= 0.047) and 36º/s (r= 0.20; p= 0.038). Longer antisaccade latency was associated with lower SPEM velocity gain at all three target velocities (12°/s: r= -0.17; all p= 0.08, 24°/s: r= -0.27; p= 0.005, 36°/s: r= -0.34; p< 0.001) and with higher saccade frequency at 12º/s (r= 0.27; p= 0.006).

COMT val^{158}met (II, III)

Genotype, demographic and clinical data

Genotype and eye movement data were obtained from 111 schizophrenia patients and 97 controls. In the patient group there were 19 (17%) val^{158} homozygotes, 53 (48%) val^{158}met heterozygotes, and 39 (35%) met^{158} homozygotes. The control group included 13 (13%) val^{158} homozygotes, 53 (55%) val^{158}met heterozygotes, and 31 (32%) met^{158} homozygotes. The *COMT* val^{158}met allele distribution in the sample did not differ significantly from a distribution expected under Hardy-Weinberg

equilibrium (χ^2= 0.23; df= 1; p= 0.89). The allele frequencies did not differ significantly between the patient and control groups (χ^2= 1.10; df= 2; p= 0.58).

No gender differences were found between genotype groups among patients, controls or the combined subject sample (all p> 0.1). No Genotype association was found with age (F[2,207] = 2.04; p= 0.13) and there was no Diagnosis-by-Genotype interaction (F[2,199]= 0.26; p= 0.77). No associations were found between Genotype and total PANSS score (R^2= 0.01; β= -0.10; p= 0.25) or the individual PANSS sub-scores (all p> 0.4). Genotype, demographic and clinical statistics are summarized in Table 17.

Table 17
Demographic and clinical variables by diagnosis and *COMT* val^{158}met genotype

	Patients			Controls		
	val/val	val/met	met/met	val/val	val/met	met/met
N (%)	19 (17)	53 (48)	39 (35)	13 (13)	53 (55)	31 (32)
Gender ratio (male %)	84	68	72	84	68	72
Mean age (SD)	38 (10.4)	43 (9.3)	40 (10.4)	39 (7.1)	42 (8.8)	39 (10.9)
PANSS negative symptoms (mean[SD])	19.7 (7.0)	20.1 (6.4)	21.6 (8.5)			
PANSS positive symptoms (mean[SD])	14.3 (4.7)	14.9 (5.3)	15.5 (6.8)			
PANSS general (mean[SD])	36.9 (10.9)	37.9 (9.8)	39.3 (11.9)			
PANSS total (mean[SD])	70.9 (21.4)	72.9 (18.0)	76.3 (23.5)			

Footnote: PANSS = Positive and Negative Syndrome Scale

COMT val^{158}met and SPEM (II)

Smooth pursuit data for one patient and one control could not be analyzed due to poor quality. Descriptive statistics for SPEM velocity gain and saccade frequency by genotype and diagnosis are shown in Table 18.

As previously described (Table 8) the main effects of Velocity and Diagnosis on SPEM velocity gain were significant (both p< 0.001) and there was a significant Velocity-by-Diagnosis interaction (p< 0.001). There were no significant Diagnosis-by-Genotype, Velocity-by-Genotype or Velocity-by-Diagnosis-by-Genotype interactions (Table 19).

No significant Genotype-by-Gender interactions were found for SPEM in patients or controls (all p> 0.09).

Table 18
Descriptive statistics of smooth pursuit variables

	Patients			Controls		
	val/val	val/met	met/met	val/val	val/met	met/met
N (%)	19 (17)	52 (47)	39 (38)	13 (14)	53 (55)	30 (31)
Gain % (SD)						
12º/s	90.2 (11.4)	92.0 (11.1)	94.1 (10.4)	95.3 (10.4)	94.9 (6.8)	95.5 (9.1)
24º/s	81.7 (16.1)	84.2 (14.3)	84.4 (16.6)	91.0 (15.0)	93.1 (11.0)	92.3 (10.0)
36º/s	64.0 (21.5)	64.9 (18.5)	69.3 (21.8)	80.4 (17.5)	79.1 (17.3)	80.5 (13.7)
Saccades N/s (SD)						
12º/s	1.46 (0.66)	1.53 (0.55)	1.54 (0.55)	1.40 (0.91)	1.06 (0.43)	1.24 (0.51)
24º/s	2.43 (0.87)	2.37 (0.68)	2.17 (0.71)	1.78 (0.96)	1.83 (0.71)	2.06 (0.89)
36º/s	3.01 (1.20)	3.05 (0.89)	2.83 (0.90)	2.47 (0.84)	2.58 (0.75)	2.67 (1.06)

Data are given in means (standard deviations) for smooth pursuit variables by diagnosis (patient, control) and COMT genotype (val/val, val/met, met/met)

Table 19
Repeated measures ANOVAs for SPEM variables

	Velocity-Genotype interaction	Diagnosis-Genotype interaction	Velocity-Diagnosis-Genotype interaction
Velocity gain	F[3,314]= 0.63 p= 0.60	F[2,200]= 0.25 p= 0.26	F[4,194]= 0.1 p= 0.95
Saccade frequency	F[3,192]= 0.92 p= 0.44	F[2,192]= 1.2 p= 0.32	F[4,192]= 1.7 p= 0.16

Within subjects variable: Velocity (12º/s, 24º/s and 36º/s) Between subjects variables: *COMT* genotype (val/val, val/met, met/met), Diagnosis (patient, control)

Although no significant Genotype effects were found on velocity gain an inspection of the descriptive statistics in Table 18 reveals that for all three target velocities the patient val/val homozygotes had numerically lower (3-5%) velocity gain than the patient met/met homozygotes with small effect sizes (d= 0.16-0.23). A power calculation showed that 230 subjects for both genotype groups are needed for the difference to be significant at 12°/s and 400-500 subjects for the 24°/s and 36°/s target velocities (α error= 5%; β error= 20%).

As previously described there was a main effect of Velocity and Diagnosis for SPEM saccade frequency (both $p< 0.001$) but there was no Velocity-by-Diagnosis interaction ($p= 0.74$) (see Table 8). The Diagnosis-by-Genotype, Velocity-by-Genotype and Velocity-by-Diagnosis-Genotype interactions were not significant

(Table 19). Also, there were no significant Gender-Genotype interactions (all p> 0.1). Inspection of the descriptive statistics in Table 18 shows that there was only 1-2% difference in saccade frequency between val/val and met/met subjects and the direction of this genotype difference was not consistent between target velocities.

COMT val^{158}met and antisaccade eye movements (III)

Antisaccade data for six patients and two controls could not be analyzed due to poor quality. Descriptive statistics for antisaccade variables are presented in Table 20.

Table 20
Antisaccade variables by diagnosis and *COMT* genotype

	Patients			Controls		
	val/val	val/met	met/met	val/val	val/met	met/met
N (%)	19 (18)	50 (48)	36 (34)	13 (14)	52 (55)	30 (31)
Errors %	62.3 (24.4)	57.8 (20.2)	63.0 (22.1)	19.1 (11.2)	28.9 (17.1)	35.9 (24.4)
Error correction %	91.7 (16.3)	92.3 (10.4)	90.0 (9.8)	100.0 (0.0)	97.6 (4.8)	99.3 (1.6)
Latency ms	312.0 (66.0)	330.9 (79.2)	341.2 (80.3)	288.4 (45.5)	285.9 (42.5)	307.7 (43.1)
Variability of latency	58.5 (23.9)	76.9 (42.2)	79.5 (34.8)	56.8 (26.3)	52.7 (15.6)	60.3 (21.2)
Gain %	96.3 (35.5)	93.7 (29.8)	89.7 (25.5)	106.7 (19.6)	108.5 (27.6)	104.1 (26.4)
Variability of gain	48.1 (20.0)	47.0 (20.2)	45.4 (18.2)	46.2 (12.6)	46.6 (18.5)	48.9 (19.5)
Spatial error %	43.4 (15.5)	44.4 (12.9)	43.4 (12.7)	37.1 (10.4)	39.2 (13.7)	40.5 (12.6)
Variability of spatial error	5.5 (1.2)	5.4 (1.2)	5.2 (1.1)	5.4 (0.9)	5.2 (0.9)	5.5 (1.3)

Data represent means (standard deviations) of antisaccade variables by diagnosis (patient, control) and COMT genotype (val/val, val/met, met/met)

Regression analyses showed significant relationships of Diagnosis with reflexive error rate, amplitude gain, spatial error, latency and the variability of latency (all p≤ 0.02; see Table 21). Schizophrenia patients had significantly higher error rate, lower amplitude gain, higher spatial error and longer and more variable latency than controls. The relationships with variability of amplitude gain and spatial error were not significant.

Table 21
Regression analyses of associations of *COMT* val^{158} genotype and diagnosis of schizophrenia with antisaccade performance measures

		Schizophrenia		val^{158}		Schizophrenia-val^{158} interaction
	R^2	β	p	β	p	p
Reflexive errors	0.37	-0.60	< 0.001	-0.11	0.056	0.11
Error correction	0.15	0.38	< 0.001	0.04	0.58	0.53
Latency	0.10	-0.29	< 0.001	-0.14	0.045	0.91
Latency SD	0.10	-0.28	< 0.001	-0.15	0.028	0.35
Amplitude gain	0.07	-0.25	< 0.001	-0.07	0.34	0.82
Amplitude gain SD	<0.01	<0.01	0.81	0.01	0.94	0.46
Spatial error	0.03	-0.17	0.02	-0.03	0.68	0.52
Spatial error SD	0.00	<0.01	0.95	0.02	0.77	0.25

The number of val^{158} alleles was significantly related to antisaccade latency (p= 0.045) and the variability of antisaccade latency (p= 0.028) but there were no Diagnosis-by-Genotype interactions (Table 21). Antisaccade latency and variability of latency decreased with increasing number of val^{158} alleles. The relationship between reflexive error rate and number of val^{158} alleles fell marginally short of being significant (p= 0.056) and there was no Diagnosis-by-Genotype interaction (Table 21). More val^{158} alleles were non-significantly related to lower reflexive error rate. Figure 14 shows the COMT val^{158}met effects on antisaccade error rate, antisaccade latency and latency variability.

There were no significant effects of Genotype or Genotype-by-Diagnosis interactions for error correction rate, antisaccade amplitude gain, antisaccade spatial error or the variability of amplitude gain and spatial error (Table 21).

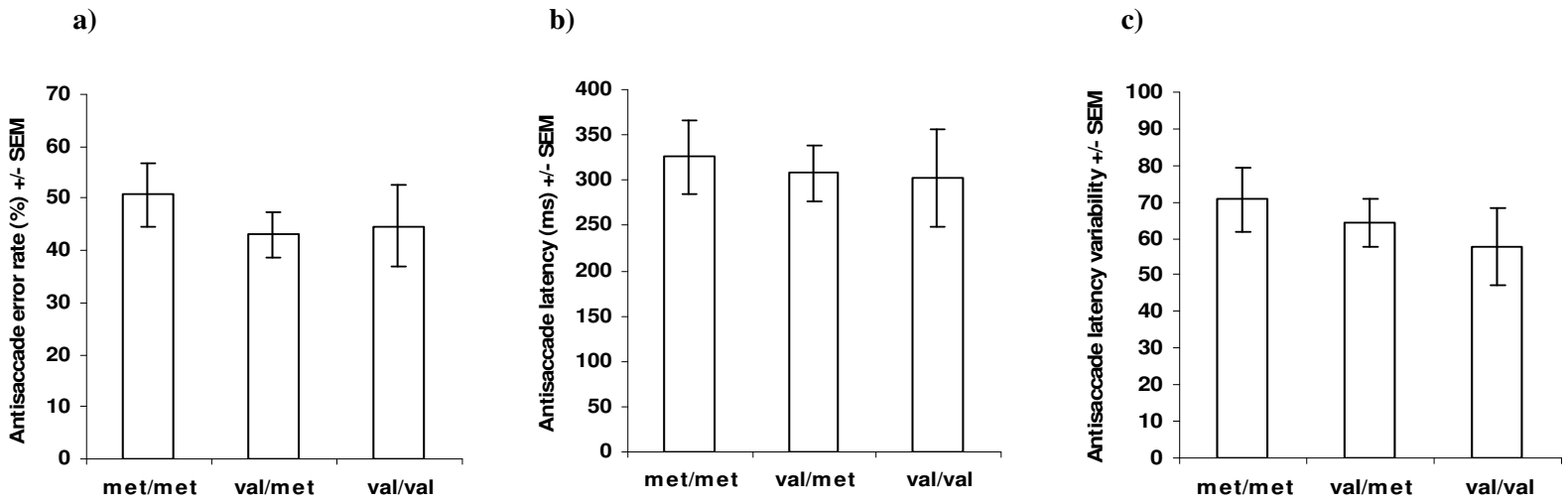

Figure 14

Antisaccade performance by *COMT* val^{158}met genotype

Error bars indicate ± 1 standard error of the mean. The figure shows mean antisaccade error rate (a), antisaccade latency (b) and latency variability c) by *COMT* val^{158}met genotype (met/met, val/met, val/val)

COMT val^{158}met and prosaccade eye movements

Prosaccade data for three patients and two controls could not be analyzed due to poor quality. Descriptive statistics for prosaccade variables are presented in Table 22.

Table 22
Prosaccade variables by diagnosis and *COMT* genotype

	Patients			Controls		
	val/val	val/met	met/met	val/val	val/met	met/met
N (%)	20 (18)	51 (46)	39 (36)	13 (14)	51 (54)	31 (33)
Latency ms	184.6 (31.2)	186.1 (28.9)	191.6 (30.3)	179.5 (17.3)	175.7 (16.4)	181.1 (27.9)
Variability of latency	32.5 (13.5)	38.9 (15.0)	40.2 (12.1)	28.6 (9.2)	30.7 (9.9)	31.9 (9.4)
Gain %	93.6 (7.8)	91.9 (12.5)	91.7 (11.4)	94.3 (6.9)	96.1 (9.4)	92.7 (10.1)
Variability of gain	17.7 (9.7)	17.3 (6.6)	18.3 (6.7)	15.0 (6.4)	14.6 (4.8)	14.4 (5.3)
Spatial error %	17.1 (10.2)	17.7 (8.2)	18.1 (6.9)	13.5 (4.9)	14.2 (4.9)	15.3 (5.8)
Variability of spatial error	11.5 (5.8)	11.8 (5.0)	12.3 (4.5)	9.3 (3.8)	9.8 (3.4)	9.4 (2.9)

Data represent means (standard deviations) of prosaccade variables by Diagnosis (patient, control) and COMT Genotype (val/val, val/met, met/met)

Regression analyses showed significant relationships of Diagnosis with prosaccade latency, spatial error and the variability of latency, amplitude gain and spatial error (all $p \leq 0.007$; see Table 23). Schizophrenia patients had significantly longer latency, higher spatial error and and more variable latency amplitude gain and spatial error than controls. The relationship of Diagnosis with amplitude gain was not significant.

Table 23

Regression analyses of associations of *COMT* val^{158} genotype and diagnosis of schizophrenia with prosaccade performance measures

		Schizophrenia		val^{158}		Schizophrenia-val^{158} interaction
	R^2	β	p	β	p	p
Latency	0.04	-0.19	0.007	-0.08	0.25	0.73
Latency SD	0.11	-0.30	< 0.001	-0.14	0.032	0.45
Amplitude gain	0.02	0.13	0.072	0.07	0.32	0.72
Amplitude gain SD	0.06	-0.24	0.001	-0.01	0.84	0.58
Spatial error	0.06	-0.22	0.001	-0.09	0.20	0.91
Spatial error SD	0.07	-0.26	< 0.001	-0.05	0.45	0.72

The number of val^{158} alleles was significantly related to the variability of prosaccade latency (p= 0.032) but there was no Diagnosis-by-Genotype interaction (Table 23). Variability of prosaccade latency decreased with increasing number of val^{158} alleles. There were no other significant relationships between *COMT* val^{158} dose and prosaccade performance. However, in the patient group there was a consistent numerical difference between val^{158} and met^{158} homozygotes (2-7%; d= 0.1-0.2) with val^{158} homozygotes having shorter latency, higher amplitude gain, lower spatial error and less variability of amplitude gain and spatial error (Table 22).

COMT val^{158}met and visual fixation

Descriptive statistics for *COMT* val^{158}met and visual fixation are shown in Table 24.

Table 24
Fixation saccades by diagnosis and *COMT* genotype

	Patients			Controls		
	val/val	val/met	met/met	val/val	val/met	met/met
N (%)	19 (18)	48 (47)	36 (35)	11 (12)	52 (55)	31 (33)
Saccade frequency (N/s)	0.11 (0.11)	0.09 (0.10)	0.08 (0.09)	0.01 (0.12)	0.06 (0.08)	0.04 (0.07)

Data represent means (standard deviations) of fixation saccades by Diagnosis (patient, control) and COMT Genotype (val/val, val/met, met/met)

Regression analysis showed that there was a significant relationship of Diagnosis with frequency of fixation saccades (r^2= 0.09; β= -0.3; p< 0.001). Patients had significantly more frequent saccades than controls. Number of val^{158} alleles was not related to saccade frequency (r^2= 0.09; β= 0.01; p= 0.84).

***NRG-1* (IV)**

Genotype, demographic and clinical data

Eye movement and SNP8NRG222662 genotype data were obtained from 113 schizophrenia patients and 106 controls. Due to assay problems one patient and four controls could not be genotyped for SNP8NRG243177. Forty-two % of patients and

39% of controls were carriers of the SNP8NRG222662 G risk allele and 57% of patients and 56% of controls were carriers of the SNP8NRG243177 T risk allele.

There were no significant associations of gender with allele status in the patient group, control group and the combined sample (all p> 0.17).

There were no significant age differences between G carriers and non-G carriers in patients, controls or the combined sample (all p> 0.20). However, for SNP8NRG243177 there was a significant age difference between T carriers and non-T carriers in the patient group (p= 0.036) but not in the control group (p= 0.66). Patient T carriers were significantly older than the non-T carriers. In the combined sample the T carriers fell just short of being older than the non-T carriers (p= 0.06). Therefore all analyses of SNP8NRG243177 Genotype effects on eye movements were performed with age as a covariate.

Neither genotype was associated with the patients' age of illness onset (both p> 0.30), total PANSS score (both p> 0.25) or the individual PANSS sub-scores (all p> 0.18). Demographic and clinical statistics by diagnosis and genotype are summarized in Table 25.

NRG-1 and SPEM (IV)

Smooth pursuit data from four patients and two controls could not be analyzed due to poor quality. Descriptive statistics for SPEM velocity gain and saccade frequency by diagnosis and *NRG-1* genotype are shown in Table 26.

As previously described the main effects of Velocity and Diagnosis on SPEM velocity gain were significant and there was a significant Velocity-by-Diagnosis interaction (all p< 0.001; see Table 8). For SPEM saccade frequency the main effects of Velocity and Diagnosis were significant (both p< 0.001) but the Velocity-by-Diagnosis interaction was not significant (p= 0.74; see Table 8).

SNP8NRG222662: For velocity gain there were no significant Velocity-by-Genotype, Diagnosis-by-Genotype or Velocity-by-Diagnosis-by-Genotype interactions (Table 27). At all three target velocities the G carriers had slightly lower velocity gain (0.5-5.0%) than non-G carriers (all d= 0.1). Power calculations showed that 395 participants are needed in each genotype group for the difference in velocity gain to become significant at 36°/s, 1210 subjects at 24°/s and 5820 subjects at 12°/s.

For saccade frequency the Velocity-by-Genotype, Diagnosis-by-Genotype and Velocity-by-Diagnosis-by-Genotype interactions were not significant (Table 27). Here the risk allele carriers had numerically fewer saccades than non-carriers at 12°/s (5%) and 36°/s (1%) but there was no difference at 24°/s (0%).

SNP8NRG243177: No significant Velocity-by-Genotype, Diagnosis-by-Genotype or Velocity-by-Diagnosis-by-Genotype interactions were found for velocity gain (Table 27). For all three target velocities the risk carriers had numerically lower velocity gain than the non-carriers (0.5-7%, d= 0.1-0.3) and power calculations revealed that 173 subjects are needed in each genotype group at 36°/s for the difference in velocity gain to become significant, 248 subjects at 24°/s and 7400 at 12°/s.

For saccade frequency there were no significant Velocity-by-Genotype, Diagnosis-by-Genotype or Velocity-by-Diagnosis-by-Genotype interactions (Table 27). For all three target velocities the carriers of the risk allele had numerically higher saccade frequency than the non-carriers (3-5%, d= 0.1). Power calculation showed that for these differences to become significant 870-2200 subjects are needed in each genotype group.

Table 25
Demographic and clinical statistics by diagnosis and *NRG-1* genotype

	Patients				Controls			
	SNP8NRG222662		SNP8NRG243177		SNP8NRG222662		SNP8NRG243177	
	G	non-G	T	non-T	G	non-G	T	non-T
N (%)	47 (36)	66 (64)	64 (57)	48 (43)	41 (39)	65 (61)	57 (56)	45 (44)
Male %	79	68	75	71	63	62	58	71
Mean age (SD)	42 (9.7)	40 (10.0)	43 (9.5)	39 (10.1)	41 (9.5)	40 (8.8)	41 (8.9)	40 (9.2)
Mean age of illness onset (SD)	24 (6.0)	23 (4.8)	23 (5.8)	22 (4.7)				
PANSS negative symptoms (SD)	20.2 (7.2)	20.6 (7.4)	19.8 (6.6)	21.5 (8.1)				
PANSS positive symptoms (SD)	14.7 (5.4)	15.1 (6.0)	14.9 (5.3)	15.0 (6.4)				
PANSS general(SD)	36.7 (9.5)	38.8 (11.6)	36.8 (9.6)	39.5 (12.2)				
PANSS total (SD)	71.6 (18.6)	74.5 (22.1)	71.4 (17.8)	76.0 (24.1)				

Footnote: PANSS = Positive and Negative Syndrome Scale

Table 26
Descriptive statistics of SPEM variables by diagnosis and *NRG-1* genotype

	Patients				Controls			
	SNP8NRG222662		SNP8NRG243177		SNP8NRG222662		SNP8NRG243177	
	G	non-G	T	non-T	G	non-G	T	non-T
N (%)	46 (41%)	65 (59)	63 (57)	47 (43)	40 (38)	64 (62)	55 (55)	45 (45)
Velocity gain %								
12º/s	91.8 (10.6)	92.9 (11.1)	92.4 (10.5)	92.6 (11.6)	95.8 (8.8)	95.3 (7.7)	95.1 (8.7)	95.6 (7.4)
24º/s	81.5 (16.8)	85.6 (14.0)	81.6 (16.9)	87.3 (12.4)	94.0 (13.2)	92.1 (11.2)	92.8 (12.9)	92.6 (9.5)
36º/s	62.8 (21.1)	68.9 (19.2)	62.9 (20.7)	71.6 (18.3)	79.6 (18.0)	79.5 (14.9)	79.3 (17.8)	79.9 (14.6)
Saccades N/s								
12º/s	1.48 (0.51)	1.56 (0.61)	1.54 (0.55)	1.48 (0.60)	(1.11 (0.54)	1.20 (0.53)	1.19 (0.59)	1.16 (0.48)
24º/s	2.25 (0.67)	2.34 (0.78)	2.31 (0.66)	2.30 (0.84)	1.91 (0.69)	1.84 (0.84)	1.92 (0.75)	1.84 (0.83)
36º/s	2.88 (0.78)	3.01 (1.06)	2.64 (0.87)	2.51 (0.77)	2.57 (0.77)	2.60 (0.93)	2.64 (0.87)	2.51 (0.77)

Data represent means (standard deviations) of SPEM variables by Diagnosis (patient, control) and NRG-1 Genotype (SNP8NRG222662 G/non-G, SNP8NRG243177 T/non-T).

Table 27
Repeated measures ANOVAs for *NRG-1* genotype effects on SPEM

	Velocity-Genotype interaction	Diagnosis-Genotype interaction	Velocity-Diagnosis-Genotype interaction
		SNP8NRG222662	
Velocity Gain	F[2,211] = 1.0 p = 0.35	F[2,211] = 0.8 p = 0.39	F[2,211] = 0.9 p = 0.38
Saccade Frequency	F[2,209] = 0.2 p = 0.77	F[1,209] = 0.4 p = 0.54	F[2,209] = 0.5 p = 0.58
		SNP8NRG243177	
Velocity Gain	F[2,206] = 2.6 p = 0.21	F[1,206] = 1.9 p = 0.29	F[2,206] = 2.7 p = 0.13
Saccade Frequency	F[2,203] = 0.1 p = 0.86	F[1,203] = 0.04 p = 0.72	F[2,203] = 0.2 p = 0.80

Within subjects variable: Velocity (12º/s, 24°/s and 36º/s)Between subjects variables: Diagnosis (patient, control), Genotype (risk allele carrier, non-risk allele carrier)

NRG-1 and antisaccade eye movements (IV)

Data from seven patients and three controls could not be analyzed due to poor quality related to difficulties the participants had in performing the task. Descriptive antisaccade statistics by diagnosis and *NRG*-1 genotype are demonstrated in Table 28.

As previously described there were significant effects of Diagnosis on reflexive error rate, latency, latency SD and amplitude gain (all $p < 0.005$) but not on spatial error, and the variability of amplitude gain and spatial error (Table 11).

SNP8NRG222662: There were no significant main effects of the SNP8NRG222662 Genotype on reflexive error rate, latency, amplitude gain, spatial error or the variability of latency and amplitude gain (Table 29). There was a trend towards a difference in the variability of spatial error ($p= 0.068$), suggesting greater variability in risk G allele carriers than non-carriers. There were no significant Diagnosis-by-Genotype interactions (all $p> 0.15$). However, for all antisaccade variables, except latency variability, carriers of the risk allele had numerically (4-10%) worse performance with small effect sizes ($d= 0.2$-0.3).

SNP8NRG243177: There were no significant main effects of SNP8NRG243177 genotype on reflexive error rate, latency, or amplitude again

(Table 29). For spatial error there was a trend (p= 0.09), suggesting poorer antisaccade spatial error in risk T allele carriers than non-carriers. The Genotype effect on the variability of antisaccade spatial error fell marginally short of being significant (p= 0.050) with carriers of the risk allele having larger variability of spatial error than non-carriers. The Genotype effect on the variability of antisaccade latency and amplitude gain were not significant. There were no significant Diagnosis-by-Genotype interactions (all p> 0.1).

Similar to what was seen for SNP8NRG222662, carriers of the SNP8NRG243177 risk allele generally had numerically worse antisaccade performance (1-13%; d= 0.1-0.3) on all variables except latency variability.

Table 28
Descriptive statistics of antisaccade variables by diagnosis and *NRG-1* genotype

	Patients				Controls			
	SNP8NRG222662		SNP8NRG243177		SNP8NRG222662		SNP8NRG243177	
	G	non-G	T	non-T	G	non-G	T	non-T
N (%)	44 (42)	61 (58)	60 (58)	44 (42)	39 (38)	63 (62)	54 (55)	44 (45)
Reflexive errors %	61.1 (20.1)	59.9 (22.9)	61.3 (20.4)	58.2 (23.1)	34.1 (24.0)	28.4 (18.2)	33.6 (20.0)	26.8 (19.2)
Error correction %	90.3 (13.2)	92.5 (9.9)	91.5 (12.0)	91.3 (10.9)	96.8 (6.7)	98.7 (4.7)	97.2 (6.8)	98.7 (3.7)
Latency ms	339.0 (75.3)	324.8 (78.2)	331.9 (80.1)	330.5 (73.7)	296.2 (43.7)	291.5 (41.9)	296.2 (45.5)	292.7 (38.9)
Variability of latency	80.4 (38.4)	70.3 (36.1)	76.6 (40.2)	73.3 (32.5)	54.3 (18.6)	56.2 (19.8)	56.1 (20.3)	56.4 (17.7)
Amplitude gain %	94.8 (30.2)	91.6 (28.6)	93.4 (29.2)	91.8 (29.6)	110.2 (27.19)	107.1 (28.7)	108.5 (30.4)	109.3 (25.4)
Variability of amplitude gain	49.1 (18.4)	44.6 (19.9)	49.7 (19.5)	42.7 (18.3)	48.3 (19.7)	47.1 (18.9)	47.0 (18.3)	49.1 (19.5)
Spatial error %	45.9 (12.0)	42.1 (14.0)	45.5 (11.8)	41.9 (14.3)	40.6 (16.6)	40.3 (13.2)	42.1 (15.6)	39.1 (12.8)
Variability of spatial error	32.1 (14.8)	28.0 (13.4)	31.6 (14.8)	27.5 (13.0)	32.2 (16.2)	29.1 (12.1)	32.2 (15.4)	28.5 (11.0)

Data represent means (standard deviations) of antisaccade variables by Diagnosis (patient, control) and NRG-1 Genotype (SNP8NRG222662 G/non-G, SNP8NRG243177 T/non-T)

Table 29
Univariate ANOVAs for *NRG-1* genotype effects on antisaccade eye movements

	SNP8NRG222662		SNP8NRG243177	
	Genotype effect	DiagnosisGenotype interaction	Genotype effect	Diagnosis-Genotype interaction
Reflexive error	F[1,208] = 1.3 p = 0.25	F[1,208] = 0.6 p = 0.46	F[1,203] = 1.7 p = 0.19	F[1,203] = 0.4 p = 0.53
Error correction	F[1,197] = 2.6 p = 0.11	F[1,197] = 0.01 p = 0.92	F[1,193] = 0.24 p = 0.63	F[1,193] = 0.4 p = 0.52
Latency	F[1,207] = 1.3 p = 0.29	F[1,207] = 0.3 p = 0.59	F[1,202] = 0.03 p = 0.85	F[1,202] = 0.01 p = 0.91
Latency SD	F[1,204] = 0.8 p = 0.37	F[1,204] = 2.1 p = 0.15	F[1,199] = 0.01 p = 0.94	F[1,199] = 0.1 p = 0.78
Amplitude gain	F[1,206] = 0.6 p = 0.60	F[1,206] < 0.01 p = 0.99	F[1,201] = 0.01 p = 0.91	F[1,201] = 0.1 p = 0.77
Amplitude gain SD	F[1,206] = 1.1 p = 0.29	F[1,206] = 0.4 p = 0.54	F[1,201] = 0.7 p = 0.39	F[1,201] = 2.9 p = 0.09
Spatial error	F[1,205] = 1.1 p = 0.30	F[1,205] = 0.7 p = 0.39	F[1,201] = 2.9 p = 0.09	F[1,201] = 0.03 p = 0.86
Spatial error SD	F[1,203] = 3.4 p = 0.068	F[1,203] = 0.2 p = 0.68	F[1,198] = 4.0 p = 0.050	F[1,198] = 0.08 p = 0.77

Between subjects variables: Diagnosis (patient, control), NRG-1 genotype (risk allele carrier, non-risk allele carrier

NRG-1 and prosaccade eye movements

As previously described there were significant effects of Diagnosis on prosaccade, latency, spatial error and the variability of latency, amplitude gain and spatial error (all $p \leq 0.002$) but not on amplitude gain (Table 14). Descriptive prosaccade statistics by diagnosis and genotype are shown in Table 30.

There were no significant main effects of either SNP8NRG222662 or SNP8NRG243177 on prosaccade latency, amplitude gain, spatial error or the variability of latency and amplitude gain (Table 31). The effects of SNP8NRG243177 on variability of spatial error fell short of being significant ($p= 0.052$) indicating that T risk allele carriers came close to having greater spatial error

variability than non-T allele carriers. There were no significant Diagnosis-by-Genotype interactions (Table 31).

In the patient group carriers of SNP8NRG222662 and carriers of SNP8NRG243177 risk alleles had numerically (1-20%) worse performance on all prosaccade variables, except variability of amplitude gain for SNP8NRG222662, with small effect sizes (d= 0.1-0.4).

Table 30
Descriptive statistics of prosaccade variables by diagnosis and *NRG-1* genotype

	Patients				Controls			
	SNP8NRG222662		SNP8NRG243177		SNP8NRG222662		SNP8NRG243177	
	G	non-G	T	non-T	G	non-G	T	non-T
N (%)	47 (42)	64 (58)	63 (57)	47 (43)	41 (39)	65 (61)	56 (50)	45 (41)
Latency ms	190.8 (30.7)	185.7 (28.8)	189.7 (30.3)	185.5 (29.1)	176.1 (17.9)	179.3 (21.8)	176.5 (17.8)	180.9 (23.4)
Variability of latency	38.7 (13.9)	37.8 (13.9)	38.5 (13.9)	37.9 (14.0)	31.0 (9.7)	30.3 (9.5)	31.0 (8.9)	29.6 (10.4)
Amplitude gain %	90.8 (11.7)	93.2 (11.0)	91.8 (12.3)	92.6 (10.0)	93.6 (7.2)	95.1 (11.0)	94.5 (10.2)	93.6 (7.9)
Variability of amplitude gain	17.3 (7.7)	17.9 (6.9)	18.6 (7.7)	16.3 (6.3)	13.9 (5.7)	15.5 (5.4)	15.0 (6.1)	14.4 (4.4)
Spatial error %	18.0 (9.0)	17.4 (7.3)	18.8 (8.8)	16.1 (6.8)	13.3 (5.0)	15.5 (5.9)	14.9 (6.4)	14.4 (4.4)
Variability of spatial error	12.4 (5.8)	11.5 (4.2)	12.7 (5.5)	10.6 (3.6)	9.5 (3.9)	10.1 (3.5)	10.1 (4.3)	9.5 (2.6)

Data represent means (standard deviations) of antisaccade variables by Diagnosis (patient, control) and NRG-1 Genotype (SNP8NRG222662 G/non-G, SNP8NRG243177 T/non-T)

Table 31

Univariate ANOVAs for *NRG-1* genotype effects on prosaccade eye movements

	SNP8NRG222662		SNP8NRG243177	
	Genotype effect	Diagnosis-Genotype interaction	Genotype effect	Diagnosis-Genotype interaction
Latency	F[1,214] = 0.08 p = 0.78	F[1.214] = 1.4 p = 0.25	F[1,209] < 0.00 p = 0.99	F[1,209] = 1.5 p = 0.23
Latency SD	F[1,216] = 0.3 p = 0.62	F[1,216] = 0.004 p = 0.95	F[1,211] = 0.4 p = 0.55	F[1,211] = 0.05 p = 0.83
Amplitude gain	F[1,216] = 1.2 p = 0.17	F[1,216] = 0.1 p = 0.76	F[1,211] = 0.004 p = 0.95	F[1,211] = 0.4 p = 0.54
Amplitude gain SD	F[1,212] = 1.2 p = 0.24	F[1,212] = 0.3 p = 0.61	F[1,208] = 2.3 p = 0.13	F[1,208] = 1.0 p = 0.32
Spatial error	F[1,214] = 1.0 p = 0.32	F[1.214] = 2.0 p = 0.16	F[1,210] = 1.9 p = 0.17	F[1,210] = 1.2 p = 0.27
Spatial error SD	F[1,214] = 0.053 p = 0.82	F[1,214] = 1.3 p = 0.26	F[1,210] = 3.8 p = 0.052	F[1,210] = 1.7 p = 0.19

Between subjects variables: Diagnosis (patient, control), *NRG-1* genotype (risk allele carrier, non-risk allele carrier)

NRG-1 and visual fixation

Descriptive statistics for *NRG-1* genotypes and saccade frequency during visual fixation are shown in Table 32. There were no main effects of either SNP8NRG222662 ($F[1,206]= 0.04$; $p= 0.84$) or SNP8NRG243177 ($F[1,201]= 2.7$; $p= 0.10$) on saccade frequency.

Table 32
Fixation saccades by diagnosis and *NRG-1* genotype

	Patients				Controls			
	SNP8NRG222662		SNP8NRG243177		SNP8NRG222662		SNP8NRG243177	
	G	non-G	T	non-T	G	non-G	T	non-T
N (%)	44 (42)	60 (58)	59 (57)	44 (43)	40 (39)	63 (61)	56 (57)	43 (43)
Saccade frequency (N/s)	0.09 (0.09)	0.10 (0.10)	0.10 (0.11)	0.08 (0.09)	0.05 (0.08)	0.04 (0.06)	0.05 (0.07)	0.04 (0.05)

Data represent means (standard deviations) of fixation saccades by Diagnosis (patient, control) and NRG-1 Genotype (SNP8NRG222662 G/non-G, SNP8NRG243177 T/non-T)

Copy number variations and eye movements

All the patients in the present study had been participants in a previous investigation of association of recurrent CNVs with schizophrenia (Stefansson et al., 2008). Two independent multicenter studies found deletions on chromosomes *1q21.1* and *15q13.3* to be associated with significantly increased risk for schizophrenia (International schizophrenia consortium, 2008, Stefansson et al., 2008). Therefore the present patient sample was screened for CNVs on *1q21.1* and *15q13.3*. Three out of 118 patients had CNVs on the two loci. Two had a deletion on chromosome *15q13.3* and one had a duplication on chromosome *1q21.1*. In Table 33 descriptive statistics of SPEM and antisaccade performance for the three CNV patients are shown along with the mean performance and SD of all patients. The patients with CNVs had similar antisaccade and SPEM task performance to the other patients on most measures. However, the patient with *1q21.1* duplication had reflexive error rate that was 1.2 SDs higher and spatial error that was 1.6 SDs lower than the patient mean (Figure 15). One of the patients with *15q13.3* deletion had lower SPEM velocity gain at all target velocities (1.8-2.2 SDs) compared to the patient group (Figure 16). The other *15q13.3* deletion patient had higher velocity gain at 24°/s (2.4 SDs) than the patient mean and the patient with *1q21.1* duplication had higher

velocity gain at 36º/s (1.3 SDs). The *15q.13.3* patient who had lower SPEM velocity gain at all target velocities had higher SPEM saccade frequency at 12º/s (2.6 SDs) and lower saccade frequency at 36º/s (1.4 SDs) than all patients.

Table 33
Antisaccade and SPEM performance in three patients with CNVs compared to mean performance of all patients

	ANTISACCADE				SPEM					
					VELOCITY GAIN			SACCADE RATE		
	Errors (%)	Latency (ms)	Amplitude gain (%)	Spatial error (%)	12°/s	24°/s	36°/s	12°/s	24°/s	36°/s
15q13.3(A) deletion	66.7	326.3	65.3	48.6	68.8	50.5	31.1	3.00	2.79	1.64
15q13.3(B) deletion	70.6	400.6	97.7	34.0	99.3	119.6	83.7	1.21	2.55	2.82
1q21.1 duplication	86.1	395.7	77.9	22.4	94.7	86.5	91.9	1.36	1.70	2.00
Mean all patients (SD)	60.4 (21.7)	330.8 (77.0)	93.0 (29.2)	43.7 (13.2)	92.5 (10.8)	83.9 (15.3)	66.4 (20.1)	1.52 (0.57)	2.30 (0.73)	2.96 (0.95)

CNV: Copy Number Variation

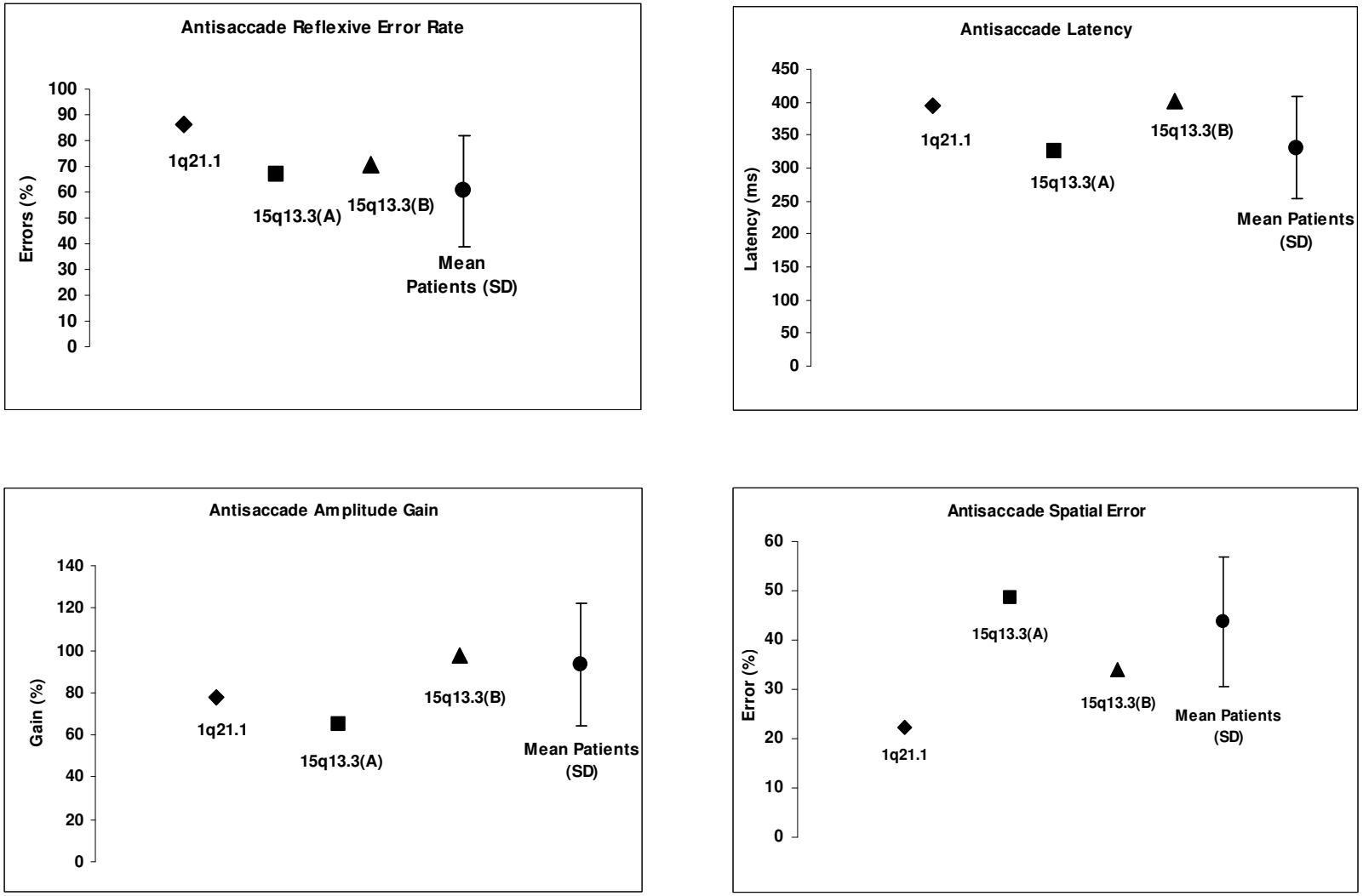

Figure 15
Antisaccade performance in three patients with CNVs on chromosomes *1q21.1* and *15q13.3* compared to mean (SD) performance

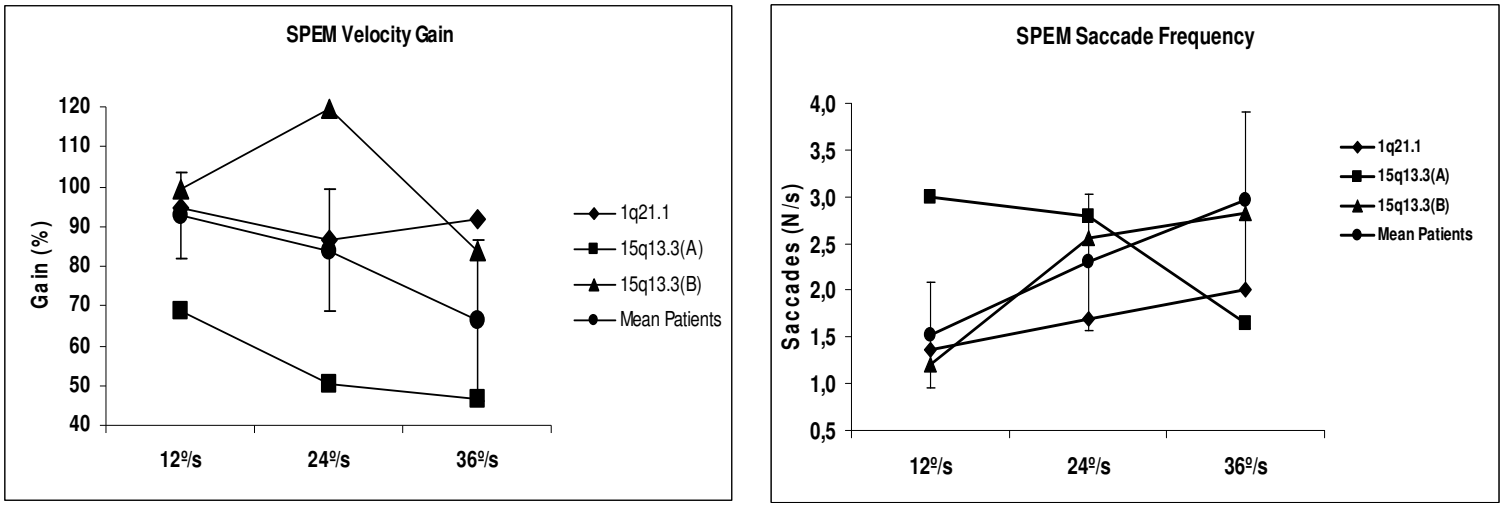

Figure 16
SPEM performance in three patients with CNVs on chromosomes *1q21.1* and *15q13.3* compared to the mean (SD) performance in all patients

DISCUSSION

The main objective of the present thesis was to confirm the well-known observation of impaired SPEM and antisaccade eye movement deficits in schizophrenia patients drawn from a homogenous Icelandic sample, and then to investigate the associations of these deficits with the putative schizophrenia risk genes *COMT* val^{158}met and *NRG-1*. Additionally, the relationship between SPEM and antisaccade performance was examined and associations of eye movement performance and the two risk genotypes with clinical measures of schizophrenia were investigated. In this chapter the results of the present thesis are discussed in relation to previous research. Then, strengths and limitations of the studies included in the thesis are considered. Finally, conclusions are formulated and future directions for further research are discussed.

SPEM in schizophrenia patients and controls

The finding of significantly lower velocity gain and higher saccade frequency in schizophrenia patients than controls for all three target velocities (12°/s, 24°/s and 36°/s) on the SPEM task replicates what most previous studies using similar methods have found (Abel et al., 1991, Friedman et al., 1991, Hutton & Kennard, 1998, Hutton et al., 2004, Radant & Hommer, 1992, Sweeney et al., 1998, Yee et al., 1987). Furthermore, SPEM performance deteriorated with increasing target velocity in both patients and controls. The velocity effect on gain was significantly stronger in the patient than the control group but no interaction with group was found for saccade frequency. A similar interaction was observed for velocity gain in a previous study comparing chronic schizophrenia patients, first episode patients and healthy controls at four target velocities (10, 20, 30, and 36°/s) (Hutton et al., 2001). However, a recent meta-analysis of SPEM studies in schizophrenia did not find significant moderating effects of target velocity on SPEM performance differences between schizophrenia patients and controls (O'Driscoll & Callahan, 2008).

Studies have shown that schizophrenia patients and their relatives have impaired motion perception (Chen et al., 1999a) and these impairments correlate with SPEM deficits (Chen et al., 1999b, Stuve et al., 1997). Sensitivity to perception

of velocity was associated with measures of pursuit gain but not saccade frequency in schizophrenia patients (Chen et al., 1999b). Recent fMRI studies have shown that decreased activity in motion perception area V_5 of the brain is associated with SPEM deficits in schizophrenia patients (Lencer et al., 2005) and lesions to this area cause SPEM impairments in non-human primates (Newsome et al., 1985). The present findings add to the evidence that schizophrenia is associated with motion processing deficits and suggest that the difference in SPEM velocity gain between patients and controls increases with increasing target velocity. These results are strengthened by the fact that the present study is one of the largest studies of SPEM in schizophrenia patients and controls.

There was good internal consistency for both SPEM velocity gain and saccade frequency in patients and controls (all Cronbach's alpha > 0.85). This is similar to what has previously been reported in healthy individuals (Ettinger et al., 2003a) and schizophrenia patients (Cegalis & Sweeney, 1979). The high internal consistency indicates that inter-individual differences in SPEM performance are consistent throughout the test sessions and that these differences can be reliably measured.

Some systematic within-session performance changes of SPEM performance were found and most of them were similar in patients and controls. Overall, SPEM velocity gain decreased with time. At the fastest target velocity (36°/s) there was an interaction effect due to an increase in gain in the second quarter of the test session, which was followed by a linear decline in patients. This may be explained by increasing fatigue or boredom with time, which affected patients more than controls. Saccade frequency decreased with time in both patients and controls, which may be ascribed to a fast learning effect allowing subjects to optimally stabilize their gaze on the target. Similar reduction in catch-up saccades was observed in healthy subjects in a previous study (Ettinger et al., 2003a).

Antisaccade eye movements in schizophrenia patients and controls

Patients had significantly higher reflexive error rate, lower amplitude gain and longer and more variable latency on the antisaccade task than healthy individuals. Both patients and controls had high rates of corrective antisaccades (initiation of an antisaccade after a reflexive error), which may suggest that the participants generally understood and were willing to perform the task.

All previous studies of antisaccades in schizophrenia have found an increased rate of reflexive errors in patients compared to controls (Calkins et al., 2008, Hutton & Ettinger, 2006). The present study supports that schizophrenia patients have difficulties inhibiting reflexive saccades during the antisaccade task. This impairment may be related to lack of inhibitory control in the prefrontal cortex (McDowell & Clementz, 2001). The role of impaired prefrontal inhibition in antisaccade deficits in schizophrenia is supported by studies showing that preservative errors on the WCST are associated with reflexive error rate in schizophrenia patients (Crawford et al., 1995a, Crawford et al., 1995b, Crawford et al., 1996, Karoumi et al., 1998, Radant et al., 1997, Rosse et al., 1993, Tendolkar et al., 2005, Tien et al., 1996).

Apart from response inhibition there have been numerous cognitive explanations for the occurrence of reflexive errors on the antisaccade task. Increased reflexive error rate in patients may also be associated with impaired attention, (Radant et al., 1997, Tendolkar et al., 2005) working memory (Hutton et al., 2004) or the ability to appropriately activate a volitional antisaccade response (Reuter et al., 2005). Studies have shown that increased reflexive error rate in schizophrenia patients correlates with measures of attention and working memory deficits (Hutton et al., 2004, Radant et al., 1997).

The finding of longer latencies to correct antisaccades in patients replicates what several previous studies have demonstrated (Fukushima et al., 1990, Karoumi et al., 1998, Spengler et al., 2006) and supports that schizophrenia patients have deficits in volitional response generation (Reuter & Kathmann, 2004). Additionally, patients had higher standard deviations of antisaccade latencies than controls, which is in agreement with evidence of increased intra-individual variability in neuropsychological task performance in schizophrenia (Kaiser et al., 2008). Kaiser et al (2008) observed elevated intra-individual reaction time variability on a Go/Nogo

task among schizophrenia patients. Increased reaction time variability may be associated with impaired neural timing mechanisms and deficient top-down attentional control in patients with schizophrenia (Kaiser et al., 2008).

The present study replicates several previous studies, which have found decreased antisaccade amplitude gain in patients with schizophrenia (Ettinger et al., 2004a, Ettinger et al., 2004b, Karoumi et al., 1998, McDowell et al., 1999). The ability to match saccade amplitude to target amplitude depends on sensorimotor processes involved in transforming the covertly encoded visual target location into a motor output. Recent functional imaging studies have demonstrated that this is a process that requires a shift in signal processing from the intraparietal sulcus to FEF (Medendorp et al., 2005, Moon et al., 2007).

Although the study found patients to have significantly lower antisaccade amplitude gain than controls the difference was due to the fact that the controls had a mean gain of 107% (overshooting) and the patients had a mean gain of 93% (undershooting). The mean gain scores of the two groups were therefore equally far (in opposite directions) from a perfect gain score of 100%. Consequently, the measure of spatial error, which provides a spatial accuracy score independent of hypo- or hypermetria, did not differ between the two groups.

All antisaccade variables, except spatial error in patients, displayed very good internal consistency ($\alpha > 0.75$). This is similar to what was reported in a previous study in healthy subjects (Ettinger et al., 2003a). Internal consistency of antisaccade performance has not previously been examined in schizophrenia patients.

Some within-session or task duration effects on antisaccade performance were observed in both patients and controls. Reflexive error rate first decreased and then increased in both groups. This may suggest that it took the subjects some time to adapt to the task and improve their performance, but towards the end fatigue started having an effect. A similar task duration effect on reflexive error rate was observed in a large study of healthy males (Smyrnis et al., 2002). The present study shows that this effect is also present in schizophrenia patients, thus representing an adaptive process that may be unimpaired in schizophrenia.

Antisaccade amplitude gain became smaller over time in both patients and controls, indicating that antisaccade hypometria might be related to task duration.

This finding suggests that longer task duration may increase demands on sensory-motor pathways involved in processing the target location information into a motor response. A previous study observed similar effects on saccade amplitudes. Mosimann et al (2004) showed that making saccades volitional by adding verbal instructions (top down control) to standard pro- and antisaccade tasks resulted in hypometric saccades. This suggests that an increased volitional component or effort may be associated with saccade hypometria. Some previous studies have found that schizophrenia patients and their relatives have hypometric antisaccade amplitudes compared to controls (Ettinger et al., 2004b, Ettinger et al., 2006) but the factors accounting for this have not been identified.

Finally, there was a moderate linear increase in antisaccade latency with time in both patients and controls. This gradual increase in reaction time may have been related to fatigue or any other factor increasingly impairing performance over the session.

Prosaccade eye movements in schizophrenia patients and controls

Schizophrenia patients had significantly longer saccade latencies, higher spatial error and more variable latency, amplitude gain and spatial error on the prosaccade task than controls. Most previous studies of prosaccade eye movements in schizophrenia have not observed significant differences in prosaccade latency and spatial accuracy between patients and controls (Clementz et al., 1994, Crawford et al., 1998, Karoumi et al., 1998, Krebs et al., 2001, Sweeney et al., 1997). However, some studies have demonstrated prolonged latency (Evans & Schwartz, 1997, Mackert & Flechtner, 1989) and reduced accuracy (Cegalis et al., 1982, Schwartz et al., 1995) of prosaccades in schizophrenia. This inconsistency may be related to differences in eye movement recording techniques and target presentation between studies. It is also possible that some subtle prosaccade deficits may be associated with schizophrenia. It has been shown that by slightly increasing the difficulty of a prosaccade task patients perform worse than controls (Done & Frith, 1984) and recent functional imaging studies have demonstrated that schizophrenia patients show subtle deficits in brain activity while performing prosaccades (Keedy et al., 2006).

Similar to what was observed for antisaccades, prosaccade amplitudes decreased with time in the present study. There was also a task duration effect on prosaccade latency. This effect was quadratic with a shorter reaction time in the second of four time segments. This may have been because of adaptation to the task, followed by a slower response, possible because of fatigue. There was also a task duration-by-diagnosis interaction due to a linear decrease in latency in controls suggesting a stronger improvement effect in controls.

Visual fixation in schizophrenia patients and controls

Patients made significantly more saccades during visual fixation than controls ($p< 0.001$). The frequency of intrusive saccades is the most commonly used performance measure of visual fixation (Curtis et al., 2001b, Gooding et al., 2000a, Kissler & Clementz, 1998). Previous studies of visual fixation in schizophrenia have provided contradictory results. While some studies have found fixation to be normal in schizophrenia patients (Gooding et al., 2000a, Kissler & Clementz, 1998) others have not (Amador et al., 1995, Curtis et al., 2001b). These contradictory findings may possibly be explained by heterogeneity in subject populations and variations in task instructions as well as methods of measuring and analyzing eye movements. The present study indicates that schizophrenia patients have deficits in saccadic inhibition during visual fixation. Future larger studies using equally homogenous subject samples and well defined and standardized methods may help clarifying whether schizophrenia patients have abnormal visual fixation or not.

Internal consistency of fixation performance was high for both patients ($\alpha= 0.86$) and controls ($\alpha= 0.92$) and there were no significant within-session performance changes. In a previous study of healthy individuals using a similar fixation task no significant performance changes were observed with time but internal consistency was lower ($\alpha= 0.45$) than in the present study (Ettinger et al., 2003a).

Relationship of clinical variables with eye movement performance

The only eye movement variable that correlated with PANSS scores of schizophrenia symptoms was antisaccade correction rate. Higher total and negative PANSS scores

were weakly associated with lower antisaccade correction rate (r= -0.24 and r= -0.29, respectively). This finding is in line with many previous studies, which have not found significant associations between schizophrenia symptom levels and performance on SPEM and antisaccade tasks (Curtis et al., 2001a, Flechtner et al., 2002, Gooding et al., 1994, Hutton et al., 2004, Karoumi et al., 1998, Litman et al., 1997, Louchart-de la Chapelle et al., 2005, Raemaekers et al., 2002, Schlenker et al., 1994). Curtis et al. (2001a) investigated antisaccade eye movements in groups of patients with acute schizophrenia and schizophrenia patients whose illness was in remission. Even though the clinical states were markedly different the antisaccade task performance was equally impaired in both patient groups.

Because of the alleged associations of negative symptoms (Weinberger et al., 2001) and eye movement deficits (Keedy et al., 2006, McDowell et al., 2002, O'Driscoll et al., 1999) with frontal brain dysfunctions the relationship between negative symptoms and eye movement endophenotypes has been investigated in many studies. Although some studies have shown associations between negative symptoms and deficits on both SPEM (Ciuffreda et al., 1994, Katsanis & Iacono, 1991, Matsue et al., 1993, Roitman et al., 1997, Sweeney et al., 1994) and antisaccade tasks (Ettinger et al., 2004a, Ettinger et al., 2006, Nkam et al., 2001), there is a similar number of studies that have not found such associations (Flechtner et al., 1992, Flechtner et al., 2002, Karoumi et al., 2001, Kelly et al., 1990, Lee et al., 2001, Lieberman et al., 1993, Litman et al., 1997, Rosse et al., 1993, Sweeney et al., 1999). The inconsistent findings of these studies may be related to small (n= 20-50) and heterogenous subject samples including both first episode and chronic schizophrenia patients. It is also possible that the effects of antipsychotic medications confounded the results.

The results of the present study, which is one of the largest studies of eye movements in schizophrenia patients (n= 118), are in keeping with findings of two studies on over 100 first episode patients (Hutton et al., 2004) and over 100 chronic schizophrenia patients (Louchart-de la Chapelle et al., 2005) that found no associations of SPEM or antisaccade eye movements with negative or positive symptoms of schizophrenia.

The present findings suggest that SPEM and antisaccade performance is not associated with levels of negative or positive symptoms and support the notion that SPEM and antisaccade deficits are state independent schizophrenia endophenotypes.

Patients' age of illness onset did not correlate with eye movement performance. However, longer illness duration was moderatly associated with decreased SPEM velocity gain at 24°/s and 36°/s (r= -0.36 and r= -0.34, respectively) and weakly associated with increased saccade rate during visual fixation (r= 0.23) and lower correction rate on the antisaccade task (r= -0.27). Although, most previous studies have not found significant association between SPEM and age of illness onset, duration of illness or number of hospitalizations (Flechtner et al., 2002, Katsanis & Iacono, 1991, Schlenker et al., 1994), there are studies which have shown worse SPEM performance with higher age at onset of psychosis (Siever et al., 1986, Sweeney et al., 1994) and longer duration of illness (Litman et al., 1997). A study including an equally large patient sample as the present study (n= 111) found that lower SPEM gain correlated signficantly with longer duration of illness (Louchart-de la Chapelle et al., 2005). The present study supports these findings and suggests that SPEM gain deteriorates with longer illness duration. This weakens the conception that SPEM gain is an endophenotype independent of disease chronicity.

Type of antipsychotic medication (typical, atypical or both typical and atypical compounds) was not associated with eye movement performance in the patient group. Most studies find that SPEM performance of schizophrenia patients is unaffected by typical antipsychotics (Reilly et al., 2008b). There is some evidence that atypical antipsychotics, particularly clozapine, may impair SPEM but this needs to be investigated further (Lencer et al., 2008, Reilly et al., 2008b). Studies of the effects of typical antipsychotics on antisaccade eye movements have provided mixed results but there are indications from recent studies that atypical antipsychotics such as risperidone and olanzapine may improve antisaccade performance in schizophrenia patients (Reilly et al., 2008b).

No effects of smoking on eye movements were observed in the present study. Several recent studies suggest that nicotine can improve performance on several neuro-cognitive tasks, including SPEM and antisaccade tasks (Depatie et al., 2002, Ettinger et al., 2009). However, in those studies nicotine administration was

experimentally manipulated and eye movements were measured within minutes of nicotine use or following abstinence.

Relationship between SPEM and antisaccade eye movements

As discussed in the introduction both SPEM and antisaccade deficits have been associated with impaired frontal brain function and both deficits have been proposed as promising endophenotypes in schizophrenia (Calkins & Iacono, 2000). However, it is not known whether or to which degree they represent the same risk genes.

Only moderate associations were found between some measures of SPEM and antisaccade task performance in the present study. Furthermore, associations that were observed in the combined sample of participants were not always significant in the separate groups of patients and controls. This finding indicates that performance on the two eye movement tasks is unlikely to reflect the same underlying genetic effects and because the sample size is quite large the present study would have been expected to detect clear associations between the two tasks if they really existed.

Relatively few previous studies have examined the relationship between SPEM and antisaccade task performance and their findings are contradictory. While some studies have found higher reflexive error rate on the antisaccade task to correlate with worse SPEM performance (Louchart-de la Chapelle et al., 2005, Matsue et al., 1994, Schlenker & Cohen, 1995, Sereno & Holzman, 1995) others have not (Hutton et al., 1998, Nkam et al., 2001, Tien et al., 1996, Zanelli et al., 2005). Recent functional brain imaging studies have demonstrated that although many brain areas are involved in both tasks some neural networks are more specific to either SPEM or antisaccades. SPEM is primarily mediated by a discrete neural network involving the FEFs and motion processing areas (Lencer et al., 2004) while antisaccades are mediated by areas involved in cognitive function such as the DLPFC (DeSouza et al., 2003, Ford et al., 2005).

Associations of *COMT* val^{158}met and *NRG-1* with eye movements

The main rationale for the present thesis was to investigate relationships between putative risk markers of the *COMT* and *NRG-1* genes and eye movement endophenotypes in order to help clarifying the mechanistic effects of these genes on brain function in schizophrenia.

As previously described, there is evidence that impaired frontal brain function plays a key role in the pathophysiology of schizophrenia (Weinberger et al., 2001). Variants of the *COMT* and *NRG-1* genes have been associated with frontal brain cognitive impairments (Egan et al., 2001, Goldberg et al., 2003, Hall et al., 2006, Stefanis et al., 2007) and series of lesion and imaging studies have shown that deficits on SPEM and antisaccade tasks in schizophrenia patients are associated with impaired prefrontal brain functions (Lencer & Trillenberg, 2008, McDowell et al., 2008). Finding associations between putative risk markers of the *COMT* and *NRG-1* genes and eye movement endophenotypes may help us understand which neural mechanisms these genes influence in schizophrenia.

COMT val^{158}met

Because of the role of COMT in prefrontal dopamine activity and the putative role of dopamine circuits and frontal brain function in schizophrenia the *COMT* gene has been extensively studied in relation to schizophrenia. Previous studies of the association of *COMT* val^{158}met with schizophrenia have provided inconsistent results. While some have shown association with the met^{158} allele (Ohmori et al., 1998, Sazci et al., 2004), others have found association with the val^{158} allele (Egan et al., 2001, Kremer et al., 2003) but most studies have not reported any association (Daniels et al., 1996, Karayiorgou et al., 1998, Nunokawa et al., 2007). Furthermore, recent meta-analyses did not find support for significant association between *COMT* val^{158}met polymorphism and schizophrenia (Fan et al., 2005, Glatt et al., 2003, Munafo et al., 2005, Okochi et al., 2009). In the present study the number of *COMT* val/val, val/met and met/met carriers did not differ between schizophrenia patients and healthy controls.

It is unlikely that a potential relationship between *COMT* and schizophrenia is limited to a main effect of the val^{158}met polymorphism. Therefore, researchers have

investigated the possibility that *COMT* val^{158}met may interact with other potential genetic and environmental risk factors for schizophrenia. A recent study found that val^{158} carriers had an increased risk of developing schizophrenia if they used cannabis (Caspi et al., 2005) and another study found an association between several SNPs in the *COMT* gene and SNPs in other potential schizophrenia risk genes (Nicodemus et al., 2007). These findings of environmental interactions with the *COMT* gene and epistatic interactions with other genes as well as the role of COMT in dopamine regulation in the brain, suggest that the *COMT* gene might still represent a minor candidate gene for schizophrenia.

There were no significant differences in gender ratio between *COMT* genotype groups among patients, controls or the combined subject sample. There is published data suggesting that COMT activity predisposes to psychiatric disorders differently in men and women (Harrison & Tunbridge, 2008). Gender differences in functional variants of the *COMT* gene have been observed in schizophrenia patients (Shifman et al., 2002) and a recent study of a homogenous Spanish population found an overrepresentation of *COMT* val^{158} homozygotes and underreprentation of *COMT* val^{158}met heterozygotes in male schizophrenia patients (Hoenicka et al., 2009). The present study does not support that the *COMT* val^{158}met allele ratio differs between males and females.

No effects of *COMT* val^{158}met genotype were found on positive or negative symptoms of schizophrenia as determined by the PANSS. This finding is in accordance with a recent study, which also did not find any relationship between *COMT* val^{158}met and PANSS scores in schizophrenia patients (Strous et al., 2006). Another recent study did not observe any association between deficit/non-deficit symptoms of schizophrenia and *COMT* val^{158}met (Wonodi et al., 2006b). However, two studies reported associations between the low activity met^{158} allele and aggressive (Strous et al., 2003) and suicidal (Nolan et al., 2000) behavior in schizophrenia patients.

COMT val^{158}met and SPEM

In the present study no significant association was observed between *COMT* val^{158}met and SPEM steady state gain or saccade frequency in schizophrenia patients and healthy controls. However, in the patient group val^{158} homozygotes had numerically lower pursuit gain than met^{158} homozygotes at all three target velocities (d= 0.16-0.23), which is in keeping with findings of worse neurocognitive performance in val^{158} allele carriers (Egan et al., 2001, Goldberg et al., 2003). It is therefore possible that the present study lacks power to detect a small effect of *COMT* val^{158}met on SPEM velocity gain in schizophrenia patients. A power analysis showed that each genotype group would have to include 230 subjects for the *COMT* effect at 12º/s to be significant and 400-500 subjects for 24º and 36º/s.

Only two smaller previous studies have investigated the relationship between *COMT* val^{158}met and SPEM in schizophrenia (Rybakowski et al., 2002, Thaker et al., 2004). Similar to the present study Thaker et al (2004) did not find a relationship between *COMT* val^{158}met and maintenance pursuit gain in 53 healthy subjects and 62 schizophrenia patients. They also examined the association between *COMT* val^{158}met and predictive pursuit and found that healthy participants with met/met genotype had higher predictive pursuit gain than healthy participants with val/val, while met/met patients had non-significantly lower predictive pursuit than patients with val/val genotype (Thaker et al., 2004). In the predictive pursuit task the visual target is intermittently masked in order to distinctively test extra-retinal brain processes involved in SPEM, whereas the traditional steady-state pursuit task involves both retinal and extra-retinal processes (Hong et al., 2005, Lencer et al., 2004). The findings of Thaker et al (2004) therefore suggest that extra-retinal SPEM processes may be more sensitive to differences in prefrontal dopamine levels and that the effects differ between patients and controls. Hong et al (2006) found that performance on a predictive pursuit task had stronger sibling pair correlation and larger heritability estimates than the steady-state SPEM task. Predictive pursuit deficits may represent a more specialized endophenotype with less complex genetic foundations than steady-state pursuit deficits. Therefore, the reason no *COMT* val^{158}met effects were observed on pursuit gain in the present study might be related

to the use of a steady-state SPEM task, which may give a more global assessment of the pursuit system than the predictive pursuit task.

Another previous study of *COMT* val^{158}met and SPEM found that male schizophrenia patients with met/met had lower mean saccade intensity than patients with val/met and val/val but no significant *COMT* genotype effects were observed in female patients or healthy controls (Rybakowski et al., 2002). They did, however, not directly study saccade frequency but instead they qualitatively classified the intensity of saccade disturbance into four categories using a 0-3 scale, ranging from no saccades to high saccade frequency, and then compared clinical and genotype groups using non-parametric tests. No Genotype-by-Gender interactions were found for SPEM velocity gain or saccade frequency in patients or controls in the present study. The differences in saccade analysing methods make it difficult to compare these results with the results of the present thesis.

COMT val^{158}met and antisaccade eye movements

In the present research a greater number of val^{158} alleles was significantly associated with shorter and less variable antisaccade latency and fell just short of being significantly related to a lower number of reflexive errors. The *COMT* val^{158}met genotype status was not associated with antisaccade gain or spatial error and there were no significant Diagnosis-by-Genotype interactions for any antisaccade variables. This is the first study of associations between *COMT* val^{158}met and antisaccade eye movements in schizophrenia. Two previous studies examined *COMT* val^{158}met and antisaccades in healthy individuals (Ettinger et al., 2008, Stefanis et al., 2004). Neither study found significant association between *COMT* val^{158}met carrier status and antisaccade task performance, although one reported a trend toward an association of higher reflexive error rate with the val^{158} allele (Stefanis et al., 2004).

There are several potential explanations for the finding of better antisaccade performance in val^{158} carriers than non-val^{158} carriers in the present study. First, the results may be reconciled with a recent theory suggesting that the *COMT* val^{158} allele is associated with better performance on tasks involving cognitive plasticity, while the met^{158} allele is hypothesized to be beneficial on tasks requiring cognitive stability (Bilder et al., 2004). The theory suggests that the high activity val^{158} allele is

associated with decreased tonic and increased phasic dopamine release subcortically and decreased dopamine cortically and the opposite is thought to be associated with the low activity met^{158} allele. Cognitive stability is required in tasks involving sustained attention, whereas cognitive plasticity is necessary in tasks involving e.g. shifts in rules, updating of working memory and monitoring and correction of response errors (Bilder et al., 2004). The antisaccade task can be conceptualized as a measure of cognitive plasticity such as inhibition of inappropriate responses, online monitoring of errors, and rapid generation of corrections. Additionally, it has been demonstrated that antisaccade performance is sensitive to reward incentives (Duka & Lupp, 1997, Jazbec et al., 2005), in line with the hypothesized properties of plasticity tasks (Bilder et al., 2004). However, like most complex cognitive tasks, the antisaccade task also involves elements of cognitive stability because constant alertness and sustained attention is necessary for adequate performance.

A second possible explanation for better antisaccade performance with higher number of val^{158} alleles may be the potential role of the met^{158} allele in anxiety and anxiety-related traits as well as risk for other psychopathologies. There have been reports of met^{158} being associated with increased anxiety (Enoch et al., 2003, Woo et al., 2004) and OCD (Karayiorgou et al., 1997). The *COMT* met^{158} allele has also been associated with other psychiatric disorders such as bipolar disorder (Li et al., 1997), ADHD traits (Reuter et al., 2006), and depression (Ohara et al., 1998). State-dependent anxiety (Smyrnis et al., 2003), OCD (Rosenberg et al., 1997a, Tien et al., 1992) and affective disorders (Katsanis et al., 1997, Sereno & Holzman, 1995) have been associated with impaired antisaccade performance. Hence, it is possible that anxiety may impair performance of met^{158} carriers on the antisaccade task in the present study. However, no dimensional measures of anxiety, affective or ADHD symptoms were obtained for participants and, therefore, this hypothesis will need to be investigated in future studies.

A third speculative explanation may be related to alterations in prefrontal dopamine levels caused by interactions between the antisaccade task and activity of the COMT enzyme. There is evidence for prefrontal cognitive function having an inverted U-shaped relationship with dopamine levels (Goldman-Rakic et al., 2000, Tunbridge et al., 2006). This means that prefrontal cognitive function is optimal at

intermediate dopamine levels but worsens in hypo- or hyperdopaminergic states. It is possible that antisaccade task procedures have some arousing effects on the frontal cortex pushing the dopamine level too far to the right on the U-shaped curve. The more effective *COMT* val^{158} may then counter-balance this effect better than the less efficient *COMT* met^{158} and bring the dopamine level closer to what is optimal for antisaccade performance.

A neurobiological explanation for better antisaccade performance with greater number of val^{158} alleles may be provided by a recent fMRI study. Ettinger et al (2008) found that val^{158} carriers demonstrated deactivations of medial frontal brain areas during antisaccade task performance, whereas non-carriers did not. It has been shown that deactivation of medial frontal brain areas is associated with better antisaccade performance (Polli et al., 2005) and more efficient stimulus processing on a selective-attention task (Weissman et al., 2006). It is, therefore, possible that val^{158} carrier status is associated with a higher signal to noise ratio in medial frontal cortex and more effective neural processing during the antisaccade task.

The lack of significant diagnosis-by-genotype interactions in the present study suggests that the *COMT* val^{158}met polymorphism is associated with task performance irrespective of whether the subject has schizophrenia or not. However, inspection of the antisaccade reflexive error rate (Table 20) suggests that the statistically non-significant effect is largely driven by performance in the controls but not the schizophrenia patients. The modulating effects of *COMT* val^{158}met on antisaccade performance may therefore be relatively stronger in controls than schizophrenia patients.

The *COMT* val^{158}met genotype status did not relate to antisaccade amplitude gain and spatial error. These performance parameters are measures of the ability to match saccade amplitude to target amplitude. They are heavily dependent on the dorsal (magnocellular) visual stream, which is specialized for processing information on spatial orientation and transforming this signal into a motor output (Ungerleider et al., 1998). The present findings suggest that antisaccade amplitude gain and spatial error may be influenced by genotypes other than *COMT* val^{158}met.

Relationship of *COMT* val^{158}met with prosaccade eye movements and visual fixation

Only one previous study has examined the relationship of *COMT* val^{158}met genotype with prosaccade eye movements. Ettinger et al (2008) did not observe significant association of *COMT* val^{158}met with prosaccade latency in a group of 36 healthy individuals. In the present study higher number of val^{158} alleles was significantly associated with less variability of prosaccade latency (p= 0.032) but there was not a significant genotype-by-diagnosis interaction. There were no other significant *COMT* val^{158}met effects on prosaccade performance measures. However, in the patient group val^{158} homozygotes consistently had numerically (2-7%) better performance than met^{158} homozygotes with shorter latency, higher amplitude gain, lower spatial error and less variability of gain and spatial error (d= 0.1-0.2). There were also small numerical differences in the control group but they did not consistently follow the val^{158} allele dosage. Future studies will need much larger subject samples for determining whether *COMT* val^{158}met is associated with prosaccade task performance.

Frequency of visual fixation saccades was not associated with *COMT* val^{158}met genotype in the present study. The relationship of *COMT* val^{158}met genotype with visual fixation has been investigated in one previous study. Rybakowski et al (2002) found that male schizophrenia patients with met/met genotype had significantly less fixation disturbances than male patients with val/met or val/val. They did not directly measure saccade frequency during fixation but classified fixation disturbances into four categories using a 0-3 scale, ranging from no disturbances to high frequency of intrusive saccades. They then compared the genotype groups using non-parametric tests. This method is different from the one used in the present thesis where the number of saccades was counted and divided by the time of task duration to yield saccade frequency (N/s). Therefore it is difficult to compare the results of the two studies.

NRG-1 schizophrenia risk genotypes

In the present study two key *NRG-1* schizophrenia risk polymorphisms (SNP8NRG222662/rs4623364 and SNP8NRG243177/rs6994992) were not significantly associated with SPEM and antisaccade eye movement task performance

in schizophrenia patients and healthy controls. The participants were drawn from an Icelandic sample in which an association between *NRG-1* and risk for schizophrenia was previously demonstrated (Stefansson et al., 2002). SNP8NRG222662 is a good surrogate marker for the originally described core risk haplotype (r^2= 1) (Decode Genetics unpublished data) and SNP8NRG243177 is part of the original haplotype and has been associated with inter-individual differences in a variety of brain functions. The SNP8NRG243177 disease-linked T allele has been associated with increased expression of NRG-1 type IV isoform in the brain of both healthy and schizophrenia subjects (Law et al., 2006) and with decreased fronto-temporal brain activation and decreased IQ in individuals with high risk for schizophrenia (Hall et al., 2006). This risk allele has also correlated with decreased white matter density (McIntosh et al., 2008), reduced spatial working memory (Stefanis et al., 2007) and higher neuroticism (Krug et al., 2008) in healthy subjects, with increased unusual thoughts in schizophrenia patients (Keri et al., 2009) and with lowered expression of α7-nicotinic acetylcholine receptors in dorsolateral prefrontal cortex of schizophrenia patients and healthy controls (Mathew et al., 2007).

The subject sample in the present study was enriched for carriers of the SNP8NRG222662 G risk allele. While this enrichment reduces the representativeness of the sample, it was necessary in order to obtain power for investigating the association of *NRG-1* genotypes with eye movement performance.

The *NRG-1* genotypes were not associated with the patients' age of illness onset, duration of illness or with any PANSS symptom scores. Few previous studies have looked for associations between *NRG-1* and clinical measures and the findings are inconclusive. The SNP8NRG243177 T risk allele was associated with increased risk for developing psychotic symptoms in a group of young people with high genetic risk of schizophrenia (Hall et al., 2006). Another *NRG-1* SNP (rs392499) has been associated with positive psychotic symptoms in individuals with late onset Alzheimer's disease (Go et al. , 2005). One study found SNP8NRG221533, which has shown strong links with the original Icelandic risk haplotype (Stefansson et al., 2003), to be associated with non-deficit schizophrenia (Bakker et al., 2004) but an opposite finding was described in an Icelandic sample where the *NRG-1* core haplotype was associated with deficit schizophrenia (Einarsson et al., 2004).

Relationship of *NRG-1* risk genotypes with SPEM and antisaccade performance

There were no significant associations of *NRG-1* SNP8NRG222662 and SNP8NRG243177 genotypes with SPEM or antisaccade task performance in the present study and there were no significant Diagnosis-by-Genotype interactions. Therefore, the present findings do not suggest that *NRG-1* is associated with neural processes critically involved in SPEM and antisaccade tasks. Genes other than *NRG-1* may determine variance in SPEM and antisaccade performance in schizophrenia patients and healthy individuals.

Although no significant effects of *NRG-1* genotypes on eye movement task performance were observed, some small and fairly consistent differences in most SPEM and antisaccade measures were associated with both SNPs. Risk allele carriers for both SNPs had numerically lower SPEM velocity gain (0.5-7%) at all three target velocities and carriers of the SNP8NRG243177 risk T allele had higher saccade frequency (3-5%) at all target velocities. Both risk alleles were associated with numerically worse performance on all antisaccade measures (1-13%) except latency variability. Notably, the differences in spatial error variability for SNP8NRG222662 ($p= 0.068$; $d= 0.26$) and spatial error ($p= 0.09$; $d= 0.25$) and spatial error variability ($p= 0.05$; $d= 0.30$) for SNP8NRG243177 fell just short of being significant.

The consistency of these non-significant trends between the risk alleles and less spatial accuracy of antisaccades indicates that *NRG-1* risk allele carriers may have more difficulties in positioning their eyes accurately during the antisaccade task. There is evidence from functional imaging studies that posterior brain regions such as the posterior parietal cortex are involved in the sensory-motor transformation necessary for generating spatially accurate antisaccades (Medendorp et al., 2005, Moon et al., 2007). It is possible that *NRG-1* is associated with impaired activity in the dorsal (magnocellular) stream connecting the visual cortex with areas of the parietal and frontal cortex.

The present study was not powered to detect small genotype effects. Such effects would require larger samples, e.g. to bring the small differences in SPEM and antisaccade performance to statistical significance. It is possible that the *NRG-1* effects on brain function are so subtle that eye movement measures are not sensitive

enough to detect them. Previous studies have shown significant genotype effects on brain activity measured with functional brain imaging techniques but no significant effects were found on behavioral task performance (Ettinger et al., 2008, Hariri & Weinberger, 2003, Heinz & Smolka, 2006). In a recent fMRI study of healthy individuals, the *COMT* val^{158}met polymorphism was associated with frontal brain activation during an antisaccade task but no significant *COMT* effects were observed on antisaccade behavioral performance measures (Ettinger et al., 2008). The small *NRG-1* genotype effects on SPEM and antisaccade performance in the present study may therefore reflect variations in brain activity, which might possibly be detected at significant levels with functional imaging techniques such as fMRI.

Relationship of *NRG-1* risk genotypes with prosaccades and visual fixation

This is the first study examining the effects of *NRG-1* risk genotypes on prosaccade and visual fixation performance. There were no significant main effects of either *NRG-1* genotype on any prosaccade or visual fixation performance measures. However, the effects of SNP8NRG243177 on prosaccade spatial error variability fell short of being significant (p= 0.052). The T risk allele carriers came close to having greater spatial error variability than non-T allele carriers (d= 0.4). Furthermore, in the patient group both carriers of the SNP8NRG222662 risk G allele and the SNP8NRG243177 risk T allele had numerically (1-16%) worse performance on all prosaccade measures (d= 0.1-0.3). The present study is not powered for detecting small differences and future studies will need larger samples for determining whether putative *NRG-1* risk genotypes are associated with prosaccade performance.

Copy number variations and eye movements

As described in the introduction CNVs, which are deletions and duplications of DNA fragments, are quite common and widespread within the human genome. These CNV segments vary in size and are either inherited from parent to offspring or caused by *de novo* mutations. Most small *de novo* segmental deletions are probably not related to pathological phenotypes (Lupski, 2007). However, recent association studies have found that some CNVs may contribute to the risk for several neuropsychiatric and neurodevelopmental disorders (Cook & Scherer, 2008, Guilmatre et al., 2009). Two

recent large multicenter studies showed that *de novo* microdeletions on chromosomes *1q21.1* and *15q13.3* are associated with a significantly increased risk for schizophrenia (International schizophrenia consortium, 2008, Stefansson et al., 2008). Deletions and duplications at these loci have also been associated with mental retardation, autism, microcephaly and other developmental and behavioural abnormalities (Ben-Shachar et al., 2009, Brunetti-Pierri et al., 2008). The patients in the present study were all participants in the CNV study by Stefansson et al (2008). Therefore the present patient sample was screened for CNVs on *1q21.1* and *15q13.3.* Three out of 118 patients had CNVs at these two loci. Two had deletion on chromosome *15q13.3* and one had duplication on chromosome *1q21.1.* Genetic markers in these two loci have not been investigated in relation to eye movement task performance.

Antisaccade and SPEM performance in the patients with CNVs was mostly similar to the mean performance of the patient group. Each of them had antisaccade or SPEM measures that deviated 1-2 SDs from the mean of all patients but these deviations were not persistently worse or better than the mean performance (see Table 33 and Figures 15 and 16). No conclusions can be drawn from these findings due to the small number of subjects with CNVs. Larger subject samples are needed to investigate whether and how CNVs may affect SPEM and antisaccade eye movements.

Outcome regarding hypotheses and research questions under investigation

1. *Hypothesis: Schizophrenia patients will perform worse than healthy subjects on the SPEM and antisaccade tasks.*
   Hypothesis is supported.

   Research question: *Will schizophrenia patients show similar prosaccade and visual fixation task performance as healthy controls?*
   Schizophrenia patients had worse prosaccade and visual fixation performance than controls.

Research question: *What is the internal consistency and within-session performance variability on antisaccade, prosaccade, SPEM and visual fixation tasks in patients and controls?*

Internal consistency was high on all measures except antisaccade spatial error and within-session performance changes were similar in patients and controls.

2. *Research question*: *Will increasing target velocity affect SPEM performance differently in patients vs. controls?*

   Increasing target velocity was associated with lower SPEM velocity gain and higher saccade frequency and for velocity gain the effect was significantly stronger in patients than controls

3. *Hypothesis: Low to moderate correlations between SPEM and antisaccade task performance are expected.*

   Present data support this hypothesis.

4. *Research question*: *How is eye movement task performance associated with schizophrenia symptoms, nicotine use and type of antipsychotic medication?*

   Only antisaccade correction rate correlated with higher PANSS total and negative scores. Only antisaccade correction rate, SPEM velocity gain at 24º/s and 36º/s and frequency of fixation saccades were associated with duration of illness.

5. *Hypothesis*: *SPEM and antisaccade performance will be associated with COMT val^{158}met genotype. A higher number of val^{158} alleles will be associated with worse performance.*

   Hypothesis is not supported by present data. SPEM performance was not associated with *COMT* val^{158}met. A higher number of val^{158}

alleles was associated with better antisaccade performance irrespective of the diagnosis of schizophrenia.

7. *Hypothesis*: *Carriers of the NRG-1 SNP8NRG222662 and SNP8NRG243177 at risk genotypes will perform worse on the SPEM and antisaccade tasks than non-carriers.*
   Hypothesis is not supported. However, a small genotype effect can not be ruled out. Larger subject samples are needed to answer this more definitely.

8. *Research question: How will patients with CNVs on chromosomes 1q21.1 and 15q13.3 perform on SPEM and antisaccade tasks compared to other patients?*
   Patients with *1q21.1* and *15q13.3* CNVs had similar SPEM and antisaccade performance as patients who did not have these CNVs.

Limitations and strengths

Limitations

While the sample size of the present thesis is large for a study on eye movement abnormalities, it is rather small for a genetic study (118 patients and 109 controls). Schizophrenia is probably a complex polygenic disorder with each gene making a relatively small contribution to the overall risk. Therefore, it is likely that very large subject samples will be needed to study genotype-phenotype associations. Related to this, the present work can also be criticized for not employing power analyses, prior to subject recruitment, in order to estimate the number of participants in each group needed for obtaining statistically significant differences in eye movement performance. Power analyses would have required one to set hypothetical minimum performance differences between genotype groups. The smaller a hypothesized difference is the more subjects are needed. However, this difference would have been completely speculative since little was known at the time of planning of this study

about how genes contribute to variance in SPEM and antisaccade eye movement task performance both in healthy individuals and patients with schizophrenia.

A general problem in studying the molecular genetic basis of eye movements is the possibility that genotype-phenotype relationships may be affected by factors such as interactions between the gene and some environmental factors (Caspi et al., 2005), epistatic interactions between the gene and some other gene/genes (Meyer-Lindenberg & Weinberger, 2006), interactions with undetected CNVs (Stefansson et al., 2008) or effects of epigenetic phenomena such as DNA methylation (Tsankova et al., 2007).

It is a limitation that the present study did not correct for effects of multiple testing. The association of *COMT* val^{158} with shorter and less variable antisaccade latency and the trends for associations of *COMT* val^{158} with fewer reflexive errors and *NRG-1* with higher spatial accuracy would not have been observed if stringent corrections for multiple testing had been applied. However, since very little is known about the association of *COMT* val^{158}met with SPEM and the relationships of *COMT* val^{158}met with antisaccades and *NRG-1* with SPEM and antisaccades have not been previously investigated, an exploratory genotype-phenotype association approach is justified. Such pioneering studies, although underpowered, may provide indications and raise research questions that can then be investigated further in larger studies using more stringent statistics.

Another limitation is that most of the patients were taking antipsychotic medications, some of which have been shown to affect SPEM and antisaccade task performance (Reilly et al., 2008b). It is possible that medication effects interact with genotype effects and studying medication naïve patients would have provided different results. However, no difference was found between the major classes of antipsychotic medications (typical, atypical) in the present patient sample. Studying the effects of medications is problematic because it is difficult to recruit large numbers of medication naïve patients and such patients are often too ill for participating in eye movement studies.

Finally, participants were not assessed for symptoms of anxiety, which would have been interesting given previous findings of *COMT* met^{158} being associated with

anxiety (Woo et al., 2004) and that anxiety has been associated with impaired antisaccade task performance (Smyrnis et al., 2003, Tien et al., 1992).

Strengths

An advantage of this study is that the subject sample was drawn from the relatively homogenous population of Iceland (Helgason et al., 2005). Population structure can influence association studies of how genetic variants may underlie human diseases. If allele frequencies differ markedly within subpopulations of participants, false associations of alleles with phenotypes may be observed or true associations may be missed. By examining subjects who share the same ethnic background the possibility of such stratification problems is reduced.

The same research group recruited all patients in the same psychiatric department. This reduced the likelihood of bias due to different recruitment methods. Because this psychiatric department treats over 90% of all schizophrenia patients in the country, the patient sample in this study is likely to represent the general schizophrenia patient population in Iceland.

All eye movements were measured and analysed by the same investigator (Magnus Haraldsson) and a subgroup of 15 participants were also tested and analysed by an experienced eye movement specialist (Ulrich Ettinger). The inter-rater reliability between the two investigators was very high for all eye movement performance measures (r= 0.95-0.99). Furthermore, the finding of high internal consistency of almost all eye movement measures and similar intra-session performance variability in patients and controls confirms that inter-individual performance differences are consistent throughout the test sessions and that these differences can be reliably measured.

An advantage for the examination of the relationship between *NRG-1* and eye movement task performance is the fact that all participants in this study participated in a previous study, in which the association between the original 5 SNP *NRG-1* haplotype and schizophrenia was first discovered (Stefansson et al., 2002). A series of other studies have demonstrated association between *NRG-1* and schizophrenia

but the disease associated SNPs often differ between populations and they may have different functions.

Conclusions

The present research confirms the presence of impaired SPEM and antisaccade eye movement deficits in patients with schizophrenia drawn from the homogenous population of Iceland. The finding of increasing difference in SPEM velocity gain between patients and controls with increasing target velocity supports previous reports of motion processing deficits in schizophrenia patients. High internal consistency and similar intra-session performance variability in patients and controls suggest that the eye movement measures are reliable. Several clinical measures such as PANSS scores, age of illness onset, duration of illness and type of antipsychotic medication were generally not associated with eye movement task performance. It is therefore concluded that the present study supports the validity of SPEM and antisaccade tasks as endophenotypes, that can be useful in the ongoing study of how recently identified putative risk genes contribute to the complex syndrome we call schizophrenia. Also, the steadily increasing knowledge of the neurophysiological substrates involved in SPEM and antisaccade deficits from functional imaging studies may provide us with important tools for understanding, which neurological processes are, affected in schizophrenia.

The findings of visual fixation and prosaccade performance deficits in schizophrenia patients compared to controls cast doubt on the common notion of unimpaired performance on these tasks in schizophrenia. The observation of only moderate relationships between SPEM and antisaccade performance indicates that deficits on the two tasks most likely reflect separate sources of genetic risk.

Similar to most previous studies the present study does not suggest that *COMT* val^{158}met allele frequencies differ between patients and controls and no associations were found between *COMT* val^{158}met and symptoms of schizophrenia.

COMT val^{158}met did not affect SPEM steady-state gain or saccade frequency. While a greater number of val^{158} alleles was significantly associated with better performance on the antisaccade task, there were no diagnosis-by-genotype

interactions. This indicates that the efficiency of dopamine degradation in the frontal cortex affects performance on the antisaccade task irrespective of the diagnosis of schizophrenia. These findings also support that SPEM and antisaccade eye movements are based on separate neurophysiological processes.

This first study of *NRG-1* and eye movements in schizophrenia did not show significant genotype effects on SPEM and antisaccade performance and the two *NRG-1* risk genotypes were not associated with clinical measures of schizophrenia. However, *NRG-1* risk allele carriers had numerically worse performance on most eye movement performance measures, especially on measures of antisaccade spatial accuracy. Therefore, while a large genotype effect can be excluded, insufficient power to examine the weak effects must be kept in mind. It remains possible that *NRG-1* modulates oculomotor endophenotypes to a minor degree.

Future directions

The primary aim of the present thesis was to investigate the relationship of the putative schizophrenia risk genes *COMT* val^{158}met and *NRG-1* with SPEM and antisaccade task performance in schizophrenia patients and healthy controls. *COMT* val^{158} was associated with better antisaccade performance in both patients and controls. No other significant genotype effects were observed but there were some consistent numerical differences and trends for both genes. The present study may lack power to detect small *COMT* val^{158}met and *NRG-1* effects on SPEM and antisaccade eye movements. The finding of *COMT* effects on antisaccade task performance needs to be replicated and the possible association of *NRG-1* with impaired spatial accuracy of antisaccades will have to be studied further in future studies, preferably including larger but equally homogenous subject samples. These studies should also include neurophysiological measures, such as regional brain activity measured with functional brain imaging techniques, because they may reflect gene action more directly than behavioral measures.

Future studies of the effects of putative schizophrenia susceptibility genes on eye movements should also include participants from schizophrenia spectrum populations such as first-degree relatives of schizophrenia patients. Relatives are

likely to share risk genes with their patient relatives but are unaffected by possible confounding effects of medications, co-morbidity and disease chronicity.

It is possible that *NRG-1* SNPs other than the ones examined in the present study are associated with eye movement deficits in schizophrenia. Studies have shown that *NRG-1* risk SNPs and haplotypes differ widely between populations (Munafo et al., 2006). Future studies should examine the association of other *NRG-1* SNPs and haplotypes with eye movement performance.

Another relevant area of further study is the association of eye movement deficits and other endophenotypes with recently discovered CNVs (Stefansson et al., 2008, Xu et al., 2008) and significant risk SNPs implicated in recent GWAS of schizophrenia (Stefansson et al., 2009).

As described in the introduction the neurological basis and cognitive control of SPEM and antisaccade eye movements is highly complex. Deficits on these tasks are accordingly not simple to delineate. It is important to continue research on the neurocognitive processes involved in SPEM and antisaccade eye movements in order to set a proper basis for investigating how these processes are impaired in schizophrenia. Future functional imaging studies including large enough and homogenous subject samples may provide more information on how eye movement task performance is associated with activation of specific neural processes. It may also be helpful to try to refine the eye movement endophenotypes by modifying the tasks to more specific neurological or cognitive components. One example of this might be the use of predictive pursuit tasks to study extra-retinal motion processing. There are indications that schizophrenia patients and their relatives have impaired extraretinal motion processing and depend more on retinal motion information for performing smooth pursuit (Hong et al., 2005).

By identifying homogenous subgroups of patients with similar functional deficits, endophenotypes may become useful in future GWAS searching for genes that are associated with schizophrenia.

Recent advances in genetic research and the discovery of several promising candidate risk genes has set the pace for steadily increasing knowledge of the causes and pathophysiology of schizophrenia. Detecting endophenotypes that signal specific neurophysiological deficits may provide remarkable opportunities for developing

novel treatments for schizophrenia. Identification of endophenotypes offers the possibility of developing animal models applicable to studies of human psychopathology and search for new treatments. Endophenotypes, such as eye movement deficits, may represent distinct brain defects associated with specific genetic markers that could provide targets for drug treatment development (Thaker, 2007). Hopefully, such research will soon lead to discovery of more effective treatments for this chronic and debilitating disorder.

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