

# **Neurocognition, Cognitive Remediation and Functional Outcome in Schizophrenia Spectrum Disorders**

Doctoral Thesis

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## List of papers

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- III. Lystad, J.U., Falkum, E., Haaland, V.Ø., Bull, H.C., Evensen, S., McGurks, S.R. and Ueland, T. (2016). Cognitive Remediation and Occupational Outcome in Schizophrenia Spectrum Disorders: A 2 year follow-up study. (*Submitted*).





## Summary

Employment rates in schizophrenia are consistently low. Considerable research has identified both societal/external barriers and internal, illness related barriers to employment. Neurocognitive impairments are a hallmark of schizophrenia spectrum disorders, contributing to impaired real-world functioning in general and significant occupational disability in particular. The consequences of these deficits are profound and largely consistent over time. The main aim of the current thesis was to further investigate neurocognition in participants with broad schizophrenia spectrum disorders as measured with the MATRICS Consensus Cognitive Battery (MCCB). Findings from Paper I revealed significant impairments on all neurocognitive domains, supporting findings from similar studies. Neurocognitive performance differentiated between academic levels and previous work history and overlapped with social functioning.

Further we sought to investigate whether neurocognitive test performance was associated with different aspects of occupational outcome; i.e. workplace assessments. Paper II found significant associations between all MCCB domains except Verbal Learning and vocational cognitive functioning at the beginning of vocational rehabilitation. Processing Speed and Attention predicted work behavior and neurocognitive performance was also associated with task complexity and type of work. Participants performing low complexity jobs performed worse on all neurocognitive domains with a similar pattern emerging for participants in sheltered work, performing poorer on all neurocognitive tests than participants in competitive work.

In Paper III, we examined the effects of the Job Management Program (JUMP); i.e. cognitive remediation (CR) in combination with vocational rehabilitation on neurocognition and occupational outcomes compared to cognitive behavioral therapy techniques (CBT) augmented vocational rehabilitation (VR). We found neurocognition to improve after both CBT- and CR-augmented vocational rehabilitation, with the greatest improvement in the CR group. There was also an increase in number of participants working and the amount of time they were working throughout the project period. The positive change in Working Memory and the Neurocognitive Composite Score predicted number of hours worked in the CR group.

These findings indicate neurocognitive dysfunctions in participants with schizophrenia spectrum disorders and that these dysfunctions are relevant for occupational functioning. Particularly, Processing Speed and Attention predicted different aspects of work behavior. This ties in with findings from similar studies, showing Processing Speed to be one of the strongest corre-

lates to functional outcome and Attention to be of particular relevance at the beginning of vocational rehabilitation. Our findings further indicate that implementing a combination of vocational rehabilitation, cognitive behavioral techniques or cognitive remediation may help participants attain and maintain work. Employment numbers increased significantly throughout the intervention period and remained high at follow-up. Positive neurocognitive change between baseline and post treatment in the Working Memory domain and the Neurocognitive Composite Score predicted number of hours worked 2 years after inclusion in the study.

Our findings underline the need for future studies that investigate which subgroups profit more (or less) from cognitive remediation and vocational rehabilitation. Stratifying on degree of impairment may thus shed further light on this matter. Also, assessing learning potential and motivation as possible mediators between neurocognition and real-world functioning may be of importance. Lastly, additive effects of strategy learning, both in general and task specific should be addressed as it may enhance gains on neurocognitive performance and in turn, functional outcome.

## Abbreviations

ANOVA	Analysis of Variance
BVMT-R	Brief Visuospatial Memory Test-Revised
BACS	Brief Assessment of Cognition in Schizophrenia: Symbol Coding
CBT	Cognitive Behavioral Therapy
CPT-IP	Continuous Performance Test, Identical Pairs version
CR	Cognitive Remediation
DDD	Defined Daily Dosage
DSM-IV	Diagnostic and Statistical manual of Mental Disorders – IV
FEP	First-episode Psychosis
Fluency	Category Fluency: Animal Naming
HC	Healthy Controls
HVLT-R	Hopkins Verbal Learning Test-Revised
IQ	Intelligence Quotient
JUMP	Job Management Program
LMM	Linear Mixed Models
LNS	Letter-Number Span
MANOVA	Multivariate Analysis of Variance
MCCB	Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery
MSCEIT	Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions
NAB Mazes	Neuropsychological Assessment Battery: Mazes
NIMH	National Institute of Mental Health
SCI-PANSS	Structured Clinical Interview for the Positive and Negative Syndrome Scale
SFS	Social Functioning Scale
SPSS	Statistical Package for the Social Science
SZ	Schizophrenia
TMT A	Trail Making Test, part A
VR	Vocational Rehabilitation
WASI	Wechsler Abbreviated Scale of Intelligence
WM	Working Memory
WMS-III	Wechsler Memory Scale-Third Edition: Spatial Span



# 1. Introduction

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

*“Because” – “the ideas I had about supernatural beings came to me the same way that my mathematical ideas did. So I took them seriously.”*

Professor George Mackey, Harvard University & John Forbes Nash

John Forbes Nash, an American mathematician and Nobel laureate in Economic Sciences, was diagnosed with schizophrenia at the age of 31. After the onset of schizophrenia symptoms, Nash was impaired in several aspects of his life. He had problems in interpersonal relations, lost his job, experienced a lack of academic progress (except for during brief remissions) and had difficulty both attaining and maintaining work positions (Nasar, 1998).

In addition to psychotic symptoms such as delusions and hallucinations, Nash experienced considerable neurocognitive impairments, particularly in the domains of memory, processing speed and problem solving (Nasar, 1998).

High neurocognitive ability is what distinguishes humans from other primates. Human activities, such as planning for the future, learning and holding a large amount of complex information and social interaction are all examples of high neurocognitive performance. If some of these functions are lost or even impaired, other activities will be disrupted as a consequence.

Neurocognitive impairment is a cardinal symptom in schizophrenia spectrum disorders<sup>1</sup> and has been reported ever since the syndrome was first described by Kraepelin and Bleuler. Kraepelin showed that individuals with schizophrenia often displayed functional impairments, involving attention, motivation and problemsolving and Bleuler described neurocognitive impairment as a central element in the clinical picture of the disease that could give rise to the splitting and disruption of personal identity. Since then, considerable research has documented neurocognitive dysfunction in individuals with schizophrenia (Green, 1996; Green et al., 2000; Heinrichs and Zakzanis, 1998; Szoke et al., 2008).

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<sup>1</sup> Psychotic disorders are intertwined with the concept of schizophrenia in the literature. The terms psychosis, schizophrenia and (broad) schizophrenia spectrum disorders are used somewhat interchangeably when referring to other research

Neurocognitive dysfunction is broad-based and seriously affects different areas of real-world functioning. Neurocognitive deficits contribute substantially to low occupational attainment and poor occupational outcomes (Christensen, 2007; Kukla et al., 2012; Lystad et al., 2015; Strassnig et al., 2015; Vargas et al., 2014). Impaired neurocognition is also a potent predictor of poor engagement in vocational rehabilitation programs (O'Connor et al., 2011).

Despite evidence that people with schizophrenia could benefit from employment and repeatedly express the need and wish for occupational training (Bevan, 2013), extensive research has shown that employment rates are consistently low, estimates ranging from only 10 % to 25 % (Bond, 2004; Evensen et al., 2015; Marwaha and Johnson, 2004; Tandberg et al., 2011). Employment, particularly competitive employment, is a fundamental goal for persons afflicted and a key treatment outcome. Work is positively related to self-esteem, recovery and symptom remission as well as increased income, improved quality of life and lower relapse rates (Bond et al., 2001; Bryson et al., 2002; Bush et al., 2009; Lieberman et al., 2008; McGurk and Mueser, 2004). Heightened self-confidence, self-sufficiency and improved stress management are further benefits associated with employment (Schennach et al., 2012).

The personal, societal and economic costs associated with unemployment in schizophrenia are comprehensive (Evensen et al., 2015). Determinants of occupational status and occupational functioning are multifaceted and employment is determined by a number of both internal and external factors. An important research focus has thus been to investigate predictors of occupational functioning and to develop vocational rehabilitation programs facilitating the transition to employment for this group. In the current thesis, the main focus is on neurocognitive predictors of occupational outcomes and how a cognitive intervention can be implemented in a broader context; to enhance occupational functioning by targeting neurocognitive impairments.

The strong relationship between neurocognition and functional outcome underlines the importance of targeting neurocognitive dysfunctions through psychosocial interventions such as cognitive remediation (CR) as a means to improve occupational functioning, social inclusion and economic outcomes. Cognitive remediation is a behavioral training-based intervention aiming to improve neurocognitive processes with the goal of durability and generalization (Harvey and Bowie, 2012; Wykes and Spaulding, 2011). Recent meta-analyses show small to moderate effects of CR on global neurocognition and beneficial effects on symptoms and psychosocial functioning (McGurk et al., 2007; Wykes et al., 2011). CR has proven to be more effective

when integrated with rehabilitation. More specifically, CR seems to maximize benefits of vocational rehabilitation, allowing participants to apply their enhanced neurocognitive skills in real-world (occupational) settings (McGurk et al., 2007).

In addition to neurocognitive deficits, individuals with schizophrenia spectrum disorders also face challenges such as psychotic symptoms, comorbid mood- or anxiety disorders and social impairments (Buckley et al., 2009; Milev et al., 2005; Morrison, 2009) affecting quality of life and outcome. These core symptoms can be targeted with Cognitive Behavioral Therapy (CBT). There is strong support for a range of CBT programs in improving symptoms, social relations and occupational outcome (Nordentoft and Austin, 2014; Rector and Beck, 2001; Tarrier and Wykes, 2004). More recently, CBT programs designed to enhance occupational functioning have been developed (Kukla et al., 2014; Lecomte et al., 2014). Although evidence is still scant regarding CBT programs adjunct to vocational rehabilitation, results are promising (Davis et al., 2008; Lecomte et al., 2014; Lysaker et al., 2009).

The main aim of this thesis was to further explore neurocognition as measured with the MATRICS Consensus Cognitive Battery (MCCB) in individuals with schizophrenia spectrum disorders and how it is related to different aspects of functional outcome, in particular occupational functioning. The thesis further sought to examine the short- and long-term effects of CR compared to CBT augmented vocational rehabilitation in participants with broad schizophrenia spectrum disorders on neurocognition and occupational functioning.

## **1.1 Psychotic disorders in an historical perspective**

There is no single symptom picture that fully describes or is unique to psychosis. This fact complicates the definition of the disorder and has consequently led to numerous different classifications throughout history. The contemporary definition of psychosis involves the presence of symptoms indicating a loss of contact with reality. Characteristic symptoms are hallucinations and delusions (APA, 1994) and may also include disorganized speech and behavior (APA, 1994).

Psychosis was initially referred to as *dementia praecox* (premature dementia), a term coined by Kraepelin in 1893 (Hoenig, 1983). This previous name reflects that Kraepelin regarded neurocognitive decline as central to the disorder (Frangou and Murray, 2000) in addition to positive and negative symptoms. Kraepelin's views were manifested in his famous work *Psychiatrie*

(Kraepelin, 1908-1913), which has become a widely read and highly influential textbook in the field of psychiatry.

Critics of Kraepelin's description of dementia praecox argued that the so called "psyche" was missing from the clinical picture, i.e. premorbid functioning, life history and the persons own understanding of the illness (Hoenig, 1983). Bleuler was one of the first scholars of psychosis to try to reclaim "the psyche" in the definition of dementia praecox. He also challenged the idea of a deteriorating course of illness, arguing that no conclusive evidence was present to support a global dementing process, i.e. to justify the term dementia praecox. Bleuler distinguished between primary and secondary symptoms. *Primary or fundamental psychic* symptoms were unknown and could be an anatomical cerebral disease or an infection, whereas *secondary or accessory symptoms*, symptoms of dementia praecox (delusions, thought inhibition etc.), were brought about as a reaction by certain psychic mechanisms. The distinction between different *psychic symptoms* led Bleuler to rename the disorder from dementia praecox to schizophrenia, showing that this split of several psychic functions was an important characteristic of the illness; "Ich nenne die Dementia praecox Schizophrenie, weil, wie ich zu zeigen hoffe, die Spaltung der verschiedensten psychischen Funktionen eine ihren wichtigsten Eigenschaften ist" ((Bleuler, 1911), page 5.) Bleulers attempt to describe the splitting of psychic functions has had considerable influence on the contemporary classification of psychotic disorders.

German psychiatrist Kurt Schneider has also exerted strong influence on the psychosis field (Beer, 1995). Initially concerned with the kraepelinian "somatic psychiatry" (Hoenig, 1983), Schneider further elaborated the primary and accessory/secondary psychic symptoms as described by Bleuler. He introduced the terms 1<sup>st</sup> and 2<sup>nd</sup> rank symptoms as a step towards creating an enduring set of empirical diagnostic criteria (Beer, 1995). With the introduction of antipsychotic medication and continuous research on etiology, course of illness and real-world outcome of psychosis, the view and definition of the illness has greatly evolved. Clinical psychiatric history thus illuminates that previous controversies outlined in this brief overview are still not settled and that defining psychosis and schizophrenia continues to be a work in progress. The contemporary classification of the disorder is the result of not one definition but rather the patchwork of clinical features plucked from several different definitions and traditions.



The concepts of psychotic disorder and schizophrenia are interwoven. In this thesis, the DSM-IV diagnostic groups included are Schizophrenia, Schizoaffective Disorder, Delusional Disorder and Psychotic Disorder Not Otherwise Specified (APA, 1994). These diagnostic categories are referred to as broad schizophrenia spectrum disorders.

## **1.2 Schizophrenia Spectrum Disorders; a clinical description**

Schizophrenia is a type of psychosis and among the most severe psychiatric disorders with symptoms including distorted conceptions of reality, hallucinations, delusions, and flat or blunted emotions (Frangou and Murray, 2000). Prevalence rates vary between reports, but current estimates indicate that approximately 1% of the population over the age of 18 (Jablensky, 2000) suffers from the disorder.

Schizophrenia is a heterogeneous disorder in terms of symptomatology, neurocognitive functioning and functional outcome. This heterogeneity is clinically manifested in many ways, with afflicted individuals varying in symptom severity, number of episodes, comorbidity and treatment response. The course of the illness is often chronic and high relapse rates have been widely documented (Robinson et al., 1999). The disorder is also regularly associated with neurocognitive impairment (Green et al., 2000).

Despite the fact that the proportion of the population suffering from schizophrenia is very low, the disease has a high impact on the individuals affected, their families and on society.

There are two main classifications of symptoms in schizophrenia: positive and negative (Frangou and Murray, 2000). Positive symptoms include hallucinations (auditory, visual and/or sensory), delusions, and disorganization such as inappropriate affect, thought disturbances and impaired reality testing (Kay et al., 1987; Salokangas, 1997; Tamminga et al., 1998). They are often conceptualized as “reality distortions” (Kay et al., 1987; Klingberg et al., 2006). Positive symptoms are the most frequently reported features of schizophrenia (Lecrubier et al., 2007), yet they are not strongly associated with prognosis or functional outcome (Velligan et al., 1997). Positive symptom load tends to diminish over time and this symptom category responds reasonably well to antipsychotic treatment (Lecrubier et al., 2007).

Negative symptoms are defined as the absence of behaviors normally shown (Zubin, 1985). These deficits influence neurocognitive, affective and social functions and include social withdrawal (Kay et al., 1987), apathy, avolition and fatigue (Lecrubier et al., 2007). Negative symptoms are often associated with poor prognosis and poor functional outcome such as limited

social contacts and poor occupational functioning and tend to have an earlier onset than positive symptoms (Tamminga et al., 1998). Negative symptoms do not respond well to pharmacological treatment, and may increase over time (Lecrubier et al., 2007; Mancevski et al., 2007; Tamminga et al., 1998; Zubin, 1985). Consequently, they are identified as particularly important in terms of the ability to attain and maintain employment.

The most frequently accepted etiological theory in schizophrenia is the stress-diathesis model (Walker and Tessner, 2008; Walker and Diforio, 1997). A diathesis is a hereditary predisposition to an illness, stress thus refers to the level of stress experienced by an individual, eliciting pathology i.e., schizophrenia.

Schizophrenia has a high heritable component, with genetic factors accountable for approximately 80 % of the probability to develop the disorder (Crow, 2007; Seidman et al., 2006; Sullivan et al., 2003). Although the illness only occurs in about 1 percent of the general population, it occurs in 10 percent of people who have a first-degree relative with the disorder. Further, individuals who have second-degree relatives with the disease also develop schizophrenia more often than the general population (NIMH, 2016). Further, the genetic transmission appears to be of a polygenetic nature, there is no one schizophrenia gene (Walker and Tessner, 2008).

Several environmental factors are also associated with an increased risk of developing schizophrenia, such as infections and malnutrition during pregnancy (Murray and Lewis, 1987; Penner and Brown, 2007; Weinberger, 1987), birth complications (Cannon et al., 2002), advanced paternal age (Messias et al., 2007; Sipos et al., 2004), autoimmune diseases (DeLisi et al., 1991; Eaton et al., 2004; Messias et al., 2007), illicit drug use/cannabis use (Arendt et al., 2005; Hall and Degenhardt, 2000), ethnicity (Leao et al., 2006), psychosocial stress (Jablensky, 2000) and urban residence (van Os et al., 2005) to name a few. Determinants of both occurrence and expression of schizophrenia are multifaceted and it still remains unclear how environmental and genetic factors interact. Thus efforts are made to study risk factors *in combination* (van Os and Kapur, 2009).

Evidence suggests great variation in the prognosis of schizophrenia. The disorder can develop into a severe form or into varying degrees of recovery (Tandon et al., 2009).

Many individuals with schizophrenia have several relapses resulting in multiple hospital stays, making it a leading cause of disability worldwide. In developed countries, the direct costs of

schizophrenia range from 1.3 per cent and 2.5 per cent of the total health expenditure and represent the highest proportion of total costs for mental illnesses (Andrew et al., 2012).

Although often chronic, schizophrenia today is a manageable condition. Advances in treatment and support, including antipsychotic medication, psychosocial therapy, and rehabilitation, now enable many people with schizophrenia to recover and live productive and fulfilling lives (Bevan, 2013). Still, schizophrenia is associated with numerous negative outcomes, such as reduced quality of life (Eack and Newhill, 2007), higher mortality rates due to heightened suicidal risk (Pompili et al., 2007), cardiovascular disease (Ringen et al., 2014) and consistently low employment rates (Evensen et al., 2015; Marwaha and Johnson, 2004; Vargas et al., 2014).

### **1.3 Schizophrenia Spectrum Disorders; a diagnostic description**

DSM-IV (APA, 1994) subcategorizes “Schizophrenia and Other Psychotic Disorders” into subgroups based on varying criteria, however, with psychotic symptoms as the common denominator.

#### **1.3.1 Schizophrenia**

Schizophrenia is characterized by at least one month of active phase symptoms, including two or more of the following; delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior and/or negative symptoms (criterion A). These symptoms are associated with markedly reduced social or occupational functioning for a significant proportion of the time since illness onset (criterion B), and there are continuous signs of the disturbance for at least six months (criterion C). Symptoms must not be a result of an underlying medical condition or substance use disorder or better explained by a pervasive developmental disorder (APA, 1994)

#### **1.3.2 Schizoaffective Disorder**

Schizoaffective disorder is characterized by the same symptom criterion as Schizophrenia (criterion A) in addition to the presence of affective symptoms for a significant period of the total illness duration. During the same period of illness, there have to be delusions or hallucinations for at least 2 weeks without prominent affective symptoms.

### **1.3.3 Delusional Disorder**

Delusional Disorder is defined by the presence of one or more non-bizarre delusions (situations that may actually occur in real life) that continue for at least 1 month. Other active phase symptoms of schizophrenia (criterion A) have never been met. Function is not markedly impaired.

### **1.3.4 Psychotic Disorder Not Otherwise Specified (Psychosis NOS)**

Psychosis NOS is a diagnostic category that also includes non-organic psychotic syndromes that do not meet the criteria for any of the Psychotic Disorders, or psychotic presentations where there are inadequate or contradictory information, precluding conclusive diagnostic evaluation.

## **1.4 Neurocognition and neurocognitive functioning**

As previously outlined, both the etiological understanding and treatment approaches have undergone developments with changing conceptual and descriptive foci throughout history. However, one aspect has remained relatively constant; even recognized by some of the earliest scholars in the field and although not a formal part of current diagnostic criteria, schizophrenia has been and still is associated with severe neurocognitive impairment.

### **1.4.1 Terminology**

*Cognition* originally stems from the Latin word *cognoscere*, which means to conceptualize or recognize, i.e. to think (Cariani, 2012). Today, the term cognition is somewhat loosely applied to describe a faculty for the processing of information and applying of knowledge in humans. The concept of cognition is thereby closely linked to concepts as mental functions, mental processes, reasoning, perception, intelligence, learning, decision making, planning, and many others that describe the numerous capabilities of the human mind. There are the obvious applications of conscious reasoning— for example playing chess or deconstructing Hamlet—but thinking also takes many subtler forms, such as interpreting sensory input, planning motor behavior, or empathizing with others. All cognition is a product of the brain and the result of neurological activity (Lezak, 2012). The neural basis of cognition can thereby be considered at two levels of description; the neuronal level (one or a small number of separate neurons) or the neural systems level (a large number of neurons serving a similar function or localized together (localization or function); for example the cerebral cortex).

*Neuropsychological function* is a concept covering a wide range of cognitive functions or cognitive domains such as general cognitive ability, attention, processing speed, learning and memory and executive functioning.

*Cognitive neuropsychology* is the discipline aiming to understand how the structure and function of the brain relate to specific psychological processes as well as to detecting and understanding cognitive deficits using (among others) neuropsychological tests. It is the study of the neurological basis of cognitive processing (as revealed by measures of normal brain functioning and disrupted performance due to brain injury or illness).

*Neurocognition* is a relatively new term describing the relationship between neuroscience and cognitive psychology. Neurocognitive functions are thus cognitive functions connected to the function of particular brain areas, cortical networks and neural pathways, especially those dealing with memory, sensation and perception, problem solving, language processing and motor functions. Traditionally, these functions have been referred to as neuropsychological or cognitive. In the present thesis, these three terms will be used interchangeably.

*Neurocognitive impairment*, *neurocognitive deficits* and *neurocognitive dysfunction* refer to reductions in neurocognitive functioning (one or several domains). These terms are also used synonymously in the present thesis.

*Clinically significant neurocognitive impairment.* Numerous studies have reported neurocognitive deficits in schizophrenia (August et al., 2012; Holmen et al., 2010; Lystad et al., 2014; Meier et al., 2014), mostly based on comparisons between patients and healthy controls on neuropsychological test performance. Results indicate that individuals with schizophrenia have poorer neurocognitive function than healthy controls on a group level, however, they reveal little information concerning the magnitude or actual consequences of these impairments on the individual level. Neurocognitive impairment can thus be defined in more ways than one. For instance, an ipsative approach to neuropsychological assessment may reveal differences between individual test scores, i.e. a decrease from premorbid level of functioning. Neurocognitive impairment may however also refer to the degree of deficit expected to influence different aspects of functioning, i.e. *clinically significant impairment*. Clinically significant neurocognitive impairment is not a fixed dimension but generally varies between 1, 1.5 and 2 standard deviations below the mean of a healthy control group on one measure or in at least one or more

neurocognitive domains (Simonsen et al., 2010). Consequently, the number of individuals suffering from neurocognitive impairments may vary greatly between reports, both with regard to individuals with schizophrenia as well as to healthy control participants.

#### **1.4.2 Neurocognitive functioning in schizophrenia**

Neurocognitive dysfunction is prominent in schizophrenia and extensively documented in the literature (Dickinson et al., 2004; Green et al., 2000; Reichenberg et al., 2009). Neurocognitive impairment represents a core feature of the illness, not directly correlated with positive or negative symptoms (Gold, 2004; Lewis, 2004), only moderately associated with duration of untreated psychosis (DUP) (Oie and Rund, 1999) and often present in adolescence prior to the onset of illness (Lewis, 2004; Tamminga et al., 1998). Unlike psychotic symptoms, neurocognitive impairment is relatively stable across clinical stage and over the life span (Barder et al., 2013; Barder et al., 2015; Hughes et al., 2003; Lewis, 2004; Rund, 1998).

Evidence is still scant regarding the genetic relationship between neurocognition and schizophrenia (Toulopoulou et al., 2010). Neurocognitive impairments are however evident in unaffected relatives (Sitskoorn et al., 2004) and findings from a recent report indicate genetic overlap between schizophrenia and childhood cognitive ability (Hubbard et al., 2015). Neurocognitive deficit has also been proposed as a potential endophenotypic marker of schizophrenia (Swerdlow et al., 2015).

While neurocognitive dysfunction is a principal feature of schizophrenia, not all persons are affected with up to 30 % maintaining intact neurocognitive function (Heinrichs and Zakzanis, 1998; Kremen et al., 2000; Mesholam-Gately et al., 2009; Rund, 1998). That is, although about 70 % perform below the mean of the general population, a significant proportion overlaps with healthy individuals on several neurocognitive domains. Intact neurocognitive functioning does however not rule out ipsative decrements. Consequently, some individuals may have experienced decline from premorbid level of functioning although they are not impaired in terms of neuropsychological test performance.

Individuals experiencing impairment display various degrees of decline from expected level of neurocognitive functioning (Keefe et al., 2005). The majority function at a level at least one standard deviation below that of healthy controls, with impairment already present in first-episode psychosis (Flashman and Green, 2004; Zanelli et al., 2010), and enduring after pharmacological treatment of psychotic symptoms (van Os and Kapur, 2009).

A variety of neurocognitive impairments are consistently linked to the diagnosis of schizophrenia (August et al., 2012; Heinrichs and Zakzanis, 1998). Impairments are found in the domains of attention, verbal learning, memory, working memory, processing speed, problem solving/executive functioning and social cognition, in addition to a global cognitive deficit (Flashman and Green, 2004; Reichenberg, 2010). Moderate to large effect sizes are documented across all neurocognitive domains (Heinrichs and Zakzanis, 1998). The presence of neurocognitive impairments is further associated with a more severe course of illness and a higher rate of use of health services (Harvey and Sharma, 2002).

### **1.4.3 Factors influencing neurocognition in schizophrenia**

Several different factors can potentially influence neurocognition in schizophrenia spectrum disorders, such as for example *psychotic symptoms* and *antipsychotic medication*.

The relationship between neurocognition and psychotic symptoms differs across symptom dimensions. Neurocognition appears to be more strongly linked to negative symptoms (August et al., 2012; Dominguez Mde et al., 2009; Frydecka et al., 2015) than to other symptom dimensions (Dominguez Mde et al., 2009). Psychotic symptomatology and neurocognition are thus not orthogonal concepts, rather it is suggested that different cerebral mechanisms underlie the clusters of the different symptom categories (Dominguez Mde et al., 2009).

The increasing awareness of the implications of neurocognitive impairment in schizophrenia and recent insights into potential causes and mechanisms have triggered substantial efforts to develop pharmacologic treatments in order to restore neurocognitive functions (Ahmed and Bhat, 2014; Millan et al., 2012). The effect of currently available antipsychotic medication on neurocognitive deficits is however broadly debated and findings are inconclusive. Results from the large Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) compared effects of first- and second generation antipsychotics on neurocognition in chronic schizophrenia. A small, but significant improvement was found after two months of treatment, but there were no differences between first- and second generation medication (Keefe et al., 2007). In the European First Episode Schizophrenia Trial (EUFEST) (Davidson et al., 2009), similar findings were reported, i.e. antipsychotic treatment was associated with improvements on neuropsychological tests, but as in the CATIE study, no differences between 1<sup>st</sup> and 2<sup>nd</sup> could be established. Furthermore, the improvements in neurocognition were linked to symptom change. Other reviews also document moderate positive effects of both first and second generation antipsychotics on neurocognitive domains (Harvey et al., 2015; Hill et al., 2010; Mishara and Goldberg,

2004), with the exception of motor function, which was negatively influenced by 1<sup>st</sup> generation medication (Mishara and Goldberg, 2004). In summary, currently available antipsychotics have only small to moderate effects on cognitive deficits (Keefe et al., 2007) , but not in a manner that restores neurocognitive functioning to the level found in healthy controls.

The delineation of separable neurocognitive domains has been an important focus in schizophrenia research (Gold, 2004; McCleery et al., 2015; Nuechterlein et al., 2004), yet there is still uncertainty regarding the nature of neurocognitive deficits – whether they are better categorized in terms of independent factors or reflect a more generalized deficit at the core of the disorder (Blanchard and Neale, 1994; Dickinson and Harvey, 2009; Dickinson et al., 2004; Twamley et al., 2002).

Evidence of a generalized deficit has emerged in the recent past and the literature is replete with evidence that many, if not most, individuals afflicted by schizophrenia have a generalized deficit (Blanchard and Neale, 1994; Dickinson and Harvey, 2009; Dickinson et al., 2004; Heinrichs and Zakzanis, 1998; Twamley et al., 2002). This is further substantiated by findings of moderate to strong relationships between neurocognitive domains (Burton et al., 2013). The issue of generalized versus specific neurocognitive deficits is not only of academic interest, it may also have clinical implications with regard to cognitive rehabilitation strategies (Gold, 2004).

Ultimately, the most important issue is the assessment and identification of the neurocognitive domains that best characterize clinical and functional consequences for the actual individual, in order to customize therapy, cognitive remediation and rehabilitation.

#### **1.4.4 The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)**

As the awareness of neurocognitive impairment and its strong impact on functional outcome has increased, so has interest in possible interventions, both psychological and pharmacological, to alleviate neurocognitive deficits in schizophrenia. Thus far, the numerous studies conducted on neurocognition in schizophrenia have however employed a wide range of different assessment batteries depending on the preferences of different research teams, making comparison across studies difficult. This stressed the need for a standardized test battery to measure neurocognition in schizophrenia trials, allowing comparison across studies.



Thus, in 2004, the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative was launched to foster the development of a cognitive consensus battery for use in clinical trials (Buchanan et al., 2005; Kern et al., 2008; Millan et al., 2012; Nuechterlein et al., 2008). The initiative was supported by the National Institute of Mental Health (NIMH) in collaboration with the US Food and Drug Administration (FDA) and had three main objectives:

- i) To establish consensus with respect to the nature of neurocognitive impairment in schizophrenia
- ii) To improve the assessment and evaluation of neurocognitive impairments in schizophrenia
- iii) To produce a framework for the formal recognition of treatments that explicitly address neurocognitive impairments in schizophrenia (e.g. independent of psychotic symptoms)

(Barch, 2010; Buchanan et al., 2005; Kalkstein et al., 2010; Keefe et al., 2011; Millan et al., 2012; Young et al., 2009).

In order to select what would be the final test-battery, a multi-stage procedure was generated, beginning with the identification of which major neurocognitive domains to incorporate. Several criteria were applied in this process, including high test-retest reliability, applicability in terms of repeated assessments (measures without considerable practice effects), association with functional outcome and tolerability and practicability for test person and test administrator.

Seven separable domains were eventually identified representing the fundamental dimensions of neurocognitive impairments in schizophrenia; Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning and Memory, Visual Learning and Memory, Reasoning and Problem Solving and Social Cognition.

After identifying the neurocognitive domains that best characterized neurocognitive deficits in schizophrenia, the MATRICS initiative devised a neuropsychological consensus cognitive battery (MCCB) consisting of ten test for the clinical assessment of neurocognition in schizophrenia. The seven neurocognitive domains covered by the MCCB are outlined below. The subtests are described in the Methods section, chapter 3.7.2.

### ***Speed of Processing***

Speed of processing refers to the rate at which different neurocognitive operations are successfully undertaken. In most cases, this domain is viewed in terms of information processing, but it also applies to the rapidity of retrieval and is operationalized using reaction time. Impairment in processing speed affects performance in many tasks and serves as a constraint on general performance because other neurocognitive operations are speed dependent (Dickinson et al., 2007b; Millan et al., 2012). Impairments in this area may hamper daily life activities, job tenure and the ability to lead an independent life (Brekke et al., 1997; Evans et al., 2003; Gold et al., 2002)

### ***Attention/Vigilance***

Attention refers to awareness and attendance to a single stimulus or a set of stimuli (Millan et al., 2012). This dimension highly depends on perception, selection and filtering of information and sensory input. It thus requires both an active focus on salient information as well as active suppression of non-relevant information. In neuropsychology, attention is often sub-divided into more specific components and individuals with schizophrenia typically show impairments in three areas; selective, sustained (vigilance) and divided attention (Tyson et al., 2008). Selective attention is the capability to focus on a pertinent subset of stimuli, avoiding, suppressing or screening out distraction (Tyson et al., 2008). As we are often confronted with competing stimuli, selective attention is a constantly ongoing process and crucial in dual task information processing. Sustained attention or vigilance refers to the capacity to maintain attention over an extended period of time (Green et al., 2000; Millan et al., 2012) whereas divided attention is the ability to attend to simultaneous multiple stimuli (Tyson et al., 2008). Intact vigilance is important for social activities such as being able to follow a conversation or reading a book. Divided attention may imply executive shifts in selective attention depending on the task at hand. Each of the attentional sub-systems is crucial in order to maintain coherent behavior when confronted with competing stimuli or numerous response alternatives, as is often the case in everyday life or in an occupational setting. Attentional impairments are proposed as markers of genetic vulnerability (Chen and Faraone, 2000). Particularly vigilance deficits are strongly related to functional outcome with regard to skills acquisition, social- and community- functioning (Green, 1996; Green et al., 2000).

### ***Working Memory***

Working memory is typically defined as the ability to hold a small amount of information in the mind over a short period of time (i.e. for a few seconds). It is a limited capacity system that permits online evaluation, manipulation and synthesis of newly acquired information (Millan et al., 2012). Information is kept in mind while required and then either transferred to the processes that prepare it for long-term storage or is discarded (Harvey and Sharma, 2002). Working memory also retains information regarding the source of information, spatial location, emotional significance etc. Baddeley's prominent model of the working memory consists of two components; the central executive and brief storage systems (so called slave systems), namely the phonological loop and the visuospatial sketchpad (Baddeley and Hitch, 1974). Working memory is thus featured as a multi-store process with each of the slave systems sensory modality specific and limited in capacity. Baddeley's model was later revised and hypothesized to include a further component, the episodic buffer. The slave systems are thought to retain information without any manipulation or modification. Information is then manipulated in the central executive system, a system that also adapts to change in neurocognitive load and determines which information will be transferred to long-term memory and which may be forgotten. Working memory operates in short-term memory, but the two concepts are not identical. Working memory is closely linked to and interacts with numerous other domains such as attention and executive function and has accordingly been suggested as a core feature of neurocognitive dysfunction in schizophrenia (Gogos and Gerber, 2006; Silver et al., 2003). It is closely connected to both job tenure (Gold et al., 2002) and occupational status (Lysaker and Bell, 1995) In the MCCB, working memory contains both verbal and non-verbal tasks.

### ***Verbal Learning and Memory and Visual Learning and Memory***

Learning refers to an active-, experience-, and/or training-driven acquisition of information whereas memory constitutes a faculty permitting consolidation, retention and retrieval of information from numerous sensory dimensions. Memory consists of several sub-components such as short-term memory (immediately available information maintained for up to 30 seconds) and long-term memory (in theory, unlimited capacity to store information both in quantity and time). Learning and memory are consistently affected in schizophrenia (Green et al., 2000; Millan et al., 2012). In general, persons with schizophrenia tend to have greater impairments in learning than in retention.

Verbal learning refers to the ability to learn verbal material exceeding the working memory capacity. Verbal learning is robustly linked to both real-world functioning and social functioning (Green, 1996; McClure et al., 2007).

Visual learning was included based on the finding that individuals with schizophrenia commonly display deficits in either visual or verbal learning rather than in both domains (Nuechterlein et al., 2004), however, visual learning has been suggested to be somewhat less impaired than verbal learning (Heinrichs and Zakzanis, 1998). Bivariate correlations with occupational status and tenure are modest (Gold et al., 2002; Gold et al., 2003), visual learning however seems to be more powerfully related to functional capacity (Twamley et al., 2002)

### ***Reasoning and Problem Solving***

Reasoning and Problem Solving is frequently used interchangeably with executive function, however these terms are not synonymous. Problem Solving has been defined as a goal-directed neurocognitive activity that arises in situations for which no response is immediately apparent or available (Rath et al., 2004). In such situations, the individual must use neurocognitive skills to go beyond the information given in order to find a solution to the problem at hand. Reasoning and Problem Solving contains sub-processes such as foresight, planning, decision making, cognitive flexibility and impulse control. Reasoning and Problem Solving as part of executive functions are strongly related to different aspects of functional outcome (Evans et al., 2004; Velligan et al., 2000)

### ***Social Cognition***

Social cognition has been defined as the mental operations underlying social interactions including the human ability to perceive the intentions and dispositions of others (Vaskinn et al., 2013). Social cognition is related to real-world functioning in schizophrenia and entails a wide set of neurocognitive skills (Fett et al., 2011).

Social Cognition was incorporated in the MCCB not through factor analysis, but due to its promising nature in terms of mediation between neurocognition and measures of functional outcome (Nuechterlein et al., 2008).

### **1.4.5 Neurocognition and functional outcome in schizophrenia**

Spurred by influential literature (Green, 1996; Liberman and Kopelowicz, 2005) and a (paradigm) shift from symptom management to the goal of recovery, the understanding and importance of functional outcome/real-world functioning in schizophrenia has become more elaborate over the past decades. By definition, a decline in functioning that has prevailed for a minimum of six months is required for a diagnosis of schizophrenia. Accordingly, functional deficits are present in most individuals with schizophrenia. Disruptions in social functioning, independent living and occupational functioning are characteristic of schizophrenia and the level of impairment is often quite substantial (Harvey and Sharma, 2002). It was previously assumed that one of the main reasons for poor functional outcome in schizophrenia was the reduced sense of reality, delusions and hallucinations. Today, there is a general consensus that the problem is far more complex, and that multiple facets of the illness contribute to different aspects of functional outcome (Perlick et al., 2008; Ventura et al., 2009). Neurocognitive impairment represents one important facet. A meta-analysis by Green and colleagues found that neurocognitive impairment accounts for as much as 20-60% of the variance in different functional outcome areas (Green et al., 2000), exceeding the association found between symptoms and outcome (Christensen, 2007; Velligan et al., 1997).

As a consequence, measures of attention, processing speed, language and memory have been used to predict employment status (Shamsi et al., 2011), social functioning (Torgalsboen et al., 2014), and social skills (Penn et al., 1995), effects in social and vocational training programs as well as interpersonal problem solving (Bellack, 2004; Xiang et al., 2006). Additional evidence has also shown neurocognitive deficits to be associated with skill acquisition in rehabilitation programs (Green et al., 2004), poor financial skills (Niekawa et al., 2007) and self-care (executive functioning) (Schutt et al., 2007).

It should however be noted that neurocognition accounts for different amounts of variance in different contexts. The validity of neurocognition as a predictor of functional outcome in schizophrenia varied between 4 % and 23 % in a recent meta-analysis by Fett and colleagues (Fett et al., 2011), indicating that numerous other factors beyond neurocognition influence a person's behavior in real-world settings, i.e. functional performance (Green, 2006).

There are a number of different ways to describe and measure functional outcome. Recent studies (Bowie et al., 2008; Bromley and Brekke, 2010; Gupta et al., 2012; Vesterager et al., 2012) delineate functional outcome in functional capacity and functional performance with functional

outcome as the umbrella term, encompassing both capacity and performance. *Functional capacity* is the ability to perform a task if given the opportunity, and functional performance or *real world functioning* refers to the ability to perform actual activities such as daily living skills or occupational functioning (Bromley and Brekke, 2010; Gupta et al., 2012). Increasing focus is given this competence-performance distinction (Gupta et al., 2012), as functional capacity does not necessarily translate into actual performance, i.e. what a person is able to do in terms of functional capacity, he or she does not necessarily do in everyday life or in an occupational setting. The relationship may be strongly influenced by both external factors such as benefits, labor market and stigma and internal factors such as motivation, apathy etc. The complexity of functional outcome has paved the way for use performance-based proxy measures such as the University of California Performance Skills Assessment (UPSA) in schizophrenia, avoiding complications such as level of insight (Harvey et al., 2007) or the lack of a real-world setting in which actual performance can be assessed.

## **1.5 Occupational status and occupational functioning**

*“Far and away the best prize that life offers is the chance to work hard at work worth doing”*

Theodore Roosevelt, 1903

Employment is an important and defining role in life, also for people with psychotic disorders. Employment not only provides income, it structures life and is an important source of social contact and fosters a positive self-image and personal identity (Nordt et al., 2007). In addition to financial benefits, employment is associated with improved levels of self-esteem, quality of life and therapeutic effects such as lowered relapse rates in schizophrenia (Bond et al., 2001; Bryson et al., 2002; Bush et al., 2009; Lieberman et al., 2008; McGurk and Mueser, 2004). It also helps promote rehabilitation and recovery (Waddell and Burton, 2006). Unemployment on the other hand, has been found to be detrimental to the health of the general population (Bartley, 1994) and is an important expression of the social exclusion faced by many persons with schizophrenia (Boardman et al., 2003). Broad interdisciplinary consensus has shown unemployment to be strongly associated with poor general health, high mortality, psychological distress, high medical consultation rates and medication use (Waddell and Burton, 2006). Concerning re-employment and claimants moving off social security benefits, comprehensive research has shown these to be important agents in regaining self-esteem and that it has comparable effects to employment with reference to the lowering of psychological distress and improved mental and physical health (Claussen et al., 1993; Pattani et al., 2004).

Beyond economic and moral arguments that employment and re-employment are efficient ways to improve the general welfare of individuals, their families and communities there is also increasing awareness that not belonging to the workforce may actually even be harmful to mental health. Hence, increasing employment and supporting people into work are key elements of government's public health and welfare reform agendas.

A considerable proportion of individuals with schizophrenia are willing and able to work. Despite repeatedly expressing the need for occupational training, placement and support, this group encounters one of the highest unemployment rates among all vocationally disadvantaged groups (Bevan, 2013; Kilian and Becker, 2007). Actually, when asked to rank their top three life goals for the near future, first-episode patients listed employment and education as their main priorities, whilst symptom remission was reported as less important (Ramsay et al., 2011). Considerable research has however shown that employment rates in schizophrenia are consistently low, estimates ranging from 10 % to 25 % (Bond, 2004; Evensen et al., 2015; Marwaha and Johnson, 2004; Mueser and McGurk, 2014; Tandberg et al., 2011). Together, schizophrenia and schizoaffective disorder constitute the fifth leading cause of disability and schizophrenia alone is ranked as the ninth cause of disability among all illnesses worldwide (World Health, 2008). Data on employment rates among individuals with schizophrenia in Norway are sparse, but one study indicates high unemployment numbers (94 %) (Evensen et al., 2015; Melle et al., 2000). Most commonly, schizophrenia has its onset at the threshold of early adulthood, a phase in which most young people devote their time to educational attainment and make their transition to independent living. The early onset and the course of illness are factors that strongly contribute to the high unemployment rate at about 80% in schizophrenia samples (Gaite et al., 2002; Mangalore and Knapp, 2007; Marwaha et al., 2007). Even when individuals with schizophrenia attain work, they frequently have difficulty maintaining employment, with as many as 50 % experiencing unwanted job discontinuations (Bond et al., 2008). Consequently, many afflicted by schizophrenia are dependent upon disability compensations or the financial support of family members, or even live in poverty (Draine et al., 2002).

In summary, even though employment may not be a realistic goal for all individuals with schizophrenia, it is generally considered to have a wide range of advantages, in terms of therapeutic benefits, financial gain, in addressing social inclusion and last but not least in improving mental health and wellbeing (Marwaha and Johnson, 2004; Waddell and Burton, 2006)

### **1.5.1 Factors associated with occupational status and occupational functioning in schizophrenia**

Poor occupational outcome is a hallmark of schizophrenia and strongly influenced by illness related factors such as psychotic symptoms and neurocognitive impairment. Occupational outcome is however further heavily influenced by a wide range of external, e.g. societal and economic, factors impeding entry into the labor market. Low employment rates are thus not intrinsic to schizophrenia but rather reflect a complex interplay between social and psychological variables (Marwaha and Johnson, 2004) as will be illustrated in this section.

#### ***Illness related barriers to employment:***

Poor *premorbid functioning* is an established antecedent of the illness (MacBeth and Gumley, 2008). Difficulties in childhood and adolescence as well as impaired social functioning prior to illness onset are predictive of a worse illness trajectory in terms of both psychosocial and occupational functioning (Malla and Payne, 2005; Tsang et al., 2010).

*Positive symptoms* may interfere with the ability to work, their relevance relative to the influence of neurocognition is however still uncertain. Between 26 and 40 % of persons with schizophrenia endure persistent psychotic symptoms (Buchanan, 2007; Chue and Lalonde, 2014; Mueser et al., 1991) which have been found to influence occupational functioning (Racenstein et al., 2002). Particularly hallucinatory symptoms may interfere with occupational functioning, as they can be both distracting and distressing (Chadwick and Birchwood, 1994; Lin et al., 2013). Further, they may influence attentional capacity, compromising occupational performance (Lin et al., 2013). Delusions may also impair occupational outcomes as they can lead to odd behaviors that perhaps may be perceived as frightening or annoying by co-workers. Although positive symptoms may influence occupational functioning, a recent review concluded that they only have a peripheral effect on work behavior (Christensen, 2007).

*Negative symptoms* tend to have a relatively stable course over time and may also impact work performance. They are well-established predictors of occupational performance in schizophrenia (Christensen, 2007; McGurk and Mueser, 2004) with apathy most robustly associated with impaired functional outcome (Chang et al., 2016). Negative symptoms are also found to mediate the relationship between neurocognitive- and occupational- functioning (Ventura et al., 2009).



As previously mentioned, *neurocognitive impairment* often precedes illness onset and is a prominent predictor of functional outcome in general and occupational functioning in particular (August et al., 2012; Green, 1996; Reichenberg et al., 2009; Shamsi et al., 2011; Vargas et al., 2014). The literature is replete with evidence of poor neurocognitive functioning being a major limitation in occupational functioning, cross-sectional, prospectively and retrospectively (August et al., 2012; Chang et al., 2014; Gold et al., 2002). In addition, neurocognitive dysfunction is associated with attenuated response to vocational rehabilitation (O'Connor et al., 2011), making it difficult to engage properly in rehabilitation programs and to properly profit from them. Regarding occupational performance, verbal memory and executive functioning have been found to be of particular importance (Christensen, 2007) whereas occupational status was more closely linked to attention/vigilance. In general, persons employed tend to have better neurocognitive performance than unemployed persons with schizophrenia (August et al., 2012; Christensen, 2007; Shamsi et al., 2011).

### ***External barriers to employment***

Circumstances in the general *labor market* influence employment rates in schizophrenia. In times of high unemployment, persons with lower levels of education or fragmented work history are less likely to obtain work, particularly if they are suffering from a highly stigmatized illness such as schizophrenia (Bevan, 2013).

*Curtailed level of academic acquisition* is often the result of a progressive deterioration experienced by people with schizophrenia (Gould et al., 2013; Harvey et al., 2012). Psychotic symptoms marking the onset of illness are often preceded by a range of difficulties including depression, social dysfunction and neurocognitive deficits influencing several areas of functioning (Haefner and An der Heiden, 2008). This functional decline prior to onset often results in a poor academic trajectory with persons often unable to complete educational milestones. Education is also an important determinant of the probability of finding a good job-match (Baldwin, 2016). Better educated persons are thus more likely to attain work where their functional impairments have less impact on important job functions. Individuals with schizophrenia may for instance be distracted by noise and may consequently be more successful at his or her job if placed in a separate office instead of in an open space. Education increases the value of these persons on the labor market, making it more likely to find work that accommodates their functional impairments (Baldwin, 2016)

Considerable research has documented that persons with schizophrenia experience *stigma* in several areas of their lives, particularly with reference to work (Schulze and Angermeyer, 2003; Thornicroft et al., 2009). Employers and co-workers frequently have limited knowledge of and little experience with severe mental illness, often resulting in mistrust, critical remarks or discrimination. In a survey of employers, 67 % reported they were uncomfortable employing a person taking antipsychotic medicine and 53 % expressed discomfort working with individuals who had been hospitalized in a mental institution (Scheid, 2005). In contrast, employers (15 %) conveyed far less distress working with individuals having physical handicaps. Beliefs of potential employers regarding mental illness may thus strongly influence their compliance when it comes to engaging persons with a history of or ongoing severe mental illness in their organizations.

*Low expectations* arguably constitute another prominent barrier to employment and often occur on different levels. Firstly, some mental health care professionals, for several reasons, tend to belittle the work capacity of their clients and as a consequence, work is not a goal of treatment outcome (Bevan, 2013), or if, only non-competitive work (Marwaha et al., 2009). Frequently documented reasons are low commendation of employment as a desirable treatment outcome, concern for mental well-being and main focus on symptom remission (i.e. symptoms must cease before work is a possibility). Secondly, this may nourish self-doubt and fear, potentially leading to internalization and self-stigma and finally, employers have been reported to believe that persons with schizophrenia are only capable of performing low-skill/low-level tasks (Baron and Salzer, 2002)

*Welfare systems* that provide relatively high social security benefits for unemployed persons with schizophrenia may embody an actual disincentive toward work. In fear of losing benefits or experience financial worsening, some persons may not be economically motivated to find work or participate in vocational rehabilitation (Burns and Patrick, 2007; Tandberg et al., 2011). Faced with the possibility of insufficient or lower income, people do not attempt to work even if they potentially could, which is referred to as the *benefit trap*. It should also be noted that the mere fear of losing benefits is associated with the ability to work, i.e. a reduction in work ability (Griggs and Evans, 2010). In general, poor access to vocational rehabilitation and support services means that assistance in finding work is also often lacking.

### **1.5.2 Vocational rehabilitation**

Vocational rehabilitation (VR) in schizophrenia is an approach or an intervention aimed at helping individuals attain and/or maintain work. Traditionally, it was considered a gradual process (train, then place) taking participants through pre-vocational training, periods of assessment and tailored occupational assistance. Unpaid positions and sheltered work were considered helpful or even necessary to prepare people for competitive employment (Waghorn et al., 2014). Over the past two decades, spurred by several influential and persuasive articles (Bond, 2004; Bond et al., 2012; Kinoshita et al., 2013), vocational rehabilitation has broadened beyond old benchmarks like pre-vocational training and sheltered work to include competitive work, integration of health and welfare services and payment. Briefly described, there are two vocational rehabilitation models most commonly implemented for persons with schizophrenia; pre-vocational training (train and place) and Supported Employment (SE) (place and train).

Pre-vocational training is thought to prepare a person prior to seeking competitive employment with regard to general skills and workplace demands and is often referred to as the medical model of rehabilitation (Corrigan and McCracken, 2005; Twamley et al., 2003).

SE focuses on competitive employment, swift job search followed by training and support on the job. That is, no pre-vocational training is required and attention is paid to client preferences in terms of type of work. The main difference between the two models is that in SE, competitive employment is considered the beginning rather than the end point of vocational rehabilitation. Although evidence suggests that pre-vocational training is not a successful model with regard to helping clients attain competitive work, it is still implemented on a large scale (Burns et al., 2009; Rinaldi et al., 2010).

Supported employment (SE) and its manualized form, Individual Placement and Support (IPS) are the principle evidence-based approaches in vocational rehabilitation for people with severe mental disorders (Allott et al., 2013; Bond et al., 2007; Killackey et al., 2006) with beneficial short- and long-term effects (Hoffmann et al., 2014). Participants in IPS programs are more likely to obtain competitive employment, work more hours and earn higher wages than participants in conventional programs.

In SE/IPS programs, competitive employment, defined as part- or full-time work in a position that is open to anyone, is the main goal. Services in the Nordic countries however routinely offer sheltered work in a train and place tradition (Hagen et al., 2011), considering all types of

employment (competitive, sheltered or work placement) to be of importance. Vocational training is thus offered in sheltered workshops if competitive work for different reasons is not possible. Work placement is work in a competitive setting financed through the Norwegian Labor and Welfare Administration (NAV) through so called work assessment allowance or disability benefits. Work demands are however equal to those in competitive employment. This so-called “Nordic Model” is underpinned by a combination of flexibility and security for all involved parties. On the one hand, laws make it relatively easy for companies not to hire individuals with functional limitations and implement more economic business models. On the other hand, employees are supported by generous social welfare programs and employment protection legislation, resulting in a system that treats all citizens equally and encourages workforce participation. This Nordic model is thus based on a high level of employment with a social safety net to provide generous financial security for individuals without a job, while at the same time the welfare society is financed primarily on the basis of incomes created through employment (Andersen, 2007; Vidje, 2012). This social contract ensures equal access to health and welfare services for all citizens and also regulates employment protection in terms of working environment, wages and sick leave. VR services are typically outsourced to agencies providing a broad range of employment options; competitive employment, sheltered work and work placement (Spjelkavik, 2012). The study presented in this thesis is carried out within this Nordic tradition, thus considering all types of employment a success.

As vocational rehabilitation gains momentum in clinical guidelines, the implementation of SE/IPS programs for people with schizophrenia has increased accordingly. Nevertheless, research shows that SE/IPS does not lead to high rates of stable competitive employment for the targeted group and that jobs obtained within the IPS model are frequently of a short-term entry-level part-time character (Baldwin, 2016; Lucca et al., 2004). Despite superior SE/IPS outcomes regarding competitive employment rates (Bond et al., 2012; Marshall et al., 2014), people with schizophrenia still face numerous occupational challenges. In a study by Allott and colleagues (Allott et al., 2013), there were no differences in employment duration between participants in an IPS program and a treatment as usual group. Further, many struggle to maintain employment after termination of SE/IPS programs (McGurk and Meltzer, 2000) and as many as 50 % experience unwanted job discontinuations (Bond et al., 2008). Hence, there is still much room for improvement and augmenting SE/IPS programs in order to optimize occupational outcomes may be advantageous.

## 1.6 Cognitive remediation and vocational rehabilitation

The strong relationship between neurocognition and functional outcome underlines the importance of targeting neurocognitive dysfunctions through psychosocial interventions such as cognitive remediation (CR) as a means to improve occupational functioning, social inclusion and economic outcomes.

Cognitive remediation refers to nonpharmacological interventions aiming to improve neurocognitive functioning in persons with severe mental illness (Galletly and Rigby, 2013). It has been defined by an expert consensus group as “a behavioral-training based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition, or metacognition) with the goal of durability and generalization” (Cognitive Remediation Experts Workshop (CREW), Florence, April 2010). CR programs thus seek to lessen the influence of neurocognitive impairment as a rate-limiting factor in rehabilitation and/or to provide alternative strategies to compensate for neurocognitive deficits. CR refers to process of thought and not thought content as is mainly the case in CBT.

Cognitive remediation approaches can be conceptualized based on their hypotheses with reference to how neurocognitive change occurs. They are most commonly divided into two main categories; *compensatory* and *restorative* (Medalia and Saperstein, 2013).

Restorative methods propose restitution or actual repair of neurocognitive processes based on theories of neuronal plasticity (Medalia and Choi, 2009). Restorative methods apply both bottom-up and top-down approaches in training; bottom-up approaches address basic neurocognitive skills such as attention at the beginning and then progress to more complex skills such as problem solving. Bottom-up approaches typically involve repetitive drill and practice with similar (or even identical) exercises to enhance automatization and effectiveness of neurocognitive processing (Barlati et al., 2013). Top-down processes on the other hand use more complex skills to improve specific neurocognitive domains and typically involve strategy learning and guided problem solving training adapted to individual resources (Wykes et al., 1999).

Compensatory methods are based on the notion that new skills can replace or compensate for impairments in neurocognition. Compensatory strategies thus bypass specific dysfunction or aims to minimize its influence by utilizing residual neurocognitive capacity or environmental resources (Barlati et al., 2013). In practice this means acquiring new skills through learning

strategies or verbalization and employing them in a way that enables task performance (Velligan et al., 2008).

Cognitive remediation applies a series of different methods and training techniques in order to improve neurocognition (Wykes and Reeder, 2005).

*Drill and practice* or *massed practice* consists of several task repetitions to facilitate retention and ultimately increase neurocognitive skills. The process of learning through massed practice is debated, but one assumption is that it increases automatization, hence require less neurocognitive effort.

*Motivation* can be defined as an internal state or condition that serves to activate or energize behavior and give it direction (Velligan et al., 2006). Given that the functional disability of schizophrenia is at least partly caused by deficits within the neurocognitive/motivational system, this system may be a critical, explicit target for remediation efforts (Medalia and Saperstein, 2011; Velligan et al., 2006). CR interventions may profit from using high levels of positive social feedback or token reward for task performance.

*Errorless learning* is a technique with the objective to improve performance through a high degree of success during learning (Wykes and Reeder, 2005). Working memory impairment is a core feature of schizophrenia, making it difficult for persons both to identify correct responses (versus incorrect) and to remember correct responses in training trials. By reducing the number of incorrect responses encoded in implicit memory, errorless learning enables fewer errors in explicit recall. Errorless learning can be facilitated through different methods, for example through adjustment of difficulty level or backward chaining and has been found to positively influence self-esteem during cognitive remediation (Wykes and Spaulding, 2011).

*Scaffolding* originates from pedagogical psychology (Wood, 1998) and describes the increase of task complexity to be just at the limit of current competence in order to encourage effort. The theory behind scaffolding is that a certain degree of effort has to be made to perform a task, but a relatively high degree of success is ensured with a minimal number of errors. A tutor, in this case cognitive trainer/cognitive specialist, considers a person's neurocognitive profile and offers support (verbal instructions) so that the client can perform a task successfully at a higher level than he or she would be able to on their own. This support is then gradually withdrawn and the client is capable of solving the task independently. The relationship between the cognitive specialist and the client is of a collaborative nature and it is of great importance that strategy

ownership is assigned to the client, e.g. performance was successfully carried out by the client, not the cognitive specialist.

These, and several other methods, are applied in different ways and to different extents in cognitive remediation programs – some even combined.

Cognitive remediation programs are frequently delivered as a package with a standard set of tasks or it can be personalized to address particular impairments in individuals. Programs however differ across a number of dimensions; they may be broad-based targeting several neurocognitive domains or specific (Barlati et al., 2013), regarding methods and technology (paper-pencil versus computerized), the presence of a cognitive specialist or not, in group or individual sessions or with reference to durability.

This range of different cognitive remediation approaches has led to an explosive growth in research and clinical interest and numerous RCT's have been conducted within the framework of cognitive remediation (Barlati et al., 2013; McGurk et al., 2007; Medalia and Choi, 2009; Wykes et al., 2011). In terms of establishing effects of CR programs, two relatively recent meta-analyses provide scientific evidence (McGurk et al., 2007; Wykes et al., 2011). The meta-analysis carried out by McGurk (2007) included 26 randomized controlled trials and documented a moderate effect of CR on neurocognitive functioning (.41), a small effect on psychotic symptoms (.28) and a moderate effect on functional outcome (.36) (Cohen's  $d$ ; .20 = small; .50 = medium; .80 = large (Wilkinson, 1999) ). Interestingly, additional analyses suggested stronger effects on functional outcome when cognitive remediation was provided in combination with rehabilitation. Similar findings were reported in the meta-analysis by Wykes and colleagues (Wykes et al., 2011). Forty studies were included and a moderate effect of CR on neurocognition was found (.45). Similar to the first meta-analysis, only a small effect was established with regard to symptom reduction and a moderate effect on functional outcome (.43). Exploratory analyses were carried out to examine the effects of cognitive remediation with adjunctive rehabilitation. Findings demonstrated stronger effects of CR on functional outcome when combined with rehabilitation than when CR was provided alone (Wykes et al., 2011). These findings indicate that improved neurocognition facilitates rehabilitation, i.e. enable participants to learn and benefit from different forms of rehabilitation to a greater extent. CR was also more effective when strategy coaching was additionally implemented (Wykes et al., 2011)

Results from the two meta-analyses provide robust documentation of the effect of CR. The effect sizes were small to moderate, but should not be neglected. As with findings from the

CBT literature, these effect sizes reflect illness severity (Sarin et al., 2011). Several randomized controlled trials have documented beneficial effects of CR embedded in vocational rehabilitation on occupational outcome compared to vocational rehabilitation alone (Au et al., 2015; Bell et al., 2014; Wykes et al., 2011). The mechanisms driving these effects are however still relatively unknown and research is still needed to determine the most favorable approach to augmenting vocational rehabilitation with CR.

## **1.7 Cognitive Behavioral Therapy and vocational rehabilitation**

Individuals with schizophrenia spectrum disorders also face challenges such as psychotic symptoms, comorbid mood- or anxiety disorders and social impairments (Buckley et al., 2009; Milev et al., 2005; Morrison, 2009). These core symptoms can be targeted with Cognitive Behavioral Therapy (CBT). CBT was originally intended to address positive symptoms in schizophrenia but has later been adapted to also help afflicted individuals cope with negative symptoms (Warman et al., 2005). There is strong support for a range of CBT programs in improving symptoms, social relations and occupational outcome (Rector and Beck, 2001; Sarin et al., 2011; Tarrier and Wykes, 2004). More recently, CBT programs designed to enhance occupational functioning have been developed (Kukla et al., 2014; Lecomte et al., 2014). Although evidence is still scant regarding CBT programs adjunct to vocational rehabilitation, results are promising (Davis et al., 2008; Lecomte et al., 2014; Lysaker et al., 2009). CBT is not a main aim of the current thesis and will thus not be described with the same level of detail as the CR intervention.

## **1.8 Synopsis and topics that need further elaboration**

It is well established that neurocognitive impairment and psychotic symptoms account for a significant part of the psychosocial challenges and illness burdens associated with schizophrenia, for example attaining and maintaining employment. Exploring this relationship is important in order to help identify illness related characteristics that may affect employment outcome.

Meanwhile, the MCCB has been translated into several different languages and is rapidly becoming commercially available (Shi et al., 2015). The process of translation and adaptation in order to achieve an instrument that is conceptually equivalent in different countries and cultures is challenging. Consequently, an important step in the validation process of this translated test battery was to document neurocognitive functioning within the current cultural framework. At the time the current study was initiated, the MCCB had only investigated in a population of



early-onset patients with schizophrenia in Norway. There was thus a need to describe neurocognitive functioning as measured with the Norwegian version of the MCCB in an adult clinical sample; i.e. adults with psychotic disorders.

Different approaches to vocational training have emerged over the years and plentiful evidence suggests that work rehabilitation is effective in schizophrenia (Twamley et al., 2003). The growing interest in programs helping affected individuals return to work increases the need for assessment tools measuring occupational functioning. Whether and how neurocognitive functioning as measured with the MCCB was reflected in workplace assessments thus required further investigation, particularly in light of participants taking part in a vocational rehabilitation study.

Finally, although substantial research has documented effects of cognitive remediation, both as stand-alone interventions and combined with rehabilitation, further research is needed to elaborate studies on cognitive remediation embedded in vocational rehabilitation.



## **2. Aims**

The main aim of the present thesis was to investigate neurocognition as measured with the MCCB and different aspects of functional outcome in persons with broad schizophrenia spectrum disorders. The thesis further sought to examine the effects of a cognitive remediation program on short- and long term neurocognitive and occupational functioning.

### **Paper I**

The main aim of Paper I was to describe neurocognitive function as measured with the Norwegian version of the MCCB in a sample of adult patients with psychotic disorders entering a vocational rehabilitation program compared to an age and gender matched sample of healthy controls. We further sought to determine whether the Norwegian translation of the MCCB produced comparable patterns of neurocognitive performance and impairments in both healthy controls and patients based on US norms parallel to the US standardization study. Finally, we aimed to examine relationships between neurocognition and different measures of functioning in the patient group, specifically between neurocognitive performance and education, previous employment and social functioning. We hypothesized higher levels of education as well as previous employment to be reflected in better neurocognitive performance and patients with better neurocognitive performance to attain higher levels of social functioning.

### **Paper II**

The aim of Paper II was to expand findings from Paper I and investigate the relationship between neurocognitive performance as measured by the MCCB and different measures of occupational functioning at the beginning of a vocational rehabilitation program. To uncover this, we employed three workplace assessments; the Vocational Cognitive Rating Scale (VCRS) (Greig et al., 2004), the Work Behavior Inventory (WBI) (Bryson et al., 1997) and the Complexity Scale (CS) (Bell et al., 2009). The hypothesis was that MCCB scores would predict VCRS and WBI scores and that participants carrying out low complexity tasks or working in a sheltered environment would perform more poorly on the MCCB than participants having average or higher complexity jobs or working in a competitive environment at the beginning of a vocational rehabilitation program.

## **Paper III**

The main aim of Paper III was to examine the effects of a CR compared to a CBT augmented vocational rehabilitation program, the Job Management Program (JUMP), on neurocognition and occupational functioning. Specifically, we wanted to examine both the short-and long-term trajectory of neurocognitive performance as measured with the MCCB as well as explore the predictive value of neurocognitive change on occupational status and number of hours worked two years after inclusion.

## **3. Methods**

### **3.1 The Job Management Program Study (JUMP)**

The present thesis is part of the JUMP study, a multisite hybrid vocational rehabilitation program for adults with psychotic disorders in Norway. JUMP is a collaborative effort between health and welfare services with the overall goal of enhancing occupational outcomes for persons with psychotic disorders. Participants were offered a 10 month extensive vocational rehabilitation program consisting of competitive or sheltered work, close collaboration between health and vocational services, employers and employment specialists in addition to either cognitive remediation (CR) or cognitive behavioral therapy techniques (CBT).

### **3.2 JUMP Interventions**

JUMP was equally organized on all sites with a team consisting of a mental health coordinator, a welfare services coordinator and an employment specialist and consists of the following components: Education on psychosis (symptoms, course, treatment, prevention, rehabilitation and prognosis)(Harsvik et al., 2008), supervision, CBT or CR in addition to vocational rehabilitation.

The element of education was identical in both intervention groups. Further, employment specialists in both groups received weekly supervision by an experienced mental health professional (the site coordinator) throughout the project. The mental health professional was also easily available for consultations when problems arose between meetings. Employment specialists implemented the CBT or CR intervention and were committed to competitive work as an attainable goal for persons with severe mental illness.

#### ***Vocational Rehabilitation***

Overall, JUMP employment specialists focused rapid work placement in positions matched to participants' preferences and work history with continuous job support. The JUMP study was carried out within the Nordic tradition of routinely offering sheltered work in VR (Hagen et al., 2011), consequently, all types of employment were considered a success. Although employment specialists were based in sheltered workshops, they were encouraged to aim for competitive employment whenever possible, as many participants stated this as a primary goal. Vocational training in sheltered workshops was offered if competitive work was not possible. Participants were thus offered a job either in the sheltered workshop or attained competitive work

in terms of work placement (work in a competitive setting financed through the Norwegian Labor and Welfare Administration through so called work assessment allowance or disability benefits) or regular competitive employment. Additionally, support and if necessary, task adaptive accommodations were provided.

JUMP participants were also assisted by the employment specialists in completing career profiles, incorporating previous work history and if relevant, disclosing mental illness to potential employers. The employment specialist collaborated closely with treatment providers and the mental health coordinator throughout the project period. Lastly, employment specialists conducted continuous job search directed to positions individualized to the interests of their participants.

### ***Cognitive remediation***

The employment specialists in the CR group received education about neurocognitive impairment in psychotic disorders, i.e. characteristics, prevalence and stability, interaction with other symptoms, and consequences for functioning in general and occupational functioning in particular. Furthermore, employment specialists were taught the basic principles of cognitive remediation, use of the computer software, strategies to enhance motivation and performance and transfer of knowledge and skills acquired through training to the work setting. The training lasted 40 hours and was provided by psychologists with experience in cognitive remediation for patients with psychotic disorders. The CR program included the following elements: Feedback from the neurocognitive assessment, setting up personal aims for the training, psychoeducation about cognitive impairment, and two hours weekly of computer based training with focus on transfer between training and the work situation. The computer programs targeted attention/vigilance, working memory, learning and memory, reasoning and problem solving, and processing speed. The tasks originated from four different programs: COGPACK (Marker Software), Vision Builder (Haraldseth Software), Brain Fitness and InSight (PositScience). The computerized training program contained elements based on a combination of bottom-up and top-down processes. On the one hand, participants carried out repetitive drill-and-practice tasks to enhance and automatize neurocognitive processing (bottom-up). On the other hand (when tasks allowed), strategy learning was also implemented (top-down).

### ***Cognitive Behavioral Therapy***

Employment specialists in the CBT intervention group received training in the basic methods of CBT, focusing on frequently encountered work related problems in vocational rehabilitation

for persons with psychotic disorders. This included social withdrawal, apathy, passivity, fear of contact, informal conversation and common meals, drug abuse, and delusions and hallucinations that interfere with work ability. In addition, the training addressed basic concepts (such as expressed emotion) and ways of reasoning in the psychoeducative tradition (Butzlaff and Hooley, 1998; Leff and Vaughn, 1984). The training lasted 40 hours. It should be emphasized that what we call CBT oriented vocational rehabilitation is not psychotherapy in the strict sense, but application of central CBT methods in an occupational context. Participants were also assigned homework to promote further cognitive restructuring between meetings. The participants had individual meetings with the employment specialist two hours weekly.

### **3.3 Design**

Three counties were randomized to receive the CBT intervention; Nord-Trøndelag, Oppland and Oslo whereas Buskerud, Telemark and Vest-Agder were randomized to the CR intervention.

Participants were assessed at baseline, post treatment approximately 10 months after baseline and 2 years after inclusion in the program (follow-up).

### **3.4 Procedure**

Participants were referred to the study from local mental health centers and vocational services. Self-referral was also possible. All participants provided written informed consent after complete description of the study. The recruitment and inclusion period was from August 2009 to March 2013.

Participants went through a broad range of assessments. First, in order to establish whether the diagnostic criteria were fulfilled, a diagnostic interview was conducted together with an assessment of current levels of psychotic symptoms. If inclusion criteria were fulfilled, neuropsychological assessment was carried out. The clinical and neuropsychological assessments were conducted by trained clinicians (psychologists, a psychiatrist and an occupational therapist). A neuropsychological report was written and sent to the treatment unit after completion. Results from the neuropsychological assessment were used in the VR program in both intervention groups in order to better tailor the program as well as meet task adaptation needs in the work setting. The remaining assessment steps were carried out by experienced mental health professionals and employment specialists. A more detailed description follows in the assessment sub-section.

The healthy control participants included in paper I had been recruited through advertisements in local newspapers in Oslo and the Southeastern region of Norway and through electronic advertisements on the Vestre Viken Hospital Trust (VVHF) homepage. The VVHF provides state-funded healthcare to the south-eastern part of Norway and consists of rural areas as well as city centers. The healthy control group was recruited as part of the MCCB Standardization Study in Norway (Mohn et al., 2012). Healthy controls received a fee of NOK 400 (approximately 70 US\$, January 2011) for participating in the study. All participants provided written informed consent before assessment and the study was approved by the Regional Committees for Medical and Health Research Ethics (REK).

### **3.5 Inclusion and exclusion criteria**

#### ***The JUMP study***

Participants in the JUMP study had to be between 18 and 65 years of age, motivated for work and able to understand and speak Norwegian to assure valid neurocognitive test performance. Participants further had to meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (APA, 1994) criteria for a broad schizophrenia-spectrum disorder to be included (295.1, 295.2, 295.3, 295.6, 295.7, 295.9, 297.1, 298.9).

Exclusion criteria were head injury with loss of consciousness for more than ten minutes or requiring medical treatment, neurological disorder, IQ below 70, unstable or uncontrolled medical condition interfering with brain function and age outside the range of 18-65. Further, participants scoring 3 or more on violent behavior, severe alcohol and/or drug dependence and suicidal ideation as measured with the Health of the Nation Outcome Scales (Wing et al., 1998) were excluded.

#### ***Healthy controls***

Participants in the healthy control group in paper I were screened for mental problems with the MINI International Neuropsychiatric Interview screening module (Sheehan et al., 1998). Exclusion criteria were history of schizophrenia or other severe mental illness, mental retardation, any history of neurological disease, head injury and/or loss of consciousness for more than 10 min, current use of psychotropic medication, chronic somatic illness causing significant fatigue or pain, history of alcohol or substance abuse, dyslexia, significant learning disabilities and inability to understand spoken and written Norwegian sufficiently enough to comprehend testing instructions. All control participants were asked to refrain from drinking alcohol or taking



sleeping pills the day before assessment. From a pool of 250 healthy controls, 137 were group-wise matched to patients on age and gender.

### **3.6 Participants**

At baseline, the full JUMP study sample consisted of 148 participants meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (APA, 1994) criteria for a schizophrenia spectrum disorder. Of these, 137 participants completed the neurocognitive assessment at baseline. Due to the neurocognitive focus in the three papers included in the present thesis, six non-native speakers were excluded from analyses because their language abilities were thought to impact negatively on their neurocognitive performance. A total of 131 participants were thus included; 88.5% with schizophrenia, 7.6% with schizoaffective disorder, 2.3% with delusional disorder and 1.6% with psychotic disorder not otherwise specified.

Eighty seven percent had Norwegian as their mother tongue. The remaining 13% could be tested and interviewed in Norwegian. Only 5.3% of the patients were not medicated at time of assessment; the remaining participants were treated with antipsychotics. Sixty four percent were medicated with atypical antipsychotic medication and 23% were medicated with more than one type of antipsychotic medication. In all three papers, the JUMP sample consisted of the same 131 participants. In Papers I and II, baseline analyses were carried out for the complete JUMP sample (N=131), in Paper III, longitudinal analyses were performed and the JUMP sample was split into intervention groups;  $N_{CR} = 63$ ,  $N_{CBT} = 68$ . The participant flow is depicted in Figure 1. One hundred and thirty one healthy controls were included at baseline.

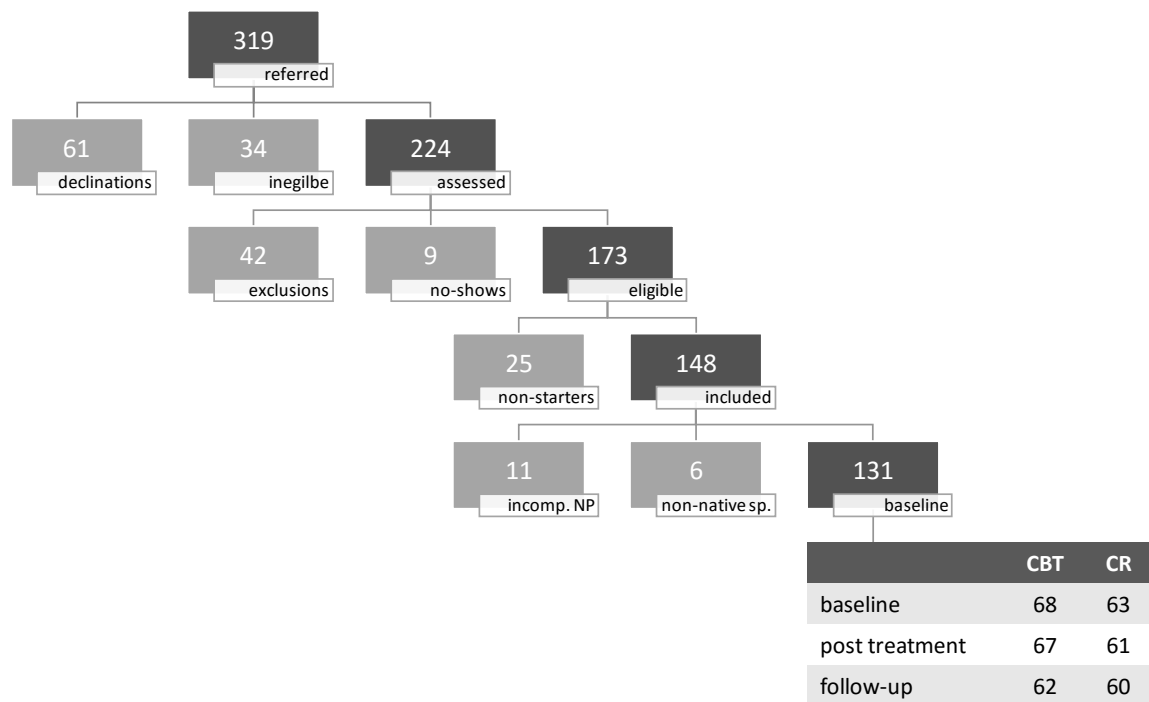


Figure 1: Subject flow in the JUMP study; referrals, baseline and follow-up assessments. NP = neuropsychological assessment.

A complete overview of the JUMP sample including a description of the healthy control group is shown in Appendix 1. The JUMP sample split into intervention groups is described in Appendix 2.

### 3.7 Assessments

JUMP participants underwent an extensive test battery, including clinical, neurocognitive and functional measures. Only the measures relevant for the current thesis are described here.

#### 3.7.1 Clinical assessment

##### *Diagnostic assessment*

Clinical assessment was carried out by trained clinicians. The Norwegian version of M.I.N.I PLUS (Sheehan et al., 1998) modules A, C, D, K, L, and M was used for diagnostic purposes. All assessors were trained and calibrated on the use of MINI PLUS. During assessment, the Longitudinal, Expert, All Data (LEAD) (Kranzler et al., 1994; Spitzer, 1983) procedure was applied when necessary, with additional course-relevant data collected from physicians, mental health professionals, care providers etc.

### ***Psychotic symptoms***

Current levels of psychotic symptoms were rated using the Structural Clinical Interview of the Positive and Negative Syndrome Scale (SCI-PANSS)(Kay et al., 1987).

### ***Duration of illness***

Duration of illness was retrieved from hospital journals and was defined as the time from the first contact with the mental health services for psychotic symptoms to the participant's entry into the JUMP study.

### ***Antipsychotic medication***

Medication was assessed by recording whether or not the participant was using antipsychotic medication, if yes, type (typical versus atypical antipsychotics), dosage and number of months participants had use their main antipsychotic medication. For statistical purposes, main dosages were converted to a measure of defined daily dose (DDD)(WHO, 2011). The DDD measure indicates the relative potency of intake of antipsychotic medication, with the value of 1 expressing the standard daily dose of a specific drug. The DDD system has been established to reliably standardize antipsychotic dosages (Nose et al., 2008).

## **3.7.2 Neurocognitive assessment**

The neurocognitive assessment was carried out by clinicians trained in standardized neuropsychological testing. All tests were administered in a fixed order with in between breaks.

### ***Intelligence Quotient (IQ)***

Current IQ was estimated with the Wechsler Abbreviated Scale of Intelligence (WASI, 2007), two subtests form. This form includes Vocabulary and Matrix Reasoning and provides a full scale IQ score (FSIQ).

### ***The MCCB neurocognitive domains***

Neurocognition was assessed with the MCCB except for the Mayer-Salovey Emotional Intelligence Test (MSCEIT), which was not part of the JUMP test protocol. Thus, the battery consisted of nine subtests to assess six cognitive domains including:

1. *Speed of Processing* using the Trail Making Test (TMT A) (United States War Department, 1944), the Brief Assessment of Cognition in Schizophrenia (BACS)

(Keefe, 1999); Symbolcoding and Category Fluency: Animal naming (Blair and Spreen, 1989).

The TMT A is a timed paper-pencil test in which participants draw a line to connect consecutively numbers randomly placed on a sheet of paper. Total completion time is obtained.

The BACS is a symbol coding test that involves writing numbers corresponding to non-sense symbols as fast as possible for 90 seconds. Scores are obtained for the correct number of symbols coded.

Category fluency is an oral test in which participants are required to name as many animals as possible in 60 seconds. Scores are obtained for the number of animals produced.

2. *Attention/Vigilance* using the Continuous Performance Test—Identical Pairs (CPT-IP) (Cornblatt et al., 1988).

The CPT-IP is a computer-administered test of sustained attention. Participants press a response key whenever two identical numbers appear consecutively. Mean  $d'$  values are obtained across 2-, 3- and 4-digit trials,  $d'$  represents the computed index of signal/noise discrimination.

3. *Working Memory* using the University of Maryland -Letter-Number Span (LNS) (Gold et al., 1997) and the Wechsler Memory Scale (WMS®-III) (Wechsler, 1997): Spatial Span.

The LNS requires participants to mentally reorganize an orally presented list of numbers and letters and then repeating them to the test administrator. The total numbers of correct letter-number-strings are obtained.

The WMS requires participants to tap blocks placed on a board in a) the same and b) the reverse order as the administrator. A sum score consisting of both conditions (forwards and backwards) is obtained.

4. *Verbal Learning and Memory* using the Hopkins Verbal Learning Test—Revised™ (HVLT-R™) (Brandt and Benedict, 2001).

The HVLT-R is an orally administered test in which a list of 12 words from three different categories is presented. Participants are instructed to recall as many words as possible after each of three trials. The sum of correct repeated words is used as a measure of verbal learning ability.

5. *Visual Learning and Memory* using the Brief Visuospatial Memory Test—Revised (BVMT-R™) (Benedict, 1997).

The BVMT-R is a test that requires participants to observe six geometric figures on a sheet of paper for ten seconds and then reproduce as many as possible after each of three trials. The total sum of number of points awarded for recalled drawings is used as the score of visual learning.

6. *Reasoning and Problem Solving* using the Neuropsychological Assessment Battery (NAB®) (White, 2003): Mazes.

Mazes is a timed paper-and-pencil test with gradually increasing difficulty. Points are given based on the time used to solve each of seven mazes.

A modified MCCB neurocognitive composite score was calculated using the mean of the nine demographically corrected domain T-scores (Burton et al., 2013; Vargas et al., 2014)

### **3.7.3 Functional assessment**

#### ***Education and previous employment***

Education level was assessed through structured interviews performed by site coordinators. Participants were asked about their highest level of education which was recorded as number of years. Employment history was registered as total number of months in part time or full time competitive employment or work placement. Participants who were working at baseline assessment were either trying to transit from sheltered to competitive employment or were not coping with the current job demands and were in need of support in order to maintain employment. Education and previous employment were entered into analyses in paper I of the present thesis.

#### ***Self-rated Social Functioning***

Social functioning was measured with the Norwegian version of the Social Functioning Scale (SFS) (Birchwood et al., 1990), yielding information about both *competence* and *performance of activities* important for everyday functioning (Burns and Patrick, 2007). This self-report scale comprises of 76 items and assesses seven subscales; *Withdrawal*, *Interpersonal behavior*, *Pro-social activities*, *Recreation*, *Independence-competence*, *Independence-performance* and *Employment*. Norms are based on the performance of patients with schizophrenia and high scores indicate better performance. Each subscale has a standardized mean of 100 with a standard deviation of 15. The Norwegian version of the SFS is validated for use in both patients with schizophrenia and bipolar disorder (Hellvin et al., 2010). A full scale SFS total score was calculated based on the seven subscales. The SFS was used in paper I of the current thesis.

### ***The Vocational Cognitive Rating Scale (VCRS)***

The VCRS (Greig et al., 2004) was developed to assess neurocognitive demands on-the-job in persons with severe mental illness. The Norwegian version of the VCRS was translated by Torill Ueland and back-translated to English. It has been approved as the official Norwegian version by the original developers. The VCRS consists of 16 items anchored along a five point scale, 1 = *consistently inferior performance* to 5 = *consistently superior performance*, giving a total score, ranging from 16 to 80. The VCRS was rated by trained employment specialists after a 15 minute observation of the participant at work and an interview with the immediate supervisor.

### ***The Work Behavior Inventory (WBI)***

The WBI (Bryson et al., 1997) was developed for the assessment of occupational functioning for people with severe mental illness. The Norwegian version of the WBI was translated by Torill Ueland and Beathe Haatveit and back-translated to English. It has been approved as the official Norwegian version by the original developers. It consists of 36 items distributed on five sub-scales, and one global score rating general occupational functioning. The five sub-scales are Social skills, Cooperativeness, Work quality, Work habits and Personal presentation. Items are rated on a five-point scale, 1 = “*Consistently an area needing improvement*” to 5 = “*Consistently an area of superior performance*”. The WBI total score is computed by adding all subscale scores. The WBI Global score is the rater’s judgment about overall work performance and differs from the Total score in that it reflects the rater’s global evaluation without equally weighting each subscale. In Paper II, the WBI Total and Global scores are reported. The WBI was rated by trained employment specialists based on a 15-minute on-the-job behavioral observation and an interview with the immediate supervisor.

To ensure consistency and reliability of rating across the study, employment specialists were trained with and calibrated on the WBI and the VCRS using manuals and videotape material. Similar training in previous studies resulted in VCRS and WBI global and total scores with excellent inter-rater reliability (Bell et al., 2009; Bryson and Bell, 2003; Greig et al., 2004). Assessments were continuously discussed among employment specialists on each site to ensure consensus ratings.

### ***The Complexity Scale***

Job complexity was rated using a complexity scale (Bell et al., 2009). The Complexity Scale ranges from 1 to 5, with higher scores indicating that the job requires multiple tasks, greater autonomy and more interpersonal contact. 1 = *Consistently Low Level of Complexity*, 3 = *Average Level of Complexity* and 5 = *Consistently High Level of Complexity*. To ensure equal ratings, all work tasks were discussed within the JUMP research team. Complexity was divided into two groups, low complexity (1 and 2) and average to high complexity (3, 4 and 5).

The VCRS, WBI and Complexity Scale were employed in Paper II of the present thesis. All three instruments were scored *before* the beginning of the CR and CBT interventions. Participants had worked an average of 6.5 weeks (SD 5.65) prior to these work assessments.

### ***Type of work***

Type of work was categorized as competitive (including work placement in a competitive setting) or sheltered work in Paper II.

Occupational status, categorized as working (sheltered work, competitive work or work placement in a competitive setting) versus not working and number of hours worked per week among participants working at follow-up were recorded in Paper III. Work placement in a competitive setting is a time-limited placement in a competitive job where the person works for benefits without receiving wages.

## **3.8 Statistical analyses**

The Statistical Package for the Social Sciences (IBM SPSS) version 20.0 (2011) was used for all statistical analyses.

All MCCB raw scores were converted to T-scores based on published US norms for the tests (Kern et al., 2008). A modified MCCB neurocognitive composite score was calculated using the mean of the nine demographically corrected domain T-scores. All tests were two-tailed if not indicated otherwise. Chi Square tests were applied when comparing categorical data, Student t-tests and analysis of variance (ANOVA) for group comparisons of continuous data and Pearson's  $r$ /Spearman's  $\rho$  for correlations. Levels of significance were set at  $p = .05$ . Effect sizes were calculated with *Cohen's d* (Paper I and II) or *partial eta squared*,  $\eta_p^2$  (Paper III). Bonferroni corrections were applied to counteract the problem of multiple comparisons.

Multiple hierarchical linear regression and logistic regression analyses were applied to examine the predictive values of neurocognition in all three papers.

Linear mixed models (LMM) for repeated measures were applied to analyze longitudinal effects in Paper III.

In Paper I a 2 (group) X 7 (neurocognitive domains) multivariate analysis of variance (MANOVA) was conducted with group (JUMP participants versus healthy controls) as the between-subjects variable and the MCCB domain scores as the dependent variables. Further, the proportion of impaired patients and controls on each domain was calculated, with 1.5 and 2 standard deviations below the mean of the healthy controls set as threshold for clinically significant impairment. T-tests were carried out to determine differences in the magnitude of impairments between the two groups. Within the patient group, we conducted a one-way ANOVA to measure differences in neurocognitive performance with regard to level of education. Further, we explored associations between the MCCB domains and employment history. Hierarchical multiple regression analysis was carried out to further explore the underlying relationship between previous employment and neurocognitive functioning as measured with the neurocognitive composite score, supplemented with age, gender, and education. Finally, bivariate correlations between the MCCB domains and SFS subscales were examined, followed by a multiple hierarchical linear regression analysis with demographic variables and the MCCB domains as predictor variables and SFS total score as criterion.

In Paper II, correlations between the MCCB domains and workplace assessments were carried out. Given significant correlations, MCCB domains were entered in hierarchical multiple linear regression analyses with VCRS Total, WBI Total and WBI Global scores as criterion variables controlling for age, gender, educational level, previous employment and length of time between the beginning of work and work assessments in the vocational rehabilitation program. Further, participants were categorized as “Low Complexity” or “Higher Complexity” workers based on CS scores (ratings of 1 or 2 = Low Complexity; 3, 4 or 5 = Higher Complexity) and on competitive versus sheltered employment. These categories were then compared on MCCB performance employing Student’s t-tests.

Finally, in Paper III linear mixed models (LMM) for repeated measures were applied to analyze the neurocognitive course by treatment group, using intercepts as random effects.



Multiple logistic regression analyses were applied to explore group differences in occupational status and multiple hierarchical regression analyses to examine predictors of hours worked.

A thorough description of the statistical analyses used in this thesis is presented in the three papers.

### **3.9 Ethical Considerations**

The JUMP study was approved by the Regional Committee of Medical Research Ethics and the Norwegian Data Protection Authority. ClinicalTrials.gov Identifier: NCT01139502.

All participants provided written informed consent after a complete description of the study. Information explaining purpose, procedures, data collection, data security and confidentiality was presented both orally and written. Being diagnosed with a psychotic disorder involves having periods of impaired ability to test reality or even reality loss. Consequently, only participants who had a clear understanding of the protocol and who could give informed consent were included.

Another important issue with reference to ethics is the time consuming test protocol including a wide range of clinical, neuropsychological and functional measures. To ensure that the study protocol was not too overwhelming, assessors were flexible with regard to time and place of assessments and frequent breaks were included.

Some of the information collected was also very personal and of a sensitive nature. Thus, assessors sought to create an empathic and warm atmosphere during measurement sessions.

Individuals with severe mental illness frequently receive disability benefits. In addition, they can earn a certain amount of money without having their allowances shortened as part of a 'permitted work' arrangement. Some JUMP participants however feared exceeding this threshold or losing benefits. Efforts were made to prevent this from happening in terms of offering work placement. NAV coordinators also provided exact information regarding security benefits and extra earnings threshold so that participants would not experience economic loss as a consequence of taking part in the JUMP study.

In order to avoid workplace stigma and discrimination, individuals with schizophrenia will usually go to great lengths to ensure that coworkers and employers do not find out about their

illness. Participating in a psychosis research program may thus be stigmatizing. Disclosure, if desirable, was discussed with the employment specialist and strategies were developed as to how and what to divulge in the work setting. If this was the case, education about psychotic illness was then provided by the local health coordinator to employers and co-workers in order to reduce stigma and promote employment equity for people with mental disabilities.

All participants were informed that they could withdraw from the study at any given time and that this would have no negative consequence for future treatment or cooperation with health- or welfare services.

## 4. Summary of papers

### ***Paper I: The MATRICS Consensus Cognitive Battery (MCCB): performance and functional correlates***

*Background:* Neurocognitive impairment is a core feature in psychotic disorders and the MATRICS Consensus Cognitive Battery (MCCB) is now widely used to assess neurocognition in this group. The MCCB has been translated into several languages, including Norwegian; although this version has yet to be described in an adult clinical population. Further, the relationship between the MCCB and different measures of functioning needed examination. The purpose of this study was to investigate neurocognition assessed with the Norwegian version of the MCCB in a sample of patients with psychotic disorders compared to age and gender matched healthy controls and to examine the association with educational-, occupational- and social functioning in the patient group.

*Methods:* One hundred and thirty one patients and 137 healthy controls completed the MCCB. In the patient group, all participants were assessed with the Social Functioning Scale. In addition, previous employment and level of education were recorded.

*Results:* The Norwegian version of the MCCB was sensitive to the magnitude of neurocognitive impairments in patients with psychotic disorders, with patients displaying significant impairments on all sub-tests and domains relative to healthy controls. Neurocognition was also related to both self-rated and objective functional measures such as social functioning, educational- and employment history.

*Conclusions:* The study replicated findings from similar MCCB studies from other countries; patients display significant impairments on all MCCB domains. The Norwegian version of the MCCB was thus sensitive in detecting differences between patients and healthy controls, supporting the robustness of the MCCB for use in different countries. Visual Learning and Processing Speed were the most afflicted domains both with regard to magnitude and number of patients impaired. Working Memory was the least impaired neurocognitive domain. The MCCB further differentiated between different levels of academic achievement and employment history. There were only moderate bivariate associations between neurocognition and social functioning, probably due to the self-rating nature of the SFS. Working Memory however does seem to overlap with social functioning.

## ***Paper II: Neurocognition and Occupational Functioning in Schizophrenia Spectrum***

### ***Disorders: The MATRICS Consensus Cognitive Battery (MCCB) and Workplace Assessments***

*Background:* The MCCB is widely used in clinical trials of schizophrenia, but its relationship to occupational functioning still needs further elaboration. While previous research has indicated that various domains of neurocognition assessed by individual tests are related to work functioning, these reports preceded the development of the MCCB as the standard neurocognitive test battery in the field. The purpose of the current study was to investigate the relationship between MCCB performance and different measures of occupational functioning.

*Methods:* In the current study, the vocational functioning of 131 Norwegian participants with schizophrenia spectrum disorders who were enrolled in a vocational rehabilitation program were assessed on the Vocational Cognitive Rating Scale (VCRS), the Work Behavior Inventory (WBI), and the Complexity Scale (CS) as well as on the MCCB. Type of work (sheltered versus competitive work) was also recorded.

*Results:* Significant correlations were found between most MCCB domains and VCRS Total Score. MCCB Processing Speed and Attention were most powerfully related to and predictive of WBI scores. When participants were divided into “low complexity” or “higher complexity” work categories, participants in the “low-complexity” group performed significantly worse than participants in the “higher-complexity” group on Processing Speed, Working Memory, Visual Learning and the Composite Score. The same pattern emerged for participants working in sheltered compared to competitive jobs.

*Conclusions:* The VCRS, WBI and CS may be useful in vocational rehabilitation. They bridge an important gap between laboratory test- and occupational setting, providing valuable information about impairments related to occupational functioning. We found the MCCB to be sensitive to occupational functioning as measured by VCRS, WBI and CS and with regard to type of work, with neurocognition accounting for a small but significant proportion of the variance in these different measures of occupational functioning.

## ***Paper III: Cognitive Remediation and Occupational Outcome in Schizophrenia Spectrum***

### ***Disorders: A 2 year follow-up study***

*Background:* Neurocognitive impairment is prominent in schizophrenia and significantly contributes to poor occupational outcomes. Neurocognitive deficits also predict poor engagement in vocational rehabilitation programs. Employment is a commonly sought goal for people with

schizophrenia, yet employment rates are consistently low. SE/IPS programs are frequently implemented to counteract high unemployment rates. However, despite superior competitive employment outcomes, people with schizophrenia still face numerous occupational challenges such as neurocognitive impairments and psychotic symptoms. Hence, augmenting SE/IPS to address illness-related factors in order to optimize occupational outcomes may be advantageous. The aim of this study was to examine the effects of a CR- compared to a CBT-augmented vocational rehabilitation program (JUMP) on neurocognition and occupational functioning in participants with schizophrenia spectrum disorders. Specifically, we evaluated the effects of the interventions on neurocognitive and occupational outcomes over a two year period.

*Methods:* One hundred and thirty one participants were included in the study, 68 and 63 respectively allocated to the CBT and CR interventions. Participants underwent MCCB assessment at baseline, at post treatment and 2 years after inclusion in the JUMP study. Occupational status and number of hours worked were recorded. Linear mixed model for repeated measures were applied to analyze changes in neurocognitive variables by intervention group. Differences in occupational status and number of hours worked were examined and finally, separate regression analyses for the two intervention groups were conducted to establish whether neurocognitive change predicted occupational status and number of hours worked.

*Results:* There were no significant differences regarding demographic, clinical, neurocognitive or medication variables between the participants in the two intervention groups at baseline except for gender, which was consequently entered as a covariate in all between group analyses. Both intervention groups improved on several neurocognitive domains, although all improvements were in favor of the CR group. There was a significant main effect for CR for Verbal Learning and a significant time x intervention effect for Working Memory and the Neurocognitive Composite Score. For occupational status and number of hours worked, there was a significant increase in number of participants working and the number of hours they worked in both intervention groups, with no between group differences. With reference to predictors of occupational status at 2 year follow-up, we found a significant model for the CR group only. Number of received intervention hours was the significant predictor. Number of hours worked was predicted by change in Working Memory and change in the Neurocognitive Composite Score in the CR group. We could not establish any significant models for the CBT intervention.

*Conclusions:* CBT- and CR-augmented vocational rehabilitation induced improvements in several neurocognitive domains, the greatest enhancements were however in favor of the CR

group. Particularly Verbal Learning and Working Memory, which were central elements in the CR program, improved. Concerning occupational outcome, the major implication of our findings is that the combination of vocational rehabilitation and CR or CBT enabled a significant proportion of JUMP participants to attain and maintain work. Neurocognitive change was not predictive of occupational status after 2 years. However, number of hours worked was significantly predicted by Working Memory change and the change in the Neurocognitive Composite Score in the CR group, which is in keeping with results from similar studies.

## 5. Discussion

### 5.1 Summary of main findings

The main aim of the current thesis was to investigate neurocognition in participants with broad schizophrenia spectrum disorders. Further we sought to investigate whether neurocognitive performance as measured with the MATRICS Consensus Cognitive Battery was reflected in different aspects of functional outcome; i.e. social functioning, type of work and different workplace assessments. Lastly, we examined the effects of CR in combination with vocational rehabilitation on neurocognition and occupational outcomes compared to CBT augmented VR. The main findings were:

#### *Paper I*

- I. Participants with schizophrenia spectrum disorders performed significantly poorer on all sub-test and domains as measured with the MCCB except for the WMS-SS. The Norwegian version of the MCCB was sensitive to neurocognitive impairments, supporting the robustness of the MCCB for cross-cultural use.
- II. Neurocognitive performance was reflected in measures of functioning. The MCCB differentiated between different levels of education and previous employment. Further, there was significant overlap between neurocognition and social functioning, with Working Memory predictive of the SFS Total Score.

#### *Paper II*

- III. There were significant associations between all MCCB domains except Verbal Learning and neurocognitive functioning on the job as measured with the VCRS at the beginning of the vocational rehabilitation program. No single MCCB domain predicted vocational cognitive functioning, but the Neurocognitive Composite Score did.
- IV. Processing Speed predicted the Work Behavior Inventory Total Score whereas Attention predicted the Global Score. The latter score was also predicted by the Neurocognitive Composite Score in a separate analysis.
- V. Neurocognitive performance was associated with both task complexity and type of work. Participants performing low complexity jobs performed worse on all neurocognitive domains. A similar pattern emerged for participants in sheltered work, performing poorer on all neurocognitive tests than participants in competitive work.

### ***Paper III***

- VI. Neurocognitive performance improved after both CBT- and CR-augmented vocational rehabilitation, with the greatest improvement in the CR group. The number of participants working increased between inclusion and follow-up as did also the number of hours worked. Number of received intervention hours predicted occupational status at follow-up in the CR group. Positive change in Working Memory and the Neurocognitive Composite Score predicted number of hours worked in the CR group. No regression models were significant for the CBT group.

## **5.2 Neurocognitive performance as measured with the Norwegian version of the MCCB**

In the first study, we found that patients not only performed poorer on all MCCB domains than healthy controls, they also had a much greater magnitude of neurocognitive dysfunction, illustrated by the high effect sizes particularly regarding Processing Speed and Visual Learning. These findings are in keeping with the performance patterns described in the substantial body of previous research reporting that persons with schizophrenia suffer from dysfunctions across an array of neurocognitive domains (August et al., 2012; Kern et al., 2011; Shamsi et al., 2011). The finding of poor neurocognitive function in participants with schizophrenia spectrum disorders as measured with the MCCB seems consistent with both previous (August et al., 2012; Shamsi et al., 2011) and later findings (Durand et al., 2015; Vargas et al., 2014).

### ***The particular role of Processing Speed***

Particularly, our findings confirm the constraints in the Processing Speed domain. Processing Speed has in meta-analytical findings been proposed to represent a general confinement on neurocognitive functioning (Dickinson et al., 2007b). Several sub-processes such as the handling of sensory information; encoding, manipulation and information retrieval are speed reliant. In addition, other higher rank operations such as Problem Solving and Decision Making, are largely speed dependent. Hence, overall neurocognitive performance is weakened when processing is slow due to the fact that relevant operations cannot be executed or that crucial information is no longer available as a result of time limitations (Salthouse, 1996).

Our findings, both in Papers I and II, indicated processing speed impairments and associations with functional outcome. Processing Speed was significantly and robustly associated with previous employment, vocational cognitive functioning and work behavior as well as a marker of



task complexity. Beyond bivariate relationships, Processing Speed predicted total work behavior with impairment mirroring poorer work performance. Thus, findings reported in this thesis seem to be concurrent with similar research (August et al., 2012; Milev et al., 2005) and at a practical level speed impairment may be a strong marker of task adaptation needs in supported employment programs or a potential target in cognitive remediation programs.

Processing Speed is also interesting in view of measurement. It is the only domain assessed with a total of three subtests in the MCCB. Consequently, it can be speculated that Processing Speed is particularly sensitive in detecting associations with functional outcome in general and occupational outcome in particular (Reddy and Kern, 2014).

### ***Neurocognition; educational and occupational correlates***

Considering the neurocognitive impairment displayed by the JUMP participants at inclusion in the study, i.e. before the beginning of the two interventions, we hypothesized that this would impact their functional outcome. In the first study, we found performance differences in accordance with academic level, that is, neurocognitive performance increased with higher level of education. Other studies have also reported that participants in school outperform participants not enrolled in an educational program across a series of domains, particularly sustained attention, working memory and problem solving (Lysaker and Bell, 1995; McGurk and Meltzer, 2000). This is also true for employed versus unemployed individuals. We also compared neurocognition with reference to work history. Most likely, participants had gathered most of their work experience before illness onset and/or had a less severe course of illness enabling them to work, i.e. better neurocognitive functioning would predict a longer period of employment. We did find that almost all participants had some previous work experience and that this was related to neurocognition, with several overlaps between MCCB domains and months of previous employment. The literature is replete with evidence of neurocognition strongly influencing work outcomes (Christensen, 2007; Green, 1996) and that better neurocognitive performance predicts more favorable outcomes of vocational rehabilitation (Bell and Bryson, 2001; McGurk and Mueser, 2004). As yet, little has however been done to examine the effects of work or vocational rehabilitation on neurocognitive performance. Interestingly, in exploratory analyses, we found previous employment to predict neurocognitive performance and not vice versa. This finding lends some support to the notion that work perhaps in some way adds to maintenance of neurocognition or serves as a 'cognitive rehabilitation arena' for participants with neurocognitive impairments. There is also some support in the literature for this (Bio and Gattaz, 2011;

Suresh Kumar, 2008). Performance on executive measures seems to particularly benefit from vocational rehabilitation, but also memory and vigilance performance increases as a result of work or vocational rehabilitation (McGurk and Meltzer, 2000). In summary, our findings with reference to the effects of work on neurocognition receive some support from previous findings. The cross-sectional nature of these studies do however not allow a conclusion to be drawn as to whether superior neurocognitive performance in the previously employed groups was a result of the working itself.

### ***Neurocognition and Social Functioning***

Education and previous employment are objective measures of functioning. We also investigated the relationship between neurocognitive performance and self-rated social functioning in Paper I. Functioning can thereby be delineated into *functional capacity* reflecting the ability to perform a task if given the opportunity and *real world functioning* reflecting actual performance (Bromley and Brekke, 2010). Our results tie in with findings from several other studies as we found significant relationships between social functioning and neurocognition (Simonsen et al., 2010; Tandberg et al., 2012). In the first study, we mainly found associations between competence related aspects of social functioning and neurocognition. The MCCB domain most strongly linked with social functioning was working memory, significantly associated with three of the subscales and a significant predictor of the SFS Total score. Impairments in working memory may possibly affect both the encoding and organization of (social) information as the correct handling of social or interpersonal situations often requires attention to multiple strings of information (Bowie and Harvey, 2006). Although we established some degree of overlap between neurocognition and self-rated social functioning, relationships were in general relatively moderate and in particular stronger for competence than performance. This may on the one hand be rooted in methodology as self-rated measures typically do not relate strongly with objective neurocognitive measures (Harvey et al., 2007; Nuechterlein et al., 2008; Sabbag et al., 2011). Further, the evaluation of one's own competence is frequently more robustly linked with neurocognition than actual performance (Green et al., 2004). On the other hand, other factors may be more predictive of social functioning than neurocognition. Current level of psychotic symptoms has been found to contribute to self-rated psychosocial functioning in some recent studies (Leifker et al., 2009; Perlick et al., 2008; Simonsen et al., 2010) and this may also be the case in Paper I. We did not enter PANSS scores into the regression analysis; hence, it would be speculative to presume such a prediction. Results regarding the longitudinal predictive value of neurocognition on social functioning are thus far inconsistent in the literature. In

Paper I, social functioning was assessed at the same time as neurocognition, e.g. in a cross-sectional design. It may be that the longitudinal relationship is stronger, which was found in a different study (Tabares-Seisdedos et al., 2008) with neurocognition as the strongest predictor of functioning in schizophrenia and bipolar disorder.

In sum, participants in the JUMP study displayed significant neurocognitive impairment which in turn was moderately associated with social functioning. We could not establish a strong predictive relationship, suggesting that other factors such as symptoms or duration of illness may be more relevant for social functioning or possibly mediating the path from neurocognition to social functioning as also proposed by Ventura and colleagues (Ventura et al., 2009). Moreover, some participants may be able to compensate for their neurocognitive impairments in the highly structured test-setting. That is, the association between neurocognitive performance and social functioning is partly concealed by the effort invested in the test situation. In social settings however, with an uninterrupted stream of information in need of processing, this compensation is more likely to be unsuccessful and the neurocognitive impairment becomes relevant. Findings from Ramsey et al (Ramsey et al., 2002) lend some support to this hypothesis. They found patients with schizophrenia to show elevated activity on performance-corrected tasks and that task engagement was an important predictor of performance. The strength of our correlational findings may further depend on several other factors such as the rating scale, relapse rate, insight, actual possibilities to perform social tasks and self-awareness. To summarize, our findings are essentially within the range of previous findings of similar studies both regarding neurocognitive impairment in schizophrenia and the concurrent associations with functional outcome measures. Neurocognitive performance was impaired in JUMP participants compared to healthy controls and to some degree reflected in social functioning, educational achievement and previous work.

### **5.3 Neurocognition and occupational functioning: The MCCB and workplace assessments**

The present thesis established several coexisting relationships between neurocognition and workplace assessments, strengthening the occupational relevance of the MCCB.

Various observations have led to the hypothesis that compromised neurocognitive functioning is fundamentally intertwined with occupational outcome (Bowie and Harvey, 2005; Keefe and Harvey, 2012; Nuechterlein et al., 2011; Reichenberg, 2010; Shamsi et al., 2011) which ties with our findings in paper II.

### ***Vocational cognitive function***

In accordance with findings from the standardization study, neurocognitive performance corresponded with ratings on the Vocational Cognitive Rating Scale (Greig et al., 2004). Greig and colleagues also found strong relationships between measures of neurocognition and cognitive functioning on-the-job. The VCRS thus seems to capture some of the neurocognitive challenges participants display in a structured test-setting, in the real world. Based on this finding, the VCRS is a promising tool in vocational rehabilitation programs for persons with schizophrenia, as it may point to particular accommodation needs.

In the national Norwegian Guidelines for Psychosis Assessment and Treatment (Helsedirektoratet, 2013), neuropsychological assessment is recommended as part of the standard assessment regime for individuals with schizophrenia. The recommendation is rooted in the notion that neuropsychological assessments may be helpful in understanding the unique neurocognitive dysfunction of an individual as well as offer guidance in the planning of treatment and rehabilitation. Despite being strongly advised, neuropsychological assessment is not a standard part of diagnostic protocols in psychoses, often due to lack of time and resources in clinical settings. The VCRS cannot by any standard replace a neuropsychological assessment, but it may be sensible to use it as a screening tool in order to enable individualized tailoring in vocational rehabilitation. Hence, the VCRS may be a strong supplement to help clients who struggle in vocational settings to achieve optimal occupational functioning.

### ***Work Behavior***

Several domains of the MCCB tapped into the two aspects of work behavior as assessed in the second study. The Work Behavior Inventory offers valuable information regarding work performance, beyond a dichotomized categorization or the recorded number of hours worked in a defined period of time. Comparing our findings with those of other vocational rehabilitation studies, they are consistent in suggesting that the WBI is sensitive to neurocognitive impairment in different stages of illness and after different treatment and rehabilitation programs (Bell et al., 2009; Bryson and Bell, 2003; Choi and Medalia, 2005; Wykes et al., 2012). Typically, the five WBI subscales and the WBI total score are criterion variables in rehabilitation studies. To our knowledge, few studies have examined the relationships between neurocognition and the WBI global score. As opposed to the Total Score, the arithmetic sum of all subscales, the Global Score reflects the general rating of work behavior. Hence, the latter does not equally weigh the subscales but is the evaluation of the rater (in this case, the employment specialist) based on

interview and brief observation. It may be that the Global Score captures something slightly different in terms of general work performance and that this may point to readiness for competitive employment. It seems to be a reliable and important supplement to the sub-scales and the total score.

Verbal Learning and Memory has previously been robustly linked to occupational outcome (Bowie and Harvey, 2006; Green, 1996; McClure et al., 2007). This thesis found no concurrent associations between the verbal learning domain and the VCRS or WBI. As we have speculated in paper II, this may be due to the stage of vocational rehabilitation. Literature suggests that verbal learning may gradually become more important as rehabilitation progresses and that other domains such as attention and working memory are more relevant at the beginning of vocational programs (Toulopoulou and Murray, 2004). Another possible explanation for the lacking relationship between Verbal Learning and occupational functioning may be the nature of the Verbal Learning/Memory assessment in the MCCB, specifically the HVLT-R (Brandt and Benedict, 2001). The HVLT-R has been reported to be a valuable screening tool for impairments related to verbal material. However, in the MCCB a delayed recall trial is not included which in turn may limit the assessment of information retention, a key component in the examination of memory (Lacritz and Cullum, 1998). Lacritz and Cullum investigated verbal learning and memory performance in Alzheimer disease (Lacritz et al., 2001) and proposed ceiling effects on the HVLT-R that may not be present in the California Verbal Learning test (CVLT) (Stone et al., 2015); that is, the list learning task may not be difficult or long enough to extract recall errors (the HVLT-R contains 12 while the CVLT-II contains 16 words). This may also be the case in schizophrenia patients. Although JUMP participants did show significant impairment on this particular domain, perhaps this does not translate into occupational performance. Nonetheless, the HVLT-R was sensitive in differentiating patients and healthy controls and thus provides a brief and valid measure of verbal learning in schizophrenia spectrum disorders.

### ***Task Complexity and Type of Work***

The importance of neurocognitive impairment for occupational outcome was also evident in the Paper II. MCCB performance differentiated between high and low task complexity and sheltered versus competitive work setting. All effect sizes were in the moderate range regarding job complexity, with the MCCB neurocognitive composite score even more powerful in separating the two categories. With reference to type of work, effect sizes were somewhat lower,

although participants in sheltered work performed consistently poorer than those working competitively. These findings are fairly consistent with similar studies, suggesting that participants with larger neurocognitive impairments may require higher levels of support during vocational rehabilitation (McGurk et al., 2003). Further, participants with poorer neurocognition may benefit from closer monitoring, more frequent prompts and more redirection to sustain occupational performance.

To summarize, few studies have yet investigated the relationships between the MCCB and occupational performance beyond occupational status or other dichotomized categories (good versus poor etc.). Employing the VCRS, the WBI, Job Complexity and type of work showed that the neurocognitive impairments found in JUMP participants were reflected in occupational functioning. Particularly, working memory and visual learning seemed to relate to level of functioning. These findings may expand our understanding of how neurocognitive factors are related to occupational outcomes and how to use vocational rehabilitation services in an optimal manner. Clients with less neurocognitive impairment may need less vocational training and support in vocational rehabilitation programs in order to maintain work, whereas service use will tend to be higher with more neurocognitive dysfunction. Also, our findings point to the importance of enhancing VR with cognitive remediation. Augmenting vocational programs with cognitive remediation, particularly addressing working memory, attention and processing speed, may lead to better work outcomes in terms of competitive employment and better work performance, in turn enabling sustained employment.

#### **5.4 Cognitive remediation, Vocational Rehabilitation and Occupational Outcome – longitudinal findings**

Our main aim in Paper III was to evaluate the short- and long-term effects of a CR augmented compared to a CBT augmented vocational rehabilitation program.

##### ***Longitudinal course of neurocognition***

Both intervention groups showed improvements in several different areas of neurocognition with the greatest enhancements in the CR group. This thesis thus adds to the comprehensive literature on the effects of CR on neurocognition in schizophrenia (Eack et al., 2009; McGurk et al., 2015; Ostergaard Christensen et al., 2014; Penades et al., 2006). Verbal Learning and Working Memory were particularly responsive to the CR program which is in line with other research (McGurk et al., 2009; Ostergaard Christensen et al., 2014). The improvement in these

neurocognitive domains may on the one hand be rooted in the computer-based training program focusing on tasks related to Verbal Memory and Working Memory. On the other hand, compensatory and practical elements incorporated in the CR intervention and the fact that participants were able to practice these CR strategies for occupational functioning may have enhanced the effects on these particular domains.

Another possible explanation for positive effects of CR on neurocognition is a more sufficient allocation of neurocognitive resources (Storzbach, 1996). The employment specialist guided participants through all sessions of CR, verbalizing goals and strategies, bridging them to real-world settings (occupational settings). Consequently, participants may be able to better focus their processing capacity on salient stimuli, e.g. the task at hand. Further, automatization may have occurred, releasing neurocognitive capacity as load decreases or task irrelevant stimuli are excluded. CR has perhaps facilitated automatization of neurocognitive processes through drill and practice, repetitions and task strategies suggested by the cognitive trainer.

Problem Solving was the domain to improve the least in the CR group. Another study has also reported this (Ostergaard Christensen et al., 2014) and attributed the finding to ceiling effects on the NAB Mazes test. In accordance with their findings, we also found relatively little impairment in the CR group at baseline in this domain. Hence, participants in our study may have reached a plateau with little room for improvement. It may also be speculated that the high level of performance on the NAB Mazes makes the measurement more inaccurate; differentiation and sensitivity to change may become more difficult at either ends of the performance scale.

The immediate effect on Verbal Learning in the CR group is important, given the indication by longitudinal studies that there may be a long-term decline of Verbal Learning in schizophrenia (Bozikas and Andreou, 2011) in addition to the strong link with functional outcome and the ability to profit from rehabilitation (Green, 1996). If CR is implemented early and has effects on verbal learning and memory, it can significantly reduce the influence of this particular domain as a rate limiting factor in vocational rehabilitation.

The longitudinal course of neurocognition in the JUMP participants still improved in the CBT group, however less marked and even decreasing slightly with regard to working memory and verbal learning. A Spanish study found similar results when comparing CBT and CR (Penades et al., 2006), indicating that CBT also may be associated with neurocognitive improvements. CBT combined with VR thus also provided the opportunity to acquire and practice new neu-

rocognitive skills. Finally, the two intervention groups aligned toward the follow-up assessment, possibly pointing to the importance of booster sessions and the importance of the employment specialist implementing compensatory strategies. Regarding intervention effects on neurocognition, it seems sensible to conclude that the two interventions target different areas; CR targets neurocognition whereas CBT mainly targets psychotic symptoms.

### ***Occupational outcomes***

Our next aim was to evaluate the occupational outcome of the JUMP program. Both the short- and long-term effects of JUMP participation are striking, with significant increases between baseline and post treatment and the high level of employment even at follow-up assessment. In accordance with similar findings, we found that a considerable proportion of participants with broad schizophrenia spectrum disorders willing and able to work, given the possibility and adequate support (Bell et al., 2005; Bevan, 2013; Mueser and McGurk, 2014). Much of the discourse regarding the employment of persons with schizophrenia derives from the perspective of the needs of individuals living with the illness. It is however essential to also consider the perspective of welfare services and employers. The JUMP study aimed to make it easier for employers to employ persons with schizophrenia by providing them with the support they need to stay in work, which seems to have succeeded. The long-term effects on occupational status may imply that even after the active intervention period and less support from the employment specialist, the employers were more likely to see and value the skills and experience of the individual and keep them on.

Although we found an increase in participants working competitively throughout the assessment period, numbers were not as high as in SE/IPS studies. This must be interpreted in light of the strong tradition within the Nordic welfare model to routinely offer sheltered work or work placement for lengthy periods in order to obtain competitive employment (Hagen et al., 2011; Spjerkavik, 2012). The goal of open paid employment is important and work placement may be a stepping stone on the path to competitive work. Nevertheless, in Norway, work placement rarely translates into competitive employment (Spjerkavik, 2012). This tradition, in addition to relatively high social security benefits, provides a framework that is somewhat different than in other welfare systems, and may shed light on competitive employment numbers in the JUMP study. Considering all kinds of employment (competitive, sheltered or work placement) may thus be of importance when interpreting and comparing results from different countries. It appears however to be a development in the use of SE/IPS programs in Norway. Further,



competitive employment may not be attainable or desirable for some individuals with schizophrenia. Sheltered work may in these cases provide a different but important pathway to work or activity. Some persons with severe mental illness may even choose to do voluntary work. Volunteering can thereby provide the added satisfaction of helping others in addition to function as work preparation.

The combined elements of the JUMP study also have unspecific effects on neurocognition, psychotic symptoms and occupational functioning. We thus speculate that barriers often obscured by the diagnosis of schizophrenia gradually became less salient and less important through the JUMP study.

Although JUMP participants showed clinically significant neurocognitive impairment at inclusion, neurocognitive improvement only had limited predictive value on long-term occupational status and number of hours worked, indicating that other factors perhaps override the influence of neurocognition. It may also indicate that occupational status and number of hours worked are less sensitive to neurocognitive change than perhaps to occupational performance. We did not have WBI or VCRS data at follow-up assessment, perhaps bereaving us of the possibility of detecting associations.

### ***Neurocognitive predictors of occupational outcome***

Working memory change was a strong predictor of number of hours worked at follow-up in the CR group, highlighting the key role of working memory in schizophrenia (Lee and Park, 2005; Perry et al., 2001). Lee & Park define working memory as the mechanism where information is represented, maintained and updated for a short duration of time. The MCCB working memory tests, LNS and WMS-SS, however also require manipulation of representation. Including this executive process (manipulation and re-organization) as in the MCCB, working memory improvements predict occupational outcome. The importance of working memory should to be considered in light of a possible general factor accounting for neurocognitive dysfunction in schizophrenia or along with the nature of the MCCB tests.

In summary, our findings correspond with similar research regarding both vocational rehabilitation and cognitive remediation. Cognitive remediation of neurocognitive deficits seems to make sense in a twofold fashion: It may enhance neurocognition directly and seems to positively contribute to occupational outcomes indirectly via improved neurocognitive domains.

JUMP participation (working) in general also seems to have had a beneficial influence on neurocognitive functioning, as improvements were also present in the CBT group. Effects may however be hampered by several other factors, both illness related and external. This thesis confirms the importance of neurocognition and cognitive remediation in occupational functioning, although the predictive value of neurocognitive improvements was limited.

## **5.5 Methodological issues**

### **5.5.1 Representativity and generalizability**

The participants included in the JUMP study were recruited from six different counties and different services, as they were referred from both mental health and welfare services and self-referral was possible. This gives a relatively high degree of representativity. Representativity may however be slightly compromised by the ability to endure the projects test protocol and the ability to work. This implies that participants in acute illness phases are indirectly excluded. Persons willing, but not able due to symptom exacerbation at the time of recruitment should however be offered the possibility to participate at a later stage. It is also possible that participants with a general higher level of functioning and less influenced by symptoms may have been more likely to participate in the JUMP study.

In order to ensure valid neurocognitive assessment, we also excluded participants from all three papers based on language ability, which may also compromise representativity and exclude those with immigrant background and poor functioning. However, regarding language ability, this was done post-hoc, so that all potential participants were initially recruited regardless of origin.

In conclusion, participants in JUMP were recruited from well-defined services and areas with no a priori control of significant clinical or personal factors. As a result, the findings in this thesis should be generalizable to the clinically heterogeneous group of individuals with schizophrenia.

### **5.5.2 Measurements**

In the present thesis, phenomena have been studied by means of standardized and widely accepted measures with good psychometric properties.

In order to assure reliable assessments, all assessors were trained, calibrated and continuously supervised throughout the JUMP study. Nevertheless, some aspects of assessment need further addressing.

The collection and use of retrospective data warrant careful interpretation. Data collected on previous work, symptom onset and progression, substance use etc. may be difficult to remember precisely. This is particularly the case for persons with low level of insight. In order to balance this, objective data was gathered where possible, for example with regard to duration of illness. Another aspect of measurement and self-report is related to the nature of the JUMP study. Participants may have held back information regarding both symptoms and illicit substance use out of fear of being excluded from the study and thus to lose the possibility of employment. We tried to counteract this by creating a trusting and warm assessment situation and to assure participants that this would not have negative consequences for participation.

Neuropsychological assessment was undertaken with the MCCB. The MCCB represents the gold standard in the field and covers the domains most significantly impaired in schizophrenia. The battery has excellent psychometric properties and was also found in the current thesis to be sensitive in detecting neurocognitive impairment and to distinguish between patients and controls.

The assessment of self-rated social functioning is associated with some challenges. Subjective data are quantified by the participants. On the one hand, neurocognitive impairment may influence the ability to both remember and reflect concerning the statements in the SFS. It has also been found that impaired individuals tend to overestimate their own level of social functioning (Sabbag et al., 2011). On the other hand, significant overlap with the GAF-F score suggests that participants are able to evaluate functioning (Hellvin et al., 2010).

Workplace assessments were carried out by trained employment specialists. It may be methodologically challenging to secure equal ratings across all the six sites, however all assessors were trained and calibrated by the research team in a thorough manner. Recording of hours worked and occupational status was executed by the employment specialist based on reports from employers, producing objective data.

The use of occupational status as an outcome measure is somewhat challenging. There is no consensus on how to define employment in the literature which makes comparison across studies difficult. In the current thesis, we have defined work to include all types of employment

(sheltered work, competitive work and work placement) as this is in keeping with the Nordic model. This may however not be the case in other vocational studies, where employment might be defined in a different manner.

### **5.5.3 Possible confounders**

#### ***IQ and education***

Although IQ and education were significantly different in patients and healthy controls, we chose not to co-vary for the two measures. In several studies, healthy controls and patients are matched on IQ and education, but we argue that matching on these characteristics may lead to incorrect conclusions regarding neurocognitive functioning in schizophrenia (Miller and Chapman, 2001). Individuals with schizophrenia are typically intellectually compromised (Vaskinn et al., 2014); hence, controlling for IQ may in fact remove a central aspect of the disease. The same may be argued for education. Having the illness itself may disrupt educational achievements and differences between controls and patients may reflect symptom severity rather than neurocognitive functioning.

#### ***Antipsychotic medication***

The use of antipsychotic medication may affect neurocognitive function in schizophrenia spectrum disorders. Although we controlled for medication in terms of use and defined daily dosage of the main antipsychotic, we cannot fully disentangle effects of medication from neurocognitive functioning. This is rooted in the numerous different combinations of medicine regimens used by the JUMP participants. Data beyond main antipsychotic, such as the use of other antipsychotics or anti-depressants were not recorded. Although analyses did not reveal medication effects and that little effect has been found on neurocognition (Keefe et al., 2007), we cannot fully rule out medication effects in general.

#### ***Gender***

The JUMP sample was skewed on gender distribution, with significantly more men participating than women. We found some gender differences in the current thesis, particularly in study II, in which better workplace performance was associated with female gender. Regarding overall neurocognitive performance, we could however not establish gender differences and thus we draw the conclusion that gender did not confound results regarding neurocognition or how it translates into social and occupational functioning.

## 5.6 Strengths and limitations

Several strengths and limitations have already been discussed in the respective papers included in the present thesis but some issues require further discussion.

With the current studies we have extended the investigation of neurocognition as assessed with the MCCB in schizophrenia spectrum disorders. We have examined not only the sensitivity of the battery in distinguishing between patients and healthy controls, but the magnitude of impairment in both groups.

We have further sought to provide support for the occupational validity of the MCCB and showed that neurocognition is relevant for real-world functioning in terms of occupational performance.

Finally, the JUMP study examined the effects of CR versus CBT augmented supported employment. That is, two strong interventions were compared as opposed to intervention versus treatment as usual as is often the case (Au et al., 2015; Eack et al., 2009). This encompasses both a methodological strength and a limitation. We found no between group differences regarding long term occupational outcome, indicating that the JUMP package also carries unspecific effects.

With regard to limitations, particularly in study III, the sample size should be acknowledged. More statistical power could have enabled us to detect between group differences between the CR and CBT groups. Hence, the lack of significant differences on the majority of MCCB domains may represent type II errors.

We had no measure of social cognition in the JUMP study. This particular domain has been found to be associated with both neurocognition and occupational outcome (Dickinson et al., 2007a; Vauth et al., 2004) and could potentially have influenced our findings, i.e. have mediated the path from neurocognition to functional outcome.

The lack of a control group in paper III, receiving only vocational rehabilitation without the addition of CR or CBT, is also a limitation making it challenging to disentangle specific effective elements in the JUMP program.

## 5.7 Clinical implications

The clinical implications of the findings in the current thesis are threefold.

First, neurocognition as measured with the MCCB, seems to be an important marker of occupational functioning and thus of particular relevance in vocational rehabilitation. Neurocognitive impairments are reflected in several aspects of occupational functioning and should be addressed. Further, the Norwegian version of the MCCB may be a valuable instrument for both clinical and research purposes. Pragmatic considerations must however also be taken: Detailed assessments of neurocognitive functioning may be too costly in time and professional expertise to be implemented in most psychiatric rehabilitation services. A compromise could perhaps be found in a neuropsychological screening procedure or by means of for example the VCRS.

Second, CR effectively enhances neurocognitive functioning and the effect of CR seems to be optimized through adjunctive vocational rehabilitation. CR should thus be made available to both persons with long and short duration of illness and tailored to individual needs and goals regarding educational and occupational functioning.

Third, this thesis supports the increasing evidence that people with schizophrenia are able and willing to work, even competitively when given the opportunity and adequate support. Tailoring vocational rehabilitation programs to individual needs may help increase employment numbers in this group.

## 6. Conclusion and future questions

This thesis investigated whether neurocognition as measured with the Norwegian version of the MCCB was impaired in participants with broad schizophrenia spectrum disorders and whether the proposed impairment was reflected in functional outcome measures. JUMP participants were significantly impaired on all MCCB domains and impairments were mirrored in lower levels of academic functioning as well as poorer social functioning. This not only underlines the sensitivity of the MCCB, but the functional relevance of the battery. Measures of occupational functioning mirrored neurocognitive performance. Particularly attention, working memory and processing speed were relevant for work behavior, making them important targets for cognitive remediation interventions.

Cognitive remediation adjunct to vocational rehabilitation is effective in improving neurocognitive functioning as well as help people attain and maintain employment. Future research would profit from investigating whether particular subgroups would profit more (or less) from cognitive remediation and vocational rehabilitation, that is stratifying on degree of impairment may shed further light on this matter. Also, assessing learning potential and motivation as possible mediators between neurocognition and real-world functioning may be of importance. Lastly, additive effects of strategy learning, both in general and task specific should be addressed as it may enhance gains on neurocognitive performance and in turn, functional outcome.

To summarize, our findings indicate that participants with schizophrenia have significant neurocognitive impairments and thus face occupational challenges. Our findings however also offer an optimistic interpretation, as JUMP participants are able to work in spite of these impairments. We also demonstrated the dynamic nature of neurocognition, as dysfunctions may be successfully targeted with cognitive remediation strategies.

*“I am working”* John Forbes Nash once stated to a *Times* reporter (Nasar, 1998). He had returned to mathematics and was happy to do serious work and to make a contribution. Work is important and clearly beneficial. It is our hope that these findings may contribute in a small manner to a better understanding of neurocognition in schizophrenia, the functional consequences and last but not least to show that, with appropriate mental health policies and the opportunity, there can be a full life and productive work after schizophrenia.





## 7. References

2011. IBM SPSS Statistics for Windows, Version 20.0. IBM Corp., Armonk, NY.
- Ahmed, A.O., Bhat, I.A., 2014. Psychopharmacological treatment of neurocognitive deficits in people with schizophrenia: a review of old and new targets. *CNS drugs* 28(4), 301-318.
- Allott, K.A., Cotton, S.M., Chinnery, G.L., Baksheev, G.N., Massey, J., Sun, P., Collins, Z., Barlow, E., Broussard, C., Wahid, T., Proffitt, T.M., Jackson, H.J., Killackey, E., 2013. The relative contribution of neurocognition and social cognition to 6-month vocational outcomes following Individual Placement and Support in first-episode psychosis. *Schizophrenia research* 150(1), 136-143.
- Andersen, T.B., Holmström, B., Honkapohja, S., Korkman, S., Söderström, H.T. & Vartiainen, J., 2007. The Nordic Model. Embracing globalization and sharing risks. The Research Institute of the Finnish Economy (ETLA).
- Andrew, A., Knapp, M., McCrone, P.R., Parsonage, M., Trachtenberg, M., 2012. Effective interventions in schizophrenia: the economic case.
- APA, 1994. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV.
- Arendt, M., Rosenberg, R., Foldager, L., Pertto, G., Munk-Jorgensen, P., 2005. Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases. *The British journal of psychiatry : the journal of mental science* 187, 510-515.
- Au, D.W., Tsang, H.W., So, W.W., Bell, M.D., Cheung, V., Yiu, M.G., Tam, K.L., Lee, G.T., 2015. Effects of integrated supported employment plus cognitive remediation training for people with schizophrenia and schizoaffective disorders. *Schizophrenia research* 166(1-3), 297-303.
- August, S.M., Kiwanuka, J.N., McMahon, R.P., Gold, J.M., 2012. The MATRICS Consensus Cognitive Battery (MCCB): clinical and cognitive correlates. *Schizophrenia research* 134(1), 76-82.
- Baddeley, A.D., Hitch, G.J., 1974. Working Memory. Oxford Academic Press.
- Baldwin, M.J., 2016. Beyond Schizophrenia
- Living and Working with a Serious Mental Illness. Rowman & Littlefield, New York.
- Barch, D.M., 2010. Pharmacological strategies for enhancing cognition in schizophrenia. *Current topics in behavioral neurosciences* 4, 43-96.
- Barder, H.E., Sundet, K., Rund, B.R., Evensen, J., Haahr, U., Ten Velden Hegelstad, W., Joa, I., Johannessen, J.O., Langeveld, H., Larsen, T.K., Melle, I., Opjordsmoen, S., Rossberg, J.I., Simonsen, E., Vaglum, P., McGlashan, T., Friis, S., 2013. Neurocognitive development in first episode psychosis 5 years follow-up: associations between illness severity and cognitive course. *Schizophrenia research* 149(1-3), 63-69.
- Barder, H.E., Sundet, K., Rund, B.R., Evensen, J., Haahr, U., ten Velden Hegelstad, W., Joa, I., Johannessen, J.O., Langeveld, J., Larsen, T.K., Melle, I., Opjordsmoen, S., Rossberg, J.I., Simonsen, E., Vaglum, P., McGlashan, T., Friis, S.P., 2015. 10 year course of IQ in first-episode psychosis: relationship between duration of psychosis and long-term intellectual trajectories. *Psychiatry research* 225(3), 515-521.
- Barlatti, S., Deste, G., De Peri, L., Ariu, C., Vita, A., 2013. Cognitive remediation in schizophrenia: current status and future perspectives. *Schizophr Res Treatment* 2013, 156084.
- Baron, R.C., Salzer, M.S., 2002. Accounting for unemployment among people with mental illness. *Behavioral sciences & the law* 20(6), 585-599.
- Bartley, M., 1994. Unemployment and ill health: understanding the relationship. *Journal of Epidemiology and Community Health* 48(4), 333-337.
- Beer, M.D., 1995. Psychosis: from mental disorder to disease concept. *History of psychiatry* 6(22 Pt 2), 177-200.
- Bell, M., Tsang, H.W., Greig, T.C., Bryson, G.J., 2009. Neurocognition, social cognition, perceived social discomfort, and vocational outcomes in schizophrenia. *Schizophrenia bulletin* 35(4), 738-747.

- Bell, M.D., Bryson, G., 2001. Work rehabilitation in schizophrenia: does cognitive impairment limit improvement? *Schizophrenia bulletin* 27(2), 269-279.
- Bell, M.D., Choi, K.H., Dyer, C., Wexler, B.E., 2014. Benefits of cognitive remediation and supported employment for schizophrenia patients with poor community functioning. *Psychiatric services (Washington, D.C.)* 65(4), 469-475.
- Bell, M.D., Fiszdon, J.M., Greig, T.C., Bryson, G.J., 2005. Can older people with schizophrenia benefit from work rehabilitation? *The Journal of nervous and mental disease* 193(5), 293-301.
- Bellack, A.S., 2004. Skills training for people with severe mental illness. *Psychiatric rehabilitation journal* 27(4), 375-391.
- Benedict, R.H.B., 1997. Brief Visuospatial Memory Test–Revised.
- Bevan, S.G., J. Steadman, K.; Taskila, T.; Thomas, R.; Moise, A., 2013. Working with Schizophrenia: Pathways to Employment, Recovery & Inclusion. The Work Foundation.
- Bio, D.S., Gattaz, W.F., 2011. Vocational rehabilitation improves cognition and negative symptoms in schizophrenia. *Schizophrenia research* 126(1–3), 265-269.
- Birchwood, M., Smith, J., Cochrane, R., Wetton, S., Copestake, S., 1990. The Social Functioning Scale. The development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. *The British journal of psychiatry : the journal of mental science* 157, 853-859.
- Blair, J.R., Spreen, O., 1989. *Clinical Neuropsychology* 3(null), 129.
- Blanchard, J.J., Neale, J.M., 1994. The neuropsychological signature of schizophrenia: generalized or differential deficit? *The American journal of psychiatry* 151(1), 40-48.
- Bleuler, E., 1911. Dementia praecox oder Gruppe der Schizophrenien. *Handbuch der psychiatrie*.
- Boardman, J., Grove, B., Perkins, R., Shepherd, G., 2003. Work and employment for people with psychiatric disabilities. *British Journal of Psychiatry* 182, 467-468.
- Bond, G.R., 2004. Supported employment: evidence for an evidence-based practice. *Psychiatric rehabilitation journal* 27(4), 345-359.
- Bond, G.R., Drake, R.E., Becker, D.R., 2008. An update on randomized controlled trials of evidence-based supported employment. *Psychiatric rehabilitation journal* 31(4), 280-290.
- Bond, G.R., Drake, R.E., Becker, D.R., 2012. Generalizability of the Individual Placement and Support (IPS) model of supported employment outside the US. *World psychiatry : official journal of the World Psychiatric Association (WPA)* 11(1), 32-39.
- Bond, G.R., Resnick, S.G., Drake, R.E., Xie, H., McHugo, G.J., Bebout, R.R., 2001. Does competitive employment improve nonvocational outcomes for people with severe mental illness? *J Consult Clin Psychol* 69(3), 489-501.
- Bond, G.R., Salyers, M.P., Dincin, J., Drake, R., Becker, D.R., Fraser, V.V., Haines, M., 2007. A randomized controlled trial comparing two vocational models for persons with severe mental illness. *Journal of Consulting and Clinical Psychology* 75(6), 968-982.
- Bowie, C.R., Harvey, P.D., 2005. Cognition in schizophrenia: impairments, determinants, and functional importance. *The Psychiatric clinics of North America* 28(3), 613-633, 626.
- Bowie, C.R., Harvey, P.D., 2006. Cognitive deficits and functional outcome in schizophrenia. *Neuropsychiatric disease and treatment* 2(4), 531-536.
- Bowie, C.R., Leung, W.W., Reichenberg, A., McClure, M.M., Patterson, T.L., Heaton, R.K., Harvey, P.D., 2008. Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. *Biological psychiatry* 63(5), 505-511.
- Bozikas, V.P., Andreou, C., 2011. Longitudinal studies of cognition in first episode psychosis: a systematic review of the literature. *The Australian and New Zealand journal of psychiatry* 45(2), 93-108.
- Brandt, J., Benedict, R.H.B., 2001. The Hopkins Verbal Learning Test–Revised.
- Brekke, J.S., Long, J.D., Nesbitt, N., Sobel, E., 1997. The impact of service characteristics on functional outcomes from community support programs for persons with schizophrenia: a growth curve analysis. *J Consult Clin Psychol* 65(3), 464-475.

- Bromley, E., Brekke, J.S., 2010. Assessing function and functional outcome in schizophrenia. *Current topics in behavioral neurosciences* 4, 3-21.
- Bryson, G., Bell, M., Lysaker, P., Zito, W., 1997. 623 - The work behavior inventory: A scale for the assessment of work behavior for clients with severe mental illness. *Schizophrenia research* 24(1-2), 220.
- Bryson, G., Bell, M.D., 2003. Initial and final work performance in schizophrenia: cognitive and symptom predictors. *The Journal of nervous and mental disease* 191(2), 87-92.
- Bryson, G., Lysaker, P., Bell, M., 2002. Quality of life benefits of paid work activity in schizophrenia. *Schizophrenia bulletin* 28(2), 249-257.
- Buchanan, R.W., 2007. Persistent negative symptoms in schizophrenia: an overview. *Schizophrenia bulletin* 33(4), 1013-1022.
- Buchanan, R.W., Davis, M., Goff, D., Green, M.F., Keefe, R.S., Leon, A.C., Nuechterlein, K.H., Laughren, T., Levin, R., Stover, E., Fenton, W., Marder, S.R., 2005. A summary of the FDA-NIMH-MATRICES workshop on clinical trial design for neurocognitive drugs for schizophrenia. *Schizophrenia bulletin* 31(1), 5-19.
- Buckley, P.F., Miller, B.J., Lehrer, D.S., Castle, D.J., 2009. Psychiatric comorbidities and schizophrenia. *Schizophrenia bulletin* 35(2), 383-402.
- Burns, T., Catty, J., White, S., Becker, T., Koletsi, M., Fioritti, A., Rossler, W., Tomov, T., van Busschbach, J., Wiersma, D., Lauber, C., for the EQOLISE Group, 2009. The impact of supported employment and working on clinical and social functioning: results of an international study of individual placement and support. *Schizophrenia bulletin* 35(5), 949-958.
- Burns, T., Patrick, D., 2007. Social functioning as an outcome measure in schizophrenia studies. *Acta psychiatrica Scandinavica* 116(6), 403-418.
- Burton, C.Z., Vella, L., Harvey, P.D., Patterson, T.L., Heaton, R.K., Twamley, E.W., 2013. Factor structure of the MATRICS Consensus Cognitive Battery (MCCB) in schizophrenia. *Schizophrenia research* 146(1-3), 244-248.
- Bush, P.W., Drake, R.E., Xie, H., McHugo, G.J., Haslett, W.R., 2009. The long-term impact of employment on mental health service use and costs for persons with severe mental illness. *Psychiatric services (Washington, D.C.)* 60(8), 1024-1031.
- Butzlaff, R., Hooley, J., 1998. Expressed emotion and psychiatric relapse: A meta-analysis. *Archives of general psychiatry*(6), 547-552.
- Cannon, M., Jones, P.B., Murray, R.M., 2002. Obstetric complications and schizophrenia: historical and meta-analytic review. *The American journal of psychiatry* 159(7), 1080-1092.
- Cariani, P., 2012. Mind, a Machine? Review of "The Search for a Theory of Cognition: Early Mechanisms and New Ideas" edited by Stefano Franchi and Francesco Bianchini. *Constructivist Foundations* 7(3), 222-227.
- Chadwick, P., Birchwood, M., 1994. The omnipotence of voices. A cognitive approach to auditory hallucinations. *The British journal of psychiatry : the journal of mental science* 164(2), 190-201.
- Chang, W.C., Hui, C.L., Chan, S.K., Lee, E.H., Chen, E.Y., 2016. Impact of avolition and cognitive impairment on functional outcome in first-episode schizophrenia-spectrum disorder: a prospective one-year follow-up study. *Schizophrenia research* 170(2-3), 318-321.
- Chang, W.C., Man Tang, J.Y., Ming Hui, C.L., Wa Chan, S.K., Ming Lee, E.H., Hai Chen, E.Y., 2014. Clinical and cognitive predictors of vocational outcome in first-episode schizophrenia: a prospective 3 year follow-up study. *Psychiatry research* 220(3), 834-839.
- Chen, W.J., Faraone, S.V., 2000. Sustained attention deficits as markers of genetic susceptibility to schizophrenia. *American journal of medical genetics* 97(1), 52-57.
- Choi, J., Medalia, A., 2005. Factors associated with a positive response to cognitive remediation in a community psychiatric sample. *Psychiatric services (Washington, D.C.)* 56(5), 602-604.

- Christensen, T.O., 2007. The influence of neurocognitive dysfunctions on work capacity in schizophrenia patients: a systematic review of the literature. *International journal of psychiatry in clinical practice* 11(2), 89-101.
- Chue, P., Lalonde, J.K., 2014. Addressing the unmet needs of patients with persistent negative symptoms of schizophrenia: emerging pharmacological treatment options. *Neuropsychiatric disease and treatment* 10, 777-789.
- Claussen, B., Bjorndal, A., Hjort, P.F., 1993. Health and re-employment in a two year follow up of long term unemployed. *Journal of epidemiology and community health* 47(1), 14-18.
- Cornblatt, B.A., Risch, N.J., Faris, G., Friedman, D., Erlenmeyer-Kimling, L., 1988. The Continuous Performance Test, identical pairs version (CPT-IP): I. New findings about sustained attention in normal families. *Psychiatry research* 26(2), 223-238.
- Corrigan, P.W., McCracken, S.G., 2005. Place first, then train: an alternative to the medical model of psychiatric rehabilitation. *Social work* 50(1), 31-39.
- Crow, T., 2007. Genetic hypotheses for schizophrenia. *The British journal of psychiatry : the journal of mental science* 191, 180; author reply 180-181.
- Davidson, M., Galderisi, S., Weiser, M., Werbeloff, N., Fleischhacker, W.W., Keefe, R.S., Boter, H., Keet, I.P., Prelipceanu, D., Rybakowski, J.K., Libiger, J., Hummer, M., Dollfus, S., Lopez-Ibor, J.J., Hranov, L.G., Gaebel, W., Peuskens, J., Lindfors, N., Riecher-Rossler, A., Kahn, R.S., 2009. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). *The American journal of psychiatry* 166(6), 675-682.
- Davis, L.W., Ringer, J.M., Strasburger, A.M., Lysaker, P.H., 2008. Participant evaluation of a CBT program for enhancing work function in schizophrenia. *Psychiatric rehabilitation journal* 32(1), 55-58.
- DeLisi, L.E., Boccio, A.M., Riordan, H., Hoff, A.L., Dorfman, A., McClelland, J., Kushner, M., Van Eyl, O., Oden, N., 1991. Familial thyroid disease and delayed language development in first admission patients with schizophrenia. *Psychiatry research* 38(1), 39-50.
- Dickinson, D., Bellack, A.S., Gold, J.M., 2007a. Social/communication skills, cognition, and vocational functioning in schizophrenia. *Schizophrenia bulletin* 33(5), 1213-1220.
- Dickinson, D., Harvey, P.D., 2009. Systemic hypotheses for generalized cognitive deficits in schizophrenia: a new take on an old problem. *Schizophrenia bulletin* 35(2), 403-414.
- Dickinson, D., Iannone, V.N., Wilk, C.M., Gold, J.M., 2004. General and specific cognitive deficits in schizophrenia. *Biological psychiatry* 55(8), 826-833.
- Dickinson, D., Ramsey, M.E., Gold, J.M., 2007b. Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Archives of general psychiatry* 64(5), 532-542.
- Dominguez Mde, G., Viechtbauer, W., Simons, C.J., van Os, J., Krabbendam, L., 2009. Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. *Psychological bulletin* 135(1), 157-171.
- Draine, J., Salzer, M.S., Culhane, D.P., Hadley, T.R., 2002. Role of social disadvantage in crime, joblessness, and homelessness among persons with serious mental illness. *Psychiatric services (Washington, D.C.)* 53(5), 565-573.
- Durand, D., Strassnig, M., Sabbag, S., Gould, F., Twamley, E.W., Patterson, T.L., Harvey, P.D., 2015. Factors influencing self-assessment of cognition and functioning in schizophrenia: implications for treatment studies. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* 25(2), 185-191.
- Eack, S.M., Greenwald, D.P., Hogarty, S.S., Cooley, S.J., DiBarry, A.L., Montrose, D.M., Keshavan, M.S., 2009. Cognitive enhancement therapy for early-course schizophrenia: effects of a two-year randomized controlled trial. *Psychiatric services (Washington, D.C.)* 60(11), 1468-1476.
- Eack, S.M., Newhill, C.E., 2007. Psychiatric symptoms and quality of life in schizophrenia: a meta-analysis. *Schizophrenia bulletin* 33(5), 1225-1237.

- Eaton, W., Mortensen, P.B., Agerbo, E., Byrne, M., Mors, O., Ewald, H., 2004. Coeliac disease and schizophrenia: population based case control study with linkage of Danish national registers. *BMJ (Clinical research ed.)* 328(7437), 438-439.
- Evans, J.D., Bond, G.R., Meyer, P.S., Kim, H.W., Lysaker, P.H., Gibson, P.J., Tunis, S., 2004. Cognitive and clinical predictors of success in vocational rehabilitation in schizophrenia. *Schizophrenia research* 70(2-3), 331-342.
- Evans, J.D., Heaton, R.K., Paulsen, J.S., Palmer, B.W., Patterson, T., Jeste, D.V., 2003. The relationship of neuropsychological abilities to specific domains of functional capacity in older schizophrenia patients. *Biological psychiatry* 53(5), 422-430.
- Evensen, S., Wisloff, T., Lystad, J.U., Bull, H., Ueland, T., Falkum, E., 2015. Prevalence, Employment Rate, and Cost of Schizophrenia in a High-Income Welfare Society: A Population-Based Study Using Comprehensive Health and Welfare Registers. *Schizophrenia bulletin*.
- Fett, A.K., Viechtbauer, W., Dominguez, M.D., Penn, D.L., van Os, J., Krabbendam, L., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neuroscience and biobehavioral reviews* 35(3), 573-588.
- Flashman, L.A., Green, M.F., 2004. Review of cognition and brain structure in schizophrenia: profiles, longitudinal course, and effects of treatment. *Psychiatric Clinics of North America* 27(1), 1-18, vii.
- Frangou, S., Murray, R., 2000. *Schizophrenia* Martin Dunitz Lt., London.
- Frydecka, D., Beszlej, J.A., Goscimski, P., Kiejna, A., Misiak, B., 2015. Profiling cognitive impairment in treatment-resistant schizophrenia patients. *Psychiatry research*.
- Gaite, L., Vazquez-Barquero, J.L., Borra, C., Ballesteros, J., Schene, A., Welcher, B., Thornicroft, G., Becker, T., Ruggeri, M., Herran, A., 2002. Quality of life in patients with schizophrenia in five European countries: the EPSILON study. *Acta Psychiatrica Scandinavica* 105(4), 283-292.
- Galletly, C., Rigby, A., 2013. An Overview of Cognitive Remediation Therapy for People with Severe Mental Illness. *ISRN Rehabilitation* 2013, 6.
- Gogos, J.A., Gerber, D.J., 2006. Schizophrenia susceptibility genes: emergence of positional candidates and future directions. *Trends in pharmacological sciences* 27(4), 226-233.
- Gold, J.M., 2004. Cognitive deficits as treatment targets in schizophrenia. *Schizophrenia research* 72(1), 21-28.
- Gold, J.M., Carpenter, C., Randolph, C., Goldberg, T.E., Weinberger, D.R., 1997. Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. *Archives of general psychiatry* 54(2), 159-165.
- Gold, J.M., Goldberg, R.W., McNary, S.W., Dixon, L.B., Lehman, A.F., 2002. Cognitive correlates of job tenure among patients with severe mental illness. *The American journal of psychiatry* 159(8), 1395-1402.
- Gold, J.M., Wilk, C.M., McMahon, R.P., Buchanan, R.W., Luck, S.J., 2003. Working memory for visual features and conjunctions in schizophrenia. *Journal of abnormal psychology* 112(1), 61-71.
- Gould, F., Sabbag, S., Durand, D., Patterson, T.L., Harvey, P.D., 2013. Self-assessment of functional ability in schizophrenia: milestone achievement and its relationship to accuracy of self-evaluation. *Psychiatry research* 207(1-2), 19-24.
- Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? *The American journal of psychiatry* 153(3), 321-330.
- Green, M.F., 2006. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *The Journal of clinical psychiatry* 67(10), e12.
- Green, M.F., Kern, R.S., Braff, D.L., Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophrenia bulletin* 26(1), 119-136.
- Green, M.F., Kern, R.S., Heaton, R.K., 2004. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophrenia research* 72(1), 41-51.
- Greig, T.C., Nicholls, S.S., Bryson, G.J., Bell, M.D., 2004. The Vocational Cognitive Rating Scale: A scale for the assessment of cognitive functioning at work for clients with severe mental illness. *Journal of Vocational Rehabilitation* 21(2), 71-81.

- Griggs, J., Evans, M., 2010. Sanctions within conditional benefit systems: A review of evidence. Joseph Roundtree Foundation.
- Gupta, M., Bassett, E., Iftene, F., Bowie, C.R., 2012. Functional outcomes in schizophrenia: understanding the competence-performance discrepancy. *Journal of psychiatric research* 46(2), 205-211.
- Haefner, H., An der Heiden, W., 2008. *Course and outcome*. Guilford Press, New York.
- Hagen, B., Härkäpää, K., Spjeltkavik, Ø., 2011. Supported Employment in the Nordic countries, in: (AFI), W.R.I. (Ed.), Oslo: Work Research Institute, p. 91.
- Hall, W., Degenhardt, L., 2000. Cannabis use and psychosis: a review of clinical and epidemiological evidence. *The Australian and New Zealand journal of psychiatry* 34(1), 26-34.
- Harsvik, T., Opdahl Mo, T., Steihaug, S., 2008. *Jobbmestrende oppfølging, Andre delrapport SINTEF Helse*. SINTEF, Oslo.
- Harvey, P.D., Bowie, C.R., 2012. Cognitive enhancement in schizophrenia: pharmacological and cognitive remediation approaches. *The Psychiatric clinics of North America* 35(3), 683-698.
- Harvey, P.D., Sabbag, S., Prestia, D., Durand, D., Twamley, E.W., Patterson, T.L., 2012. Functional milestones and clinician ratings of everyday functioning in people with schizophrenia: overlap between milestones and specificity of ratings. *Journal of psychiatric research* 46(12), 1546-1552.
- Harvey, P.D., Sharma, T., 2002. *Understanding and Treating Cognition in Schizophrenia. A Clinician's Handbook*. Martin Dunitz, London.
- Harvey, P.D., Siu, C.O., Ogasa, M., Loebel, A., 2015. Effect of lurasidone dose on cognition in patients with schizophrenia: post-hoc analysis of a long-term, double-blind continuation study. *Schizophrenia research* 166(1-3), 334-338.
- Harvey, P.D., Velligan, D.I., Bellack, A.S., 2007. Performance-based measures of functional skills: usefulness in clinical treatment studies. *Schizophrenia bulletin* 33(5), 1138-1148.
- Heinrichs, R.W., Zakzanis, K.K., 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* 12(3), 426-445.
- Hellvin, T., Sundet, K., Vaskinn, A., Simonsen, C., Ueland, T., Andreassen, O.A., Melle, I., 2010. Validation of the Norwegian version of the Social Functioning Scale (SFS) for schizophrenia and bipolar disorder. *Scandinavian journal of psychology* 51(6), 525-533.
- Helsedirektoratet, 2013. *Nasjonal faglig retningslinje for utredning, behandling og oppfølging av personer med psykoselidelser*.
- Hill, S.K., Bishop, J.R., Palumbo, D., Sweeney, J.A., 2010. Effect of second-generation antipsychotics on cognition: current issues and future challenges. *Expert review of neurotherapeutics* 10(1), 43-57.
- Hoenig, J., 1983. The concept of Schizophrenia. Kraepelin-Bleuler-Schneider. *The British journal of psychiatry : the journal of mental science* 142, 547-556.
- Hoffmann, H., Jackel, D., Glauser, S., Mueser, K.T., Kupper, Z., 2014. Long-term effectiveness of supported employment: 5-year follow-up of a randomized controlled trial. *The American journal of psychiatry* 171(11), 1183-1190.
- Holmen, A., Juuhl-Langseth, M., Thormodsen, R., Melle, I., Rund, B.R., 2010. Neuropsychological profile in early-onset schizophrenia-spectrum disorders: measured with the MATRICS battery. *Schizophrenia bulletin* 36(4), 852-859.
- Hubbard, L., Tansey, K.E., Rai, D., Jones, P., Ripke, S., Chambert, K.D., Moran, J.L., McCarroll, S.A., Linden, D.E., Owen, M.J., O'Donovan, M.C., Walters, J.T., Zammit, S., 2015. Evidence of Common Genetic Overlap Between Schizophrenia and Cognition. *Schizophrenia bulletin*.
- Hughes, C., Kumari, V., Soni, W., Das, M., Binneman, B., Drozd, S., O'Neil, S., Mathew, V., Sharma, T., 2003. Longitudinal study of symptoms and cognitive function in chronic schizophrenia. *Schizophrenia research* 59(2-3), 137-146.
- Jablensky, A., 2000. Epidemiology of schizophrenia: the global burden of disease and disability. *European Archives of Psychiatry and Clinical Neuroscience* 250(6), 274-285.

- Kalkstein, S., Hurford, I., Gur, R.C., 2010. Neurocognition in schizophrenia. *Current topics in behavioral neurosciences* 4, 373-390.
- Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia bulletin* 13(2), 261-276.
- Keefe, R.S., Bilder, R.M., Davis, S.M., Harvey, P.D., Palmer, B.W., Gold, J.M., Meltzer, H.Y., Green, M.F., Capuano, G., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Davis, C.E., Hsiao, J.K., Lieberman, J.A., 2007. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Archives of general psychiatry* 64(6), 633-647.
- Keefe, R.S., Eesley, C.E., Poe, M.P., 2005. Defining a cognitive function decrement in schizophrenia. *Biological Psychiatry* 57(6), 688-691.
- Keefe, R.S., Fox, K.H., Harvey, P.D., Cucchiaro, J., Siu, C., Loebel, A., 2011. Characteristics of the MATRICS Consensus Cognitive Battery in a 29-site antipsychotic schizophrenia clinical trial. *Schizophrenia research* 125(2-3), 161-168.
- Keefe, R.S., Harvey, P.D., 2012. Cognitive impairment in schizophrenia. *Handbook of experimental pharmacology*(213), 11-37.
- Keefe, R.S.E., 1999. *Brief Assessment of Cognition in Schizophrenia*.
- Kern, R.S., Gold, J.M., Dickinson, D., Green, M.F., Nuechterlein, K.H., Baade, L.E., Keefe, R.S., Mesholam-Gately, R.I., Seidman, L.J., Lee, C., Sugar, C.A., Marder, S.R., 2011. The MCCB impairment profile for schizophrenia outpatients: results from the MATRICS psychometric and standardization study. *Schizophrenia research* 126(1-3), 124-131.
- Kern, R.S., Nuechterlein, K.H., Green, M.F., Baade, L.E., Fenton, W.S., Gold, J.M., Keefe, R.S., Mesholam-Gately, R., Mintz, J., Seidman, L.J., Stover, E., Marder, S.R., 2008. The MATRICS Consensus Cognitive Battery, part 2: co-norming and standardization. *The American journal of psychiatry* 165(2), 214-220.
- Kilian, R., Becker, T., 2007. Macro-economic indicators and labour force participation of people with schizophrenia. *Journal of Mental Health* 16(2), 211-222.
- Killackey, E.J., Jackson, H.J., Gleeson, J., Hickie, I.B., McGorry, P.D., 2006. Exciting career opportunity beckons! Early intervention and vocational rehabilitation in first-episode psychosis: employing cautious optimism. *The Australian and New Zealand journal of psychiatry* 40(11-12), 951-962.
- Kinoshita, Y., Furukawa, T.A., Kinoshita, K., Honyashiki, M., Omori, I.M., Marshall, M., Bond, G.R., Huxley, P., Amano, N., Kingdon, D., 2013. Supported employment for adults with severe mental illness. *The Cochrane database of systematic reviews* 9, Cd008297.
- Klingberg, S., Wittorf, A., Wiedemann, G., 2006. Disorganization and cognitive impairment in schizophrenia: independent symptom dimensions? *European Archives of Psychiatry and Clinical Neuroscience* 256(8), 532-540.
- Kraepelin, E., 1908-1913. *Psychiatrie*. Bart, Leipzig.
- Kranzler, H.R., Kadden, R.M., Babor, T.F., Rounsaville, B.J., 1994. Longitudinal, expert, all data procedure for psychiatric diagnosis in patients with psychoactive substance use disorders. *The Journal of nervous and mental disease* 182(5), 277-283.
- Kremen, W.S., Seidman, L.J., Faraone, S.V., Toomey, R., Tsuang, M.T., 2000. The paradox of normal neuropsychological function in schizophrenia. *Journal of abnormal psychology* 109(4), 743-752.
- Kukla, M., Bond, G.R., Xie, H., 2012. A prospective investigation of work and nonvocational outcomes in adults with severe mental illness. *The Journal of nervous and mental disease* 200(3), 214-222.
- Kukla, M., Davis, L.W., Lysaker, P.H., 2014. Cognitive behavioral therapy and work outcomes: correlates of treatment engagement and full and partial success in schizophrenia. *Behavioural and cognitive psychotherapy* 42(5), 577-592.

- Lacritz, L.H., Cullum, C.M., 1998. The Hopkins Verbal Learning Test and CVLT: a preliminary comparison. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists* 13(7), 623-628.
- Lacritz, L.H., Cullum, C.M., Weiner, M.F., Rosenberg, R.N., 2001. Comparison of the hopkins verbal learning test-revised to the California verbal learning test in Alzheimer's disease. *Applied neuropsychology* 8(3), 180-184.
- Leao, T.S., Sundquist, J., Frank, G., Johansson, L.M., Johansson, S.E., Sundquist, K., 2006. Incidence of schizophrenia or other psychoses in first- and second-generation immigrants: a national cohort study. *The Journal of nervous and mental disease* 194(1), 27-33.
- Lecomte, T., Corbiere, M., Lysaker, P.H., 2014. [A group cognitive behavioral intervention for people registered in supported employment programs: CBT-SE]. *L'Encephale* 40 Suppl 2, S81-90.
- Lecrubier, Y., Perry, R., Milligan, G., Leeuwenkamp, O., Morlock, R., 2007. Physician observations and perceptions of positive and negative symptoms of schizophrenia: a multinational, cross-sectional survey. *Eur.Psychiatry* 22(6), 371-379.
- Lee, J., Park, S., 2005. Working memory impairments in schizophrenia: a meta-analysis. *Journal of abnormal psychology* 114(4), 599-611.
- Leff, J., Vaughn, C., 1984. *Expressed emotion in families: Its significance for mental illness*. Guilford Press.
- Leifker, F.R., Bowie, C.R., Harvey, P.D., 2009. Determinants of everyday outcomes in schizophrenia: the influences of cognitive impairment, functional capacity, and symptoms. *Schizophrenia research* 115(1), 82-87.
- Lewis, R., 2004. Should cognitive deficit be a diagnostic criterion for schizophrenia? *Journal of Psychiatry and Neuroscience* 29(2), 102-113.
- Lezak, H., Bigler & Tranel, 2012. *Neuropsychological Assessment*, 5 ed. Oxford University Press, New York.
- Lieberman, R.P., Kopelowicz, A., 2005. Recovery from schizophrenia: a concept in search of research. *Psychiatric services (Washington, D.C.)* 56(6), 735-742.
- Lieberman, J.A., Drake, R.E., Sederer, L.I., Belger, A., Keefe, R., Perkins, D., Stroup, S., 2008. Science and recovery in schizophrenia. *Psychiatric services (Washington, D.C.)* 59(5), 487-496.
- Lin, C.H., Huang, C.L., Chang, Y.C., Chen, P.W., Lin, C.Y., Tsai, G.E., Lane, H.Y., 2013. Clinical symptoms, mainly negative symptoms, mediate the influence of neurocognition and social cognition on functional outcome of schizophrenia. *Schizophrenia research* 146(1-3), 231-237.
- Lucca, A.M., Henry, A.D., Banks, S., Simon, L., Page, S., 2004. Evaluation of an Individual Placement and Support model (IPS) program. *Psychiatric rehabilitation journal* 27(3), 251-257.
- Lysaker, P., Bell, M., 1995. Work rehabilitation and improvements in insight in schizophrenia. *The Journal of nervous and mental disease* 183(2), 103-106.
- Lysaker, P.H., Davis, L.W., Bryson, G.J., Bell, M.D., 2009. Effects of cognitive behavioral therapy on work outcomes in vocational rehabilitation for participants with schizophrenia spectrum disorders. *Schizophrenia research* 107(2-3), 186-191.
- Lystad, J.U., Falkum, E., Haaland, V.O., Bull, H., Evensen, S., Bell, M.D., Ueland, T., 2015. Neurocognition and occupational functioning in schizophrenia spectrum disorders: The MATRICS Consensus Cognitive Battery (MCCB) and workplace assessments. *Schizophrenia research*.
- Lystad, J.U., Falkum, E., Mohn, C., Haaland, V.O., Bull, H., Evensen, S., Rund, B.R., Ueland, T., 2014. The MATRICS Consensus Cognitive Battery (MCCB): Performance and functional correlates. *Psychiatry research*.
- MacBeth, A., Gumley, A., 2008. Premorbid adjustment, symptom development and quality of life in first episode psychosis: a systematic review and critical reappraisal. *Acta psychiatrica Scandinavica* 117(2), 85-99.
- Malla, A., Payne, J., 2005. First-episode psychosis: psychopathology, quality of life, and functional outcome. *Schizophrenia bulletin* 31(3), 650-671.



- Mancevski, B., Keilp, J., Kurzon, M., Berman, R.M., Ortakov, V., Harkavy-Friedman, J., Rosoklija, G., Dwork, A.J., 2007. Lifelong course of positive and negative symptoms in chronically institutionalized patients with schizophrenia. *Psychopathology* 40(2), 83-92.
- Mangalore, R., Knapp, M., 2007. Cost of schizophrenia in England. *J.Ment.Health Policy Econ.* 10(1), 23-41.
- Marshall, T., Goldberg, R.W., Braude, L., Dougherty, R.H., Daniels, A.S., Ghose, S.S., George, P., Delphin-Rittmon, M.E., 2014. Supported employment: assessing the evidence. *Psychiatric services (Washington, D.C.)* 65(1), 16-23.
- Marwaha, S., Balachandra, S., Johnson, S., 2009. Clinicians' attitudes to the employment of people with psychosis. *Social psychiatry and psychiatric epidemiology* 44(5), 349-360.
- Marwaha, S., Johnson, S., 2004. Schizophrenia and employment - a review. *Social psychiatry and psychiatric epidemiology* 39(5), 337-349.
- Marwaha, S., Johnson, S., Bebbington, P., Stafford, M., Angermeyer, M.C., Brugha, T., Azorin, J.M., Kilian, R., Hansen, K., Toumi, M., 2007. Rates and correlates of employment in people with schizophrenia in the UK, France and Germany. *British Journal of Psychiatry* 191, 30-37.
- McCleery, A., Green, M.F., Helleman, G.S., Baade, L.E., Gold, J.M., Keefe, R.S., Kern, R.S., Mesholam-Gately, R.I., Seidman, L.J., Subotnik, K.L., Ventura, J., Nuechterlein, K.H., 2015. Latent structure of cognition in schizophrenia: a confirmatory factor analysis of the MATRICS Consensus Cognitive Battery (MCCB). *Psychological medicine* 45(12), 2657-2666.
- McClure, M.M., Bowie, C.R., Patterson, T.L., Heaton, R.K., Weaver, C., Anderson, H., Harvey, P.D., 2007. Correlations of functional capacity and neuropsychological performance in older patients with schizophrenia: evidence for specificity of relationships? *Schizophrenia research* 89(1-3), 330-338.
- McGurk, S.R., Meltzer, H.Y., 2000. The role of cognition in vocational functioning in schizophrenia. *Schizophrenia research* 45(3), 175-184.
- McGurk, S.R., Mueser, K.T., 2004. Cognitive functioning, symptoms, and work in supported employment: a review and heuristic model. *Schizophrenia research* 70(2-3), 147-173.
- McGurk, S.R., Mueser, K.T., DeRosa, T.J., Wolfe, R., 2009. Work, recovery, and comorbidity in schizophrenia: a randomized controlled trial of cognitive remediation. *Schizophrenia bulletin* 35(2), 319-335.
- McGurk, S.R., Mueser, K.T., Harvey, P.D., LaPuglia, R., Marder, J., 2003. Cognitive and Symptom Predictors of Work Outcomes for Clients With Schizophrenia in Supported Employment. *Psychiatric Services* 54(8), 1129-1135.
- McGurk, S.R., Mueser, K.T., Xie, H., Welsh, J., Kaiser, S., Drake, R.E., Becker, D.R., Bailey, E., Fraser, G., Wolfe, R., McHugo, G.J., 2015. Cognitive Enhancement Treatment for People With Mental Illness Who Do Not Respond to Supported Employment: A Randomized Controlled Trial. *The American journal of psychiatry* 172(9), 852-861.
- McGurk, S.R., Twamley, E.W., Sitzer, D.I., McHugo, G.J., Mueser, K.T., 2007. A meta-analysis of cognitive remediation in schizophrenia. *The American journal of psychiatry* 164(12), 1791-1802.
- Medalia, A., Choi, J., 2009. Cognitive remediation in schizophrenia. *Neuropsychology review* 19(3), 353-364.
- Medalia, A., Saperstein, A., 2011. The role of motivation for treatment success. *Schizophrenia bulletin* 37 Suppl 2, S122-128.
- Medalia, A., Saperstein, A.M., 2013. Does cognitive remediation for schizophrenia improve functional outcomes? *Current opinion in psychiatry* 26(2), 151-157.
- Meier, M.H., Caspi, A., Reichenberg, A., Keefe, R.S., Fisher, H.L., Harrington, H., Houts, R., Poulton, R., Moffitt, T.E., 2014. Neuropsychological decline in schizophrenia from the premorbid to the postonset period: evidence from a population-representative longitudinal study. *The American journal of psychiatry* 171(1), 91-101.
- Melle, I., Friis, S., Hauff, E., Vaglum, P., 2000. Social functioning of patients with schizophrenia in high-income welfare societies. *Psychiatric Services* 51(2), 223-228.

- Mesholam-Gately, R.I., Giuliano, A.J., Goff, K.P., Faraone, S.V., Seidman, L.J., 2009. Neurocognition in first-episode schizophrenia: a meta-analytic review. *Neuropsychology* 23(3), 315-336.
- Messias, E.L., Chen, C.Y., Eaton, W.W., 2007. Epidemiology of schizophrenia: review of findings and myths. *The Psychiatric clinics of North America* 30(3), 323-338.
- Milev, P., Ho, B.C., Arndt, S., Andreasen, N.C., 2005. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *The American journal of psychiatry* 162(3), 495-506.
- Millan, M.J., Agid, Y., Brune, M., Bullmore, E.T., Carter, C.S., Clayton, N.S., Connor, R., Davis, S., Deakin, B., DeRubeis, R.J., Dubois, B., Geyer, M.A., Goodwin, G.M., Gorwood, P., Jay, T.M., Joels, M., Mansuy, I.M., Meyer-Lindenberg, A., Murphy, D., Rolls, E., Saletu, B., Spedding, M., Sweeney, J., Whittington, M., Young, L.J., 2012. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nature reviews. Drug discovery* 11(2), 141-168.
- Miller, G.A., Chapman, J.P., 2001. Misunderstanding analysis of covariance. *Journal of abnormal psychology* 110(1), 40-48.
- Mishara, A.L., Goldberg, T.E., 2004. A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. *Biological psychiatry* 55(10), 1013-1022.
- Mohn, C., Sundet, K., Rund, B.R., 2012. The Norwegian standardization of the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery. *Journal of clinical and experimental neuropsychology* 34(6), 667-677.
- Morrison, A.K., 2009. *Cognitive Behavior Therapy for People with Schizophrenia*. *Psychiatry (Edgmont)* 6(12), 32-39.
- Mueser, K.T., Douglas, M.S., Bellack, A.S., Morrison, R.L., 1991. Assessment of enduring deficit and negative symptom subtypes in schizophrenia. *Schizophrenia bulletin* 17(4), 565-582.
- Mueser, K.T., McGurk, S.R., 2014. Supported employment for persons with serious mental illness: current status and future directions. *L'Encephale* 40 Suppl 2, S45-56.
- Murray, R.M., Lewis, S.W., 1987. Is schizophrenia a neurodevelopmental disorder? *British medical journal (Clinical research ed.)* 295(6600), 681-682.
- Nasar, S., 1998. *A beautiful mind / Sylvia Nasar*. Simon & Schuster, New York, NY.
- Niekawa, N., Sakuraba, Y., Uto, H., Kumazawa, Y., Matsuda, O., 2007. Relationship between financial competence and cognitive function in patients with schizophrenia. *Psychiatry and clinical neurosciences* 61(5), 455-461.
- NIMH, 2016. Schizophrenia, [http://www.nimh.nih.gov/health/publications/schizophrenia-easy-to-read-12-2015/tr-15-3517-pdf\\_151831.pdf](http://www.nimh.nih.gov/health/publications/schizophrenia-easy-to-read-12-2015/tr-15-3517-pdf_151831.pdf).
- Nordentoft, M., Austin, S., 2014. CBT for psychotic disorders: beyond meta-analyses and guidelines - it is time to implement! *World psychiatry : official journal of the World Psychiatric Association (WPA)* 13(3), 260-261.
- Nordt, C., Muller, B., Rossler, W., Lauber, C., 2007. Predictors and course of vocational status, income, and quality of life in people with severe mental illness: a naturalistic study. *Social Science and Medicine* 65(7), 1420-1429.
- Nose, M., Tansella, M., Thornicroft, G., Schene, A., Becker, T., Veronese, A., Leese, M., Koeter, M., Angermeyer, M., Barbui, C., 2008. Is the Defined Daily Dose system a reliable tool for standardizing antipsychotic dosages? *International clinical psychopharmacology* 23(5), 287-290.
- Nuechterlein, K.H., Barch, D.M., Gold, J.M., Goldberg, T.E., Green, M.F., Heaton, R.K., 2004. Identification of separable cognitive factors in schizophrenia. *Schizophrenia research* 72(1), 29-39.
- Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese, F.J., 3rd, Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R.S., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A.S., Zalcman, S.,

- Marder, S.R., 2008. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *The American journal of psychiatry* 165(2), 203-213.
- Nuechterlein, K.H., Subotnik, K.L., Green, M.F., Ventura, J., Asarnow, R.F., Gitlin, M.J., Yee, C.M., Gretchen-Doorly, D., Mintz, J., 2011. Neurocognitive predictors of work outcome in recent-onset schizophrenia. *Schizophrenia bulletin* 37 Suppl 2, S33-40.
- O'Connor, M.K., Mueller, L., Van Ormer, A., Drake, R., Penk, W., Rosenheck, R., Semiatin, A., Drebing, C.E., 2011. Cognitive impairment as barrier to engagement in vocational services among veterans with severe mental illness. *Journal of rehabilitation research and development* 48(5), 597-608.
- Oie, M., Rund, B.R., 1999. Neuropsychological deficits in adolescent-onset schizophrenia compared with attention deficit hyperactivity disorder. *The American journal of psychiatry* 156(8), 1216-1222.
- Ostergaard Christensen, T., Vesterager, L., Krarup, G., Olsen, B.B., Melau, M., Gluud, C., Nordentoft, M., 2014. Cognitive remediation combined with an early intervention service in first episode psychosis. *Acta psychiatrica Scandinavica* 130(4), 300-310.
- Pattani, S., Constantinovici, N., Williams, S., 2004. Predictors of re-employment and quality of life in NHS staff one year after early retirement because of ill health; a national prospective study. *Occupational and environmental medicine* 61(7), 572-576.
- Penades, R., Catalan, R., Salamero, M., Boget, T., Puig, O., Guarch, J., Gasto, C., 2006. Cognitive remediation therapy for outpatients with chronic schizophrenia: a controlled and randomized study. *Schizophrenia research* 87(1-3), 323-331.
- Penn, D.L., Mueser, K.T., Doonan, R., Nishith, P., 1995. Relations between social skills and ward behavior in chronic schizophrenia. *Schizophrenia research* 16(3), 225-232.
- Penner, J.D., Brown, A.S., 2007. Prenatal infectious and nutritional factors and risk of adult schizophrenia. *Expert review of neurotherapeutics* 7(7), 797-805.
- Perlick, D.A., Rosenheck, R.A., Kaczynski, R., Bingham, S., Collins, J., 2008. Association of symptomatology and cognitive deficits to functional capacity in schizophrenia. *Schizophrenia research* 99(1-3), 192-199.
- Perry, W., Heaton, R.K., Potterat, E., Roebuck, T., Minassian, A., Braff, D.L., 2001. Working memory in schizophrenia: transient "online" storage versus executive functioning. *Schizophrenia bulletin* 27(1), 157-176.
- Pompili, M., Amador, X.F., Girardi, P., Harkavy-Friedman, J., Harrow, M., Kaplan, K., Krausz, M., Lester, D., Meltzer, H.Y., Modestini, J., Montross, L.P., Mortensen, P.B., Munk-Jorgensen, P., Nielsen, J., Nordentoft, M., Saarinen, P.I., Zisook, S., Wilson, S.T., Tatarelli, R., 2007. Suicide risk in schizophrenia: learning from the past to change the future. *Annals of general psychiatry* 6, 10.
- Racenstein, J.M., Harrow, M., Reed, R., Martin, E., Herbener, E., Penn, D.L., 2002. The relationship between positive symptoms and instrumental work functioning in schizophrenia: a 10 year follow-up study. *Schizophrenia research* 56(1-2), 95-103.
- Ramsay, C.E., Broussard, B., Goulding, S.M., Cristofaro, S., Hall, D., Kaslow, N.J., Killackey, E., Penn, D., Compton, M.T., 2011. Life and treatment goals of individuals hospitalized for first-episode nonaffective psychosis. *Psychiatry research* 189(3), 344-348.
- Ramsey, N.F., Koning, H.A., Welles, P., Cahn, W., van der Linden, J.A., Kahn, R.S., 2002. Excessive recruitment of neural systems subserving logical reasoning in schizophrenia. *Brain : a journal of neurology* 125(Pt 8), 1793-1807.
- Rath, J.F., Langenbahn, D.M., Simon, D., Sherr, R.L., Fletcher, J., Diller, L., 2004. The construct of problem solving in higher level neuropsychological assessment and rehabilitation. *Archives of Clinical Neuropsychology* 19(5), 613-635.
- Rector, N.A., Beck, A.T., 2001. Cognitive behavioral therapy for schizophrenia: an empirical review. *The Journal of nervous and mental disease* 189(5), 278-287.

- Reddy, L.F., Kern, R.S., 2014. Supported employment among veterans with serious mental illness: the role of cognition and social cognition on work outcome. *Schizophrenia Research: Cognition* 1(3), 144-148.
- Reichenberg, A., 2010. The assessment of neuropsychological functioning in schizophrenia. *Dialogues in clinical neuroscience* 12(3), 383-392.
- Reichenberg, A., Harvey, P.D., Bowie, C.R., Mojtabai, R., Rabinowitz, J., Heaton, R.K., Bromet, E., 2009. Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. *Schizophrenia bulletin* 35(5), 1022-1029.
- Rinaldi, M., Miller, L., Perkins, R., 2010. Implementing the individual placement and support (IPS) approach for people with mental health conditions in England. *International review of psychiatry (Abingdon, England)* 22(2), 163-172.
- Ringen, P.A., Engh, J.A., Birkenaes, A.B., Dieset, I., Andreassen, O.A., 2014. Increased mortality in schizophrenia due to cardiovascular disease - a non-systematic review of epidemiology, possible causes, and interventions. *Frontiers in psychiatry* 5, 137.
- Robinson, D., Woerner, M.G., Alvir, J.M., Bilder, R., Goldman, R., Geisler, S., Koreen, A., Sheitman, B., Chakos, M., Mayerhoff, D., Lieberman, J.A., 1999. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Archives of General Psychiatry* 56(3), 241-247.
- Rund, B.R., 1998. A review of longitudinal studies of cognitive functions in schizophrenia patients. *Schizophrenia bulletin* 24(3), 425-435.
- Sabbag, S., Twamley, E.M., Vella, L., Heaton, R.K., Patterson, T.L., Harvey, P.D., 2011. Assessing everyday functioning in schizophrenia: Not all informants seem equally informative. *Schizophrenia research* 131(1-3), 250-255.
- Salokangas, R.K., 1997. Structure of schizophrenic symptomatology and its changes over time: prospective factor-analytical study. *Acta Psychiatrica Scandinavica* 95(1), 32-39.
- Salthouse, T.A., 1996. The processing-speed theory of adult age differences in cognition. *Psychological review* 103(3), 403-428.
- Sarin, F., Wallin, L., Widerlov, B., 2011. Cognitive behavior therapy for schizophrenia: a meta-analytical review of randomized controlled trials. *Nordic journal of psychiatry* 65(3), 162-174.
- Scheid, T.L., 2005. Stigma as a barrier to employment: mental disability and the Americans with Disabilities Act. *International journal of law and psychiatry* 28(6), 670-690.
- Schennach, R., Musil, R., Moller, H.J., Riedel, M., 2012. Functional outcomes in schizophrenia: employment status as a metric of treatment outcome. *Current psychiatry reports* 14(3), 229-236.
- Schulze, B., Angermeyer, M.C., 2003. Subjective experiences of stigma. A focus group study of schizophrenic patients, their relatives and mental health professionals. *Social science & medicine* (1982) 56(2), 299-312.
- Schutt, R.K., Seidman, L.J., Caplan, B., Martsinkiv, A., Goldfinger, S.M., 2007. The role of neurocognition and social context in predicting community functioning among formerly homeless seriously mentally ill persons. *Schizophrenia bulletin* 33(6), 1388-1396.
- Seidman, L.J., Giuliano, A.J., Smith, C.W., Stone, W.S., Glatt, S.J., Meyer, E., Faraone, S.V., Tsuang, M.T., Cornblatt, B., 2006. Neuropsychological functioning in adolescents and young adults at genetic risk for schizophrenia and affective psychoses: results from the Harvard and Hillside Adolescent High Risk Studies. *Schizophrenia bulletin* 32(3), 507-524.
- Shamsi, S., Lau, A., Lencz, T., Burdick, K.E., DeRosse, P., Brenner, R., Lindenmayer, J.P., Malhotra, A.K., 2011. Cognitive and symptomatic predictors of functional disability in schizophrenia. *Schizophrenia research* 126(1-3), 257-264.
- Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of clinical psychiatry* 59 Suppl 20, 22-33;quiz 34-57.

- Shi, C., Kang, L., Yao, S., Ma, Y., Li, T., Liang, Y., Cheng, Z., Xu, Y., Shi, J., Xu, X., Zhang, C., Franklin, D.R., Heaton, R.K., Jin, H., Yu, X., 2015. The MATRICS Consensus Cognitive Battery (MCCB): Co-norming and standardization in China. *Schizophrenia research* 169(1–3), 109-115.
- Silver, H., Feldman, P., Bilker, W., Gur, R.C., 2003. Working memory deficit as a core neuropsychological dysfunction in schizophrenia. *The American journal of psychiatry* 160(10), 1809-1816.
- Simonsen, C., Sundet, K., Vaskinn, A., Ueland, T., Romm, K.L., Hellvin, T., Melle, I., Friis, S., Andreassen, O.A., 2010. Psychosocial function in schizophrenia and bipolar disorder: Relationship to neurocognition and clinical symptoms. *Journal of the International Neuropsychological Society : JINS* 16(5), 771-783.
- Sipos, A., Rasmussen, F., Harrison, G., Tynelius, P., Lewis, G., Leon, D.A., Gunnell, D., 2004. Paternal age and schizophrenia: a population based cohort study. *BMJ (Clinical research ed.)* 329(7474), 1070.
- Sitskoorn, M.M., Aleman, A., Ebisch, S.J., Appels, M.C., Kahn, R.S., 2004. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. *Schizophrenia research* 71(2-3), 285-295.
- Spitzer, R.L., 1983. Psychiatric-Diagnosis - Are Clinicians Still Necessary. *Comprehensive Psychiatry* 24, 399-411.
- Spjelkavik, Ø., 2012. Supported Employment in Norway and in the other Nordic countries. *Journal of Vocational Rehabilitation* 37, 163-172.
- Stone, W.S., Mesholam-Gately, R.I., Braff, D.L., Calkins, M.E., Freedman, R., Green, M.F., Greenwood, T.A., Gur, R.E., Gur, R.C., Lazzeroni, L.C., Light, G.A., Nuechterlein, K.H., Olincy, A., Radant, A.D., Siever, L.J., Silverman, J.M., Sprock, J., Sugar, C.A., Swerdlow, N.R., Tsuang, D.W., Tsuang, M.T., Turetsky, B.I., Seidman, L.J., 2015. California Verbal Learning Test-II performance in schizophrenia as a function of ascertainment strategy: Comparing the first and second phases of the Consortium on the Genetics of Schizophrenia (COGS). *Schizophrenia research* 163(1–3), 32-37.
- Storzbach, D.M.C., P. W., 1996. Cognitive Rehabilitation for Schizophrenia, in: Corrigan, P.W.Y., S.C. (Ed.), *Cognitive Rehabilitation for Neuropsychiatric Disorders*. American Psychiatric Press, Washington.
- Strassnig, M.T., Raykov, T., O'Gorman, C., Bowie, C.R., Sabbag, S., Durand, D., Patterson, T.L., Pinkham, A., Penn, D.L., Harvey, P.D., 2015. Determinants of different aspects of everyday outcome in schizophrenia: The roles of negative symptoms, cognition, and functional capacity. *Schizophrenia research* 165(1), 76-82.
- Sullivan, P.F., Kendler, K.S., Neale, M.C., 2003. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Archives of general psychiatry* 60(12), 1187-1192.
- Suresh Kumar, P.N., 2008. Impact of vocational rehabilitation on social functioning, cognitive functioning, and psychopathology in patients with chronic schizophrenia. *Indian Journal of Psychiatry* 50(4), 257-261.
- Swerdlow, N.R., Gur, R.E., Braff, D.L., 2015. Consortium on the Genetics of Schizophrenia (COGS) assessment of endophenotypes for schizophrenia: an introduction to this Special Issue of *Schizophrenia Research*. *Schizophrenia research* 163(1-3), 9-16.
- Szoke, A., Trandafir, A., Dupont, M.E., Meary, A., Schurhoff, F., Leboyer, M., 2008. Longitudinal studies of cognition in schizophrenia: meta-analysis. *The British journal of psychiatry : the journal of mental science* 192(4), 248-257.
- Tabares-Seisdedos, R., Balanza-Martinez, V., Sanchez-Moreno, J., Martinez-Aran, A., Salazar-Fraile, J., Selva-Vera, G., Rubio, C., Mata, I., Gomez-Beneyto, M., Vieta, E., 2008. Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. *Journal of affective disorders* 109(3), 286-299.
- Tamminga, C.A., Buchanan, R.W., Gold, J.M., 1998. The role of negative symptoms and cognitive dysfunction in schizophrenia outcome. *International Clinical Psychopharmacology* 13 Suppl 3, S21-S26.

- Tandberg, M., Ueland, T., Andreassen, O.A., Sundet, K., Melle, I., 2012. Factors associated with occupational and academic status in patients with first-episode psychosis with a particular focus on neurocognition. *Social psychiatry and psychiatric epidemiology* 47(11), 1763-1773.
- Tandberg, M., Ueland, T., Sundet, K., Haahr, U., Joa, I., Johannessen, J.O., Larsen, T.K., Opjordsmoen, S., Rund, B.R., Rossberg, J.I., Simonsen, E., Vaglum, P., Melle, I., Friis, S., McGlashan, T., 2011. Neurocognition and occupational functioning in patients with first-episode psychosis: a 2-year follow-up study. *Psychiatry research* 188(3), 334-342.
- Tandon, R., Nasrallah, H.A., Keshavan, M.S., 2009. Schizophrenia, "just the facts" 4. Clinical features and conceptualization. *Schizophrenia research* 110(1-3), 1-23.
- Tarrier, N., Wykes, T., 2004. Is there evidence that cognitive behaviour therapy is an effective treatment for schizophrenia? A cautious or cautionary tale? *Behaviour Research and Therapy* 42(12), 1377-1401.
- Thornicroft, G., Brohan, E., Rose, D., Sartorius, N., Leese, M., 2009. Global pattern of experienced and anticipated discrimination against people with schizophrenia: a cross-sectional survey. *Lancet (London, England)* 373(9661), 408-415.
- Torgalsboen, A.K., Mohn, C., Rishovd Rund, B., 2014. Neurocognitive predictors of remission of symptoms and social and role functioning in the early course of first-episode schizophrenia. *Psychiatry research* 216(1), 1-5.
- Toulopoulou, T., Goldberg, T.E., Mesa, I.R., Picchioni, M., Rijdsdijk, F., Stahl, D., Cherny, S.S., Sham, P., Faraone, S.V., Tsuang, M., Weinberger, D.R., Seidman, L.J., Murray, R.M., 2010. Impaired intellect and memory: a missing link between genetic risk and schizophrenia? *Archives of general psychiatry* 67(9), 905-913.
- Toulopoulouand, T., Murray, R.M., 2004. Verbal memory deficit in patients with schizophrenia: an important future target for treatment. *Expert review of neurotherapeutics* 4(1), 43-52.
- Tsang, H.W., Leung, A.Y., Chung, R.C., Bell, M., Cheung, W.M., 2010. Review on vocational predictors: a systematic review of predictors of vocational outcomes among individuals with schizophrenia: an update since 1998. *The Australian and New Zealand journal of psychiatry* 44(6), 495-504.
- Twamley, E.W., Doshi, R.R., Nayak, G.V., Palmer, B.W., Golshan, S., Heaton, R.K., Patterson, T.L., Jeste, D.V., 2002. Generalized cognitive impairments, ability to perform everyday tasks, and level of independence in community living situations of older patients with psychosis. *The American journal of psychiatry* 159(12), 2013-2020.
- Twamley, E.W., Jeste, D.V., Lehman, A.F., 2003. Vocational rehabilitation in schizophrenia and other psychotic disorders: a literature review and meta-analysis of randomized controlled trials. *The Journal of nervous and mental disease* 191(8), 515-523.
- Tyson, P.J., Laws, K.R., Flowers, K.A., Mortimer, A.M., Schulz, J., 2008. Attention and executive function in people with schizophrenia: Relationship with social skills and quality of life. *International journal of psychiatry in clinical practice* 12(2), 112-119.
- United States War Department, n., 1944. Army Individual Test Battery: Manual of directions and scoring.
- van Os, J., Kapur, S., 2009. Schizophrenia. *Lancet (London, England)* 374(9690), 635-645.
- van Os, J., Krabbendam, L., Myin-Germeys, I., Delespaul, P., 2005. The schizophrenia envirome. *Current opinion in psychiatry* 18(2), 141-145.
- Vargas, G., Strassnig, M., Sabbag, S., Gould, F., Durand, D., Stone, L., Patterson, T.L., Harvey, P.D., 2014. The course of vocational functioning in patients with schizophrenia: Re-examining social drift. *Schizophrenia research. Cognition* 1(1), e41-e46.
- Vaskinn, A., Sundet, K., Ueland, T., Agartz, I., Melle, I., Andreassen, O.A., 2013. Social cognition and clinical insight in schizophrenia and bipolar disorder. *The Journal of nervous and mental disease* 201(6), 445-451.
- Vaskinn, A., Ueland, T., Melle, I., Agartz, I., Andreassen, O.A., Sundet, K., 2014. Neurocognitive Decrements are Present in Intellectually Superior Schizophrenia. *Frontiers in psychiatry* 5, 45.

- Vauth, R., Rusch, N., Wirtz, M., Corrigan, P.W., 2004. Does social cognition influence the relation between neurocognitive deficits and vocational functioning in schizophrenia? *Psychiatry research* 128(2), 155-165.
- Velligan, D.I., Bow-Thomas, C.C., Mahurin, R.K., Miller, A.L., Halgunseth, L.C., 2000. Do specific neurocognitive deficits predict specific domains of community function in schizophrenia? *The Journal of nervous and mental disease* 188(8), 518-524.
- Velligan, D.I., Diamond, P.M., Mintz, J., Maples, N., Li, X., Zeber, J., Ereshefsky, L., Lam, Y.W., Castillo, D., Miller, A.L., 2008. The use of individually tailored environmental supports to improve medication adherence and outcomes in schizophrenia. *Schizophrenia bulletin* 34(3), 483-493.
- Velligan, D.I., Kern, R.S., Gold, J.M., 2006. Cognitive rehabilitation for schizophrenia and the putative role of motivation and expectancies. *Schizophrenia bulletin* 32(3), 474-485.
- Velligan, D.I., Mahurin, R.K., Diamond, P.L., Hazleton, B.C., Eckert, S.L., Miller, A.L., 1997. The functional significance of symptomatology and cognitive function in schizophrenia. *Schizophrenia research* 25(1), 21-31.
- Ventura, J., Helleman, G.S., Thames, A.D., Koellner, V., Nuechterlein, K.H., 2009. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. *Schizophrenia research* 113(2-3), 189-199.
- Vesterager, L., Christensen, T.O., Olsen, B.B., Krarup, G., Melau, M., Forchhammer, H.B., Nordentoft, M., 2012. Cognitive and clinical predictors of functional capacity in patients with first episode schizophrenia. *Schizophrenia research* 141(2-3), 251-256.
- Vidje, G., Wright, J. V., Wehner, L. W., Gudnason, M., Lybeck, M., Rosenqvist, P., Simic, N. & Lagercrantz, H. , 2012. Focus on the Nordic Welfare Model. Nordic Centre for Welfare and Social Issues.
- Waddell, G., Burton, A.K., 2006. Is work good for your health and well-being. The Stationery Office, United Kingdom.
- Waghorn, G., Dias, S., Gladman, B., Harris, M., Saha, S., 2014. A multi-site randomised controlled trial of evidence-based supported employment for adults with severe and persistent mental illness. *Australian occupational therapy journal* 61(6), 424-436.
- Walker, E., Tessner, K., 2008. Schizophrenia. *Perspectives on psychological science : a journal of the Association for Psychological Science* 3(1), 30-37.
- Walker, E.F., Diforio, D., 1997. Schizophrenia: A neural diathesis-stress model. *Psychological Review*, Vol 104 ((4), Oct ), 667-685. .
- Warman, D.M., Grant, P., Sullivan, K., Caroff, S., Beck, A.T., 2005. Individual and group cognitive-behavioral therapy for psychotic disorders: a pilot investigation. *Journal of psychiatric practice* 11(1), 27-34.
- WASI, 2007. Wechsler Abbreviated Scale of Intelligence, Norwegian Manual Supplement. Harcourt Assessment Inc., Stockholm, Sweden.
- Wechsler, D., 1997. Wechsler Memory Scale.
- Weinberger, D.R., 1987. Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of general psychiatry* 44(7), 660-669.
- White, T.S., R. A. , 2003. Neuropsychological Test Battery. FL: Psychological Assessment Resources, Lutz.
- WHO, 2011. World Health Organization: WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index 2011.
- Wilkinson, L., 1999. Statistical methods in psychology journals: Guidelines and explanations. *American Psychologist* 54(8), 594-604.
- Wing, J.K., Beevor, A.S., Curtis, R.H., Park, S.B., Hadden, S., Burns, A., 1998. Health of the Nation Outcome Scales (HoNOS). Research and development. *The British journal of psychiatry : the journal of mental science* 172, 11-18.
- Wood, D., 1998. *How Children Think and Learn*, 2 ed. Blackwell, Oxford.
- World Health, O., 2008. *The Global Burden of Disease*.

- Wykes, T., Huddy, V., Cellard, C., McGurk, S.R., Czobor, P., 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *The American journal of psychiatry* 168(5), 472-485.
- Wykes, T., Reeder, C., 2005. *Cognitive Remediation Therapy for Schizophrenia* Routledge, Hove, East Sussex.
- Wykes, T., Reeder, C., Corner, J., Williams, C., Everitt, B., 1999. The effects of neurocognitive remediation on executive processing in patients with schizophrenia. *Schizophrenia bulletin* 25(2), 291-307.
- Wykes, T., Reeder, C., Huddy, V., Taylor, R., Wood, H., Ghirasim, N., Kontis, D., Landau, S., 2012. Developing models of how cognitive improvements change functioning: mediation, moderation and moderated mediation. *Schizophrenia research* 138(1), 88-93.
- Wykes, T., Spaulding, W.D., 2011. Thinking about the future cognitive remediation therapy--what works and could we do better? *Schizophrenia bulletin* 37 Suppl 2, S80-90.
- Xiang, Y., Weng, Y., Li, W., Gao, L., Chen, G., Xie, L., Chang, Y., Tang, W.K., Ungvari, G.S., 2006. Training patients with schizophrenia with the community re-entry module: a controlled study. *Social Psychiatry and Psychiatric Epidemiology* 41(6), 464-469.
- Young, J.W., Powell, S.B., Risbrough, V., Marston, H.M., Geyer, M.A., 2009. Using the MATRICS to guide development of a preclinical cognitive test battery for research in schizophrenia. *Pharmacology & therapeutics* 122(2), 150-202.
- Zanelli, J., Reichenberg, A., Morgan, K., Fearon, P., Kravariti, E., Dazzan, P., Morgan, C., Zanelli, C., Demjaha, A., Jones, P.B., Doody, G.A., Kapur, S., Murray, R.M., 2010. Specific and generalized neuropsychological deficits: a comparison of patients with various first-episode psychosis presentations. *American Journal of Psychiatry* 167(1), 78-85.
- Zubin, J., 1985. Negative symptoms: are they indigenous to schizophrenia? *Schizophrenia bulletin* 11(3), 461-470.



## 8. Appendices

### 8.1 Appendix 1

Overview of the JUMP participants in papers I and II, including characteristics of the healthy control group in paper 1.

	<b>Patients (N = 131)</b>	<b>HC (N = 137)</b>	<b>Test Statistics</b>	<b>Group comparison (p)</b>
<b>Gender, male (%)</b>	N = 92 (70.2 %)	N = 81 (59.1)	$\chi^2 (1, n = 268) = 3.61$	ns
<b>Age, mean (SD)</b>	32.7 (7.9)	33.50 (9.4)	$t (266) = -0.78$	ns
<b>Hand dominance (R)</b>	N = 119 (86.9)	N = 120 (88.2)	$\chi^2 (1, n = 267) = 0.23$	ns
<b>Education, mean (SD) <sup>a</sup></b>	11.8 (2.4)	12.8 (2.4)	$t (266) = -3.48$	$p = 0.001$
<b>IQ, mean (SD)</b>	102.4 (13.1)	107.6 (12.2)	$t (263)^b = -3.37$	$p = 0.001$
<b>Units of DDD<sup>c</sup> main anti-psychotic, mean (SD)</b>	1.1 (1.0)			
<b>Duration of illness, mean years (DOI) (SD)</b>	6.9 (6.4)			
<b>SCI-PANSS</b>				
Positive, mean (SD)	13.4 (4.57)			
Negative, mean (SD)	16.3 (5.7)			
General, mean (SD)	29.8 (8.3)			
Total, mean (SD)	59.3 (15.4)			
<b>Substance use, n (%)</b>				
Alcohol dependence	9 (6.9)			
Alcohol abuse	13 (9.9)			
Drug dependence	8 (6.1)			
Drug abuse	4 (3.1)			
<b>Previous employment</b>				
Previously employed	84.7 %			

## 8.2 Appendix 2

Overview of the JUMP participants in paper III, split into intervention groups

	<b>CBT (N = 68)</b>	<b>CR (N = 63)</b>	<b>Test Statistics</b>	<b>Group comparison (p)</b>
<b>Diagnosis</b>			$X^2 (8, n= 131) = 0.59$	<i>ns</i>
Schizophrenia	89.6 %	87.2 %		
Schizoaffective disorder	5.9 %	9.6 %		
Psychosis NOS	1.5 %	1.6 %		
Delusional disorder	2.9 %	1.6 %		
<b>Age, mean (SD)</b>	33.2 (8.2)	32.2 (7.7)	$t (129) = 0.75$	<i>ns</i>
<b>Gender, male (%)</b>	42 (61.8 %)	50 (79.4 %)	$X^2 (1, n= 131) = 4.85$	.03
<b>Education, mean (SD)</b>	12.0 (2.6)	11.6 (2.2)	$t (129) = 1.05$	<i>ns</i>
<b>IQ, mean (SD)<sup>a</sup></b>	102.3 (13.2)	102.4 (13.1)	$t (129) = -0.05$	<i>ns</i>
<b>Units of DDD<sup>b</sup> main anti-psychotic, mean (SD)</b>	1.6 (3.0)	1.4 (1.5)	$t (129) = 0.41$	<i>ns</i>
<b>Duration of illness, mean years (DOI) (SD)</b>	7.9 (7.0)	5.9 (5.5)	$t (124) = 1.76$	<i>ns</i>
<b>SCI-PANSS</b>				
Positive, mean (SD)	12.8 (4.6)	14.0 (4.5)	$t (127) = -1.5$	<i>ns</i>
Negative, mean (SD)	16.7 (5.8)	15.9 (5.6)	$t (126) = 0.8$	<i>ns</i>
General, mean (SD)	29.3 (8.9)	30.2 (7.6)	$t (128) = -0.6$	<i>ns</i>
Total, mean (SD)	58.8 (16.5)	59.8 (14.2)	$t (125) = -0.4$	<i>ns</i>
<b>Previous competitive employment (Lifetime)</b>				
Previously employed	86.8 %	82.5 %	$X^2 (1, n=131) = 0.45$	<i>ns</i>
Months part time, mean(SD)	18 (39.2)	15.4 (31.2)	$X^2 (27, n=131) = 23.5$	<i>ns</i>
Months full time, mean (SD)	48.6 (21)	38.0 (6)	$X^2 (39, n=131) = 42.9$	<i>ns</i>
Months work placement, mean (SD)	5.5 (14.0)	4.3 (10.6)	$X^2 (15, n=131) = 10.6$	<i>ns</i>
<b>MCCB Domain T-scores, mean (SD)</b>				
Processing Speed	36.6 (10.1)	35.1 (8.6)	$t (126) = 0.89$	<i>ns</i>
Attention	39.1 (10.6)	36.9 (9.2)	$t (129) = 1.26$	<i>ns</i>
Working Memory	41.2 (9.7)	41.6 (9.5)	$t (128) = -0.24$	<i>ns</i>
Verbal Learning	38.5 (7.9)	41.0 (10.7)	$t (129) = -1.50$	<i>ns</i>
Visual Learning	36.3 (12.1)	38.0 (10.4)	$t (129) = -0.80$	<i>ns</i>
Problem Solving	44.5 (10.0)	42.3 (9.2)	$t (129) = 1.21$	<i>ns</i>
Neurocognitive Composite Score	39.5 (6.4)	39.1 (6.6)	$t (125) = 0.35$	<i>ns</i>