First-episode schizophrenia: Recovery, remission and neurocognitive predictors of functional outcome

Results from the sixth year of the Oslo Schizophrenia Recovery Study

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Abstract

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The range of outcomes in first-episode schizophrenia (FES) is heterogenous, and reaching full recovery is possible. The proportion of FES patients reaching full recovery is still somewhat unclear. Functional outcome is recognized as an important aspect of recovery, and neurocognition has emerged as a possible predictor of this. The present study combines outcome with neurocognition in FES, investigating the proportion of participants reaching full recovery, and identifying neurocognitive domains predictive of social and role functioning at six-year follow-up.

Methods: The present study is part of the Oslo Schizophrenia Recovery Study, in which individuals with first-episode schizophrenia are followed over a period of ten years. We here report on data from the six-year follow-up. The candidate was given access to the collected data. Regression analysis was used to investigate the research questions. All statistical analyses are performed by the candidate. **Results:** 45,5% of the FES participants fulfilled criteria for full recovery, 27,3% were partially recovered, and 13,6% were in remission. Attention ($\beta = 0,57$, $p<0,05$), processing speed ($\beta = -0,55$, $p<0,05$), verbal learning ($\beta = 0,50$, $p< 0,05$), reasoning and problem solving ($\beta = 0,44$, $p<0,05$) and working memory non-verbal ($\beta = 0,33$, $p < 0,05$) statistically significantly predicted social functioning at six-year follow-up. Neither of the specific cognitive domains statistically significantly predicted role functioning. **Conclusions:** The findings of the present study contribute to the knowledge on outcomes of FES. They indicate a bright outlook for the majority of FES participants. The results add to the knowledge on specific neurocognitive domains as predictors of functional outcome in FES, and further facilitate tailoring treatment according to neurocognition. We speculate that, long-term, neurocognition might be of greater importance for social- than role functioning; emphasizing the importance of a continued focus on destigmatization of schizophrenia.

Preface

I believe it was already in my first semester at the Department of Psychology, that a certain professor Torgalsbøen held a thundering lecture about schizophrenia. She talked about "schizophrenic weather" and opened my eyes to the stigmatization faced daily by individuals suffering from schizophrenia. "One *is* not a schizophrenic, rather, one *has* schizophrenia".

Something about this captured my interest, and I have since tried to gain a deeper understanding of what schizophrenia actually is. During the past six years, studying psychology, I have had the pleasure to meet and get to know several individuals with schizophrenia. The words of Torgalsbøen have rung in my head, as I have been baffled by beliefs held not only by the general public, but also by health care professionals.

As so, when the time came to write my thesis, writing about schizophrenia was the natural choice. It has not been disappointing.

I would like to thank professor Anne-Kari Torgalsbøen. Firstly, for inspiring my interest in schizophrenia. Further, for giving me the opportunity to write a thesis within the Oslo Schizophrenia Recovery Study and providing guidance through the process. I am also grateful for the trained eye and extensive knowledge of post doc Christine Mohn, not only lending me statistical advice, but also providing hope. Thanks to Nikolai Czajkowski for initial statistical advice.

Lastly, I am eternally grateful for the love, support and persistent encouragement of my mother, Marianne.

Oslo, April 2018

Rebecca Tholin

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1 Introduction

Schizophrenia entails major personal suffering and is one of the most debilitating disorders world-wide (World Health Organization, 2016). Adults with schizophrenia have the highest mortality rates compared to individuals with other disorders (Walker, McGee, & Druss, 2015), and schizophrenia also entails major societal costs (Chong et al., 2016). For many years, pessimism dominated the field regarding outcome. It was a widespread notion among clinicians and researchers that individuals with schizophrenia could be expected to have a poor outcome (Rund, 1990), likely with a progressively deteriorating course (Goldberg et al., 2009). Schizophrenia is now recognized as a disorder with major heterogeneity, possible outcomes ranging from worsening and continuation of debilitating symptoms, to that of full recovery (Carpenter & Kirpatrick, 1988; Ruggeri et al., 2004).

The concept of recovery, however, is debated, and there are several different conceptualizations of what it entails. Finding potentially treatable determinants of recovery from schizophrenia is a major goal. Functional outcome is recognized as an important aspect of recovery, mainly because of its importance for the individual, but also due to its implications for society. Today, there is a substantial amount of research on this, and neurocognition has emerged as an important predictor of later functional outcome (Green, 1996; Mesholam-Gately, Giuliano, Goeff, Faraone, & Seidman, 2009; Allott, Liu, Proffitt, & Killackey, 2011).

We will now provide a brief review of the psychological history of schizophrenia, as this provides a theoretical background for understanding current research.

1.1 From the Kraepelinian paradigm to the modern construct of schizophrenia

Schizophrenia has historically been conceptualized as a chronic, deteriorating disease with a poor outcome (Rund, 1990). This pessimism has also been evident in the diagnostic system; in the DSM III (American Psychiatric Association, 1980) remission and return to premorbid functioning was considered so rare, the clinician would probably question the original diagnosis. Although representing a somewhat more optimistic view, even in the DSM IV-TR it was stated that return to premorbid functioning was probably not common (American

Psychiatric Association, 2000). Some of this pessimism can be traced back to Emil Kraepelin, one of the first to devote his career to schizophrenia. His work has had great influence on the field (Andreasen, 1997), and he coined the term *dementia praecox*, meaning *early dementia*.

Kraepelin divided dementia praecox into different subtypes (e.g. hebephrenic, catatonic and paranoid) (Adityanjee, Aderibigbe, Theodoridis, & Vieweg, 1999), and described dementia praecox as a fundamentally chronic, degenerative disorder (Kraepelin, 1923). This implied that the illness itself causes degeneration of brain tissue within a few years of experiencing positive symptoms (Wyatt & Henter, 1998), leading to a progressively deteriorating course.

Kraepelin might have been misunderstood or over-simplified (Hoenig, 1983). For example, he found that the course of schizophrenia showed great variability in the speed of the decline, its extent, and in the frequency, extent and quality of remission (Hoenig, 1983). In one study, he found 12,5 per cent of the patients were fully recovered (Kraepelin as cited in Hoenig (1983)). Despite this, Kraepelin seemingly did not revise his view on the prognosis of schizophrenia. Rather, he argued that individuals who improved had originally been misdiagnosed (Rund, 1990). As so, regardless of potentially having been over-simplified, the work of Kraepelin has been taken as support for homogeneity in outcomes of schizophrenia (Beck, Rector, Stolar, & Grant, 2009). This has had important and perhaps negative consequences, consolidating a belief of schizophrenia as a devastating and chronic disease, without hope of recovery (Hoenig, 1983; Andreasen, 1997).

Another influential person in the history of schizophrenia is Bleuler. Disagreeing with Kraepelin's understanding of dementia praecox as invariably degenerative, he coined the term *schizophrenia* in 1911 (Bleuler, 1950). Bleuler characterized schizophrenia as a family of mental disorders – *die Gruppe der Schizophrenien.* Thus, he widened the diagnosis considerably in comparison to Kraepelin, and used a more dimensional approach (Beck et al., 2009). He considered schizophrenia as ranging from what today is known as schizotypy to full-blown chronic dementia praecox; recognizing the heterogeneity of schizophrenia (Adityanjee et al., 1999). A substantial part of the current research on schizophrenia is based on Bleuler's theories (Beck et al., 2009).

Much of the early research on schizophrenia was done with patients who had suffered from schizophrenia for many years (Mesholam-Gately et al., 2009). The patients were often institutionalized and might be considered suffering from "chronic" or long-acting

schizophrenia. This likely influenced findings of recovery rates negatively, and contributed to the pessimism concerning both the possibility and rate of recovery.

Today, in the Bleulerian tradition, schizophrenia is recognized as a disorder with major heterogeneity (Joyce, Hutton, Mutsata, & Barnes, 2005; Lally et al., 2017). Outcomes range from reaching full recovery to experiencing worsening, potentially with a chronic course (Lally et al., 2017). A substantial proportion of individuals with schizophrenia is found to have a favorable outcome.

Recognizing good outcomes as a possibility, a new question arises: Which criteria must be fulfilled to be considered fully recovered from schizophrenia?

1.2 Functional outcome and the recovery perspective

There is currently no consensus on how recovery should be conceptualized (Leucht, 2014), and different definitions of recovery are used in schizophrenia research. Agreement about the concept of recovery is important both for clarity of treatment goals and for facilitation of comparison between studies, accommodating advancement of schizophrenia research.

In the discussion of the concept of recovery and what it should include, it is increasingly embraced that researchers, clinicians and consumers of mental health services may have different perceptions of what recovery is (Barber, 2012). Traditionally, researchers have focused on the remission of psychotic symptoms. Clinicians might focus on improvement in global functioning, while consumers are often found to value the highest retaining a meaningful life within the limitations of the disorder (Slade et al., 2014; Green, 2016).

In recent years, more emphasis has been placed on recovery as a subjective orientation, taking into consideration that people can have hope, feel capable of expanding their personal abilities and make their own choices, regardless of symptoms (Barber, 2012). Thus, the symptomatic focus might decrease, acknowledging instead that other aspects of life might be more important to the individual, such as having a meaningful job and a satisfying social life. That is, elements of functional outcome. This broadening in the understanding of the concept of recovery from schizophrenia allows for a variety of other aspects than symptoms to be important in the pursuit of mental health. Such additional important aspects include being an

active part of the community, being hopeful, working towards one's goals and having working abilities (Lieberman et al., 2008).

It has also been suggested that recovery criteria need to take into consideration that functional improvement can occur in some patients in parallel with ongoing moderate symptoms, with some individuals developing coping mechanisms that enable them to function despite their illness (Andreasen et al., 2005).

Further supporting a decreased focus on symptoms in recovery is the now substantial evidence that a relatively large proportion of the general population at times have psychotic-like experiences (PLE). For example, hearing voices is quite widespread, and is not only a symptom experienced by people who suffer from a psychotic disorder. One Norwegian study found that 7,3% of their sample reported a life-time prevalence of auditory verbal hallucinations (Kråkvik et al., 2015). This study is one of many reporting that hallucinations are experienced by a substantial proportion of the general population (Stip & Letourneau, 2009). Such findings might be taken as support for understanding psychotic symptoms on a continuum between normality and pathology, rather than as categorical (Stip & Letourneau, 2009). The findings might also influence how one should conceptualize recovery. What differentiates those individuals in the general population who hear voices, or experience other psychotic symptoms, from those individuals diagnosed with schizophrenia? Quality of life and functioning in daily living might be one major difference. As so, functional outcome is a potentially important indicator of recovery.

Liberman, Kopelowicz, Ventura, and Gutkind (2002) proposed refining the concept of recovery by dividing it into different areas, such as recovery of cognitive functioning and recovery of vocational functioning. They explained the need for such a clarification by emphasizing that people with schizophrenia are considerably heterogeneous in each domain of recovery, and that the various domains of recovery are relatively independent from one another. Liberman et al. also emphasize that different interventions are effective for specific dimensions of the illness and functions, and are effective only for a proportion of patients. It therefore makes more sense to view recovery in terms of improvements in specific domains rather than globally.

As the concept of recovery has broadened, functional outcome is receiving more attention. Also considering the debilitating effects of schizophrenia, both personally and societally,

functional outcome is of major importance. Working towards facilitation of functional recovery in schizophrenia, different factors have been identified as being of importance. Neurocognition is consistently being associated with functional outcome (e.g. Green, 1996; Nuechterlein et al., 2011; Davies, Fowle, & Greenwood, 2017; Sawada et al., 2017), and is therefore an important area of research.

Regarding the concept of functional outcome, it is necessary to be aware of the difference between real-world functioning and functioning under optimal conditions (Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006). While real-world functioning is arguably of the greatest importance to daily living, the dissonance between this and performance under optimal condition might enlighten the potential of the individual and guide researchers to factors hindering optimal performance in the real world. However**,** as real-world functioning is potentially highly informative, it is often the focus of studies. Neurocognition, on the contrary, is frequently measured with standardized tests under optimal conditions. Hence, it reflects the potential of the individual, though the person might not be able to perform on this level in the real world.

Considering that schizophrenia involves great personal suffering, and also entails a substantial economic expense for society, finding potentially treatable determinants for functional outcome is highly important. Neurocognition is found to be one such area.

1.3 Neurocognition in schizophrenia

Schizophrenia is often associated with hearing voices, seeing visions, and having false beliefs about reality (Barch & Ceaser, 2012). Those symptoms, verbal and visual hallucinations, and delusions, are commonly thought to be the core characteristics of schizophrenia. However, abnormalities in cognitive functioning has long been recognized as a key component, perhaps affecting the lives and daily functioning of those with schizophrenia to a greater extent than positive and negative symptoms (Green & Nuechterlein, 2004). Cognitive deficits are now recognized as a core feature of schizophrenia (Barch & Ceaser, 2012).

Modern antipsychotic medication contribute in relieving psychotic symptoms, but the cognitive difficulties are often still an issue (Green & Nuechterlein, 2004), and residual functional disabilities persist. Several studies have found neurocognition to be associated with later functional outcome. Thus, neurocognition is potentially a predictor of outcome. If

clinicians can identify those at great risk of a poor functional outcome, they may eventually be able to target predictive factors – such as different neurocognitive domains – that are associated with functional outcome, with a goal of facilitating better functional outcome in individuals with schizophrenia (Allott et al., 2011).

There is much evidence of global cognitive deficits in patients with long-acting ("chronic") schizophrenia (Heinrichs & Zakzanis, 1998; Bowie et al., 2008; Schaefer, Giangrande, Weinberger, & Dickinson, 2013). Neurocognitive deficits among people with schizophrenia as a group are estimated to lie about one standard deviation below the norm (Moritz et al., 2017). In recent years, there has been an increased focus on cognition in individuals with first-episode psychosis (FEP) or schizophrenia (FES). Deficits in global cognition are found also in FES.

A meta-analysis performed by Mesholam-Gately et al. (2009) concludes that individuals with first episode or early phase schizophrenia show statistically significant and clinically meaningful deficits across all neuropsychological domains. These findings are supported by research repeatedly showing that individuals with schizophrenia on group level show moderate to severe cognitive deficits (Tandon, Nasrallah, & Keshavan, 2009). Their findings are also in accordance with earlier meta-analyses, such as one performed by Heinrichs and Zakzanis (1998), even though this analysis had a considerably older sample who had had schizophrenia for a longer time.

Mesholam-Gately et al. (2009) found prominent cognitive deficits in several specific domains: The cognitive impairments were greatest for verbal- and non-verbal memory, processing speed, attention, language skills, executive functions and social cognition. A review by Allott et al. (2011), examining cognitive domains separately, found that in order of highest to lowest, the frequency with which each cognitive domain significantly predicted functional outcome was verbal/language skills, global/general cognition, reasoning and problem solving, verbal learning and memory, speed of processing, motor skills, attention and vigilance, working memory, construction and visuospatial skills, visual learning and memory and verbal fluency. When including only studies that controlled for potential predictor variables, their results were largely unchanged, except for Reasoning and Problem Solving, which were then of less importance.

Summarizing, deficits in neurocognitive domains are consistently found in FES patients. Several of these domains are associated with functional outcome in schizophrenia. The domains of the greatest importance seem to be, in random order, *attention, processing speed, verbal and nonverbal memory, general cognitive ability, language functions, visuospatial abilities, executive functioning* and *working memory* (Bilder et al., 2000; Mesholam-Gately et al., 2009; Lindenmayer et al., 2017; Sawada et al., 2017). As such, most neurocognitive domains seem to be associated with deficits.

Identifying specific neurocognitive deficits might facilitate prediction of functional outcome in individuals with schizophrenia. As potential markers of illness vulnerability (Carrión et al., 2018) and outcome they might constitute the foundation for tailoring cognitive training interventions. This might, in turn, contribute to a better functional outcome. Several studies and meta-analyses have found that cognitive remediation has moderate to large effects on cognitive outcomes (Revell, Neill, Harte, Khan, & Drake, 2015; Lindenmayer et al., 2017).

The Norwegian National Guidelines for disorders in the psychosis spectrum (The Norwegian Directorate of Health, 2013) are based on relatively recent and up-to-date research. The importance of cognition in schizophrenia is recognized, and cognitive training is recommended.

1.3.1 The MATRICS initiative

Based on the importance of neurocognition for future functional outcome, the National Institute of Mental Health (NIMH) initialized the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS). The MATRICS group based their work on the assumption that cognitive deficits are core features of schizophrenia, and the premise that cognitive performance in schizophrenia is predictive of community functioning at some later point in time (Green & Nuechterlein, 2004). The NIMH recognized that there were efficacious medications for psychotic symptoms, but that, contrary to quite extensive research focusing on cognitive deficits, there was an unmet need of medication for the cognitive deficits in schizophrenia. They also recognized that this might contribute extensively in hindering many people with schizophrenia from reentering the society (Green & Nuechterlein, 2004). The NIMH-Measurement and Treatment Research to Improve Cognition in Schizophrenia wished to push toward the development of such drugs, underlining its importance. The mandate of the MATRICS group was to decide on the methods that could be

used to evaluate new drugs so that they could be approved for use on cognitive enhancement in schizophrenia; stimulating development of psychopharmacological agents to improve cognition in schizophrenia. Then, the pharmaceutical industry would have to do their part.

The main product of the extensive effort of the MATRICS working group was the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein & Green, 2006). In addition to its original purpose, the MCCB came to be important also in research focusing purely on neuropsychological functioning in schizophrenia spectrum disorders, not necessarily assessing medications.

The MCCB is frequently used in studies, such as the present, assessing the predictive value of neurocognition to functional outcome. There is evidence supporting the notion that the MCCB is sensitive both to cognitive training interventions and to pharmacological interventions (Green, Harris, & Nuechterlein, 2014), and it is frequently referred to as the gold standard of neuropsychological assessment in schizophrenia (Mohn, Sundet, & Rund, 2014).

1.4 Other factors than neurocognition associated with functional outcome

As seen, neurocognitive functioning is a much studied topic in schizophrenia research, and cognitive abilities are currently considered of the most poignant predictors of functional outcome (Bechi et al., 2017). However, neurocognition often only explains about 25-50% of the variance in functional outcome (Bowie et al., 2006), and several additional factors are found to be associated with outcome in schizophrenia. Such factors might be directly associated with outcome, or they can mediate the association between cognitive functioning and real-world functioning. Probably, multiple constructs are required to capture the complexity of functional outcome (Bowie et al., 2006).

Duration of untreated psychosis is one factor often found to be associated with outcome, elaborated below. Other factors that seemingly influence the outcome of schizophrenia are the circumstances under which the illness develops, characteristics of the illness, premorbid functioning and abilities at onset (Tandon et al., 2009). Acute onset of illness, as opposed to an insidious onset, is found in several studies to indicate a more favorable outcome (Tandon et al., 2009). Premorbid characteristics of the affected individual seem to be of importance

(Bechi et al., 2017). For example, better premorbid functioning, a multi-faceted construct, may be of importance (Tandon et al., 2009). Absence of substance abuse is also found to be associated with a more favorable outcome (Dixon, 1999). Demographic factors such as age of onset, education level, race and gender have long been seen as important predictors of later functioning (Gould, Bowie, & Harvey, 2012). Presence and degree of some specific psychopathology is also associated with real-world functioning, such as positive and negative symptoms, and depressed mood (Bechi et al., 2017).

Considering it a separate measure from neurocognitive functioning, social cognition is found to significantly explain a large proportion of the variance in functional outcome (Fett et al., 2011). Family environment and early childhood experiences have also been suggested to potentially influence outcome (Bechi et al., 2017).

1.4.1 The association between neurocognition and functional outcome

Although there is there is much research on the association between neurocognition and later functional outcome, exactly how cognition and social and role functioning is interconnected remains unclear. The association might be one of cause-effect; that is, the level of neurocognitive functioning might directly affect later functional outcome (Davies et al., 2017). An increasing amount of studies examine possible moderating and mediating variables. Moritz et al. (2017) argue that the performance of people with schizophrenia on neurocognitive measures are influenced to a considerable extent by secondary factors such as motivation and fear, and argue that factors such as these, potentially affecting the performance on neurocognitive tests, should be taken into account even before concluding that neurocognitive deficits are present in patients with schizophrenia. Stress has also been suggested to influence neurocognitive performance (Krkovic, Moritz, & Lincoln, 2017). However, laying to ground that impaired performance on neurocognitive tests actually do reflect neurocognitive deficits, a variety of different variables have been suggested to contribute to or influence the association between neurocognition and functional outcome. Metacognition (Davies et al., 2017), motivation and symptoms are examples of such variables, and have been suggested to mediate or otherwise be associated with neurocognition and functional outcome (Ventura, Hellemann, Thames, Koellner, & Nuechterlein, 2009).

Regardless of how it is associated with functional outcome, cognition in schizophrenia is marked by major heterogeneity, both concerning severity and in which areas the individual shows the greatest deficiencies. A large proportion of individuals with schizophrenia exhibit cognitive deficiencies compared to healthy control groups (Mohamed, Paulsen, O'Leary, Arndt, & Andreasen, 1999; Mesholam-Gately et al., 2009). This entails that not all individuals with schizophrenia have cognitive deficiencies. However, it is debated whether they still function at a lower cognitive level than they did before onset of the illness (Mesholam-Gately et al., 2009; Sawada et al., 2017). The field has developed beyond the Kraepelinian notion of homogeneity, and a major focus today is on the heterogeneity of schizophrenia.

1.5 Heterogeneity in schizophrenia

Homogeneity in schizophrenia was part of the Kraepelinian legacy. With the advancement of research, schizophrenia is now recognized as a disorder with major heterogeneity (American Psychiatric Association, 2013). The heterogeneity is evident in many aspects of schizophrenia, such as in the symptoms, cognition (Joyce et al., 2005), treatment response and outcome (Tandon et al., 2009).

Already in the 70ties, and probably long before, symptom heterogeneity in schizophrenia was recognized (Buchsbaum & Haier, 1978). However, in recent years, another form of heterogeneity has been in the scientific limelight. That is, heterogeneity in outcome across individuals with schizophrenia (Ruggeri et al., 2004). This could be seen in contrast to the Kraepelinian perspective of unalterably progressive deterioration (Tandon et al., 2009), assuming relative homogeneity in long-term outcomes of schizophrenia (Carpenter & Kirpatrick, 1988).

A number of varying hypotheses concerning heterogeneity have been postulated (Tsuang, Lyons, & Faraone, 1990). Some consider schizophrenia a clinical syndrome rather than a single disease entity, and suggest heterogeneity is a result of underlying differences such as subtypes of schizophrenia (Carpenter & Kirpatrick, 1988). However, the traditional subtypes do not fully explain the heterogeneity of schizophrenia (Tandon et al., 2009).

Following the first psychotic break, the course of schizophrenia varies substantially across individuals (Ruggeri et al., 2004; McGrath, 2008; Tandon et al., 2009). Different studies report somewhat different proportions, but it is estimated that about a quarter of patients

exhibit full psychopathological remission and about half show social remission (Tandon et al., 2009). More generally; about 20-40% appear to have a favorable course (American Psychiatric Association, 2013; Lally et al., 2017). This realization represents a major step away from the pessimistic notion of schizophrenia being a chronic disease without hope of recovery. Instead, schizophrenia might have many different trajectories and outcomes. It may resolve completely, end in a severe state, or in varying degrees of partial or full recovery (Tandon et al., 2009). This multitude of possible outcomes is crucial in the modern understanding of schizophrenia. A significant proportion of individuals with first-episode schizophrenia exhibit *substantial* improvement (Menezes, Arenovich, & Zipursky, 2006; Jääskeläinen et al., 2012; Lally et al., 2017).

As some individuals experience a more favorable outcome from schizophrenia than others, studying what differentiates these individuals is of major importance. Longitudinal studies with multi follow-up provide an opportunity to do this. Longitudinal research further allows for studying causation and making inferences which cannot be made from cross-sectional studies, as individuals are not followed over time. Studying individuals from their first episode of psychosis widens the scope of investigation and possible research questions further.

1.6 The importance of studying FES patients

Until the early 1990s, the majority of studies had been conducted with institutionalized patients with what could be termed "chronic" schizophrenia. The patient group studied represented those individuals with a poor outcome (Harvey, Loewenstein, & Czaja, 2013). Among these patients, measures of cognitive dysfunction are potentially confounded by effects of age, clinical symptoms, illness duration and treatment. To minimize the effects of confounding variables, there has been a growing interest in the clinical and neurocognitive characteristics of early phases of schizophrenia (Mesholam-Gately et al., 2009), especially first-episode schizophrenia. Another important reason to focus on the early phase of schizophrenia is that earlier treatment is associated with a better outcome (Wyatt & Henter, 1998; Hegelstad et al., 2012), and that the period in which the individual experiences psychosis without treatment often is both painful and frightening. Such a focus also has the potential to test Kraepelin's notion of deterioration: Neurocognitive assessment would have to be conducted at the beginning of psychosis, or as close as possible to the onset of the first

episode (Mesholam-Gately et al., 2009). Additionally, it is increasingly recognized that neurocognitive impairments are often present before the onset of psychosis (Fett et al., 2011). Focusing on FES patients also makes it possible to study whether neurocognition changes between the relatively early and later phases of illness.

1.6.1 Early intervention is associated with better outcome

The duration of untreated psychosis (DUP) is commonly defined as the period of time between the first onset of positive symptoms and the time point where the person receives appropriate care (Birnbaum, Wan, Broussard, & Compton, 2017). DUP has been established as a significant predictor of outcome in people with first episode psychosis, at least on short term (Hegelstad et al., 2012). There are major international efforts working towards reducing the DUP (Birnbaum et al., 2017), and early intervention is also encouraged in Norway (The Norwegian Directorate of Health, 2013). The rationale is that early intervention might prevent even more severe psychopathology from developing, as well as counteracting chronicity (Hegelstad, 2014). The Norwegian TIPS-project, which is a project focusing on the potential effects of reducing the DUP, has resulted in several findings supporting that duration of untreated psychosis is associated with recovery-rates. In a 10-year follow-up study, the TIPS research group reported that patients in the early-detection program had higher rates of recovery that patients who were in the usual-detection group (Hegelstad et al., 2012).

Duration of untreated psychosis is of special interest and significance as it currently is one of few potentially modifiable predictors of outcome in schizophrenia (Penttilä, Jääskeläinen, Hirvonen, Isohanni, & Miettunen, 2014). Longer DUP is associated with poorer response to treatment, including worse global, vocational, social and cognitive functioning (Birnbaum et al., 2017), as well as higher risk of relapse and lower quality of life. Longer DUP is also found to be associated with more severe positive and negative symptoms later (Penttilä et al., 2014). However, there is some contradicting evidence**.** For example, a recent meta-analysis by (Lally et al., 2017) found DUP not to be a moderator of remission and recovery rates.

While some people experience only one episode of psychosis, most do not (Hegelstad, 2014). Psychotic symptoms often occur in formative years of life (Birnbaum et al., 2017). Adolescence and early adulthood is a period of life characterized by major changes, such as establishing one's place in society and developing both personally and socially. Education, work and carrier are often central issues. As such, it is evident that developing schizophrenia

will likely have major implications for the lives of the people affected. This underlines the importance of early intervention, as we might expect it could contribute to giving people a chance to develop more age-adequately in this period.

Another reason to study individuals with first-episode schizophrenia is that it facilitates testing of the neurotoxicity hypothesis.

1.6.2 Testing the neurotoxicity hypothesis and the Kraepelinian notion of deterioration

The hypothesis of neurotoxicity, claiming that being psychotic has a toxic effect on the brain (Rund, 2014), was launched in 1991 (Wyatt, 1991). It should also been seen in the historical light of the Kraepelinian notion of deterioration (Kraepelin, 1899; Wyatt & Henter, 1998). Implying that etiologic and pathogenic factors occur (long) before the onset of psychotic symptoms, understanding schizophrenia as a neurodevelopmental disorder can be seen as opposed to the notion of deterioration (Lieberman, 1999). However, these two theories need not be mutually exclusive (McClure & Lieberman, 2003).

The neurotoxicity hypothesis has generated a great deal of research, with the potential verification of the hypothesis underlining the importance of early intervention in psychosis. If psychosis is neurotoxic, early intervention is not only humane, but also has neuroprotective effects (Goldberg et al., 2009). As the underlying neurology of the neurotoxicity hypothesis is rather complicated, this will not be reviewed in this thesis.

Duration of untreated psychosis has often been used as an important measure in studying the neurotoxicity hypothesis, with studies finding a correlation between DUP and outcome being taken as support for the hypothesis (Rund, 2014). Several studies have examined the relationship between DUP and cognition at study entry. Many of these have found no, or weak, correlations, suggesting schizophrenia is not a neurodegenerative disorder (Goldberg et al., 2009). However, the current evidence is mixed. For example, Rund (2014) found that of the 22 studies included in his review, 6 studies supported the neurotoxicity hypothesis, and 16 did not. Inconsistency across studies, both methodologically and concerning results, make it difficult to conclude concerning the hypothesis of neurotoxicity and neurodegeneration (Goldberg et al., 2009). Rund (2014), however, concludes that in general, neurocognitive studies do not provide substantial support for the hypothesis.

Today, there is a substantial amount of evidence that functional and structural changes occur before the onset of psychosis, and that these may continue after the debut of psychosis (Zipursky, Reilly, & Murray, 2013; Rund, 2014). The evidence concerning neurocognitive trajectories after the onset of psychosis, however, is somewhat unclear. There seems to be a deterioration of cognitive functioning from before onset of psychosis which stabilizes some time into the disorder (Tandon et al., 2009). The evidence for the neurotoxicity hypothesis is by several researchers deemed to be weak (Rund et al., 2016).

As this scientific debate is not yet settled, studying longitudinally the neurocognitive course of people who experience their first episode of psychosis or schizophrenia, with as short DUP as possible, creates an opportunity to further explore the notion of schizophrenia as a progressive or developmental brain disorder.

1.7 Aims of the field of research and purpose of this study

The purpose of studying cognition in first-episode schizophrenia is versatile. Firstly, by gaining insight into cognitive functioning at the onset of schizophrenia, clinicians might eventually be able to identify individuals highly vulnerable of developing schizophrenia (Carrión et al., 2018). Secondly, information on cognitive strengths and deficits in the individual makes it possible to tailor treatment and other interventions accordingly. Thirdly, studying specific cognitive deficits in FES might give insight to possible predictors of later functional outcome (Bowie et al., 2008; Green, 2016), making it possible to create cognitive training and remediation programs, thereby hopefully contributing to a better functional outcome for them.

There are several studies of the relationship between neurocognition and functional outcome in first-episode schizophrenia (e.g. Kurtz, Moberg, Ragland, Gur, & Gur, 2005; Tandberg et al., 2011; Álvarez-Jiménez et al., 2012). However, the long-term outcome for these patients in terms of remission and recovery rates remains uncertain (Lally et al., 2017), as well as the course of neurocognitive dysfunction (Mesholam-Gately et al., 2009). There has been extensive variability across studies on how cognitive functioning is measured, as well as on which definitions of remission and recovery are used. This has resulted in difficulty merging findings together and comparing across studies, potentially hindering the scientific progress.

The knowledge about neurocognition and outcomes in first-episode schizophrenia is still limited. Although numerous studies have used the Remission in Schizophrenia Working Group (RSWG) criteria (Andreasen et al., 2005), most have applied these cross-sectionally (AlAqeel & Margolese, 2012) or with a relatively short period of follow-up. Few studies have used both published criteria for remission (Andreasen et al., 2005) and the suggested criteria for full recovery (Liberman et al., 2002), combined with the MCCB to examine the association between baseline neurocognitive functioning in FES and later remission and/or full recovery. The MCCB allows facilitated comparisons across studies, and the consensus-based criteria of symptom remission and full recovery in addition to facilitate comparison permit a more reliable estimate of the degree of both symptom improvement and functional recovery.

To our knowledge, the Oslo Schizophrenia Recovery Study is the first prospective study using such a comprehensive and strict definition of full recovery in a year-by-year-assessment (at baseline, six months, and then once a year for 10 years) to investigate full recovery (Torgalsbøen, Fu, & Czajkowksi, 2018). This procedure enables us to investigate if the duration criteria of sustained remission (Andreasen et al., 2005) and full recovery (Liberman et al., 2002) are fulfilled, and to study neurocognitive change and the relationship between neurocognition and functional outcome. It offers an important contribution to present knowledge, since the sample is assessed on multiple cognitive domains as well as symptom ratings every year over a long time-period (Torgalsbøen, Mohn, & Rund, 2014; Torgalsbøen, Mohn, Czajkowksi, & Rund, 2015; Fu, Czajkowksi, Rund, & Torgalsbøen, 2017; Torgalsbøen et al., 2018). The study is ongoing, and here we report on data from the six-year follow-up assessment of the patient group. The current study addresses the following research questions:

a) How many of the FES patients meet comprehensive criteria for remission and full recovery at the six-year follow-up?

b) Which cognitive domains at baseline predict functional outcome at six-year follow-up?

2 Methods

2.1 Design

The Oslo Schizophrenia Recovery Study has a prospective longitudinal design and assesses first-episode schizophrenia patients with a total of 12 follow-up points spanning a period of 10 years (Torgalsbøen et al., 2014; Torgalsbøen et al., 2015; Fu et al., 2017; Torgalsbøen et al., 2018). Both clinical and neuropsychological assessments are made annually.

2.2 Participants

31 patients with first-episode schizophrenia were referred to the study through a period of four years (2007-2011), from mental health service institutions in the Oslo area. They were referred to the project by their treating clinicians, shortly after being admitted. 28 of the 31 patients fulfilled the following inclusion criteria: the first episode of psychosis was within the spectrum of schizophrenia according to the DSM-IV (American Psychiatric Association, 1994), age of 18 years or older. Referral was done within five months of their first contact with the mental health service institutions. All patients could read and write Norwegian fluently, and written informed consent was obtained from all participants. Exclusion criteria were having affective disorders, having experienced head trauma and having an IQ below 70.

In the follow-up period, the majority of patients were provided treatment by their local mental health service institution, independently of the study. They were treated with antipsychotic medication (primarily second-generation antipsychotics), psychoeducation and/or cognitive behavior therapy and case management. All patients were retained during the first three follow-ups. Three participants left the study at two-year follow-up, and an additional three patients dropped out during the three-year follow-up.

The study was approved by the Regional Committee for Research Ethics for Health Region South-East (REC South-East).

At six-year follow-up, 22 (78,6 %) participants were retained. Of these 22 participants, 10 are women (45,5 %), 12 (54,4 %) are men, and the mean age at baseline was 21,09 (SD = 2,67). The mean education level at baseline was 13 (SD = 2).

Table 1 *Demographic and clinical characteristics of the participants at baseline*

Age	$\bar{x}$ = 21,0 (SD=2,6)
Gender	
Women	39,3% (n=11)
Men	60,7% (n=17)
Level of education	
Elementary school	39,3% (n=11)
High school	28,6% (n=8)
Some college	25,5% (n=7)
BA degree or higher	7,2% (n=2)
Duration of untreated psychosis	$\bar{x}$ = 16,1 months, SD = 16,2
Substance abuse at baseline	3,6% (n=1)
Substance abuse earlier	64,3% (n=18)
SCI-PANSS scores	
Positive	$\bar{x}$ = 18,27, SD = 5,36
Negative	$\bar{x}$ = 20,73, SD = 4,31
Total	$\bar{x}$ = 77,18, SD = 15,77

Percentages are based on the total sample at baseline (n=28). Mean baseline PANSS scores for the participants who remain in the study at six-year follow-up (n=22) is reported.

Table 2 *Sub-diagnoses at baseline*

Diagnosis	Frequency	Percent
Schizophrenia	4	18,2
Residual schizophrenia	2	9,1
Schizoaffective disorder	6	27,3
Schizophreniform disorder	3	13,6
Paranoid schizophrenia	5	22,7
Disorganized schizophrenia	2	9,1
Total	22	100

Table 2 displays the baseline distribution of sub-diagnoses among the participants who participate in the six-year follow-up, according to the DSM-IV.

Table 3 *Baseline medication of patients (Torgalsbøen et al., 2015).*

Second generation antipsychotic	80 % (n = 20) CDD: 0,80
First generation antipsychotic	20 % (n = 5) CDD: 1,10
Antidepressive	44,0 % (n = 11) CDD: 1,20
No medication	4,0 % (n = 1)

CDD: Calculated dose of medication based on the prescribed dosage divided by the defined daily dosage.

Table 3 shows the baseline medication of the patients retained at two-year follow-up (n=25).

On every point of measurement, the participants completed the assessments described below.

2.3 Clinical instruments

The clinical interviews and assessments of the participants were done within the first 5 months of their admission to hospital or out-patient clinic. This was performed by an experienced clinical psychologist.

The diagnoses were established using the Structural Clinical Instrument of Diagnosis for DSM-IV Axis I disorders (SCID-I) modules A-D. At every point of assessment, the participants are screened for symptoms according to the Positive and Negative Syndrome Scale (PANSS). Level of social- and role functioning is measured using a semi-structured interview to assess the Global Functioning: Social (GF: Social) and the Global Functioning: Role (GF: Role) (Cornblatt et al., 2007). GF: Social and GF: Role represent two measures of social and role functioning that aim to disentangle social from role functioning domains, detect changes in functioning over time, provide brief and easy-to-use clinician ratings, while taking age and phase of illness into account (Cornblatt et al., 2007). The social scale assesses peer relationships, level of peer conflict, age appropriate intimate relationships, and involvement with family members. The role scale assesses performance in school, at work or as a homemaker. Based on this, these measures were considered appropriate for following first-episode individuals prospectively, and hence are used as the measures of functioning in the Oslo Schizophrenia Recovery Study.

The social functioning scale (GF: Social) provides a single overall score from 1-10, with a score of 1 representing *extreme social isolation* (e.g. the individual has no social contact whatsoever and does not leave his or her home), and 10 representing *superior social and interpersonal functioning* (e.g. the individual has multiple satisfying relationships). To be considered in remission, the individual must receive a score of 6 (*moderate problems*) or above. A score of 6 entails having few close friends, significant but intermittent conflicts with coworkers, friends etc., moderate difficulty in developing age-appropriate intimate relationships, but the person does occasionally seek out others. To be considered fully recovered, the individual must obtain a score of 8 (*good social and interpersonal functioning).* He/she then at the time of assessment exhibit some transient mild impairment in social functioning, being expectable following psychosocial stressors. He/she has some

meaningful interpersonal relationships with peers, and/or intimate age-appropriate relationships. The individual has infrequent conflicts with peers.

The role functioning scale (GF: Role) provides a score from 1-10, with a score of 1 representing *extreme role dysfunction* (the individual is severely disabled, and does not work for pay or attend to classes for grades, and is not living independently), and a score of 10 representing *superior role functioning* (e.g. obtains only superior performance evaluations at competitive work placement and all A's in school and generates, organizes and completes all homemaking tasks with ease). To be considered in remission, the individual must obtain a score of 6 (*moderate impairment*) or above. He/she then poor performance evaluations at work or in school, require less demanding or part-time jobs, and/or have difficulty organizing homemaking tasks, perhaps requiring some supervision, but then functions well. To be considered fully recovered, he/she must obtain a score of at least 8 (*good role functioning*). This entails that the person maintains good role functioning in demanding roles, however he/she occasionally falls behind on tasks, but always catches up. He/she obtains satisfactory performance evaluations in work or at school, and may occasionally have some difficulty organizing homemaking tasks.

2.4 Neuropsychological instruments – the MCCB

The Norwegian version of the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein & Green, 2006; Mohn, Sundet, & Rund, 2012) was used to assess the neuropsychological functioning of the participants both at baseline and at follow-ups. The MCCB was chosen mainly for its sensitivity to cognitive changes and high test-retest reliability, its suitability for repeated measures (Nuechterlein et al., 2008), and its relevance for activities of daily life. The testing was performed by graduate students of clinical psychology, trained on neuropsychological assessments.

The MCCB consists of ten subtests (table 4), loading on the seven neurocognitive domains of *processing speed, verbal learning, working memory (verbal* and *non-verbal), reasoning and problem solving, visual learning, attention/vigilance* and *social cognition*. Due to the somewhat different properties of verbal- and non-verbal working-memory (Nuechterlein et al., 2004), we here have chosen to include verbal- and non-verbal working memory as separate subscales in our analyses. The subtests of the MCCB were selected mainly based on

their high test-retest reliability, their utility as a repeated measure, their substantial relationship to self-reported functional outcome, practicality for the test administrator and tolerability for the participant (Nuechterlein et al., 2008; Green et al., 2014). The MCCB also calculates an overall Composite Score for all 10 tests. The average testing duration of the entire battery is 65 minutes.

Table 4 *MCCB domains and tests (Nuechterlein et al., 2008)*

Test	Domain
Trail Makin Test, Part A	Speed of processing
Brief Assessment of Cognition in Schizophrenia, symbol coding subtest	Speed of processing
Category Fluency Test, animal naming	Speed of processing
Continuous Performance Test, Identical Pairs Version	Attention/vigilance
Wechsler Memory Scale, 3rd edition, spatial span	Working memory (non-verbal)
Letter-Number Span Test	Working memory (verbal)
Hopkins Verbal Learning Test – Revised, immediate recall	Verbal learning
Brief Visuospatial Memory Test – Revised	Visual learning
Neuropsychological Assessment Battery, mazes subtest	Reasoning and problem solving
Mayer-Salovey-Caruso Emotional Intelligence Test, managing emotions branch	Social cognition

Below follows a description of the different cognitive domains included in the MCCB, and the tests chosen to represent these. For several of these tests, both age and education is found to be of significance for test performance (Keefe et al., 2008; Lezak, Howieson, Bigler, & Tranel, 2012).

2.4.1 Processing speed

Sufficient processing speed is important for many cognitive operations, and slowed processing speed often underlies attentional deficits (Lezak et al., 2012).

Trail making test, Part A: In the Trail making test, Part A, the participant must draw lines between consecutively numbered circles, as fast as possible, without lifting the pencil from

the paper. The Trail Making Test is thought to tap scanning abilities, visuomotor tracking, as well as processing speed (Lezak et al., 2012).

Brief Assessment of Cognition in Schizophrenia, symbol coding subtest: In this test, the participant uses a key and is to write digits corresponding to given symbols for 90 seconds. Symbol substitution tests are generally thought to tap into visual scanning, motor persistence, sustained attention, response speed, and visuomotor coordination (Lezak et al., 2012).

Category Fluency Test, animal naming: Patients are given 60 seconds to name as many different words as possible within the animal category (Keefe et al., 2008). Short-term memory is involved, as the patient has to remember what words they have already said (Lezak et al., 2012). Strategy making, i.e. forming subcategories to organize recall, and then switching between them, is also involved (Lezak et al., 2012). As such, animal naming might additionally rely on executive functioning.

2.4.2 Attention/vigilance

Many different cognitive operations require sustained, focused attention (Lezak et al., 2012). Vigilance refers to the ability to focus and sustain attention over time, this often also includes ignoring distractors.

Continuous Performance Test (CPT), Identical Pairs Version: In the CPT, the participant is to indicate when the same stimuli appears twice in a row (Rapisarda et al., 2014). This entails keeping the stimuli in working memory until it can be compared to the stimulus immediately following, and in so, working memory is also of importance.

2.4.3 Working memory

Working memory allows for information to be temporarily stored and manipulated for complex cognitive operations (Lezak et al., 2012). Involved in working memory tasks are executive control mechanisms focusing attention and combating interference.

Wechsler Memory Scale-III (WMS-III), spatial span: The WMS-III, spatial span, is used in the MCCB as an indicator of non-verbal working memory. The test measures the participant's ability to reproduce the spatial pattern of tapping sequences performed by the examiner on 10 cubes that are irregularly spaced.

Letter-Number Span Test: This test is used in the MCCB as an indicator of verbal working memory. The examiner reads aloud a list of digits and letters, and the participant is to repeat this list in alphanumeric order.

2.4.4 Verbal learning

Verbal learning requires the ability to acquire, store, and retrieve verbal information for more than a few minutes (Green, 2016). Attention is crucial in verbal learning (Lezak et al., 2012).

Hopkins Verbal Learning Test-Revised (HVLT-R): This is a word list learning task that presents 12 words, four in each of three semantic categories. In the MCCB, only the immediate recall condition is used**.** The examiner reads the list of words out loud, then the participant is to repeat as many words as he/she remembers (Lezak et al., 2012).There are six different forms of the HVLT-R, which might facilitate testing on several occasions (Nuechterlein et al., 2008).

2.4.5 Visual learning

Visual learning taps into somewhat different abilities, one of which is recognition of different visual stimuli. In the extension of this, visual learning could be of importance for example in recognizing different faces (Nuechterlein et al., 2004).

Brief Visuospatial Memory Test – Revised: Geometric figures on a sheet of paper are presented for the patient for 10 seconds (Lezak et al., 2012). The participant is then to draw as many as they he/she remembers, at correct location. There are three learning trials. There are six alternative forms of the BVMT-R.

2.4.6 Reasoning and problem solving

Reasoning is a higher cognitive function of abstraction (Lezak et al., 2012), while problem solving can be more or less complex and abstract. Executive functions contribute to the problem being recognized as a problem that needs to be solved.

Neuropsychological Assessment Battery (NAB), Mazes subtest: In this test, participants are to finish seven mazes as fast as possible, not lifting the pencil from the paper. The mazes subtest loads on executive functioning (Zgaljardic & Temple, 2010).

2.4.7 Social cognition

Social cognition is the ability to identify and interpret social cues, and impaired social cognition is associated with difficulties in processing social information, including understanding emotions and being able to mentalize sufficiently (Green, 2016). The ability to create and maintain social connection is also connected to social cognition.

The Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT), Managing Emotions Branch: This test is meant to capture the abilities of the participant to regulate moods and emotions in oneself and others (Brackett & Salovey, 2006). The examiner reads aloud short descriptions of different situations, ending in a question. The participant is then asked to choose between different alternatives what he/she finds to be the most appropriate way to respond.

2.4.8 Omitting social cognition (MSCEIT) from the analyses

The measure of social cognition, the managing emotions part of MSCEIT (Nuechterlein & Green, 2006), was omitted from the analyses in the present study. There are several contributing reasons. Firstly, MSCEIT was not originally intended to be part of the MCCB, it was added later because of its potential predictive value for functional outcome (Green & Nuechterlein, 2004; Nuechterlein et al., 2008) Secondly, since the creation of the MCCB, there has been growing awareness that social and nonsocial cognition are separable dimensions (Green et al., 2014). There is now an option for *neurocognitive composite* in the MCCB scoring program, allowing investigators to examine nonsocial cognition separately. This is based on the (likely) possibility that treatments will affect social and nonsocial cognition differently. There is some evidence that social cognition might act as a mediating or intervening variable between measures of neurocognition and functional outcome (Green, Kern, & Heaton, 2004). Some longitudinal studies using the MCCB to predict functional outcome, have found the MSCEIT not to be of great importance for functional outcome e.g. (Holmén, Juuhl-Langseth, Thormodsen, Melle, & Rund, 2010). Given the relatively small sample size of this study, it was necessary to limit the number of predictor variables, and as the focus of this study primarily is on nonsocial neurocognition in schizophrenia, excluding social cognition from the independent variables gave sense.

2.4.9 Scoring

The MCCB tests were scored using the American norms (Nuechterlein & Green, 2006). Norwegian reference data have been published (Mohn et al., 2012), and their similarity to US norms allows for US norms to be employed in Norway.

2.5 Defining remission, full recovery and partial recovery

The criteria for remission are based on the criteria proposed by Andreasen et al. (2005), and as such on the evaluation of eight dimensions of the PANSS: P1 (delusions), G9 (unusual thought content), P3 (hallucinatory behavior), P2 (conceptual disorganization), G5 (mannerisms and posturing, N1 (blunted affect), N4 (social and emotional withdrawal) and N6 (lack of spontaneity). These domains must be scored mild or less (< 3, the range is 1-7), with a duration of a minimum of six months. In addition to this, the score of both GF: Social and GF: Role must be at minimum of 6 or higher.

The full recovery criteria used in this study are a combination of the remission criteria proposed by Andreasen et al. (2005) and the operational recovery criteria by (Liberman et al., 2002). The recovery criteria are based on the evaluation of eight dimensions of the PANSS: P1 (delusions), G9 (unusual thought content), P3 (hallucinatory behavior), P2 (conceptual disorganization), G5 (mannerisms and posturing), N1 (blunted affect), N4 (social and emotional withdrawal) and N6 (lack of spontaneity). These dimensions must be scored mild or less (< 3, the range is 1-7), with a duration of minimum two years. In addition, the subject must fulfill the following criteria concerning psychosocial functioning: the participant must be in at least part-time work or school, living independently from his or her family, and socialize with peers at least one time per week or in some other way be involved in age-appropriate recreational activities, independently of professional supervision. To be considered fully recovered, a score of eight (good social/interpersonal functioning and good role functioning) on the GF: Social and GF: Role is required.

It should be noted that not all members of the general public would meet these criteria for social and role functioning, required here to be considered fully recovered. It therefore makes sense to allow minor impairments (in housing, work or intimate relationships), if they do not entail significant impairment in social and role functioning. The definition of partial recovery

is influenced by this, as it is largely identical to the definition of full recovery, with the exception of one of the psychosocial criteria not having to be met. The remission criteria must, aside from this, be fulfilled for a duration of at least two years.

2.6 Statistical analyses

All statistical analyses were performed in IBM SPSS Statistics, Version 25. For all analyses, the level of significance was set to $p = 0,05$.

Regression analysis were chosen to try to answer the research questions. There are two main reasons regression analysis was chosen as the statistical method. Firstly, we wished to explore the (long-term) predictive value of the MCCB neurocognitive domains for social- and role functioning, and so regression was a strong alternative. Secondly, the present study is part of the Oslo Schizophrenia Recovery Study, based on which are already several publications. It seemed sensible to continue using regression analyses, as has been used in several of these publications, to facilitate comparison across publications and follow-ups.

2.6.1 The predictive value of the MCCB for social- and role functioning

Firstly, linear regression analyses were performed, assessing the predictive value of the MCCB composite score for social- and role functioning, respectively. The composite score was calculated by combining the t-values of the six neurocognitive domains of the MCCB at baseline, and then dividing this score on the number of included domains.

In addition to studying the relationship between general neurocognitive functioning (the composite score) and functional outcome, we wished to uncover specific associations between each cognitive domain and functional outcome, as this might suggest particular areas of relevance for future studies. In order to determine the predictive value of the baseline measures of the neurocognitive domains (speed of processing, attention, working memory verbal, working memory non-verbal, verbal learning, visual learning, reasoning and problem solving) for social- and role functioning at six-year follow-up, multiple regression analyses were performed. The baseline measures of the neurocognitive domains were set as independent variables, and social and role functioning at six-year follow-up, respectively in two different analyses, as dependent variables.

To control for demographic and clinical variables at baseline, hierarchical regression analyses were performed, one with social functioning at six-year follow-up as the dependent variable, and one with role functioning as the dependent variable. Variables were entered in two blocks. First, the demographic and clinical characteristics were entered in block one: duration of untreated psychosis, PANSS scores, sex, age, years of education at baseline, social and role functioning at baseline. Then, the neurocognitive domains were entered in block two, allowing us to assess the predictive values of these as demographic and clinical characteristics were controlled for.

Only first-episode schizophrenia patients were included in the analyses; this study does not report on the control group.

2.6.2 Evaluation of the assumptions

The results of the evaluation of the assumptions for the different statistical analyses performed were highly similar. Therefore, they are combined in the following. The predictor variables generally correlated sufficiently with the dependent variables (Tabachnick & Fidell, 2007). The predictor variables did not correlate highly with each other, however, there were some exceptions where correlations are slightly high (Tabachnick & Fidell, 2007). Combined with the collinearity statistics of Tolerance and VIF, multicollinearity was not deemed a major issue.

An evaluation of potential outliers, normality, linearity, homoscedasticity, and independence of residuals did not give rise to concern. The normal probability plot of the regression standardized residual, social functioning, suggested no major deviations from normality. Both the assumption of normality and the assumption of linearity were deemed to be sufficiently met. There might be some heteroscedacity; however, heteroscedacity does not invalidate the analysis (Tabachnick & Fidell, 2007). The scatterplot did not indicate any evident outliers, but Cook's distance indicates there might be outliers. Summarizing, the assumptions were deemed to be only partially met. However, they were considered adequately met for it to be possible to use these analyses and allow results to be interpreted. However, the evaluation of the assumptions indicated that the results must be interpreted with caution.

3 Results

3.1 Remission and full recovery

Table 5 *Remission and recovery at six-year follow-up*

	Frequency	**Percent**
Full recovery	10	45,5
Partial recovery	6	27,3
Remission	3	13,6
Not in remission	3	13,6
Total	*22*	*100*

Based on comprehensive criteria for remission and recovery, a substantial proportion of the participants were fully recovered at six-year follow-up (table 5). Many participants were partially recovered. Merging those fully recovered and those partially recovered, a total of 16 (72,7%) participants were recovered by the six-year follow-up. A modest proportion of the participants were in remission. Only few participants were neither in remission, partially or fully recovered by the six-year follow-up.

3.2 Baseline predictors of social- and role functioning

3.2.1 Social functioning

Performing a linear regression analysis, the MCCB composite score statistically significantly (F (1, 20) = 8,11, p<0,05) predicted social functioning at six-year follow-up.

The multiple regression analysis revealed that the baseline measures of the neurocognitive domains combined explained 63,7% (F (7, 14) = 6,26, p<0,05) of the variance in social functioning at six-year follow-up, not controlling for any baseline factors.

Further, regarding specific neurocognitive domains, attention (β = 0,57, p<0,05), processing speed (β = -0,55, p<0,05), verbal learning (β = 0,50, p< 0,05), reasoning and problem solving (β = 0,44, p<0,05) and working memory non-verbal (β = 0,33, p < 0,05) contributed in explaining the variance in social functioning at six-year follow-up.

Using hierarchical analysis, predictor variables were entered in two levels**.** In model 1, duration of untreated psychosis (months), sex (male/female), age at baseline, PANSS total score at baseline, years of education at baseline, social functioning at baseline (GF: Social) and role functioning at baseline (GF: Role) were entered as independent variables. In model two, both the variables included in model 1 and the baseline values of the neurocognitive domains (reasoning and problem solving, verbal learning, working memory verbal, working memory non-verbal, visual learning, processing speed and attention) were entered as independent variables. Social functioning at six-year follow-up was set as the dependent variable.

Table 6 *Hierarchichal analysis of social functioning*

Model	R	Adjusted R Square	R Square Change	F Change
1	0,70	0,23	0,49	$1,90^{(n.s)}$
2	0,93	0,58	0,37	$2,63^{(n.s)}$

*n.s = non-significant (p>0,05)

Demographic and clinical factors (duration of untreated psychosis, sex, PANSS total score at baseline, years of education, age, social- and role functioning at baseline) alone did not statistically significantly predict social functioning at six-year follow-up, F (7, 14) = 1,90, p>0,05. Adding the neurocognitive domains, the model still did not significantly explain the variance in social functioning at six-year follow-up, F (14, 7) = 3,04, p>0,05. F change p>0,05. None of the predictor variables in model 2 statistically significantly contributed in explaining the variance in social functioning.

3.2.2 Role functioning

Performing a linear regression analysis, the MCCB composite score did not statistically significantly predict role functioning at six-year follow-up, however, the association was near-significant (F (1, 20) = 4,16, p=0,055).

As expected from the linear regression analysis, the neurocognitive domains did not statistically significantly predict role functioning at six-year follow-up (F (7, 14) = 1,84), p>0,05). All domains were far from being significant.

Using hierarchical analysis, predictor variables were entered in two levels**.** In model 1, duration of untreated psychosis (months), sex (male/female), age at baseline, PANSS total

score at baseline, years of education at baseline, social functioning at baseline (GF: Social) and role functioning at baseline (GF: Role) were entered as independent variables. In model two, both the variables included in model 1 and the baseline values of the neurocognitive variables were entered as independent variables. Role functioning at six-year follow-up was set as the dependent variable.

Table 7 *Hierarchichal analysis of role functioning*

Model	**R**	**Adjusted R Square**	**R Square Change**	**F Change**
1	0,45	$-0,19^{n.s}$	0,20	$0,51^{n.s}$
2	0,82	$0,02^{n.s}$	0,47	$1,44^{n.s}$

*n.s = non-significant (p>0,05)

Demographic and clinical factors (duration of untreated psychosis, sex, PANSS total score at baseline, years of education, age, social- and role functioning at baseline) alone did not statistically significantly predict role functioning at six-year follow-up, F (14, 7) = 1,03, p>0,05. Adding the baseline measures of the MCCB domains, the model still did not statistically significantly predict role functioning at six-year follow-up. F change was not of statistical significance. All neurocognitive domains were far from being significant.

4 Discussion

The purpose of the present study was twofold. Our first objective was to determine the rate of recovery and remission among the participants at six-year follow-up. Secondly, we aimed to identify cognitive predictors of functional outcome. We report high rates of recovery and remission, and we found several cognitive domains to significantly predict social functioning at six-year follow-up.

4.1 Recovery and remission

In the six-year follow-up of the Oslo Schizophrenia Recovery Study, 45,5% of the participants were fully recovered and 27,3% were partially recovered, accumulating to a total of 72,7% being recovered. 13,6% were in remission.

4.1.1 Follow-ups of the Oslo Schizophrenia Recovery Study

As the present study reports on data from the six-year follow-up of the Oslo Schizophrenia Recovery Study, it is of scientific interest to compare the recovery and remission rates to that reported in earlier follow-ups. At six-month follow-up, 61% of the participants were in remission (100% retention rate) (Torgalsbøen et al., 2014). At two-year follow-up, 48% of the participants were found to be in remission, while 16% fulfilled the criteria for full recovery, and 16% were partially recovered, accumulating to a total of 32% of the participants being recovered (in the second year, there were 25 participants left) (Torgalsbøen et al., 2015). At four-year follow-up, 29% of the participants were in remission and 55% were recovered (fully and partially) (Torgalsbøen et al., 2018). Comparing the remission and recovery rates at different points of follow-up, the rate of full recovery has steadily increased towards the six-year follow-up.

The remission rate should be seen in combination with the rate of recovery. As a large proportion of the participants are recovered, the corresponding rate of remission has decreased. It is possible that the participants fully recovered at the six-year follow-up had as good psychosocial functioning at earlier follow-ups, however not fulfilling the duration criterion.

4.1.2 Comparing the recovery and remission rates to that reported in other studies

The rate of full recovery at the current six-year follow-up might be considered high compared to that found in other longitudinal studies, reporting on remission and recovery in first-episode schizophrenia patients. To date, there are few meta-analyses of longitudinal studies on this patient group, and these report varying rates of remission and recovery. The most recent meta-analysis, to our knowledge, is the one by Lally et al. (2017). Using remission and recovery criteria comparable to the present study, they reported a recovery rate of 30,3% for individuals with first-episode schizophrenia, and a remission rate of 56,0%.

Jääskeläinen et al. (2012), also using recovery criteria comparable to that of the present study, reported a recovery rate of 13,5 %. This is a substantially lower percentage than both reported by Lally et al. (2017) and that found in the present study. It is worth noticing, however, that this meta-analysis includes studies of both first- and multi-episode schizophrenia, possibly influencing their results. Yet another meta-analysis, AlAqeel and Margolese (2012), report a remission-rate of 35,6% for FES, noting a quite wide range of reported remission rates in the included studies.

It is evident, then, that remission and recovery rates found in the present study are substantially higher that that reported in other similar longitudinal studies. How might these differences be explained? There are several differences between the different longitudinal studies of first-episode schizophrenia, and a multitude of factors might contribute to the significant gaps in recovery and remission rates.

Regional differences

One such variable might be the country in which the study is conducted. Lally et al. (2017), for example, reported that the rate of recovery for individuals with first-episode psychosis (FEP) was significantly higher in North America (71,0%) than in Europe (21,8%). The same trend was reported for remission: The reported remission rate for North America was 65,5%, while for Europe it was 55,1% (Lally et al., 2017). As these differences are reported for FEP, it seems likely that the same holds true for FES. Interestingly, the findings of the present study, when using the combined recovery rate, are more comparable to the North-American than the European findings.

Related to this, several studies have suggested that schizophrenia patients have more favorable outcomes in developing countries than in developed countries (Leff, Sartorius, Jablensky, Korten, & Ernberg, 1992; Harrison et al., 2001). This is conflicting to the high recovery rates reported in North-America and the finding of the present study, as Canada, the USA and Norway are all considered developed nations.

Pinpointing what differentiates the studies conducted in different regions is challenging. One possibly contributing reason might be the duration criteria applied. Lally et al. (2017) did not identify any factors clearly differentiating the European and the North-American studies; but noted that no American study used a duration criterion for recovery of more than two years, as some of the European studies did. However, as the Oslo Schizophrenia Recovery Study uses a duration criterion of minimum two years, one would expect the results to be lower rather than higher. The same would be expected as Norway is a developed country. On the basis of this, one might wonder: Is there something about conditions in Norway contributing to the high recovery and remission rates?

There are few other Norwegian studies with which we may compare our findings. One major (partly) Norwegian study, however, is the TIPS project (Rund et al., 2004; Larsen et al., 2011; Tandberg et al., 2011; Hegelstad et al., 2012)**.** Hegelstad et al. (2012) report, from a 10-year follow-up, remission rates of 47,9 % and 52,5% (usual detection versus early intervention). The corresponding recovery rates were 15,1% and 30,7% (using a one-year duration criteria) (Hegelstad et al., 2012). The recovery rate reported of the present study is higher also than these rates of recovery, suggesting that our results might be understood as reflecting specific characteristics of the present study.

Characteristics of the present study

Characteristics of the Oslo Schizophrenia Recovery Study, such as the design and sample, might be associated with observed remission and recovery rates.

The sample: Looking first at the sample, it is evident from the distribution of sub-diagnoses that a relatively large proportion of participants are diagnosed with schizoaffective disorder at baseline (27,3%). Individuals with affective psychosis are found to have a more favorable outcome than schizophrenia patients as a whole (Tondo et al., 2016). This is also supported by Lally et al. (2017), reporting a recovery rate of 84,6% for this subgroup, significantly higher

than for FES patients as a whole. The distribution of diagnoses in our sample might therefore indicate a more favorable outcome for these individuals, and thereby partially explain the high rates of recovery and remission.

The low rate of substance abuse at baseline (3,6%) could further contribute to explain the high recovery rate, as substance abuse in schizophrenia is often associated with a poorer outcome (Dixon, 1999). This is also supported by the fact that none of the recovered participants use drugs.

In an earlier follow-up in the Oslo Schizophrenia Recovery Study, Torgalsbøen et al. (2014) reported that many of the first-episode schizophrenia patients had an early improvement in both symptoms and social and role functioning. This finding indicates a positive prognosis for the participants (e.g. Schennach-Wolff et al., 2010) and might contribute in explaining the high rates of remission and recovery found at later follow-ups in the study, such as the present.

Also symptom severity at baseline is associated with later outcome in schizophrenia (Kurtz et al., 2005; Gould et al., 2012), with more severe symptoms often predicting a more pessimistic future outcome. However, as the baseline PANSS scores of the participants in the present study are comparable to that reported in other longitudinal studies of FES patients (e.g. Tandberg et al. (2011), Addington and Addington (2002)), we would not expect outcomes to be significantly influenced by the baseline level of symptoms.

There is some evidence indicating that women with schizophrenia have a more favorable outcome than men (Angermeyer, Kühn, & Goldstein, 1990; Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012). However, as the gender distribution in our sample is relatively well-balanced, and also comparable to that of other longitudinal studies (Addington & Addington, 2002; Tandberg et al., 2011), we would not be expect it to significantly influence the remission and recovery rates.

Design and other features: It seems reasonable to expect that the advancement of research and treatment in schizophrenia, and the development of second-generation antipsychotics, would contribute to better outcomes for individuals with schizophrenia receiving treatment today, than those being in treatment several years ago. However, several studies indicate that this is not the case. Recent meta-analyses report that recovery rates are not higher in more recent studies, rather, the opposite seems to be a trend (Jääskeläinen et al., 2012; Lally et al.,

2017). However, regarding remission, Lally et al. (2017) found improved remission rates in more recent studies, possibly reflecting qualities of modern treatment.

Although findings on the association between outcomes and time period in which the study is conducted are mixed, one might speculate that the period in which the current study is conducted (from 2007 and ongoing), at least to some degree influences the observed rate of remission and recovery in a positive direction. In addition to treatment of schizophrenia being increasingly evidence based (Beck et al., 2009), the evolution of modern antipsychotic medication (second generation) might contribute to more optimistic outcomes for patients with schizophrenia (Leucht et al., 2009). This is potentially reflected in our findings, but we cannot conclude whether the period in which the study is conducted and the treatment the participants receive, significantly influences recovery and remission rates.

Although we cannot conclude regarding the quality of treatment offered the participants of our study, it is worth noticing that all participants receive treatment in Norway, where treatment is free. It is therefore, at least in theory, accessible for all patients. Additionally, the treatment offered in the Norwegian health care system should be based on The Norwegian National Guidelines for disorders in the psychosis spectrum (The Norwegian Directorate of Health, 2013), which are founded on relatively up-to-date research. Hence, they could be expected to encourage high quality treatment. If it is so, that the participants in our study all receive treatment, supposedly of high quality, this might contribute to the high rates of remission and recovery we report in the present study.

It is possible that the findings of the present study reflect selection bias. The participants are referred from different institutions in the Oslo area, perhaps contributing to the sample being rather homogenous concerning where they come from and certainly where they live. This may have different implications. One possibility is that a large proportion of our participants have relatively high socioeconomic status (SES), a characteristic often associated with a more favorable outcome in a range of mental disorders (Meyer, Castro-Schilo, & Aguilar-Gaxiola, 2014). It is also possible that those individuals who agree to participate in studies such as the Oslo Schizophrenia Recovery Study have more personal resources and a lower level of symptoms than those who do not wish to participate. This remains a speculation.

Yet another aspect of the Oslo Schizophrenia Recovery Study that might contribute to the high rate of full recovery and remission is the low attrition rate. At six-year follow-up, 78,6%

of the participants are retained. Compared to other similar studies, this may be considered somewhat high, given the long follow-up period (Menezes et al., 2006; Larsen et al., 2011). We have not conducted a drop-out-analysis, but it might be that the Oslo Schizophrenia Recovery Study manages to keep *both* the recovered patients and those in remission in the study, as well as those who still suffer from schizophrenia. Lally et al. (2017) found that higher drop-out rates moderated lower rates of recovery, possibly indicating that a number of studies lose in attrition the participants who recover. As so, the high retention rate of the Oslo Schizophrenia Recovery Study might contribute to the high – and then also *realistic* – remission and full recovery rates. It is worth noticing, however, that similar studies frequently report that the participants who drop out are more symptomatic (Larsen et al., 2011; AlAqeel & Margolese, 2012).

Taking into account the reason why participants left the study at the two-year follow-up (refusal to participate due to anxiety, lack of insight in having a mental illness, and finding participation in research not useful) (Torgalsbøen et al., 2015), at least for two of three participants, is seems as though they were not recovered. This at least partially supports the idea that participants who recover are kept in the study, contributing to the high rate of recovery.

Although somewhat ambiguous, several reviews and meta-analyses report a trend of decreasing remission and recovery rates as follow-up period lengthens (Menezes et al., 2006; AlAqeel & Margolese, 2012; Lally et al., 2017). Lally et al. (2017), for example, report that studies with follow-up periods of 2-6 years and >6 years have a significantly lower recovery rate than those with a duration of 1-2 years. This could perhaps be seen in light of the association between attrition rate and rate of remission and recovery. The relatively long follow-up period of our study, six years, could be seen as predicting a more modest recovery rate. However, laying to ground the possibility that poorer remission and recovery rates are connected to attrition of participants who experience favorable outcomes, and that the Oslo Schizophrenia Recovery Study manages to keep these individuals in the study, the long follow-up period might rather positively contribute to the high rates of recovery and remission.

Other variables: Duration of untreated psychosis (DUP) is a widely researched, potentially modifiable determinant of outcome (Penttilä et al., 2014; Birnbaum et al., 2017). Several studies have found an association between these DUP and later recovery and remission rates

(AlAqeel & Margolese, 2012). However, the evidence is mixed. For example, Lally et al. (2017), in their extensive meta-analysis, and Menezes et al. (2006) in a review of longitudinal outcome studies of FES, did not find DUP to make a statistically significant contribution in either remission or recovery rates. The mean duration of untreated psychosis for the sample of the present study is, at 16,14 months, not significantly shorter than that reported in comparable studies (e.g. Álvarez-Jiménez et al. (2012), Marchesi et al. (2014) and the usual-detection group in (Larsen et al., 2011)). On the basis of this, we would not expect DUP to significantly contribute to the high rates of remission and recovery in the present study.

As schizophrenia is found to have a somewhat fluctuating course (AlAqeel & Margolese, 2012), the possibility that the high recovery and remission rates at six-year follow up are influenced by timing of the assessment, should be considered. The participants might have been assessed at time points in which they were not experiencing debilitating symptoms, and were functioning well, but still have periods outside observation in which they would be regarded as not in remission. However, this is unlikely, as participants are monitored yearly with clinical instruments. This gives reason to believe that our reported rates of full recovery are valid.

It seems, then, likely that the design of the Oslo Schizophrenia Recovery Study, with frequent follow-ups and thorough assessments would contribute to an accurate depiction of recovery and remission rates. However, findings are based on our sample, consisting of a relatively low number of participants, and might be influenced by their characteristics. Our reported results might therefore not be representative for FES patients in general. However, the results are still of scientific interest. They support the notion that a substantial proportion of individuals with first-episode schizophrenia have may experience a positive outcome. This could potentially generate both hope and optimism in what is realistic to expect in terms of outcome in first-episode schizophrenia.

In our discussion of factors potentially influencing outcomes, there is one major variable and possible predictor of outcome we have yet to mention: Neurocognitive functioning. We will now discuss the association between specific neurocognitive domains and functional outcome.

4.2 Neurocognition and functional outcome

In the present study, we found the MCCB neurocognitive domains at baseline statistically significantly predicted social functioning at six-year follow-up. More specifically, we found attention, processing speed, verbal learning, reasoning and problem solving and non-verbal working memory made a statistically significant contribution in predicting social functioning. When controlling for different demographic and clinical variables, the MCCB domains no longer significantly predicted social functioning.

This latter finding might be seen as underlining the importance of demographical and clinical characteristics at baseline, such as symptom level, age and education. As we have not conducted separate analyses for the separate characteristics, we cannot say anything about which ones might make significant contributions in predicting social functioning. However, it is evident that, as a whole, they make a contribution, but that this contribution is not of statistical significance when seen separately.

The finding that the demographic and clinical characteristics of the participants are of importance is in line with what is reported in other studies, where for example DUP, PANSS scores and gender is found to be associated with later outcome. The clinical and demographic characteristics did not alone statistically significantly predict social functioning. It is, however, evident that they made a contribution, as the neurocognitive domains no longer statistically significantly predicted social functioning when these factors were controlled for. Although the contribution of the MCCB domains was no longer significant when controlling for baseline variables, it is worth noticing that adding the MCCB variables to the model increased the explained variance in social functioning substantially.

This might have different explanations. One is that, considering our small sample size, adding more independent variables, the statistical power is lost. Another possible explanation is that the MCCB domains and the demographic and clinical characteristics are somehow interwoven, and so the effect of the demographic and clinical characteristics overshadow or masque the contribution of the MCCB domains. A third alternative, constituting a combination of the first two alternatives, is that the increasing number of independent variables weaken the statistical power, and as both demographic/clinical and the MCCB domains explain a part of the variance in social functioning, the effects are lost to the decreased power.

We could have conducted more analyses to investigate this further, such as analyzing the relationships between each demographic and clinical variable on the one hand and the functional outcome variables on the other. However, we chose not to, as further analyses on this relatively small sample would reduce the statistical power further. Therefore, we cannot conclude with certainty on which explanation, if any of these, best fit the data. However, it does seem likely that the combined explanation might at least to some degree reflect what is found, as the MCCB domains combined, not controlling for any demographic, clinical or baseline factors, statistically significantly explained 63,7% of the variance in social functioning. This finding adds evidence to the importance of neurocognitive factors in achieving a favorable functional outcome. However, a large proportion of the variance in social and role functioning is still left unexplained.

Neither the MCCB as a whole, although near-significant, or any of the baseline neurocognitive domains statistically significantly predicted role functioning. Baseline demographic and clinical characteristics did not significantly predict the variance in role functioning, and adding the MCCB domains did not significantly increase the explained variance. This might have different explanations. As similar studies frequently have reported neurocognition to be of importance for work (and school) performance (e.g. Strassnig et al., 2015; Lystad et al., 2016), and we found a near-significant association, it seems likely that our small sample size, combined with quite a few independent variables, contributed to too low statistical power to be able to detect the contributions from the neurocognitive domains. This will be explored further below.

4.2.1 Specific neurocognitive domains

As the conducted analyses do not reveal any significant associations between baseline neurocognitive domains and role functioning at six-year follow-up, we will here focus on the domains that were found to predict social functioning.

The neurocognitive domain of the greatest importance in predicting social functioning was *attention*. Attention is found in several studies to be associated with functional outcome in schizophrenia (Rapisarda et al., 2014). It is probably complexly tied to social functioning, as many cognitive operations require focused and sustained attention (Lezak et al., 2012). Social interaction requires a person to focus and ignore distractors, to pay attention to what is going

on and identify relevant information in social interactions (Green, 2016). This is part of the basis for later being able to respond in appropriate ways.

We also found *processing speed* to significantly predict social functioning. One could argue that processing speed, in addition to being complexly tied to social functioning, more specifically is crucial to understand and make sense of one's surroundings. If all processes are slow, one would probably miss a lot of potentially important social information.

Also reasoning and problem solving, verbal learning and non-verbal working memory are identified in the present study as predictors of social functioning. Working memory might reflect the ability of the participant to switch attention between tasks and maintain social conversation (Green, 2016). Adapting to social settings also requires flexibility and the ability to simultaneously process a large amount of information (Torgalsbøen et al., 2014), skills that might be seen as an extension of these cognitive domains.

We have now discussed separate properties and clinical significance of different neurocognitive domains. Doing this, one should keep in mind possible limitations of such a procedure. Although one might speak of different cognitive domains, they are often found to be highly intercorrelated and should perhaps not always be understood as completely separate entities (Dickinson, Ragland, Gold, & Gur, 2008).

This intercorrelation is evident also in the present study, as indicated by relatively high correlations between some of the neurocognitive domains. Statistically, this could result in multicollinearity. For example, slowed processing speed often underlies attentional deficits (Lezak et al., 2012), and attention is also closely tied to working memory (Rapisarda et al., 2014). As so, the different subtests of the MCCB might not be completely separate measures of the domain they are intended to represent (Nuechterlein et al., 2008). Conflicting findings regarding the factor structure of the MCCB (Burton et al., 2013; McCleery et al., 2015; Mohn, Lystad, Ueland, Falkum, & Rund, 2017) could also be taken as support for this. Illustrating that the domains are often found to be interwoven, Mesholam-Gately et al. (2009), in a meta-analyses of neurocognitive functioning in FES patients, chose to separate the attention domain into subdomains of processing speed, working memory and vigilance.

Although the MCCB is still considered one of the best test batteries for assessing neurocognition in schizophrenia, it also has some shortcomings in being such a comprised measure as it is. There are few subtests loading on each domain, some only have one single

subtest. Inherent in this is that the different domains are relatively narrowly represented. Adding more tests could have given an even more comprehensive measure of the different cognitive domains, which might in turn have contributed to the different domains being more clearly separated. However, the MCCB is a comprehensive measure of cognition, and subtests are carefully selected to best represent the different domains, in addition to being practical and possible to execute for individuals in vulnerable periods of life. It is important to find a balance between gaining sufficient information and that the test battery is practically feasible, and the MCCB does fulfill both these criteria.

4.2.2 Comparing the findings of the present study to earlier follow-ups in the Oslo Schizophrenia Recovery Study

Comparing the findings from the six-year follow-up to results from earlier follow-ups in the Oslo Schizophrenia Recovery Study, some patterns emerge. Both at six-month and two-year follow-up, attention, working memory and reasoning/problem solving have been found to be predictive of social functioning (Torgalsbøen et al., 2014; Torgalsbøen et al., 2015). Attention was also found to be associated with social functioning at the four-year follow-up (Fu et al., 2017). At the current six-year follow-up, consistent with this pattern, we found attention, processing speed, verbal learning, reasoning and problem solving, and non-verbal working memory to statistically significantly predict social functioning.

Summarizing, attention remains an important predictor of social functioning through all follow-ups. Other cognitive domains also seem to be of importance over time, such as reasoning and problem solving, and working memory. However, these domains do not hold as predictors at each time of follow-up, as attention does. This points towards attention being a potentially fruitful target for cognitive interventions. It also suggests some domains are of importance early in the course, while others, as attention, are important both short- and long-term.

The findings regarding role functioning are somewhat more mixed. Both in the six-month and the two-year follow-up, attention (and reasoning/problem solving at the two-year follow-up) was found to statistically significantly predict role functioning. Attention was, however, not found to be strongly associated with role functioning at the four-year follow-up, and at the current six-year follow-up, we did not find any neurocognitive domains to statistically significantly predict role functioning. This might indicate that attention is a predictor of

shorter-term role functioning, however, not holding as a predictor as time progresses. One might speculate that cognitive abilities at baseline might not be of as great importance in long-term role functioning as short-term functioning.

4.2.3 Comparing the findings to that of similar studies

The pattern and severity of cognitive impairment across specific domains in FES-patients remains unclear (McCleery et al., 2014). Attention has been pin-pointed as a possible predictor of functional outcome by many studies, as illustrated for example by a meta-analysis conducted by Mesholam-Gately et al. (2009) (although they also identified several additional domains to be of importance). An early meta-analysis performed by Green, Kern, Braff, and Mintz (2000) found attention (vigilance) to be a key neurocognitive domain for functional outcome in schizophrenia. They also reported it to predict social problem solving, in line with the results of the present study. More recently, and with a sample comparable to that of the present study, Fett et al. (2011) reported in a meta-analysis that social skills showed the strongest association with attention (vigilance) (however, they report "social behavior in the milieu" not to be significantly associated with attention). Concluding, different studies frequently report somewhat varying cognitive domains to be associated with functional outcome, and combining different studies, deficits are found in all domains included in the MCCB (e.g. McCleery et al., 2014).

4.2.4 Social- versus role functioning

The MCCB only significantly explained *social functioning*, and not role functioning. Following earlier points of follow-up in the Oslo Schizophrenia Recovery Study, this appears to be a pattern, as the findings for social functioning have consistently been stronger than those for role functioning. It seems plausible that we would have found an association between neurocognitive domains and role functioning if we had a larger sample, as the association between the composite score and role functioning is near-significant. However, it gives sense to assume that the differences between social- and role functioning reflect differences in properties of the two constructs.

Role functioning might be influenced by factors that social functioning is not. For example, as social functioning mostly depends on abilities (and wishes) of the individual, it could be that, with the inherent abilities, the person her- or himself could to a large extent come closer to

what is rated superior functioning, e.g. by seeking out others and avoiding major conflicts with them. It is also conceivable that reaching out to old friends, for instance, is more associated with joy and less with fear of failure.

In role functioning, however, it is possible that external factors, outside the control of the individual, influence the real-world functioning of the person to a greater extent. For example, to be able to perform superiorly, above average or good in a competitive work place one has to *have* a job to perform in. Finding and applying for jobs might in itself be demanding and draw on personal resources such as neurocognition. Being hired is arguably – at least to some extent – outside the control of the individual.

The attitudes and beliefs of the employer might influence whether an individual with a diagnosis of schizophrenia is hired for a job. A negative pattern may emerge, where the person hiring might not be well-informed on the current research on recovery in schizophrenia. He or she might therefore hold some of the old, widespread Kraepelinian beliefs. Being able to get (or keep) a job is hopefully mostly dependent on the knowledge and abilities of the individual. However, we argue that external factors might be of greater importance for performance in the domain of role functioning than social functioning.

It should also be noted that other variables than neurocognitive functioning are of importance for optimal performance in a job. For example, beliefs of personal incompetence might influence performance negatively (Lystad et al., 2017). Success in work and/or studies, at least to some degree, requires that the people surrounding the person affected with schizophrenia have faith in the person and believe that working will be beneficial for them. In light of our findings, we speculate that these variables are of greater importance for role functioning than for social functioning.

The Norwegian National Guidelines for disorders in the psychosis spectrum (The Norwegian Directorate of Health, 2013) underline the importance of being in ordinary/competitive work placement. Individual job support (IPS) is encouraged rather than re-employment or rehabilitation services. It could be questioned whether the Norwegian health care system offers adequate opportunities for people with, in remission of, or recovered from, schizophrenia. However interesting, investigating this is outside the scope of the present study.

In the four-year follow-up in the Oslo Schizophrenia Recovery Study Fu et al. (2017) found no significant differences in role functioning within the patient group. They suggest this might be attributable to extensive support provided by Norwegian health institutions to schizophrenia patients, in order for them to get back to work. Although to some degree contradictory to the explanation provided above, this is also a possible explanation for the non-significant findings on role functioning in the present study. If there are no significant differences between individuals in role functioning, one would not expect to find statistically significant associations between neurocognitive functioning and role functioning.

Although we have briefly mentioned strengths and limitations of the study through the text, a more thorough review will now be provided.

4.3 Strengths and limitations

One of the main strengths of this study is its prospective longitudinal design with multiple follow-ups. Recommended operationalized criteria of both remission (Andreasen et al., 2005) and full recovery (Liberman et al., 2002), as well as a renowned cognitive battery (the MCCB) for assessing neurocognitive functioning (Nuechterlein & Green, 2006) are used. This contributes to securing validity of measures, in addition to facilitate comparison across studies. The participants have completed all interviews and tests at each point of measurement. Also, the retention rate is high compared to many other longitudinal studies, perhaps reflecting that also participants in remission and full recovery remain in the study (Lally et al., 2017).

Another strength of the study is its naturalistic design, following the participants and the course of development they would likely follow also if they did not participate in the Oslo Schizophrenia Recovery Study. In the extension of this, the treatment the participants receive is probably representative of the treatment given in the Norwegian health care system.

Combined, the design and features of the Oslo Schizophrenia Recovery Study allow for participants to be closely followed; including both their cognitive trajectory and recovery process. It is reason to believe this would give a relatively accurate picture of the participants of the study.

This brings us to a substantial limitation of the Oslo Schizophrenia Recovery Study: Even though we may follow the participants and their process closely, the small sample size limits

the generalizability of our results. The low number of participants also influences which statistical analyses can be used, and the inferences that can be drawn from these. A small sample often entails a relatively modest statistical power, which may for example hinder controlling for all variables one could wish, such as additional baseline characteristics of the participants. However, although there are drawbacks to the small sample size, considering both the low incidence of first-episode schizophrenia, and geographical considerations, a relatively small sample is to be expected.

The frequent measurement of the Oslo Schizophrenia Recovery Study is mainly a strength, however, it might have pitfalls. For example, learning effects might be more severe with more frequent measurement. However, the MCCB is designed to minimalize such effects (Nuechterlein et al., 2008). The result could be that participants obtain higher scores than warranted by their cognitive abilities. In the two-year follow-up, Torgalsbøen et al. (2015) report significant improvement for the participants on the composite score, also for the control group. This could potentially be a result of learning. However, as the participants are relatively young, the natural development of the brain might also contribute to participants obtaining higher scores at follow-up. As so, it cannot be concluded whether learning effects influence the findings of the present study.

The scores the participants obtain at different cognitive domains might be influenced by their use of medication, possibly influencing results in either direction. As we have not in the present study assessed possible interactions and associations between medications doses and obtained scores on the MCCB, we cannot conclude regarding possible medication effects. However, as Torgalsbøen et al. (2014) found no association between daily doses of medication and neurocognitive test performance, we would assume it not to be of major influence in the six-year follow-up either. Also, antipsychotic medication is generally not found to have a major impact on cognition, as illustrated by the MATRICS initiative (Green & Nuechterlein, 2004; Green et al., 2014).

The omission of social cognition (MSCEIT) might have implications for the prediction of social and role functioning, in so that including it could have contributed to explaining more of the variance in functional outcome, and making more accurate predictions. Some studies, like a meta-analysis by Fett et al. (2011), suggest that social cognition even explains relatively more variance in community functioning than nonsocial neurocognition does, implying that

we should have included social cognition in our analyses. It is possible, however, that if we included social cognition, we would not have found any statistically significant associations.

The measurement of functional outcome, specified as social- and role functioning, possibly represents a further limitation of the study, as it solely relies on self-report. This could potentially give a somewhat erroneous image, as participants' reported functioning might not be sufficiently objective and could then be influenced by different factors (Nuechterlein et al., 2008). Although self-report entails a potential bias or misrepresentation, it is based on the participants' personal evaluation of their functioning, which in light of the recovery perspective is the most important. Self-report is also the preferred method of inquiry across studies for assessing functional outcome.

A further limitation of the present study is the fact that, although the assumptions required for the statistical analyses used here are deemed to be sufficiently met, they are not *fully* met, and so caution must be taken when interpreting the findings. However, as our results – at least partially – support that of other studies, it gives reason to believe what we report is real, and not purely a result of statistical error.

Lastly, there are several potentially mediating and moderating variables which we have not included in the analyses, or otherwise assessed. This represents a limitation of the present study.

4.4 Clinical implications and future research

The findings of the present study indicate a bright outlook for the majority of participants. Our results support the findings from earlier studies demonstrating that individuals with first-episode schizophrenia may completely recover, and that the chances for a positive outcome are good. Hopefully, this will contribute to correct the old notion of schizophrenia being a chronic, progressively deteriorating disease. Instead, the findings should generate hope for reaching full recovery, both in individuals with schizophrenia, their family and friends, and clinicians. Reduction of stigma and incorrect assumptions held by the general public could be a further positive consequence. In turn, this might contribute to facilitating recovery in first-episode schizophrenia, as job opportunities, social networks etc. might be more readily available and supportive.

Our findings support the now recognized centrality of cognitive impairments in first-episode schizophrenia, as we report neurocognitive functioning at baseline to be significantly associated with later social functioning. In the extension of this, a continued focus on neurocognition is supported. Our results, in line with other studies, indicate that neurocognition is of importance for functional outcome, and that baseline measures might predict functioning years later. Additionally, as is the basis for cognitive training, cognition is potentially modifiable, and so facilitating recovery and better functioning might be possible. However, our results indicate that a continued focus on other factors that might also be of importance for the recovery process and functional outcome is necessary, such as motivation and metacognition.

We understand our results, regarding the limited importance of neurocognition in role functioning, as emphasizing the importance of a continued focus on destigmatization of schizophrenia. If society had more positive, evidence-based beliefs and knowledge about schizophrenia, this might both influence the self-efficacy of the individual and open more possibilities as to employment and successful integration to society. Also aiming to facilitate optimal real-world functioning, we underline the importance of a continued focus on neurocognition for individually tailoring treatment and other interventions.

Our findings contribute to the knowledge on the association between specific cognitive domains and later functional outcome, and further indicate which domains could be of special interest and significance for future studies. The results also, by supporting the association between neurocognition and functional outcome, underline the importance of integrating cognition in the treatment of first-episode schizophrenia. This could potentially be done in several different ways, for example by adapting treatment to cognitive strengths and deficits of the individual, or by tailoring cognitive training or remediation programs.

Lastly, as baseline measures of the neurocognitive domains did not statistically significantly predict role functioning, and a substantial proportion of the variance in social functioning was left unexplained, our findings may be understood as suggesting the importance of other variables than neurocognition for more fully understanding functional outcome in first-episode schizophrenia. Both those variables included in the present study as baseline demographic and clinical variables, and variables which we have not assessed, might be of interest and importance for further research.

Hopefully, future follow-ups of the Oslo Schizophrenia Study will further elucidate both the recovery process and the neurocognitive functioning of individuals with first-episode schizophrenia.

4.5 Conclusion

The present study reports on the six-year follow-up of individuals with first-episode schizophrenia. We report heterogeneity of outcomes, with high rates of recovery compared to that found in similar studies. 45,5% were fully recovered, 27,3% were partially recovered, and 13,6% were in remission at the present follow-up. The findings indicate a bright outlook for the majority of participants and contribute to the knowledge base on outcomes of first-episode schizophrenia.

Neurocognitive functioning at baseline was found to be significantly associated with social functioning at follow-up. The separate domains of attention, processing speed, verbal learning, reasoning and problem solving, and non-verbal working memory statistically significantly predicted social functioning. We report no significant findings for role functioning. Our findings add to the knowledge on specific neurocognitive domains as potential predictors of functional outcome in first-episode schizophrenia. The results further suggest that, long-term, neurocognition might be of greater importance for social- than role functioning, and other variables than neurocognition might make a greater contribution in role- than social functioning.

Our findings may contribute to the advancement of tailoring treatment to the neurocognitive functioning of individuals with first-episode schizophrenia, aiming towards facilitating real-world functioning. We emphasize the importance of a continued focus on destigmatiziation of schizophrenia.

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