Full recovery in first-episode schizophrenia

Long-term cognitive functioning and functional outcome

Susie Fu

Dissertation for the degree of philosophiae doctor (PhD)

University of Oslo

Department of Psychology

Faculty of Social Sciences

University of Oslo

And

Vestre Viken Hospital Trust

Oslo, 2019

Series of dissertations submitted to the
Faculty of Social Sciences, University of Oslo
No. 745

ISSN 1564-3991

Cover: Hanne Baadsgaard Utigard.
Print production: Reprosentralen, University of Oslo.

Table of contents

Acknowledgements

I would like to thank my main supervisor Professor Anne-Kari Torgalsbøen for the opportunity to work on this research project, first as a research assistant and then as a PhD-fellow. From day one, Anne-Kari has given me freedom to define my own role within the project and encouraged me to explore research questions that I found novel and interesting. Yet, she was always within reach, providing knowledge, advice and support. Thank you for believing in me at times when I struggled to do so myself.

To my second supervisor, Associate Professor Nikolai Czajkowksi, who generously offered me his time and effort. A wonderful teacher who never failed to point me in the right direction, and yet holding back just enough for me to learn. Special thanks to the senior researches and fellows of the Research Unit of Neuropsychopathology (RUN) at Department of Psychology. This group has provided me guidance and many great discussions.

Thanks to all participants that have devoted their time to this research project. Our research would not have been possible without you. Thanks to the research assistants, especially Adrian Dahl Askelund, Bendik Rund Torgalsbøen, Kristina Aagaard and Maren Kopland, who have contributed with data collection and competent assistance.

I am grateful to "The National Program for Integrated Clinical Specialist and PhD-training for Psychologists" and the two collaborating institutions, the University of Oslo and Vestre Viken Hospital Trust, for supporting my PhD and clinical specialization. It is important to bridge the gap between research and clinical work, and I am thankful for the opportunity to share my knowledge through this program both nationally and internationally.

Lastly, I would like to thank my friends and family. To my friends, who never complained about my absence in the later stages of my doctoral work. To my mother and father, who have endured difficulties and done their utmost to give me opportunities in life that were never given to them. To my husband, Knut, who stood by my side through all the ups and downs. You never fail to put a smile on my face when work is stressful. You always managed to find in my work new achievements to celebrate.

Summary

Schizophrenia has traditionally been regarded as a severe mental illness with limited prospects of full recovery. Research on first-episode schizophrenia (FES) has provided some new insights, although there is still much to learn regarding the long-term outcomes of FES-patients. The relationship between cognitive impairments and functional outcomes remains unclear in FES. The development of individual cognitive domains over time has not yet been fully examined. The recovery rate in FES is still highly debated, and long-term use of antipsychotics is common and often regarded as necessary to prevent relapses. This thesis includes three papers that investigate the longitudinal development in cognition and functional outcomes, as well as examining the recovery rate in FES using consensus-based criteria of full recovery. This study has a prospective longitudinal multi-assessment design with a total of 12 assessments over ten years. Here, we present data up to the eight-year follow-up.

The first paper aimed to examine the developmental trajectories of functional outcome in patients with different levels of baseline cognition. The patient sample was divided into three groups based on neurocognitive scores, and their developments in role and social functioning were compared to each other. Results indicated steady improvements in role and social functioning over a four-year period. The rate of change in social outcome varied among the patients depending on their baseline level of attention and verbal working memory, with the lowest scoring subgroup showing the least improvement. This indicated that cognitive deficits that were present at the onset of the disorder were associated with limited gains in social functioning over a period of four years.

The aim of the second paper was to compare the cognitive trajectories of FES-patients to the cognitive trajectories of a pairwise matched healthy control group. Unlike paper 1, which focused on cognition at illness onset, paper 2 examined the development of different cognitive domains over six years. The results showed an overall trend in the cognitive trajectories that indicated a similar cognitive change in both groups. The patient group's improvement in reasoning/ problem solving was significantly larger than the control group, while improvement in working memory was smaller. This indicated that there existed different developmental trajectories for different cognitive domains and measuring cognition with a single global measure may not be sufficient.

The third paper aimed to examine the development in cognition, work, and social functioning in a group of fully recovered FES-patients across six to eight years. Additionally, we wanted to inspect whether changes in outcomes were similar when individuals were off medication as when they were on medication. The results showed steady improvements in cognition, social, and role functioning for all patients, but the changes in processing speed and work functioning were significantly larger when individuals were off antipsychotic medications than on medications. Unmedicated participants were not healthier than medicated participants at baseline. This indicated that long-term continuous medication treatment was not necessary for maintaining low levels of symptoms and good functioning over time.

The findings from the three papers are important as they enhance our understanding of FES. However, the results need to be replicated with studies of larger sample sizes. The results from the current thesis provide new knowledge about the long-term development in FES by providing yearly assessments over multiple years. We showed that the FES-population is highly heterogeneous and dividing the patient group into subgroups in research is feasible and useful.

Abbreviations

AIC	Akaike information criteria
CDD	Calculated daily dose
DSM-IV	Diagnostic and statistical manual of mental disorders, 4th edition
EOS	Early onset schizophrenia
FES	First-episode schizophrenia
GAF	Global assessment of functioning scale
GF: Role	Global functioning: role
GF: Social	Global functioning: social
IPII	The Indiana psychiatry illness interview
MATRICS	Measurement and treatment research to improve cognition in Schizophrenia
MCCB	MATRICS consensus cognitive battery
MLM	Multilevel modelling
PANSS	The positive and negative syndrome scale
SCID	The structural clinical interview for DSM-IV
VVHF	Vestre Viken hospital trust

List of papers

The present thesis is based upon the papers listed below.

Paper I:

The relationship between level of cognitive impairments and functional outcome trajectories in first-episode schizophrenia.

Susie Fu, Nikolai Czajkowski, Bjørn Rishovd Rund, Anne-Kari Torgalsbøen. *Schizophrenia Research.* 2017; 190: 144-149.

Paper II:

Cognitive improvement in first-episode schizophrenia and healthy controls: a 6-year multi-assessment follow-up study.

Susie Fu, Nikolai Czajkowski, Anne-Kari Torgalsbøen. *Psychiatry Research.* 2018; 267: 319-326.

Paper III:

Cognitive, work- and social outcomes in fully recovered first-episode schizophrenia: on and off antipsychotic medication

Susie Fu, Nikolai Czajkowski, Anne-Kari Torgalsbøen. *Psychiatry: Interpersonal and Biological Processes.* 2019; in press, doi: 10.1080/00332747.2018.1550735

1. Introduction

For over a century, the definition of schizophrenia has continually changed as our understanding of the condition has increased. First introduced as dementia praecox by Kraepelin as a progressive neurodegenerative disease, it was later renamed to schizophrenia by Bleuler in his attempt to reintroduce "the psyche" into the concept of schizophrenia (Hoenig, 1983). The works of Bleuler and Schneider laid the important theoretical foundations for diagnosing schizophrenia reliably. The modern thinking on schizophrenia has moved beyond the simple listing of positive (delusions, hallucinations, disorganized speech and behavior) and negative symptoms (apathy, affect flattening, social withdrawal). The research on schizophrenia spans from genomic studies to pathophysiological studies to studies of cognitive, familial, and societal factors, among others. Still, our understanding of schizophrenia is far from complete. The clinical manifestations of schizophrenia are very diverse. The boundaries around the condition remain elusive, and the diagnosis is likely a conglomerate of multiple disorders (Tandon et al., 2013).

With the current thesis, we seek to further enhance the understanding of schizophrenia by examining longitudinally some variables associated with outcome. It includes a comprehension of the global cognitive impairments associated with schizophrenia. It includes an awareness of how a disrupted mind may have vast negative impact on a person's ability to lead a normal daily life. It includes an understanding of what recovery in schizophrenia entails.

1.1 Research on first-episode schizophrenia (FES)

Schizophrenia spectrum disorders are traditionally viewed as life-long disorders requiring substantial care, with a lifetime prevalence of about 1 % (Mueser & McGurk, 2014). Poor prognosis in schizophrenia was generally agreed upon based on studies showing chronic illness courses for a majority of patients (Breier, Schreiber, Dyer & Pickar, 1991; McGlashan, 1984; Tsuang, Woolson & Fleming, 1979). Still, it has long been acknowledged that outcome in schizophrenia is highly variable with a subgroup of patients showing favorable long-term outcomes (Engelhardt, Rosen, Feldman, Engelhardt & Cohen, 1982; Harding, Brooks, Ashikaga, Strauss & Breier, 1987; Strauss & Carpenter, 1972). Many of the earlier follow-up studies were done with patients that were chronically ill with repeated hospitalizations (McGlashan, 1984). The outlook may seem especially negative as 25-50 percent of patients with schizophrenia were

not represented in these studies (Tsuang et al., 1979). Chronically ill patients are characterized by poor outcome, severe negative symptoms, and worsening of cognitive function (Hulsfoff Pol & Kahn, 2008). The use of FES-patients in research was an effort to homogenize variability among patients caused by differences in chronicity and varying stages of treatment (Keshavan & Schooler, 1992). Over the past 20 years there has been an increased focus on FES in research, shedding some new light on the chances of recovery from schizophrenia.

1.2 Definition of full recovery

A major challenge for outcome studies is the lack of consensus in the definition of the term full recovery. Full recovery from schizophrenia is a complex process, and we have yet to operationalize a clear definition that incorporates the many areas that may be afflicted when individuals experience symptoms of schizophrenia.

Symptomatic remission is perhaps the most commonly used outcome measure in research as it is clearly defined and relatively easy to measure. The criteria of remission, as defined by the Remission in Schizophrenia Working Group (Andreasen et al., 2005), map three major dimensions of psychopathology in schizophrenia: psychoticism (reality distortion), disorganization, and negative symptoms (psychomotor poverty). These groups of symptoms must be scored mild or lower. Additionally, the criteria require a minimum maintenance period of six months. However, symptomatic remission is not enough to be considered fully recovered from schizophrenia, as a lowered symptom level does not necessarily equal improved psychosocial functioning. Yet, the criteria of remission provide an important foundation to further develop a definition of full recovery. The maintenance criteria of six months especially emphasized the episodic course of schizophrenia, as it is characterized by relapses and periods of stabilization. A definition of full recovery must distinguish between recovery from the disorder itself and recovery from an illness episode (Liberman & Kopelowicz, 2005). Thus, patients have to demonstrate symptom remission and adequate functioning for a sufficiently long period of time to be considered fully recovered.

Full recovery has been conceptualized in many ways that are not mutually exclusive (Barber, 2012). Unlike past decades where outcome was defined as symptom improvements and

prevention of relapses, symptom remission and functional improvements are now identified as achievable treatment goals (Leucht & Lasser, 2006). With ties to medical models of recovery, full recovery from schizophrenia can similarly be conceptualized as an objective outcome, a subjective process and/ or as illness management. An objective measure of full recovery is sometimes equated with cure or clinical recovery, where patients are free of symptoms, function well in work and social relationships, and do not receive medication or other treatments. However, this view is generally considered outdated. Similar to persons who suffer from chronic illnesses such as hypertension and diabetes, people with schizophrenia may live a rich and meaningful life by taking on a healthy lifestyle and following an effective treatment program, despite some level of symptoms. This view of full recovery is referred to as illness management where efforts are made to minimize exacerbations of the illness (Barber, 2012). A defining feature is that it does not equate recovery with cure, nor is cure the end state that patients should strive to obtain (Torgalsbøen, 2005). This definition of full recovery does not require total symptom remission. Recovery from schizophrenia is a process that is characterized by back and forth movement in illness severity, with gradual improvement over time. Thus, patients do not have to wait to be cured before reclaiming their lives and autonomy. This highlights the possibility of living an active and meaningful life despite varying degrees of symptoms (Davidson, Schmutte, Dinzeo & Andres-Hyman, 2008). As such, the modern thinking of full recovery often requires symptomatic remission, but many definitions also include elements of functional outcomes, such as being employed and having satisfying relationships.

Full recovery is more commonly defined as either an objective outcome or a subjective process. As an objective outcome, full recovery relies heavily on clinicians having accurate appraisals of patient's recovery status (Leonhardt et al., 2017). As a process, recovery points to the subjective indicators of recovery such as hope, feelings of control and agency, feeling capable of growth, and attaining new abilities (Resnick, Rosenheck & Lehman, 2004). These subjective indicators are sensitive to treatment and may ultimately mediate the process leading towards full symptomatic and functional recovery (Torgalsbøen, 2005). Past research has shown that patients and clinicians may disagree on the clients' quality of life (Hasson-Ohayon, Roe, Kravetz, Levy-Frank & Meir, 2011; Kravetz, Faust & Dasberg, 2002), which may negatively affect patients' satisfaction with treatment (Roe, Lereya & Fennig, 2001). More importantly, it reflects the fact that patients and clinicians may have different opinions on what defines a meaningful life. It was

suggested that disagreements may result from patients' lack of insight. This has not been consistently found in research, and it has been suggested that an apparent lack of insight might rather be a defense mechanism against stigma (Hasson-Ohayon et al., 2011), as internalized stigma may have negative effects on recovery (Yanos, Roe, Markus & Lysaker, 2008). Fervaha et al. (2015) reported in their study that patients with chronic courses of schizophrenia can experience a high sense of well-being and life satisfaction despite prominent clinical and functional impairments. Using an objective definition of full recovery, this group of patients may be considered ill and their prospective chances of recovery as poor. However, from a consumer perspective, this group of people may be considered improved as they have come to terms with their illness, found a way to live with the symptoms, and report being satisfied with their lives. Thus, in defining full recovery as simply symptom remission or the number of rehospitalizations, we may fail to see the individuals that are coping with their mental illness in ways that they themselves experience as effective. Personal subjective recovery is complementary to objective measures of full recovery as it helps evaluate a person's progress along the multidimensional course of illness and recovery (Roe, Mashiach-Eizenberg & Lysaker, 2011).

From a practical point of view, full recovery must be defined in ways that promote replicable research and facilitate clinical work for patients and clinicians alike. Past research has defined full recovery inconsistently (Silverstein & Bellack, 2008). Earlier studies may use the terms recovered or improved without defining the concepts. Thus, outcome measures may simply be defined as hospitalized or discharged (Shapiro & Shader, 1979). Researchers also varied in their opinions on whether positive outcomes such as mild symptoms, no disability, and no treatment, represent full recovery or simply significant improvements in the illness (Hegarty, Baldessarini, Tohen, Waternaux & Oepen, 1994; Mason et al., 1995).

Attempts towards a consensus outcome-oriented definition of full recovery have been made based on criteria commonly used in the field (Liberman, Kopelowicz, Ventura & Gutkind, 2002). Many incorporate the criteria of remission as defined by the Remission in Schizophrenia Working Group (Andreasen et al., 2005). We have yet to agree on one set of criteria for defining recovery, but the majority of studies operationalize recovery from two groups of criteria: clinical and functional. It was proposed that symptoms and functioning should be separate criteria, as symptoms and functioning have been found to be independent domains (Carpenter & Strauss,

1991; Green, 1996), although less so for negative symptoms than for positive symptoms (Ventura, Hellemann, Thames, Koellner & Nuechterlein, 2009). Functioning has traditionally been measured with the Global assessment of functioning scale (GAF) (Hall, 1995), but recently more specific measures of functioning have been proposed to replace the GAF, as GAF may be too nonspecific to track developmental patterns of major functional domains (e.g. work and social function) (Cornblatt et al., 2007). Another criterion concerns the duration of symptomatic and functional stability. A period of two years is most widely used and is generally thought to be enough time for clinical and functional improvements to be solidified (Liberman et al., 2002).

Consensus definitions facilitate research in providing standard, operational definitions, but are limited as they are not empirically based (Bellack, 2006). The level of functioning is especially hard to determine because unlike criteria for residual symptom levels and duration, which lend themselves to be objectively evaluated, level of functioning is a multifaceted construct that is not easily measured. What level of work performance is classified as good outcome? How much support can an individual receive and still be considered fully recovered? How often should one meet up with friends, and does the requirement differ with changes in family status?

As discussed earlier, it is debated whether a definition of full recovery should include a consumer perspective as well, as the personal experience of recovery may differ from the operational measures of recovery (Bellack, 2006). Although consumer perspectives may add additional important information, consumer-oriented definitions are hard to operationalize. It is challenging to disentangle the positive experiences that may appear as part of the process of recovering from the experiences that ultimately defines good outcome (Liberman & Kopelowicz, 2002). Silverstein and Bellack (2008) note that some of the widely cited consumer definitions are created by professionals with mental illness histories. It is unclear whether these people represent a good outcome subgroup, and thus their experiences may not be generalized to the broader population of people with schizophrenia. As such, consumer-oriented definitions are not yet widely used. However, there is a growing awareness of the importance of narratives as a tool for both patients and researchers to process and understand the severe mental illness that is schizophrenia (Lysaker, Ringer, Maxwell, McGuire & Lecomte, 2010; Saavedra, Cubero &

Crawford, 2009). As Roe and Davidson (2005) commented in their article – objective measures and manuals simply cannot replace the narratives that speak to the person's own experiences.

1.3. FES and outcome

It is well-established that many individuals with FES show symptom remission within the first year of illness (Gupta et al., 1997; Ho, Andreasen, Flaum, Nopoulos & Pharm, 2000; Malla et al., 2002). However, the relapse rate is high. An increase in relapse risk is associated with poor premorbid functioning and medication discontinuation within the first two years of illness (Robinson et al., 1999, Ücok, Polat, Cakir & Genc, 2006). Further, early symptom remission was not paralleled by improvement in functioning (Gupta et al., 1997).

Before a consensus definition of full recovery was proposed, research studies varied in the definitions used. A systematic review by Menezes, Arenovich and Zipursky (2006) on outcome rates in FES found that the most common way to report outcome was to categorize patients in groups, defined as good, intermediate and poor outcomes. Good outcome was found in 42 % of the population and poor outcome in 27 %. However, as studies applied various definitions, actual comparisons were difficult, and the recovery rates remained unclear.

Jääskeläinen et al. (2012) utilized the consensus definition of full recovery described earlier and reported in their meta-analytic review a recovery percentage of 16.6 among first-episode samples. The interquartile range was 9.0 – 20.4 %, indicating large variations among studies. However, the studies that were included in the review consisted of both patients with FES and multiple episodes, and the average follow-up period was not reported. The findings from this review contrasts with a more recent meta-analytic review by Lally et al. (2017), who found a full recovery rate of 38 % in FES. Contrary to earlier beliefs, over one third of the FES population achieved full recovery, with an even higher rate of individuals meeting the criteria of remission (57.9 %). Over a mean follow-up period of seven years, the full recovery rate became stable after the first two years. The authors concluded that patients with worse outcomes may be identified already in the earlier stages of illness. However, as this was a meta-analytic review, it was not apparent whether the individuals that achieved full recovery early on maintained their recovery status over time. The Danish OPUS trial is one of the few longitudinal studies of

recovery in FES with a follow-up period of up to ten years. The research group reported an approximately similar full recovery rate at 2- and 5-year follow-ups (15.7 %), but the patients that were fully recovered at the 2-year follow-up were not the same individuals that were fully recovered at the 5-year follow-up (Albert et al., 2011). Thus, Albert et al. (2011) viewed recovery as a fairly changeable state, and it is hard to predict from the beginning who will recover from the illness.

No consensus has yet been reached on methods measuring functional outcomes (Emsley, Chiliza, Asmal & Lehloenya, 2011). Several studies use outcome measures that include some global measures of vocational and social adjustment, for instance the Global social adjustment scale, Global assessment scale (Malla & Payne, 2005), and the GAF (Jääskeläinen et al., 2012). These tests show the proportions of patients that meet the standards of good global outcome (e.g. a GAF score ≥ 61), but the information provided is still incomplete, and the study results will vary based on how stringent the applied criteria are. Liberman et al. (2002) proposed that functional outcomes should be assessed in separate dimensions of vocational functioning, independent living, and social relationships. With these assessment measures implemented, Robinson, Woerner, McMeniman, Mendelowitz and Bilder (2004) reported that after five years 25 % of a total of 118 patients met the criteria for vocational and social outcome, and 13.7 % met the criteria of full recovery. Wunderink, Sytema, Nienhuis and Wiersma (2009) reported that 19.2 % met the criteria of full recovery after a 2-year follow-up period. Sterling et al. (2003) reported from a 10-year follow-up study that 82 % lived independently for at least five years, and 22 % had been working for at least three years.

1.4 Neurocognitive functioning in schizophrenia

Although not a criterion for the diagnosis of schizophrenia, cognitive impairments are a defining characteristic of the illness. Patients with schizophrenia consistently score lower on cognitive tests than healthy controls (Fioravanti, Carlone, Vitale, Cinti & Clare, 2005; Fioravanti, Bianchi & Cinti, 2012). This also holds true for patients with FES (Mesholam-Gately, Giuliano, Goff, Faraone & Seidman, 2009), who also show larger cognitive impairments than patients with bipolar psychoses or depression (Mesholam-Gately et al., 2009; Seidman et al., 2002). Cognitive deficits in patients with schizophrenia have been clinically observed and labelled from the early

1900s, but the excitement that characterized the research on cognition did not happen until the latter part of the 20th century (Green & Harvey, 2014). With the subsequent research into predictors of positive outcomes, research on cognition boomed. Cognitive impairments are consistently associated with functioning in schizophrenia (Green, Kern, Braff & Mintz, 2000; Green, Kern & Heaton, 2004), even more so than positive and negative symptoms (Harvey et al., 1998; Velligan et al., 1997). Rehabilitation programs focused on cognitive remediation also show significant effects on improving psychosocial functioning (McGurk, Twamley, Sitzer, McHugo & Mueser, 2007; Wykes, Huddy, Cellard, McGurk, Czobor, 2011). The questions asked by researchers are no longer whether cognition affects functioning in schizophrenia, but rather: a) which cognitive domains predict good functional outcome and b) how cognition affects functioning. Some promising variables suggested to mediate the relationship between cognition and functional outcomes include social cognition (Schmidt, Mueller & Roder, 2011) and negative symptoms (Ventura et al., 2009).

Although research show consistent evidence for an association between cognition and functional outcomes, there remain some issues that are still debated. Here we present a selective review of some of the ongoing debates that create the backdrop for understanding our own research.

1.4.1 The cognitive course in schizophrenia

The main debate regarding the cognitive course in schizophrenia is about whether it follows a neurodevelopmental or neurodegenerative course (Bora & Murray, 2014, Rund, 2018). The former states that cognitive impairments are the end state of abnormal neurodevelopmental processes that are present before the illness onset (Rapoport, Giedd & Gogtay, 2012), while the latter indicates further decline in the years after illness onset (Rund, 2009).

The neurodegenerative model has got some support from longitudinal studies on elderly patients with schizophrenia. In general, studies with one or two-year follow-up periods have failed to find significant cognitive changes in elderly (Harvey et al.,1996) and out-clinic populations (Heaton et al., 2001). However, studies with longer follow-up periods have shown further cognitive worsening in a group of elderly chronically ill patients (Friedman et al., 2001;

Harvey, 2001). In comparison, a group of younger patients with good prognosis did not show the same development over time (Heaton et al., 2001). The cognitive decline seen in the patients with poor outcomes is different from deficits seen in Alzheimer's disease, which indicates that poor outcome may be a risk factor for subsequent cognitive decline in late life (Harvey, 2001). Other support for the neurodegenerative model originates from brain imaging studies. Patients with schizophrenia show progressive changes in the frontal lobes, medial temporal lobes, and neocortex temporal lobe and enlarged ventricles (Shenton, Dickey, Frumin & McCarley, 2001).

Research in favor of the neurodevelopmental model shows no indication of further cognitive decline after illness onset (Carrión et al., 2018; Keefe et al., 2006). It seems that cognitive deficits are established before the prodromal phase (Becker et al, 2010; Bora & Murray, 2014; Jahshan, Heaton, Golshan & Cadenhead, 2010). Prospective longitudinal studies of FES are especially valuable, as the cognitive function of chronically ill patients may be affected by other factors, e.g. long-term antipsychotic treatment and under-stimulation from the environment (Rund, 2009). Reviews of studies with FES-populations conclude that cognitive impairments do not progressively worsen in the first years after illness onset (Rund, 2009). However, most of the studies that include a FES-population have follow-up periods of only one or two years (Bora & Murray, 2014). Albus et al. (2006) assessed a group of FES-patients at baseline and after five years and found no cognitive deterioration. Barder et al. (2013a) reported mostly stable cognitive functioning during a follow-up period of five years, except for motor speed which declined. Only four studies of FES reported a follow-up length of ten years. Barder et al. (2013b), Hoff, Svetina, Shields, Stewart and Delisi (2005), and Rund et al. (2016) found stability in cognitive functioning over time, while Sterling et al. (2003) found deterioration in three visuospatial tasks.

A limitation with many of the current studies is the lack of healthy control groups. This especially applies to studies with follow-up periods beyond three years. These studies either did not have a healthy control group or the control group was not matched to the patient group. Without a control group, cognitive improvements may be falsely attributed to true changes in cognition, whereas some or all of the improvements may be due to practice effects (Szöke et al., 2008).

1.4.2 Generalized or specific cognitive impairments in schizophrenia

Another debate concerns whether cognitive impairments in schizophrenia are generalized or specific. Generalized cognitive deficits imply that all areas of cognition show deficits, thus most or all variance in cognitive performance is shared (Green, Horan & Sugar, 2013). In their review of the literature, Schaefer, Giangrande, Weinberger and Dickinson (2013) concluded that the evidence for generalized cognitive deficits in schizophrenia is pervasive. People with schizophrenia showed cognitive impairments relative to healthy controls across all neurocognitive measures. The impairments seem also to be consistent despite geographic and cultural variations, as well as differences in cognitive instruments and diagnostic criteria. However, Green et al. (2013) argued that the view about generalized deficits becomes problematic in instances when findings of specific cognitive deficits are interpreted as generalized deficits, and specific deficits are instead downplayed as concerns about the psychometrics of measures.

Patients with schizophrenia have demonstrated intact attention for emotionally significant stimuli (Horan, Foti, Hajcak, Wynn & Green, 2012) and intact context processing for facial emotion identification (Lee et al., 2013). Gold, Hahn, Strauss and Waltz (2009) reported evidence of preserved emotional processing, aspects of gradual learning, speed of attention shifting and selective attention for working memory storage. These findings do not support the view of generalized deficits in schizophrenia. Furthermore, patients that demonstrate preserved cognitive functioning range from 10 to 55 % (Palmer et al., 1997; Rund et al., 2006). Patients demonstrate varying degrees of cognitive impairments, with some cognitive domains showing more impairments than others, and it has been suggested that cognitive functioning may be understood along a continuum in schizophrenia (Rund et al., 2006).

Although cognitive constructs may have some variance that is shared, it does not mean that the individual constructs no longer have unique explanatory power, as shown with mediation associations (Green et al., 2013). Similarly, when considering the association between cognitive functioning and functional outcomes, it is important to identify the cognitive components that have unique predictive power, above and beyond shared variance.

1.4.3 Specific cognitive domains associated with functional outcomes

Consistent associations have been found between cognition and functional outcomes, but most of the findings are from cross-sectional studies (Green et al., 2000) or studies on chronic schizophrenia (Green et al., 2004). In comparison, the longitudinal effects of cognition on functional outcomes in FES are not as well-established (Nuechterlein et al., 2011). There are several reasons for this. Firstly, there are few longitudinal studies that include cohorts of FES-patients (Milev, Ho, Arndt & Andreasen, 2005). Secondly, before the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) was developed (Nuechterlein et al., 2008), there existed no standard for the number of cognitive domains to include in the optimal assessment of cognition. As such, Allott, Liu, Proffitt and Killackey (2011) found no two studies that examined the exact same number of cognitive domains in their meta-analytic review of the literature. Furthermore, methodological heterogeneity made it even more difficult to make direct comparisons across studies. Thirdly, when considering the scientific evidence of each cognitive domain separately, there are more null relationships between cognition and functional outcome than there are significant relationships (Allott et al., 2011). This is again largely due to heterogeneous measurements of cognition and functional outcome, as well as other specific features of the individual studies (Nuechterlein et al., 2011). Lastly, as previously mentioned, many longitudinal studies on cognition have follow-up periods of one to two years. Some studies have longer follow-up periods, but include only two measurement occasions. Multi-follow-up studies provide a more comprehensive examination of the course of cognition and functional outcome. As the number of follow-up points increases, the better the estimates of the rates of change/growth over time become.

Despite the current methodological limitations and the lack of a firm conclusion regarding the association between cognition and functional outcomes in FES, several cognitive domains have repeatedly been reported to predict later functioning. These include verbal memory, processing speed, attention, and working memory (Milev et al., 2015; Nuechterlein et al., 2011; Tandberg et al., 2011, Torgalsbøen, Mohn, Czajkowski & Rund, 2015).

1.4.4 Antipsychotic medication, cognition, and functional outcomes

In almost all episodes of acute psychosis patients with schizophrenia are treated with antipsychotic medication. Medication treatment are recommended to be initiated as soon as is clinically feasible, as acute psychosis is associated with emotional distress, disruption to the patient's life and substantial risk of dangerous behaviors (Lehman et al., 2004). Once stabilization has been achieved, the treatment plan should address whether continued treatment with medication is necessary for minimizing relapse and address possible residual symptoms. Treatment guidelines for FES recommend at least one year of antipsychotic treatment following remission (Lehman et al., 2004).

The effectiveness of antipsychotic medication in reducing relapses needs to be evaluated against the risks of harmful effects associated with long-term use of antipsychotics. At present, there are limited guidelines to guide the choice of type of antipsychotic treatment for optimal response, and the choice of antipsychotics is still based on a trial-and-error strategy (Lally & MacCabe, 2015). Old habits seem hard to break as well, as the age of the prescribing psychiatrist was found to predict the prescription of first-generation antipsychotics over second-generation antipsychotics despite the guidelines that recommend the latter. Patient variables, however, did not significantly influence treatment decisions (Hamann, Langer, Leucht, Busch & Kissling, 2004). A more user-centered approach has been recommended that focuses on a collaborative model where patients are encouraged to take part in the decision-making and make their own informed treatment choices (Alvarez-Jimenez et al., 2016; Morrison, Hutton, Shiers & Turkington, 2012). For instance, Gaebel et al. (2002) reported that FES-patients showed better treatment compliance if the medication intervention was intermittent and prodrome-based compared to maintenance treatment. In Norway, mental health care services seek to provide patients with the choice of medication free treatment if this is deemed justifiable for the individual patient. As such, the need for personalized treatment is emphasized, as medication treatment is a collaborative decision between clinicians and patients, and patients should be offered evidence-based alternative treatment if so desired. Opponents of medication free treatment in schizophrenia often point to studies that show seemingly worse outcomes in FES-patients that discontinue medication treatment in terms of higher relapse rates and an increased treatment response time if medications are restarted (Emsley, Chiliza, Asmal & Harvey, 2013;

Wyatt, Damiani & Henter, 1998; Zipursky, Menezes & Streiner, 2014). However, whether antipsychotic treatment has a long-term effect on cognition and functional outcomes is still broadly debated.

Treatment with antipsychotics has consistently shown an effect in improving positive symptoms (Leucht, Arbter, Engel, Kissling & Davis, 2009; Leucht et al., 2013). Regarding its effect on cognition, the outlook seemed promising at first (Harvey & Keefe, 2001), but the effects of antipsychotics on cognitive function have since been found to be modest (Keefe, Bilder et al., 2007; Keefe, Sweeney et al, 2007), irrespective of the type of antipsychotic used (first- vs second-generation antipsychotics) (Keefe, Bilder et al., 2007). In contrast, Woodward, Purdon, Meltzer and Zald (2004) found that second-generation antipsychotics were superior to first-generation antipsychotics in improving functioning in several cognitive domains. Regarding FES, Goldberg et al. (2007) found improvement in 9 out of 16 cognitive domains, but some of the cognitive improvements might have been due to practice effects, as the magnitude was comparable to the improvements seen in healthy controls.

Since antipsychotics are associated with symptom improvements, but not improvement in cognition, and cognition is associated with functional outcomes, Green and Harvey (2014) argued that it is unsurprising that antipsychotics have made little difference in improving overall recovery rates. This contrasts with the common perception of the importance of antipsychotics in the treatment of schizophrenia. Studies on FES have shown an increased risk of relapse following medication discontinuation (Emsley et al., 2013), with a meta-analytic review reporting a recurrence rate of 77 % within a year following antipsychotics discontinuation (Zipursky et al., 2014). If antipsychotics were successful in preventing relapses, one would expect an increase in remission rates over time. However, as recent studies demonstrate, maintenance treatment with antipsychotics seems not to prevent relapses, but only postpone them (Wunderink, Niebor, Wiersma, Sytema & Nienhuis, 2013). Similar to longitudinal studies on cognition, most studies on the long-term effects of antipsychotics have follow-up periods of one to two years (Harrow & Jobe, 2013). There is some evidence pointing towards antipsychotics losing their effectiveness over time (Leucht et al., 2012; Wunderink et al., 2013), but currently there are very few studies that have follow-up points from three years onward. As of now, it is simply difficult to tell whether long-term antipsychotic medication treatment results in better or poorer outcome than

treatment with no medication (Sohler et al., 2016). In recent years, there have accumulated quite a few studies that show subgroups of patients that demonstrate good long-term functioning without use of antipsychotics (Harrow, Jobe & Faull, 2014, Moilanen et al., 2013; Torgalsbøen, 2012; Torgalsbøen & Rund, 2010; Wils et al., 2017). Still, it is unclear if this subgroup represents a unique sample that is healthier to begin with, and thus their recovery may not be directly related to medication discontinuation.

Even though the long-term association between medication treatment and functional outcome is still unclear, antipsychotic treatment may have benefits from a consumer perspective. In their qualitative study of patient's experiences of recovery, Jenkins and Carpenter-Song (2005) found that many patients did not believe that medication could be relied on by itself in promoting recovery. Rather, antipsychotics provided them with the means to control their illness and regain autonomy of their lives. Similarly, some patients with chronic schizophrenia reported small improvements in quality of life following medication treatment (Swartz et al., 2007).

The relationship between antipsychotics and functional outcome is further complicated by other factors. For instance, the selective dropout of patients with poor outcome from longitudinal studies is a well-known issue. Non-adherence with antipsychotic medication is another problem. Non-adherence is common and predictive of poor outcome, including relapses, suicide attempts, and poor long-term functioning (Novick et al., 2010). It may be especially challenging to assess non-adherence in longitudinal studies if follow-up points are many years apart. Moreover, as antipsychotics may affect cognition, so can cognition affect medication adherence and then again affect functional outcomes. Jeste et al. (2003) reported in their study that cognitive functions were stronger patient-related predictors of medication adherence than symptom severity in a group of middle-aged outpatients.

1.5 Unanswered questions

We have come a long way in understanding schizophrenia since the condition was first defined by Kraepelin, but we still have much to learn. We seek to define schizophrenia at its core, but are instead met with the possibility of its heterogeneity. The precipitating factors may be organic or idiopathic. The course of the illness is diverse with differences in its clinical features

and prognosis. We may still be unable to give conclusive answers to some of the debates reviewed earlier, but we are gradually learning, applying developments in scientific methodology as we move along. The questions below are not a complete list of all the unanswered questions in the field of recovery and outcome in FES, but rather questions that are especially relevant for this thesis.

The use of longitudinal designs has provided valuable information about the course of schizophrenia, especially for the first two years after psychosis onset. Since there are few studies that have examined FES beyond the first two years, many questions remain about the long-term course of illness. Does the cognitive course remain stable after the first two years of illness? Do different cognitive domains develop differently, and if so are there different rates of growth? Put another way, do assessment batteries that assess separate cognitive domains convey more information than cognitive tests that measure global cognition? How is the long-term cognitive course in FES compared to the course of healthy controls?

The research on the potential benefits of medication treatment in FES is as well limited by longitudinal studies with short follow-up periods. Specifically, we wonder whether continuous long-term medication treatment is necessary to remain symptom free and show good functional outcomes, which is common practice in many healthcare systems. Of course, there are other important questions as well, for instance: what are the long-term effects of antipsychotics? How does long-term treatment of antipsychotics affect cognitive functioning?

Amidst the evidence of heterogeneity in schizophrenia, we now recognize the existence of subgroups. However, few studies have examined the long-term course of different subgroups. If poor outcome is predictive of further cognitive and functional decline later in life, then it is important to identify factors that may predict poor prognosis as early as possible.

2. Main research aims

The main purpose of this thesis is to investigate the longitudinal courses of cognitive functioning, work-, and social functioning in FES. We also want to determine the recovery rate in FES using consensus-based criteria of full recovery. In addition to using objective outcome measures, we also interviewed the participants to examine their subjective experiences of recovering from schizophrenia.

The field of recovery and the factors that contribute to good outcomes are simply too many to be included in three focused research articles. Thus, we focus our studies on cognition, functional outcomes and recovery. These are key concepts in the research on schizophrenia, with research spanning over several decades. While it has been established that impaired cognition is a core feature of schizophrenia, research has yet to conclude on its long-term course. The three papers that comprise this thesis will investigate cognition and outcome from different perspectives, and answer different aspects of the main research aim with their own delineated objectives:

> Objective of paper 1: The relationship between level of cognitive impairments and functional outcome trajectories in first-episode schizophrenia.

In our first paper, the objective was to investigate whether baseline cognition can predict later work- and social functioning. Further, since cognition is associated with functional outcomes, we wondered whether different levels of cognitive impairments will impact functioning differently over the years. We therefore divided the patient sample into three groups based on their cognitive levels at baseline. Some cognitive domains are found to be more consistent associated with functioning than others, thus we investigated the cognitive domains separately. Due to heterogeneity in outcome in schizophrenia, it is likely that patients follow different pathways on their road to recovery. If so, it is of special interest to recognize patients with poor outcomes as early as possible, as well as giving a clearer picture of the group with good outcomes beyond just stating that such a subgroup exists.

> Objective of paper 2: Cognitive improvement in first-episode schizophrenia and healthy controls: a 6-year multi-assessment follow-up study.

Since we only examined baseline cognition in our first paper, it is natural to ask ourselves next how cognition develops over the years. Research has shown that better cognitive functioning is associated with good prognosis. However, as cognitive improvements are suggested to be due to practice effects, we wanted to compare the cognitive scores of the patient group to a healthy control group to examine whether there are any developmental differences between the two groups. We do not expect either one of the groups to show larger practice effects than the other, so significant differences in change in any cognitive domains are of special interest.

Objective of paper 3: Cognitive, work- and social outcomes in fully recovered first-episode schizophrenia patients: on and off antipsychotic medication.

Our objective in the third paper is to examine whether changes in outcome seen after medication discontinuation are similar to the changes seen while under medication treatment. Based on the patient's recovery status on the 8th follow-up (approximately 6-8 years after illness onset), participants that fulfilled the criteria for full recovery were selected for analysis (n = 10). Unremitted patients are still on medication treatment, and thus unsuitable for answering our paper's objective. Since this study is ongoing, participants are at various follow-up points ranging from 8 to 11 assessments, the eighth follow-up was chosen because complete data was collected from all 28 participants. We wondered specifically whether the common perception of increased relapse risk and subsequent fall in functioning following medication discontinuation also holds true beyond the first two years of illness. We also examined whether change in medication status resulted in changes in cognitive functioning as medication treatment is commonly found to not affect cognition.

3. Methods

3.1 Oslo Schizophrenia Recovery Study

The Oslo Schizophrenia Recovery Study is a prospective longitudinal multi-follow up study of FES-patients. The main goal of the study is to examine the long-term course of schizophrenia and investigate predictors of prognosis. The study has yearly assessment points over 10 years. It is ongoing, and as of now complete data has been collected through the seventh year. The main variables are cognition, resilience, hope, self-efficacy, metacognition, and recovery. Participants were recruited over a period of four years (2007-2011) from mental health service institutions in Oslo and nearby areas. Participants for the healthy control group were recruited through inquiries at junior and senior high schools in the Oslo metropolitan region, and through electronic advertisements on the Vestre Viken Hospital Trust (VVHF) homepage. The VVHF provides state funded healthcare to the south-eastern part of Norway which consists of rural areas and cities.

In this section, we will only present methods and variables that are relevant for this thesis.

3.2 Inclusion

31 FES-patients were referred to the study by their treating clinicians at mental health service institutions. Before entry into the study, potential participants were screened using the following inclusion criteria:

- Age $\geq$ 18 years
- First episode of mental illness was within the spectrum of schizophrenia and psychosis according to DSM-IV (American Psychiatric Association, 1994)
- IQ > 70
- No evidence of affective disorders, head trauma, and primary diagnosis of substance abuse
- Referred to the study within five months of their first contact with mental health service institutions (hospital or out-patient clinic)

A total of 28 FES-patients fulfilled the inclusion criteria and were admitted to the study. Based on their gender, age, and education level (+/- one year), healthy controls were matched pairwise to the patients. Exclusion criteria for the healthy control group were:

- A history of schizophrenia or other severe mental disorder
- Mental retardation (IQ < 70)
- A history of neurological disease, head injury and/ or loss of consciousness for more than 10 minutes
- Current psychotropic medication or narcotic drug for pain
- Chronic somatic illness inducing significant fatigue or pain
- A history of alcohol and substance abuse
- Dyslexia or other significant learning difficulties

Only participants who understand spoken and written Norwegian fluently were entered into the study. The table below shows the demographic and clinical characteristics of the participants at study entry.

	Patients (*n*=28)	**Controls (*n*=28)**
Age in years	21.0 (SD 2.6)	21.1 (SD 2.7)
Gender	17 (60.7%) men, 11 women	17 (60.7%) men, 11 women
Level of education		
Elementary school	n=11 (39.3 %)	n=9 (32.1 %)
High school	n=8 (28.6 %)	n=16 (57.1 %)
Some college	n=7 (25.0 %)	n=2 (7.1 %)
BA degree or higher	n=2 (7.1 %)	n=1 (3.6 %)
Diagnoses		
Schizophrenia	21 (75.0 %)	
Schizoaffective disorder	6 (21.4 %)	
Psychotic disorder NOS	1 (3.6 %)	
Substance abuse earlier	18 (64.3 %)	
Substance abuse at baseline	1 (3.6 %)	
Treatment status		
Hospitalized	16 (57.0 %)	
Outpatient	12 (43 %)	
Duration of untreated psychosis (months)	15.9 (SD 15.4)	
Drug-naïve at baseline	2 (7.1 %)	

3.3 Procedures

Patients were tested at baseline, then six months later and thereafter once a year. On every assessment, patients completed a semi-structured interview with questions about their lives and status on their relationships, medication, treatment etc. Neurocognitive testing was completed on every assessment through the fourth year; thereafter the patients will be tested cognitively every other year. The complete assessment lasts between 1 ½ - 2 ½ hours, and 30 minutes to an hour without neurocognitive testing. Once in the follow-up period, patients will be interviewed with the IPII by the study's principal investigator. This interview is audiotaped and later transcribed by graduate students of clinical psychology trained in neuropsychological assessments.

Healthy controls complete neurocognitive testing on four occasions: at baseline, after two years, six years and ten years.

All patients were retained during the first three assessments, while three participants left the study during the 2-year follow-up and an additional three dropped out during the 3-year follow-up. Anxiety, a lack of insight into having mental illness, not finding participation in research useful, and non-response at contact were reasons for participants dropping out of the study. Regarding the healthy control group, three participants were unable to participate on the 6-year follow-up. These three were replaced by pairwise matched participants (age, gender and education level) that were picked from a pool of potential healthy controls that were tested on baseline, but until now not matched to the patient population. Thus, for these three participants we do not have data from the 2-year follow-up, but we have full data from baseline and 6-year follow-up.

3.4 Clinical and functional instruments

Diagnoses. The Structural Clinical Interview for DSM-IV (SCID-I), modules A-D, was used to establish diagnoses. Diagnoses were first set by the treating clinicians, then separately confirmed by an experienced clinical psychologist at study entry.

Criteria for remission and full recovery. The criteria for remission (Andreasen et al., 2005) in schizophrenia are based on an evaluation of 8 symptoms: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), N1 (blunted affect), N4 (social and emotional

withdrawal), N6 (lack of spontaneity), G5 (mannerisms and posturing), and G9 (unusual thought content). Symptom level is measured by The Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein & Opler, 1987). Each item is scored on a scale from 1-7, and each item must be scored 3 or less (mild) for at least six months to fulfill the criteria for remission.

The criteria for full recovery are based on the same set of symptoms as mentioned above. The full recovery definition used is a combination of Andreasen et al.'s (2005) criteria for remission and the operational recovery criteria developed by Liberman et al. (2002). Each item on PANNS must be scored 3 or less (mild) over a period of at least two years. Additionally, the following criteria must also be fulfilled:

- Full- or part-time engagement in an instrumental role activity (e.g. worker, student, volunteer) that is constructive and appropriate for culture and age.
- Living unsupervised by family or other care-givers, with the individual being responsible for her/his own day-to-day needs (e.g. self-administration of medication, money management).
- At least once a week, participating in active friendship and/or peer social relations or otherwise involved in recreational activities that are age-appropriate and independent of professional supervision.

Semi-structured interviews. A semi-structured interview was used to gather information on the following topics, amongst others: current employment status, relationship status, psychopathology, treatment status, medications, free time activities, and subjective well-being. Based on the answers from this interview, a score ranging from 1-10 is given according to the Global Functioning: Social (GF: Social) and the Global Functioning: Role (GF: Role) (Cornblatt et al., 2007). A higher score indicates better functioning. The social scale measures quantity and quality of peer relationships, level of peer conflict, age appropriate intimate relationships, and involvement with family members. The role scale assesses performances either in school, work or as a homemaker.

Based on the information gathered and the functioning scores we rate the participants as either non-remitted, in remission, partially recovered or fully recovered. Fully recovered corresponds to the criteria of full recovery by Liberman et al. (2002), while partially recovered means that symptomatic remission has been achieved, but not all of the additional criteria (work,

independent housing, social activities) have been successfully reached. Partial recovery allows minor impairments in either housing, work or intimate relationships if these do not lead to significant impairments in social and role functioning. Not all people without mental disorders would meet both criteria for good functioning as measured by GF: Social and GF: Role, thus it makes sense to define the participants that meet this level of functioning as partially recovered (Torgalsbøen, Fu, Czajkowski, 2018).

Another semi-structured interview, the Indiana Psychiatry Illness Interview (IPII) (Lysaker, Clements, Plascak-Hallberg, Knipscheer & Wright, 2002) was used to sample the patient's illness narratives. In this interview the participants are asked:

- To tell the story of their life
- Whether they think they have a mental illness
- How this condition has/ has not affected different facets of their lives
- How they control and are controlled by their condition
- How their condition affects and is affected by others
- What they expect in their future

Medicine. Calculated daily dose of medication (CDD) has been reported in a separate research article (Torgalsbøen, Mohn & Rund, 2014). Pearson's correlation analyses on the relationship between CDD and neurocognitive scores did not yield any statistically significant associations.

3.5 Neurocognitive test-battery

Cognitive functioning was measured with the MCCB (Nuechterlein et al., 2008), translated into Norwegian. Norwegian reference data have been collected, and the study concluded that US norms can be employed for the Norwegian population (Mohn, Sundet & Rund, 2012). The MCCB was developed from the National Institute of Mental Health's Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative. The goal was to create a consensus cognitive battery for use in clinical trials in schizophrenia, emphasizing characteristics such as test-retest reliability; utility as a repeated measure; relationship to functional status; potential changeability in response to pharmacological

agents; and practicality for clinical trials and tolerability for patients (Nuechterlein et al., 2008). Since its development, the MCCB has shown excellent psychometric properties, for instance high test-retest reliability and modest practice effects, as well as sensitivity to improvement from interventions (Green, Harris & Nuechterlein, 2014).

The MCCB consists of 10 tests assessing seven cognitive domains. The seven cognitive domains with their corresponding tests are:

Speed of processing.

Intact attention is a necessary precondition of both concentration and mental tracking activities. Conceptual tracking can be prevented or interrupted by slowed processing speed which is the pace information is taken in, processed and responded upon. Thus, slowed processing speed often underlies attentional deficits (Lezak, Howieson, Loring, Hannay & Fischer, 2004).

Category Fluency: Animal Naming – Verbal test where respondents are asked to name as many animals as possible in one minute;

Brief Assessment of Cognition in Schizophrenia (BACS): Symbol Coding – Timed paper-and-pencil test where respondents use a key to write digits that correspond to nonsense symbols;

Trail Making Test: Part A – Timed paper-and-pencil test where respondents connect consecutively numbered circles placed irregularly on a sheet of paper by drawing a continuous line.

Attention/ Vigilance.

Deficits in vigilance may reflect an attentional problem as vigilance is the sustained, focused attention that is required in daily tasks that involves concentration or tracking over time, and ignoring distractors (Lezak et al., 2004).

Continuous Performance Test – Identical Pairs (CPT-IP) – Computer-administered test that lasts 10 minutes where respondents press a response button only when two consecutive matching numbers show up on the screen.

Nonverbal working memory and Verbal working memory.

Working memory is associated with attention and short-term memory. Its short-term limited capacity reflects the basic dimensions of attention. Working memory taps into how much information the attentional system can process at once. The manipulation of temporarily stored information taps into short-term memory capacity (Lezak et al., 2004).

Wechsler Memory Scale – 3rd ed. (WMS-III): Spatial Span – Using a board on which 10 cubes are irregularly spaced, respondents tap cubes in same (or reverse) sequence as test administrator.

Letter-Number Span – Verbally administered test where respondents mentally reorder and repeat a string of random number and letters.

Verbal learning and Visual learning.

Memory is the ability to acquire, store, and retrieve information. Normally, testing memory requires three different procedures: immediate recall, an interference period to prevent rehearsal, and a delayed recall (Lezak et al., 2004). As none of the revised tests in the MCCB have a delayed recall condition, caution must be taken when considering the results as they only tap into the subject's ability of immediate recall.

Hopkin's Verbal Learning Test – Revised (HVLT-R) – Verbally administered test where respondents recall a list of 12 words to their best ability. There are three trials, where the same 12 words are read aloud for the respondents. Alternate forms are available.

Brief Visuospatial Memory Test – Revised (BVMT-R) – A sheet of paper with six geometric figures are shown to the respondents for 10 seconds. Upon removal of the sheet of paper, respondents are asked to reproduce the figures from memory. Alternate forms are available.

Reasoning and problem-solving.

Reasoning is thinking with a conscious intent to reach a conclusion. It requires the collaboration of different cognitive domains to be performed successfully. Executive functions contribute to purposeful problem solving: planning, purposive action, monitoring, and effective performance (Lezak et al., 2004).

Neuropsychological Assessment Battery (NAB): Mazes – Seven timed paper-and-pencil mazes of increasing difficulty.

Social Cognition.

Social cognition is the ability to process social information, including identifying emotions, interpreting other people's thoughts and feelings, and creating and maintaining social connections (Green, 2016). Mentalizing and emotion regulation are part of this social processing system (Green, 2016).

Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT): Managing Emotions – Multiple-choice test where respondents are presented with short stories and asked how effective the main characters' solutions to their problems were. All stories are about characters managing their emotions.

3.6 Characteristics of papers 1-3

The table below shows characteristics of paper 1-3 (number of participants, lengths of follow-up and test instruments).

	Paper 1	**Paper 2**	**Paper 3**
Number of participants	28 patients	28 patients 28 controls	10 patients
Follow-up length	4 years	6 years	6-8 years
Clinical and test instruments	MCCB PANSS GF: social GF: role	MCCB	MCCB PANSS GF: social GF: role Semi-structured interviews and IPII

3.7 Analyses

Analyses with multilevel modelling (MLM) were performed in all three papers. Our study has a longitudinal design with repeated measures. We have chosen to analyze our data with MLM as it is a well-suited method to analyze nested data structures. In the case of our data that are collected on multiple occasions over time, the measurement occasions are nested within individuals. Measurement occasions represent level 1 and individuals represent level 2.

A major benefit of using multilevel modelling rather than linear regression analysis is MLM's ability to handle violations of the independence assumption. Traditional analysis models require that observations are independent of each other, if not they can produce excessive Type I errors and biased parameter estimates (Peugh, 2010). Dependent observations occur in studies with repeated measures as each participant provides multiple observations, and these are usually correlated. Similarly, the residuals in level 1 will also be correlated and thus violating the assumption of independent errors. MLM lets the users handle these violations by allowing them to include random intercepts and slopes instead of treating these as fixed constants. Additionally, the user may specify a covariance model (Garson, 2013).

Another benefit with multilevel modelling is its ability to handle missing data. Missing cases is almost impossible to prevent in longitudinal studies. Typical approaches for dealing with missing data like listwise deletion or mean imputation are not optimal solutions. In multilevel models, missing cases are estimated based on available data points, thus there is no need to remove participants with incomplete data (Peugh & Enders, 2004). However, one important assumption is that data are missing at random or missing completely at random.

In all our analyses, we set up a series of growth models, starting with a simple model and then increasing the complexity while evaluating which model best fitted the observed data. All models were fitted using maximum likelihood and with an unstructured covariance structure for the random effects. The best fitting model was chosen based on the lowest Akaike information criterion (AIC) (Akaike, 1974). AIC is a goodness-of-fit measure that is corrected for the number of parameters that are estimated.

3.8 Ethics

The study was approved by the Regional Committee for Research Ethics for Health Region South-East (REC South-East). After receiving verbal and written information about the study and the procedures involved, written informed consent were obtained from all participants.

An ethical consideration regarding our study is the choice to recruit participants within five months upon their first contact with mental health services. It is likely that the patients were in a vulnerable state and experienced some levels of psychotic symptoms. Thus, it is relevant to ask whether our group of patients had the capacity or competence to consent to participate in a longitudinal study with annual measurements over ten years. Psychotic symptoms and impaired cognitive functions may influence patients' ability to fully understand the aims of a research study (Dunn, Candilis & Roberts, 2006). Yet, other studies have shown that, collectively, people with schizophrenia do not necessarily have reduced competence to consent compared to healthy controls (Dunn et al., 2006). Instead, researchers should take measures to ensure that participants with reduced decisional capacity get a more intensive educational intervention as part of the informed consent process (Carpenter et al., 2000).

We are aware that our participants may change their minds regarding their participation in our study. Thus, consistent with Norwegian ethical guidelines for health research, our participants may withdraw their consent for participation whenever they want. Before every assessment, participants are reminded of the aims of the study to ensure that they fully understand their roles as research participants and that their continued participation in the study is voluntary.

4. Summary of findings from papers 1-3

4.1 Paper 1

The relationship between level of cognitive impairments and functional outcome trajectories in first-episode schizophrenia.

In this study, we fitted a series of multilevel models to examine whether baseline cognition is associated with later social- and work outcome. The first model (model 1) showed a significant increase in both social- and role functioning over the four-year follow-up period. Cognitive functioning at baseline predicted later functional outcome. Social functioning was predicted by attention, verbal learning and verbal working memory. Role functioning was predicted by attention, verbal working memory and reasoning/ problem solving. In model 2 and 3, the patient group was divided into three approximately equally large groups based on baseline cognition T-scores to explore whether a stratification of the group would further improve the models. There were some significant differences between the subgroups. The subgroup that scored the lowest on attention and verbal working memory at baseline displayed a significantly smaller rate of change in social functioning than the other two groups. No differences were found between the medium- and high scoring groups. Nor were there any significant differences in development between the three groups in role functioning. Of all the models, model 3 had the best fit to the observed data.

The results from this study showed that a majority of FES-patients experienced improvements in social relationships and work performance over time. However, one subgroup that is characterized by poorer cognitive performance at illness onset showed limited improvements. Compared to the higher scoring groups, these patients are more socially secluded and have fewer steady friendships and intimate relationships. Their social relationships are marked by larger conflicts with peers and less involvement with family members. Interestingly, their work performances were not negatively affected, which may indicate difficulties with maintaining balance in their daily life; being able to master work, but struggling with personal relationships. Less functional improvements may also indicate that this subgroup of patients responded less effectively to rehabilitation. Thus, it may be possible to identify a subgroup of patients with personalized rehabilitation needs already within five months after first contact with mental health services.

4.2 Paper 2

Cognitive improvement in first-episode schizophrenia and healthy controls: a 6-year multi-assessment follow-up study.

Based on neurocognitive data gathered over six years, we estimated the cognitive development in FES, and compared the cognitive domain trajectories to those of healthy controls. Model 1 was performed with all participants, both patients and healthy controls, and formed the basis of comparison for subsequent models. It showed a significant linear increase in all cognitive domains. Compared to healthy controls, FES-patients scored lower on all cognitive domains at baseline except for social cognition (model 2). When considering cognitive development over time, the differences in development between the two groups were insignificant for most cognitive domains (model 3). However, the patient group showed a significantly lower increase in working memory than the control group. Meanwhile, the increase in reasoning/ problem solving was significantly larger for the patient group than the control group. For working memory and reasoning/ problem solving, model 3 had the best fit to the observed data.

The present study had some interesting findings. Firstly, the cognitive development seemed to be of comparable magnitude in the two groups. Some of the cognitive improvements may be explained by practice effects, although it seems unlikely that any cognitive deterioration in our FES-sample had been masked by practice effects. Secondly, there seemed to be different trajectories for different cognitive domains. A larger increase in reasoning/ problem solving in the patient group compared to the healthy control group suggests that patients are able to use more flexible problem-solving techniques when symptoms subside. On the other hand, the patient group showed a lower increase in working memory which indicates that the gap in performance between the two groups will only grow larger over time. This may speak in favor of a targeted rehabilitation of working memory. Thirdly, when examining our figures, the trajectory of social cognition seemed to stabilize, reaching the same level as healthy controls after one year. It remains to be determined whether this improvement in test scores will yield similar gains in real life social cognitive functioning.

4.3 Paper 3

Cognitive, work- and social outcomes in fully recovered first-episode schizophrenia patients: on and off antipsychotic medication.

In the present paper, we examined the course and outcome of fully recovered FES-patients. Table 1 shows the results from the analyses. Model 1 showed significant increases in social functioning, role functioning, and global cognition over time. Model 2 showed larger increases when patients were off medication compared to when they were on. The estimates were significant for role functioning, but not for social functioning and global cognition. However, processing speed might be more sensitive to the effects of medication, as the estimates were significant for processing speed when we analyzed the cognitive domains separately. The results showed that larger increases in processing speed were seen when patient were off medication than when they were on. Model 1 and model 2 had similar model fit to the data, so there was no clear indication for which model was better. Nevertheless, the two models showed changes that were similar in size and direction, indicating that it is possible to maintain low levels of symptoms and good functioning without long-term medication treatment.

The rate of full recovery in our sample at the 8th follow-up is 35.7%. Out of the fully recovered sample of 10 participants, six were unmedicated. Compared to the unmedicated individuals, the medicated participants experienced relapses and became fully recovered at a later point in time. Interestingly, the unmedicated participants had the largest impairments in role functioning and the highest symptom level at baseline. Both medicated and unmedicated participants reported work performance limitations, but the medicated participants also reported problems with balancing work and social activities. Negative side effects was the most common reason for medication discontinuation in our sample. Instead, most of the participants highlighted the use of other active coping strategies, such as mindful thinking and symptom awareness, when discussing the factors that contributed positively to their recovery.

Table 1. Results from paper 3.

Social functioning

	Model 1		**Model 2**	
Fixed effects	Estimate (SE)	*p*	Estimate (SE)	*p*
Intercept	6.249 (0.246)	<0.001	6.211 (0.315)	<0.001
Time	0.022 (0.003)	<0.001		
Time On			0.008 (0.005)	0.101
Time Off			0.027 (0.004)	<0.001
Random effects				
Residual	0.362 (0.062)	<0.001	0.367 (0.065)	<0.001
Intercept	0.460 (0.000)		0.842 (0.441)	0.056
Slope	0.000 (0.000)		0.000 (0.000)	
Model fit				
AIC	197.649		190.529	

Role functioning

	Model 1		**Model 2**	
Fixed effects	Estimate (SE)	*p*	Estimate (SE)	*p*
Intercept	4.032 (0.441)	<0.001	4.288 (0.462)	<0.001
Time	0.056 (0.006)	<0.001		
Time On			0.035 (0.013)	0.049
Time Off			0.060 (0.007)	<0.001
Random effects				
Residual	1.230 (0.221)	<0.001	1.273 (0.231)	<0.001
Intercept	1.865 (1.066)	0.080	1.594 (0.947)	0.092
Slope	0.002 (0.001)	0.164	0.001 (0.001)	0.301
Model fit				
AIC	288.881		289.212	

Processing speed

	Model 1		**Model 2**	
Fixed effects	Estimate (SE)	*p*	Estimate (SE)	*p*
Intercept	37.505 (2.506)	<0.001	36.914 (2.568)	<0.001
Time	0.189 (0.032)	<0.001		
Time On			0.126 (0.054)	0.022
Time Off			0.221 (0.042)	<0.001
Random effects				
Residual	41.178 (7.770)	<0.001	41.285 (7.801)	<0.001
Intercept	49.017 (29.051)	0.092	48.471 (29.806)	0.104
Slope	0.007 (0.000)		0.004 (0.000)	
Model fit				
AIC	496.200		496.457	

5. Discussion

In order to discuss our findings in a larger context, we will revisit some of the ongoing debates reviewed in the introduction section. Of course, these debates will hardly be settled just yet, as more research is needed. Yet, with a longitudinal multi-assessment design and sophisticated analytic methods, we hope to contribute to the ongoing debates with research findings from a recovery perspective.

5.1 Full recovery in FES

The rate of full recovery in our sample with a follow-up period of 6-8 years is 35.7 %. This is very close to the recovery rate of 38 % reported by Lally et al. (2017) in their meta-analytic review with a mean follow-up period of 7.2 years. However, due to large variability in methods and the definition of full recovery amongst studies, it is not possible to make direct comparisons between our findings and results from other studies. Out of the 35 studies reported by Lally et al. (2017), only 16 studies included criteria of both clinical and social dimensions, and only nine studies had a duration criterion of >2 years. When narrower criteria of recovery were applied, the imputed recovery rate was 23.3 %.

Compared to other studies of FES (Austin et al., 2013; Faber et al., 2011; Shrivastava, Shah, Johnston, Stitt & Thakar, 2010; Verma, Subramaniam, Abdin, Poon & Chong, 2012) where the age range varies with many years, our sample is relatively young with a mean age of 21 years. Younger age has been associated with higher rates of recovery (Austin et al., 2013, Shrivastava et al., 2010; Verna et al., 2012), although a non-significant age effect between recovered and non-recovered patients has also been reported (Faber et al., 2011). The age effect seems only to exist in adult onset schizophrenia though, as patients with early onset schizophrenia (EOS) are generally considered to have a particularly poor prognosis (Clemmensen, Vernal & Steinhausen, 2012). Younger age is suggested to impact recovery because it helps people maintain links with school and friends and maintain more support in achieving developmental milestones (Amminger et al., 2011; Verma et al., 2012).

Another possible explanation for our relatively high recovery rate is that 61 % of our participants have attained higher education (education beyond high school). Completed high

school has been found to be associated with recovery and has been suggested to be an indicator of the achievement of several social, educational, and vocational milestones before becoming mentally ill (Austin et al., 2013). Thus, when symptom levels subside, the patients have better foundations for regaining their previous levels of functioning.

Another possible reason for the increased recovery rate in our sample is that we managed to retain the fully recovered participants in our study, who often drop out of longitudinal studies once they are no longer in treatment (Torgalsbøen et al., 2018).

The recovery rate in FES does not seem to vary based on the length of the follow-up period. Studies that include either one or both functional criteria of recovery and have follow-up periods of two years (Faber et al., 2012; Torgalsbøen et al., 2015; Verma et al., 2012; Wunderink et al., 2009) report recovery rates that are quite similar to studies with longer follow-up periods (Albert et al., 2011; Austin et al., 2013; Robinson et al., 2004). This contrasts with earlier findings that indicate decreased rates of good outcomes when follow-up duration increases (Hegarty et al., 1994; Menezes et al., 2006). Like the more recent studies, we did not find any decline in favorable outcomes over time. Rather, the recovery rate in our sample increased over time. The recovery rate on our two-year follow-up was 16 % (Torgalsbøen et al., 2015), while we found a full recovery rate of 35.7 % by the 8th follow-up (6 – 8 years). A low relapse rate in our sample of fully recovered patients may be a possible reason for why we found an increase in recovery rate. It seemed that once patients became fully recovered in our sample, they often maintained good functioning and low symptom levels. Results from the four-year follow-up showed that 55 % of the patients sustained their status as partly or fully recovered for up to four years (Torgalsbøen et al., 2018). The apparent stable recovery rate found by Lally et al. (2017) does not necessarily imply that no more patients attain full recovery after the first two years of illness. Rather, new patients may become fully recovered while already recovered patients experience relapses. It has been reported that approximately 30-40 % of FES-patients achieved recovery at least once over the follow-up period (Austin et al., 2013; Harrow, Grossman, Jobe & Herbener, 2005). Thus, the challenge may lay in helping patients to maintain their recovery.

5.2 Long-term medication treatment in FES

A debated method for maintaining recovery and preventing relapses is the long-term use of antipsychotics. Like earlier findings (Gaebel et al., 2016; Harrow et al., 2014; Moilanen et al., 2013; Wils et al., 2017; Wunderink et al., 2013), we found a subgroup of patients that showed good functional outcomes without long-term medication treatment. Studies have reported that around 20 % (Wunderink et al., 2007; Wyatt et al., 1998) to 40 % (McGorry, Alvarez-Jimenez, Killackey, 2013) of FES-patients may recover without use of antipsychotics. However, Wunderink et al. (2007) argued that if the length of time between their two follow-ups had been longer, they would expect the percentage to decrease due to an increased probability of relapses over time. This observation is in line with the common perception that has dominated the field until recently: medication discontinuation is associated with an increased risk of relapse. Recent studies have shown that the increased relapse risk is only temporary (Wunderink et al., 2013). Supporting these findings, we found no decrease in social and role functioning following medication discontinuation. Only one participant experienced relapse, and subsequently started on medication treatment again. The others did not experience any adverse effects from discontinuing. In fact, it seemed that medication discontinuation was followed by larger positive changes in functioning compared to patients that were still on medication. However, due to the small sample size we have to be cautious when drawing conclusions since we were unable to test for group differences based on medication status.

It has been reported that antipsychotics may have reduced effects on preventing relapses over time (Wunderink et al., 2013). In line with this, we noticed that our medicated participants had relapses that occurred after the first two years of illness onset. However, once the acute symptoms had passed, the medicated patients once again showed increased levels of functioning. This contrasts with the hypothesis that antipsychotic medications produce poor long-term outcomes like medicine-induced chronicity (Whitaker, 2004). Yet, it is possible that our fully recovered sample may be less affected by the negative long-term effects of antipsychotics compared to a poor functioning group. Our findings need to be replicated by studies with larger sample sizes. As of now, available research has failed to address whether long-term antipsychotic treatment results in better or worse outcomes than treatment with no medication due to large heterogeneity in methodology among studies (Sohler et al., 2016).

We analyzed fully recovered patients' functioning level at baseline, and we found no apparent differences between individuals that were on or off medication. In fact, the individuals that later discontinued medication showed some of the largest impairments at baseline. This is interesting, as it is natural to assume that patients who show good outcomes without use of medications might be a healthier group. This is especially true for studies that compare functional outcomes in medicated and unmedicated samples, but do not divide the patient group based on recovery status. Our findings do not totally discount the assumption of a healthier group, as acute psychoses may bring an abrupt fall in functioning that is only temporary, and unmedicated patients may have inner resources that helped promote a speedier recovery. However, at least in our sample, it was not evident at the time of hospitalization or early after illness onset who had favorable characteristics and would be candidates for medication discontinuation. Since medication treatment may cause adverse effects (Artaloytia et al., 2006; Manu et al., 2015), efforts should be made to personalize treatment and detect patients that may recover with psychosocial interventions alone (McGorry et al., 2013). Current studies have failed to identify common predictors though, as no positive predictors have been found to predict successful discontinuation in more than one study. For instance, education level, sustained remission at two years, and clinician-rated good prognosis at baseline (Bowtell, Ratheesh, McGorry, Killackey & O'Donoghue, 2017)

The effects of antipsychotics on cognitive functioning remain unclear. The fully recovered patients showed improved cognition over time, but most of the cognitive domains showed no significant developmental changes as patients changed in medication status. This may indicate a limited effect of antipsychotics on cognition which is in line with the findings of other studies (Goldberg et al., 2007; Keefe, Bilder et al., 2007; Keefe, Sweeney et al., 2007). On the other hand, a significant difference in change was found for processing speed. It seems being off medications is associated with larger increases than being on medications. These results must be replicated with larger samples, but it may indicate that antipsychotics have a specific effect on processing speed. Alternatively, this effect may be indirect. For instance, antipsychotics may produce adverse effects like drowsiness and affect flattening, which in turn affects processing speed.

5.3 Full recovery in FES as a subjective process

If long-term use of medications may possibly have limited effects on relapse and recovery, what other factors may help patients achieve and maintain full recovery? Subjective accounts of what the patients themselves considered as effective strategies may eventually point us towards some possible answers.

Although medications are commonly considered the cornerstone of schizophrenia treatment by health-care professionals, the patients' view about medications are rather divided in our study. Out of the ten fully recovered patients in our sample, four have discontinued antipsychotic medications and two never started on any medication treatment. Adverse effects were the most reported reason for discontinuing antipsychotic medications. The patients experienced weight gain, slowed thinking and drowsiness from medications. However, four fully recovered patients have continuously been on antipsychotics, and report limited adverse effects.

When discussing other factors that contributed to their recovery, most patients mentioned the use of active coping strategies such as symptom awareness, regulation of activity and mindful thinking. Psychotherapy was also mentioned, but as the participants became fully recovered most of them were no longer in need of therapy on a regular basis.

The majority of the fully recovered patients still experienced work performance limitations. They reported feeling tired after work, underachieving in their current job, and having problems balancing work and social activities. Yet, these patients do consider themselves as fully recovered because they have not had any relapses in recent years. They feel in charge of their lives despite some minor impairments. They are open about their mental illnesses and accept that they have some limitations in their daily lives. Interestingly, many participants reported feeling stronger because of the mental illness. They have gained experiences that they think will be useful in life, and they report knowing themselves better. Many feel closer to their family members, and report having a supportive family as a factor in becoming fully recovered.

5.4 Long-term cognitive course in FES

Like earlier findings in favor of the neurodevelopmental model (Becker et al., 2010; Bora & Murray; 2014; Carrión et al. 2018; Keefe et al., 2006), we found no cognitive decline in the

patient group from five months after illness onset and onwards. A follow-up period of six years is relatively substantial, and we found cognitive improvements throughout the period. This is in contrast with other studies that have follow-up periods longer than five years, which mostly found stability in cognitive functioning (Barder et al., 2013b; Hoff et al., 2005; Rund et al., 2016). Studies with shorter follow-up periods that vary from one to five years, also report overall cognitive stability, but these studies differ in their results when examining specific cognitive domains. For instance, Barder et al. (2013a) reported improvements in impulsivity and working memory the first two years, while motor speed decreased. Torgalsbøen et al. (2015) found improvements in reasoning/ problem solving and social cognition and decline in verbal learning. Crespo-Facorro et al. (2009) found improved visual memory and executive functioning, and Rodríguez-Sánchez et al. (2008) reported decline in verbal learning. The seemingly disparate findings are largely due to methodological differences between studies. Yet, despite these limitations, cognition seems to remain stable over time with the possible exceptions of verbal memory and executive functioning (Bozikas & Andreou, 2011).

There are some possible explanations as to why long-term follow-up studies do not find specific developmental trajectories for different cognitive domains. Firstly, there are simply too few of such studies. Rund et al. (2016) only included a measure of global cognitive functioning, while Hoff et al. (2005) had a small sample size. Secondly, conflicting results may be due to lack of a healthy control group to take into account the influences of age, education and gender (Albus et al., 1997). Thirdly, it is possible that improvements in symptoms have a greater effect on cognitive functioning earlier in the illness (Hoff et al., 1999) and with diminishing effects over time (Hoff et al. 2005). For instance, Barder et al. (2013b) found no change in the subsequent years following the initial improvements seen in impulsivity and working memory. Interestingly, when we compared our current findings with the results from the two-year follow-up that examined the same patient sample (Torgalsbøen et al., 2015), we also found some diminishing effects on cognitive development over time.

On the two-year follow-up, the patient group showed significant improvements in reasoning/ problem solving and social cognition and decline in verbal learning compared to healthy controls (Torgalsbøen et al., 2015). At the current six-year follow-up, however, FES-patients no longer showed the same effects on social cognition and verbal learning. This indicates

that the changes seen in social cognition and verbal learning were only temporary. It seems that the patients' performance in social cognition gradually increased to the same level as healthy controls and then stabilized. However, Holmén, Juuhl-Langseth, Thormodsen, Melle and Rund (2010) also found no differences in social cognition between patients and controls with the MCCB and suggested that patients with schizophrenia may have no problems with knowing how to act in social situations, but still have problems with performing them in real life. In the MCCB, social cognition is measured as a skill in managing emotions and identifying effective ways to deal with problems. When social cognition was measured with tests of emotion perception (identify expressed emotions, discern emotional messages), social cognition was found to mediate the relationship between cognition and functional outcome (Vaskinn et al., 2008).

It is interesting that we did not find a decline in verbal learning in patients compared to healthy controls, as impairment in verbal memory has consistently been observed in schizophrenia and considered to be among the most impaired cognitive domains (Cirillo & Seidman, 2003; Kern, Hartzell, Izaguirre & Hamilton, 2010). However, impairments in verbal memory have been reported to be the greatest in the early phase of the illness (Mesholam-Gately et al., 2009), which may explain why verbal impairments were more apparent on the two-year follow-up in our patient sample. The indication that improvements in some cognitive domains in FES seem to be characterized by pronounced improvements following the acute phase and then followed by gradual stabilization (Bonner-Jackson, Grossman, Harrow & Rosen, 2010; Mesholam-Gately et al., 2009) points to the importance of having longitudinal studies that assess cognitive functioning over many years.

The cognitive improvements seen in our sample may be partly explained by practice effects. Unlike earlier studies, the patient group is matched to a healthy control group. Compared to controls, the patient group scored significantly worse on all cognitive domains except for social cognition, which supports the findings of earlier studies (Holmén et al., 2010). It has consistently been shown that patients with schizophrenia score 1-2 standard deviations below healthy controls in cognitive functioning (Fioravanti et al., 2005; Fioravanti et al., 2012). More importantly, our results showed no differences in degree of change between patients and controls in most cognitive domains. In other words, the cognitive improvements seen in the patient group

were not significantly different from the control groups' developments. Thus, we argue that no deteriorations in cognitive functioning have been masked by practice effects.

Our results showed specific cognitive trajectories for working memory and reasoning/ problem solving that differed from the developments seen in healthy controls, which supports the findings of earlier studies about specific changes in different cognitive domains. Specifically, we found that increase in working memory is smaller in patients compared to healthy controls. A smaller increase compared to the other cognitive domains may simply indicate that working memory is less affected by practice effects. Yet, working memory as a system for storing and manipulating information is crucial for thought, planning and action (Baddeley, 2003). A limited working memory capacity may underlie the low scores seen in other cognitive domains, as it has been suggested that impaired working memory may limit the performance of other cognitive operations (Silver, Feldman, Bilker & Gur, 2003).

The patient group showed a larger increase than healthy controls in reasoning/ problem solving. Reasoning/ problem solving may be categorized under executive functions, although such a categorization is not without problems as executive functions comprise of a variety of separate cognitive skills like inhibition, attention, and working memory. In fact, the long-term development of executive functions has been somewhat hard to conclude due to inconsistent definitions and measuring methods (Bozikas & Andreou, 2011). Nevertheless, a larger improvement in reasoning/ problem solving may indicate that patients were able to use more flexible problem-solving techniques as their symptoms improved.

Overall, our findings do not support a neurodegenerative model. At least in the case of FES, there seems to be no evidence of cognitive deterioration in the first six years after illness onset. Schizophrenia is a heterogenous illness, and it is possible that different groups of patients have different developmental courses. For instance, cognitive worsening has been found in a group of elderly chronically ill patients (Friedman et al., 2001; Harvey, 2001; Harvey et al., 1999). Øie, Sundet and Rund (2008) found significant deterioration in cognitive performance in EOS-patients over 13 years, although maturational processes in adolescence may have had a positive effect on cognitive functioning (Juuhl-Langseth, Holmén, Thormodsen, Øie & Rund, 2014). Alternatively, it has been suggested that early neurodevelopmental lesions render the brain vulnerable to developmental arrest before individuals transition to active psychoses (Pantelis et

al., 2005). There is simply no room for further cognitive deterioration with further brain tissue reductions (Bozikas & Andreou, 2010). Yet another possible explanation is that brain volume reductions are not expressed as cognitive impairments because patients may use other cognitive strategies than what is expected from healthy controls (Hazlett et al., 2000). As such, we cannot disregard the possibility of a neurodegenerative component in schizophrenia, although this does not seem to apply to FES.

5.5 Cognitive functioning and functional outcome

Overall, we found a significant change in both social- and role functioning for our patient group. Baseline levels of attention and verbal working memory predicted both social- and role functioning. Further, baseline verbal learning predicted social functioning and baseline reasoning/ problem solving predicted role functioning. Earlier studies could not conclude on the long-term relationship between cognition and functional outcome due to methodological differences between studies and the lack of a standard for which cognitive domains to include. A review of the available research produced a large amount of null relationships (Allott et al., 2011). Here, we wanted to examine the relationships with a consensus-based cognitive battery, consensus-based definitions of good functioning, and with repeated measurements over a longer follow-up period than earlier studies. Our results are consistent with previous findings (González-Blanch et al., 2010; Mesholam-Gately et al., 2009; Milev et al., 2005; Nuechterlein et al., 2011; Tandberg et al., 2011), confirming the association between functional outcome and cognition, in cognitive domains that are regarded as key areas of impairment (attention, verbal learning, working memory, executive functioning).

If the cognitive domains associated with functional outcome are identified, is it then necessary to divide the patient group into subgroups to examine the relationships further? We believe so. Subdividing the patient group in schizophrenia research is quite common considering the heterogeneous nature of the illness. The categorization of chronic schizophrenia, early-onset schizophrenia and first-episode schizophrenia have revealed different processes and illness progressions for different groups of patients. Regarding research on FES, the patient group has been further subdivided in the attempt to identify factors that may predict improvement or further deterioration in cognition. For instance, recognizing findings that show cognitive stabilization in

FES as a group effect that may mask substantial heterogeneity across individuals, Barder et al. (2013a) divided the patient group based on the presence of relapses. Psychotic relapses early in the illness was a potent predictor of cognitive deterioration over time, while patients with no relapses did not experience decline. Similarly, Rund et al. (2016) found that patients with stable remission in the first year had better cognitive trajectories than patients that experienced unstable remission or who remained continuously psychotic after the first year. Although cognitive functioning varies between individuals and has been consistently associated with functional outcome (Green et al., 2004; Green & Harvey; 2014), few if any have examined whether different levels of baseline cognition predicts later functional outcomes.

When we subdivided our patient group based on baseline levels of cognitive functioning, we found that individual heterogeneity had indeed been masked when we examined the patient sample as one group. We found functional improvements in subgroups with intermediate and high levels of cognition, but the subgroup that demonstrated the largest cognitive impairments at baseline showed limited improvements over four years. Specifically, low levels of baseline attention and verbal working memory were associated with poor social functioning and limited improvements over time. Compared to the other groups, this subgroup consisted of patients that had limited peer- and intimate relationships, and their relationships were marked by more conflicts. This has important clinical implications. The treatment of schizophrenia consists of a collection of various interventions like medication, psychosocial intervention, familial education, and social skill and work training. Cognitive rehabilitation is much more rarely provided. Yet, cognitive impairments may affect many facets of everyday life. A limited ability to concentrate on what other people are saying and problems with thinking flexibly may cause solitude. Similarly, poor cognitive functioning may affect how well patients respond to rehabilitation.

The hypothesis of a critical period in schizophrenia states that the early phase of psychosis is characterized by rapid deterioration, which eventually slows down and stabilizes or improves. The level of functioning by the end of the critical period sustains into the long-term (Birchwood, Todd & Jackson, 1998). Crumlish et al. (2009) have shown that further symptomatic improvements are possible between four and eight years after illness onset, and our own findings showed continued improvements in functional outcomes over time, but the question remains whether this also applies to the poorest functioning group.

5.6 Generalized vs specific cognitive impairments

Given the past and present findings on the existence of specific cognitive impairments in schizophrenia, it may seem tempting to conclude that the cognitive impairments seen in schizophrenia are specific impairments rather than generalized impairments. Yet, due to methodological heterogeneity between studies we still have to be cautious when discussing selective deficits. Although some cognitive domains seem to be more consistently impaired than others, there are also many studies that show null relationships between these cognitive domains and functional outcome (Allott et al., 2011). Differences in the reliability between tests can mimic specific cognitive deficits. That is, when tests differ in sensitivity and difficulty, the tests with the higher reliability will yield greater performance deficits for the less able participants (Chapman & Chapman, 1973; Miller, Chapman, Chapman & Collins, 1995). Further, cognitive tests are seldom, if ever, only tapping one cognitive domain, as many functions require the coordination of various cognitive domains. When tests tap into different cognitive domains, albeit some more than others, they are not diagnostic as to which specific domain is impaired (Jonides & Nee, 2005).

It is striking that patients with FES score 1-2 standard deviations below healthy controls on most cognitive domains, which can be viewed as a generalized cognitive impairment (Dickinson & Harvey, 2009; Schaefer et al., 2013). Further, the broad deficit is supported by evidence of biological abnormalities (Dickinson & Harvey, 2009). Factor analytic studies have found that a single factor accounted for the common variance in cognitive functioning among patients with chronic schizophrenia, as well as in a mixed sample of schizophrenia and bipolar patients, while cognitive performance in schizophrenia was best accounted for by multiple independent cognitive domains (Nuechterlein et al., 2004). Thus, it is important that we are precise in our definitions and use the same standard of tests to measure cognitive performances. The creation of the MCCB was an important step towards the use of a consensus-based test battery, where cognitive domains are identified through factor analytic analysis, and tests included for their sensitivity of cognitive change (Nuechterlein et al., 2004). In the same vein, efforts have been made in identifying a set of consensus-based measures for real-world functional outcomes (Leifker, Patterson, Heaton & Harvey, 2009) similar to the MATRICS initiative.

5.7 Methodological considerations

As all relevant methods for this thesis have been presented, we will discuss some methodological considerations related to the participants, choice of study design, interpretation of results, and limitations of the study design.

Study design. This study has a longitudinal multi-assessment design. Longitudinal studies are important for understanding pathways and developmental changes (Masten, 2006). Repeated year-by-year measurements are better than studies with one or two assessments that are many years apart as this is more sensitive to changes that occur in-between assessment points (Torgalsbøen et al., 2018). Moreover, since we have a small sample size, the multi-assessment design will benefit the data analyzing process, as growth curve models produce estimates that are more reliable with increasing number of assessment waves (Quené & van den Bergh, 2004).

In most of our analyses, we estimated cognitive changes with a linear slope. We are aware that not all functions change linearly over time, and while we have enough measurement points to estimate non-linear patterns of change, our sample size is too small to allow for the inclusion of a large number of parameters without affecting the statistical power of the models. By examining the plots of our outcome variables, we saw that our variables mainly had linear developments over time. Thus, the linear slope was used for estimating longitudinal change in our data.

Practice effects. A drawback with repeated measurements is the increased probability of practice effects. While some studies have shown improved or stable cognitive functioning over time in FES, others have argued that practice effects alone may account for the improvement and further, mask deterioration in some cognitive domains (Goldberg et al., 2007; Szöke et al., 2008). We have taken some pre-emptive measures to help us interpret practice effects in our results. Firstly, we have included a healthy control group. Any improvement or deterioration in FES cannot be correctly interpreted without a comparison group. Secondly, cognitive functioning is assessed with MCCB. Alternate forms were used when provided by the MCCB. The MCCB is considered the gold standard of neurocognitive evaluation in severe mental illness. This cognitive battery has shown good sensitivity to the cognitive impairments observed in schizophrenia (August, Kiwanuka, McMahon & Gold, 2012). It has shown small practice effects in validation studies (Buchanan et al., 2011; Keefe et al., 2011; Nuechterlein et al., 2008), although it may still be vulnerable (Lees et al., 2015). However, most studies that report practice effects have short

time intervals between test and retest, ranging between a few weeks to some months (Goldberg, Keefe, Goldman, Robinson & Harvey, 2010; Lees et al., 2015; Szöke et al., 2008). In our study, except for the first year where cognition was assessed every six months, cognition was measured once a year and then every other year from the seventh follow-up onwards. Nevertheless, we have to show increased awareness of practice effects as a potential source for cognitive change.

Another consideration regarding our sample is that the number of assessments differs between the patient and the control group. The patient group will be assessed neurocognitively eight times during the ten-year period, whereas the control group will be assessed four times. Given that there are practice effects when repeating cognitive tasks, it may introduce bias by overestimating a patient group's improvement in cognitive performance relative to controls. However, studies show that practice effects are largest between the initial and second assessments, with smaller increases with subsequent follow-ups (Goldberg et al., 2010), which seem also to be the case for most of the cognitive domains measured in the MCCB (Lees et al., 2015).

Psychometrics. The MCCB, PANSS, IPII, and GF: Role and GF: Social were chosen for their good psychometric properties. The MCCB consists of neurocognitive tests that were especially chosen for their good reliability and validity. High test-retest reliability, utility as a repeated measure, practicality and tolerability were considered as some of the most important features of the test battery (Nuechterlein et al., 2008). Since its creation, the MCCB has been extensively evaluated and has demonstrated impressive psychometrics, among others high test-retest reliability, data completeness, modest practice effects, as well as sensitivity to improvement from interventions (Green et al., 2014).

The psychometric properties of the PANSS are well-documented (Kay et al., 1987; Peralta & Cuesta, 1994), and it is currently the most widely used scale to assess symptoms level in patients with schizophrenia. The first construction of the PANSS divided the symptoms into three groups: positive symptoms, negative symptoms and general psychopathology. This three-factor division has later been thought of as an oversimplification, for instance Peralta and Cuesta found that the original positive subscale was composed of positive and disorganized symptoms (1994). Nowadays a five-factor model of PANSS is most commonly reported, but studies still fail to confirm the fit of the Pentagonal model with confirmatory factor analysis (Fitzgerald et al.,

2003; van der Gaag et al., 2006). In our study, we group our symptoms according to a three-factor model. As our study aims are not concerned with modelling the symptoms of schizophrenia, but rather using the symptom levels as an indication of recovery status, we find using a three-factor model when scoring unproblematic.

While the IPII is often used to assess aspects of metacognitive skills in schizophrenia (Lysaker, Damaggio, Buck, Carcione & Nicolo, 2007), we found this semi-structured interview to supply us with additional information compared to our regular interviews that are done yearly and have specific questions regarding medication, work, social relationships etc. The IPII contains a few very widely defined questions, and the interviewer is not instructed to introduce content. As a result, we get to know the patients' personal illness narratives and recovery processes without us introducing any objective measures of recovery. However, this approach has some limitations as well. First, we cannot control how detailed the individual narratives are. A seemingly scant narrative does not necessarily mean that the person has limited thoughts regarding his recovery. Secondly, when used to assess metacognitive skills, the answers are scored against four different scales of metacognition. There are no readily available scales for scoring IPII against definitions of full recovery. Since we have a small sample size though, we decided to only describe the factors that the patients reported as important on their road towards full recovery.

Both GF: role and GF: social have shown high interrater reliability and acceptable construct validity (Cornblatt et al., 2007). Based on information gathered from the interview, role and social functioning scores were rated by either the principal investigator who did the interview or the PhD-fellow. If the information from the interview was unclear, the PhD-fellow discussed the final scores with the principal investigator.

For establishing the accuracy of recovery status (remission, partly recovered and fully recovered) according to the full recovery criteria, we performed an inter-rater reliability assessment. 36 clinical protocols were rated by an independent rater, three for each patient fulfilling the criteria for either full or partial recovery at the four-year follow-up. The results showed an inter-rater reliability of 0.60 (Cohen's kappa), which indicates good inter-rater agreement.

Sample size. One major limitation of the study is the small sample size which only consists of 28 patients. Although we recruited patients from one of Norway's largest health trusts, it only delivers health services to about 490 000 individuals which is a relatively small amount of people compared to countries with larger populations. The incidence rate of first-episode schizophrenia is relatively small. Simon et al. (2017) reported an incidence rate of 86 per 100 000 per year in the US, but this rate included all patients with new onset symptoms which might later be determined to have other disorders rather than schizophrenia-spectrum disorders. Furthermore, it may have been hard for young people that were in a vulnerable state to commit to a research study that would last over ten years. We also recruited from hospitals in the capital to increase the number of participants. Taking this into consideration, we managed to recruit quite a few individuals from the catchment area. There will always be some amount of sampling bias in research, which may be especially problematic in smaller samples as some members of the population are less likely to be included than others. However, in our study, due to the small amount of people that fulfilled the inclusion criteria in the first place, we argue that all potential participants have had the same chances of being included in the sample.

Since we already have a small sample size, it seems natural to question our choice of dividing the sample into even smaller groups, as we did in paper 1 and 3. In the case of the subgroup with fully recovered FES-patients (paper 3), there are simply no other study that have yearly prospectively gathered data on this group of patients. Due to the low recovery rate in schizophrenia and an increased chance of drop out in longitudinal studies, the sample size of fully recovered patients will be low. Still, we have to be aware of the limitations. Low statistical power is inevitable, and the small sample size may limit the kind of analyses that can be performed. The results must be interpreted carefully due to the possibility of both type I and type II errors. For instance, a non-significant result may simply be a false negative due to the study being underpowered. Low statistical power may also produce significant results that have overrated effect sizes. Thus, when discussing our results, we try to be careful to not draw any firm conclusions but rather state the overall patterns of development in our sample. As this is such a unique subgroup that may contribute information to a relatively new field within schizophrenia research, we found an explorative approach to be suitable.

The existence of subgroups in schizophrenia has given rise to studies that question whether poor and good prognosis may be predicted from early illness stages. Rund et al. (2016) compared the cognitive trajectories of three subgroups of FES-patients. They found improved cognition in stable remitted patients compared to patients who experienced relapses or were in continuous psychosis. Studies on cognitive remediation have suggested that the relationship between baseline cognition and response to cognitive remediation might be nonlinear; that a predictor of good response in a low cognitively functioning group might be a predictor of poor response in a high functioning group (Green, Llerena & Kern, 2015). Such a pattern would not have been found if studies kept examining the patient sample as a whole instead of accounting for the diversity in the population. Thus, we divided the sample into three approximately equal sizes based on baseline level of cognition to examine the effects on functional outcomes (paper 1).

Generalizability of research findings. Small sample sizes decrease the generalizability of research findings. There are also other considerations about our sample that may affect generalizability that should be pointed out. An earlier article from this project reported a remission rate of 80 % and a recovery rate of 16 % amongst FES-patients on the two-year follow-up (Torgalsbøen et al., 2015), and the rates have since increased even more. Although high remission and recovery rates are not unique to our study (Lally et al., 2017), part of the good prognosis in our sample may still be attributed to the Norwegian health care system. The Norwegian health care system provides universal coverage and equal access to mental illness treatment for all regardless of socioeconomic status, ethnicity, and area of residence. Hospital treatment is provided free of charge, and outpatients services require copayments that are relatively inexpensive. The treatment can be given in specialized mental health services, municipal services that coordinate with services in the local community, and by home treatment teams that deliver acute mental health care in the community. The majority (64 %) of our participants are recruited from early intervention wards. Other studies that also focus on early-detection and recruit their patients from a similar area to ours have similarly reported a relatively high recovery rate (30 %), although the criteria for full recovery were not as strict as ours (Hegelstad et al., 2012). Recovery rates seem to be higher in North America compared to other regions, Norway included, but any service-level confounds have yet to be investigated (Lally et al., 2017). Until then, we have to be cautious when interpreting the generalizability of our findings as there is some uncertainty related to differences in the intensity and modes of treatment

provided to patients across studies. Still, the high recovery rate reported from several studies is uplifting and speaks to the potential of recovery in FES.

Another consideration related to the generalizability of our results is the multi-assessment design of our study. As time passed, the patients in our sample varied greatly in how often and what kind of treatment they received, if any. For those who have stopped receiving clinical treatments, the yearly assessments in our study was the only follow-up care they had. For some patients, this contact with an academic institution felt meaningful. It is also possible that the frequent assessments gave patients an increased sense of purpose. Although not necessarily a confounding variable, it is worth noting the ways our sample may differ from the general population of patients with first-episode schizophrenia.

5.8 Clinical implications

The main goal of the present thesis is to examine recovery in FES through investigating the longitudinal course of cognitive functioning, work- and social functioning.

Our current findings show that full recovery in schizophrenia is possible even with narrow criteria that require symptom remission, good social- and role functioning, and a duration requirement of at least 2 years (Liberman et al., 2002). There is only a subgroup of patients that meets these criteria, but it seems that the proportion of people that do is larger than what we earlier believed. If recovery is maintained, the recovery rate will increase. Maintaining recovery requires a strong tie between patients and clinicians that continues beyond the stabilization phase and into the stable phase. With continued contact with an outpatient clinic, there will be greater chances to notice any occurrence of life stressors and resurgence of symptoms that may increase the risk of relapse (Lehman et al., 2004).

Medication treatment is effective in diminishing psychotic symptoms. Yet, the long-term effectiveness of antipsychotics is debated, and the presence of side effects may be debilitating on its own. We cannot yet predict which patients are likely to discontinue medication successfully, but no patient that shows promising progress should be denied the opportunity of dose-reduction or discontinuing if they wish to do so (Wunderink, 2018). Our findings showed that not all

patients that are fully recovered need long-term maintenance treatment in order to maintain good functioning.

We found that baseline cognitive functioning is predictive of later functional outcome. Baseline attention and working memory are especially predictive of stable or improved functioning scores. It is important to detect early the subgroup that will have limited improvements in functioning, and a cognitive screening may be the solution. This subgroup of patients will have need of personalized treatment that takes into account the specific cognitive deficits the patients experience. While most patients experience some degree of cognitive impairments in FES, the poorest performing subgroup should be receiving appropriate treatment, including cognitive rehabilitation, as soon as possible as cognition shows limited change over time. The exception may be reasoning/ problem solving as we found improvement that are greater for FES-patients than healthy controls over time.

6. Revisiting the unanswered questions and concluding remarks

In this thesis, we wanted to examine some questions about recovery and outcome in FES that are yet to be answered. Even though we are unable to give definite answers due to methodological limitations, we sought to approach these questions in scientific ways that are considered novel in the field of schizophrenia research.

Our results confirm that cognitive deficits are common and a core symptom of FES. Patients seem to score lower cognitively than healthy controls, and the size of the cognitive gaps seem to remain stable over time for most cognitive domains. No further decline in cognitive functioning was found among the patients. There may even be some improvements in cognition beyond the effects of repeated assessments. A single global cognitive measure may be too limiting as different cognitive domains seem to change at different rates. Developments in reasoning/ problem solving, working memory, and social cognition may be particularly interesting areas for further research.

Cognitive impairments are associated with functional outcomes. In fact, our results indicate that there exists a subgroup of patients with poor cognitive functioning that shows limited improvements in social functioning over time. Thus, large cognitive impairments may be an early predictor of later recovery. This group of patients may have different rehabilitation needs and should get personalized treatment that takes into account their cognitive strengths and limitations.

On the other end of the recovery spectrum, a subgroup of fully recovered patients was identified. While it seems hard to predict candidates for medication discontinuation early on after illness onset, patients should not be discouraged to stop taking antipsychotics if they are showing good recovery from schizophrenia. In fact, in our subsample of only fully recovered patients, discontinuing medications is followed by larger increases in functioning and development in processing speed compared to continuous medication treatment. It seems that long-term medication treatment is not necessary for good functional outcomes. In fact, for those patients that are becoming better but are experiencing adverse effects from antipsychotics, a continued medication treatment may impede their recovery process.

Our findings support the notion that schizophrenia is a heterogeneous disease. There seems to be several possible routes towards good long-term outcomes. It is especially important to provide personalized treatment from an early phase as to enable positive developments as soon as possible, since cognitive impairments that are apparent from illness onset appear to predict later functioning. Further longitudinal research with larger samples is needed to allow for more final conclusions.

References

Akaike, H., 1974. A new look at the statistical model identification. *IEEE Trans. on Automatic Control*, *19*(6), 716-723.

Albert, N., Bertelsen, M., Thorup, A., Petersen, L., Jeppesen, P., Le Quack, P., ... Nordentoft, M. (2011). Predictors of recovery from psychosis. Analyses of clinical and social factors associated with recovery among patients with first-episode psychosis after 5 years. *Schizophrenia Research*, *125*(2-3), 257-266.

Albus, M., Hubmann, W., Mohr, F., Hecht, S. Hinterberger-Weber, P., Seitz, N. N., & Küchenhoff, H. (2006). Neurocognitive functioning in patients with first-episode schizophrenia. Results of a prospective 5-year follow-up study. *European Archives Psychiatry and Clinical Neurosciences*, *256*(7), 442-451.

Albus, M., Hubmann, W., Mohr, F., Scherer, J., Sobizack, N., Franz, U., … Wahlheim, C. (1997). Are there gender differences in neuropsychological performance in patients with first-episode schizophrenia? *Schizophrenia Research*, *28*(1), 39-50.

Allott, K., Liu, P., Proffitt, T. M., & Killackey, E. (2011). Cognition at illness onset as a predictor of later functional outcome in early psychosis: systematic review and methodological critique. *Schizophrenia Research*, *125*(2-3), 221-235.

Alvarez-Jimenez, M., O'Donoghue, B., Thompson, A., Gleeson, J. F., Bendall, S., Gonzalez-Blanch, C., … McGorry, P. D. (2016). Beyond clinical remission in first episode psychosis: thoughts on antipsychotic maintenance vs. guided discontinuation in the functional recovery era. *CNS Drugs*, *30*(5), 357-368.

American Psychiatric Association. (1994). *Diagnostic and statistical manual for mental disorders* (4th ed. revised). Washington, DC: Author.

Amminger, G. P., Henry, L. P., Harrigan, S. M., Harris, M. G., Alvarez-Jimenez, M., Herrman, H., … McGorry, P. D. (2011). Outcome in early-onset schizophrenia revisited: findings from the early psychosis prevention and intervention centre long-term follow-up study. *Schizophrenia Research*, *131*(1-3), 112-119.

Andreasen, N. C., Carpenter, W. T., Kane, J. M., Lasser, R. A., Marder, S. R., & Weinberger, D. R. (2005). Remission in schizophrenia: proposed criteria and rationale for consensus. *American Journal of Psychiatry*, *162* (3), 441-449.

Artaloytia, J. F., Arango, C., Lahti, A., Sanz, J., Pascual., A., Cubero, P., ... Palomo, T. (2006). Negative signs and symptoms secondary to antipsychotics: a double-blind, randomized trial of a single dose of placebo, haloperidol, and risperidone in healthy volunteers. *American Journal of Psychiatry*, *163*(3), 488-493.

August, S. M., Kiwanuka, J. N., McMahon, R. P., & Gold, J. M. (2012). The MATRICS consensus cognitive battery (MCCB): clinical and cognitive correlates. *Schizophrenia Research*, *134*(1), 76-82.

Austin, S. F., Mors, O., Secher, R. G., Hjorthøj, C. R., Albert, N., Bertelsen, M., … Nordentoft, M. (2013). Predictors of recovery in first episode psychosis: the OPUS cohort at 10 year follow-up. *Schizophrenia Research*, *150*(1), 163-168.

Baddeley, A. (2003). Working memory: looking back and looking forward. *Nature Reviews Neuroscience*, *4*(10), 829-839.

Barber, M. E. (2012). Recovery as the new medical model for psychiatry. *Psychiatric Services*, *63*(3), 277-279.

Barder, H. E., Sundet, K., Rund, B. R., Evensen, J., Haahr, U., Ten Velden Hegelstad, W., ... Friis, S. (2013a). Neurocognitive development in first episode psychosis 5 years follow-up: associations between illness severity and cognitive course. *Schizophrenia Research*, *149*(1-3), 63-69.

Barder, H. E., Sundet, K., Rund, B. R., Evensen, J., Haahr, U., Ten Velden Hegelstad, W., ... Friis, S. (2013b). Ten year neurocognitive trajectories in first-episode psychosis. *Frontiers in Human Neuroscience*, *7*, 643.

Becker, H. E., Nieman, D. H., Wiltink, D., Dingemans, P. M., van de Fliert, J. R., Velthorst, E., ... Linszen, D. H. (2010). Neurocognitive functioning before and after the first psychotic episode: does psychosis result in cognitive deterioration? *Psychological Medicine*, *40*(10), 1599-1606.

Bellack, A. S. (2006). Scientific and consumer models of recovery in schizophrenia: concordance, contrasts, and implications. *Schizophrenia Bulletin*, *32*(3), 432-442.

Birchwood, M., Todd, P., & Jackson, C. (1998). Early intervention in psychosis. The critical period hypothesis. *The British Journal of Psychiatry Supplement*, *172*(33), 53-59.

Bonner-Jackson, A., Grossman, L. S., Harrow, M., & Rosen, C. (2010). Neurocognition in schizophrenia: a 20-year multi-follow-up of the course of processing speed and stored knowledge. *Comprehensive Psychiatry*, *51*(5), 471-479.

Bora, E., & Murray, R. M. (2014). Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: do the cognitive deficits progress over, or after, the onset of psychosis? *Schizophrenia Bulletin*, *40*(4), 744-755.

Bowtell, M., Ratheesh, A., McGorry, P., Killackey, E., & O'Donoghue, B. (2017). Clinical and demographic predictors of continuing remission or relapse following discontinuation of antipsychotic medication after a first episode of psychosis. A systematic review. *Schizophrenia Research*. *197*, 9-18.

Bozikas, V.P., & Andreou, C. (2011). Longitudinal studies of cognition in first episode psychosis: a systematic review of the literature. *Australian & New Zealand Journal of Psychiatry*, *45*(2), 93-108.

Breier, A., Schreiber, J. L., Dyer, J., & Pickar, D. (1991). National institute of mental health longitudinal study of chronic schizophrenia. Prognosis and predictors of outcome. *Archives of General Psychiatry*, *48*(3), 239-246.

Buchanan, R. W., Keefe, R. S. E., Umbricht, D., Green, M. F., Laughren, T., & Marder, S. R. (2011). The FDA-NIMH-MATRICS guidelines for clinical trial design of cognitive-enhancing drugs: what do we know 5 years later? *Schizophrenia Bulletin*, *37*(6), 1209-1217.

Carpenter, W. T., Gold, J. M., Lahti, A. C., Queern, C. A., Conley, R. R., Bartko, J. J., … Appelbaum, P. S. (2000). Decisional Capacity for Informed Consent in Schizophrenia Research. *Archives of General Psychiatry*, *57*(6), 533-538.

Carpenter, W. T., & Strauss, J. S. (1991). The prediction of outcome in schizophrenia IV: eleven-year follow-up of the Washington IPSS cohort. *The Journal of Nervous and Mental Disease*, *179* (9), 517-525.

Carrión, R. E., Walder, D. J., Auther, A. M., McLaughlin, D., Zyla, H. O., Adelsheim, S., ... Cornblatt, B. A. (2018). From the psychosis prodrome to the first-episode of psychosis: no evidence of a cognitive decline. *Journal of Psychiatric Research*, *96*, 231-238.

Chapman, L. J., & Chapman, J. P. (1973). Problems in the measurement of cognitive deficit. *Psychological Bulletin*, *79*(6), 380-385.

Cirillo, M. A., & Seidman, L. J. (2003). Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms. *Neuropsychology Review*, *13*(2), 43-77.

Clemmensen, L., Vernal, D. L., & Steinhausen, H.-C. (2012). A systematic review of the long-term outcome of early onset schizophrenia. *BMC Psychiatry*, *12*, 150.

Cornblatt, B. A., Auther, A. M., Niendam, T., Smith, C. W., Zinberg, J., Bearden, C. E., & Cannon, T. D. (2007). Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. *Schizophrenia Bulletin*, *33*(3), 688-702.

Crespo-Facorro, B., Rodríguez-Sánchez, J. M., Pérez-Iglesias, R., Mata, I., Ayesa, R., Ramirez-Bonilla, M. L., … Vázquez-Barquero, J. L. (2009). Neurocognitive effectiveness of haloperidol, risperidone, and olanzapine in first-episode psychosis: a randomized, controlled 1-year follow-up comparison. *Journal of Clinical Psychiatry*, *70*(5), 717-729.

Crumlish, N., Whitty, P., Clarke, M., Browne, S., Kamali, M., Gervin, M., … O'Callaghan, E. (2009). Beyond the critical period: longitudinal study of 8-year outcome in first-episode non-affective psychosis. *The British Journal of Psychiatry*, *194*(1), 18-24.

Davidson, L., Schmutte, T., Dinzeo, T., & Andres-Hyman, R. (2008). Remission and recovery in schizophrenia: practitioner and patient perspectives. *Schizophrenia Bulletin*, *34*(1), 5-8.

Dickinson, D., & Harvey, P. D. (2009). Systematic hypotheses for generalized cognitive deficits in schizophrenia: a new take on an old problem. *Schizophrenia Bulletin*, *35*(2), 403-414.

Dunn, L. B., Candilis, P. J., & Roberts, L. W. (2006). Emerging Evidence on the Ethics of Schizophrenia Research. *Schizophrenia Bulletin*, *32*(1), 47-68.

Emsley, R., Chiliza, B., Asmal, L., & Harvey, B. H. (2013). The nature of relapse in schizophrenia. *BMC Psychiatry*, *13*, 50.

Emsley, R., Chiliza, B., Asmal, L., & Lehloenya, K. (2011). The concepts of remission and recovery in schizophrenia. *Current Opinion in Psychiatry*, *24*(2), 114-121.

Engelhardt, D. M., Rosen, B., Feldman, J., Engelhardt, J. A. Z., & Cohen, P. (1982). A 15-year followup of 646 schizophrenic outpatients. *Schizophrenia Bulletin*, *8*(3), 493-503.

Faber, G., Smid, H. G., Van Gool, A. R., Wunderink, L., van den Bosch, R. J., & Wiersma, D. (2012). Continued cannabis use and outcome in first-episode psychosis: data from a randomized, open-label, controlled trial. *Journal of Clinical Psychiatry*, *73*(5), 632-638.

Faber, G., Smid, H. G., Van Gool, A. R., Wunderink, L., Wiersma, D., & van den Bosch, R. J. (2011). Neurocognition and recovery in first episode psychosis. *Psychiatry Research*, *188*(1), 1-6.

Fervaha, G., Agid, O., Takeuchi, H., Foussias, G., Lee, J., & Remington, G. (2015). Clinical and functional outcomes in people with schizophrenia with a high sense of well-being. *The Journal of Nervous and Mental Disease*, *203*(3), 187-193.

Fioravanti, M., Bianchi, V., & Cinti M. E. (2012). Cognitive deficits in schizophrenia: an updated metaanalysis of the scientific evidence. *BMC Psychiatry*, *12*(64), doi: 10.1186/1471-244X-12-64.

Fioravanti, M., Carlone, O., Vitale, B., Cinti, M. E., & Clare, L. (2005). A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. *Neuropsychology Review*, *15*(2), 73-95.

Fitzgerald, P. B., de Castella, A. R., Brewer, K., Filia, K., Collins, J., Davey, P., … Kulkarni, J. (2003). A confirmatory factor analytic evaluation of the pentagonal PANSS model. *Schizophrenia Research*, *61*(1), 97-104.

Friedman, J. I., Harvey, P. D., Coleman, T., Moriarty, P. J., Bowie, C., Parrella, M., … Davis, K. L. (2001). Six-year follow-up study of cognitive and functional status across the lifespan in schizophrenia: a comparison with Alzheimer's disease and normal aging. *American Journal of Psychiatry*, *158*(9), 1441-1448.

Gaebel, W., Jänner, M., Frommann, N., Pietzcker, A., Linden, M., Müller, P., ... Tegeler, J. (2002). First vs multiple episode schizophrenia: two-year outcome of intermittent and maintenance medication strategies. *Schizophrenia Research*, *53*(1-2), 145-159.

Gaebel, W., Riesbeck, M., Wölwer, W., Klimke, A., Eickhoff, M., von Wilmsdorff, M., … Möller, H.-J. (2016). Predictors for symptom re-exacerbation after targeted stepwise drug

discontinuation in first-episode schizophrenia. Results from the first-episode study within the German research network of schizophrenia. *Schizophrenia Research*, *170*(1), 168-176.

Garson, G. D. (2013). Chapter 1. Fundamentals of hierarchical linear and multilevel modeling. In G. D. Garson (Ed.), *Hierarchical linear modeling: guide and applications* (p. 3-25). Los Angeles: SAGE Publications.

Gold, J. M., Hahn, B., Strauss, G. P., & Waltz, J. A. (2009). Turning it upside down: areas of preserved cognitive function in schizophrenia. *Neuropsychology Review*, *19*(3), 294-311.

Goldberg, T. E., Goldman, R. S., Burdick, K. E., Malhotra, A. K., Lencz, T., Patel, R. C., … Robinson, D. G. (2007). Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia. Is it practice effect? *Archives of General Psychiatry*, *64*(10), 1115-1122.

Goldberg, T. E., Keefe, R. S. E., Goldman, R. S., Robinson, D. G., & Harvey, P. D. (2010). Circumstances under which practice does not make perfect: a review of the practice effect literature in schizophrenia and its relevance to clinical treatment studies. *Neuropsychopharmacology*, *35*(5), 1053-1062.

González-Blanch, C., Perez-Iglesias, R., Pardo-García, G., Rodríguez-Sánchez, J. M., Martínez-García, O., Vázquez-Barquero, J. L., & Crespo-Facorro, B. (2010). Prognostic value of cognitive functioning for global functional recovery in first-episode schizophrenia. *Psychological Medicine*, *40*(6), 935-944.

Green, M. F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *American Journal of Psychiatry*, *153* (3), 321-330.

Green, M. F. (2016). Impact of cognitive and social cognitive impairment on functional outcomes in patients with schizophrenia. *Journal of Clinical Psychiatry*, *77*(2), 8-11.

Green, M. F., Harris, J. G., & Nuechterlein, K. H. (2014). The MATRICS consensus cognitive battery: what we know 6 years later. *American Journal of Psychiatry*, *171*(11), 1151-1154.

Green, M. F., & Harvey, P. D. (2014). Cognition in schizophrenia: past, present, and future. *Schizophrenia Research.: Cognition*, *1*(1), e1-e9.

Green, M. F., Horan, W. P., & Sugar, C. A. (2013). Has the generalized deficit become the generalized criticism? *Schizophrenia Bulletin*, *39*(2), 257-262.

Green, M. F., Kern, R. S., Braff, D. L., & Mintz, J. (2000). Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the “right stuff”? *Schizophrenia Bulletin*, *26*(1), 119-136.

Green, M. F., Kern, R. S., & Heaton, R. K. (2004). Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophrenia Research*, *72*(1), 41-51.

Green, M. F., Llerena, K., Kern, R. S., (2015). The “right stuff” revisited: what have we learned about the determinants of daily functioning in schizophrenia? *Schizophrenia Bulletin*, *41*(4), 781-785.

Gupta, S., Andreasen, N. C., Arndt, S., Flaum, M., Hubbard, W. C., Ziebell, S. (1997). The Iowa longitudinal study of recent onset psychosis: one-year follow-up of first episode patients. *Schizophrenia Research*, *23*(1), 1-13.

Hall, R. C. W. (1995). Global assessment of functioning. A modified scale. *Psychosomatics*, *36*(3), 267-275.

Hamann, J., Langer, B., Leucht, S., Busch, R., & Kissling, W. (2004). Medical decision making in antipsychotic drug choice for schizophrenia. *American Journal of Psychiatry*, *161*(7), 1301-1304.

Harding, C. M., Brooks, G. W., Ashikaga, T., Strauss, J. S., & Breier, A. (1987). The Vermont longitudinal study of persons with severe mental illness, II: long-term outcome of subjects who retrospectively met DSM-III criteria for schizophrenia. *American Journal of Psychiatry*, *144*(6), 727-735.

Harrow, M., Grossman, L. S., Jobe, T. H., & Herbener, E. S. (2005). Do patients with schizophrenia ever show periods of recovery? A 15-year multi-follow-up study. *Schizophrenia Bulletin*, *31*(3), 723-734.

Harrow, M., Jobe, & T. H. (2013). Does long-term treatment of schizophrenia with antipsychotics medications facilitate recovery? *Schizophrenia Bulletin*, *39*(5), 962-965.

Harrow, M., Jobe, T. H., & Faull, R. N. (2014). Does treatment of schizophrenia with antipsychotic medications eliminate or reduce psychosis? A 20-year multi-follow-up study. *Psychological Medicine*, *44*(14), 3007-3016.

Harvey, P. D. (2001). Cognitive impairment in elderly patients with schizophrenia: age related changes. *International Journal of Geriatric Psychiatry*, *16*(Suppl 1), S78-S85.

Harvey, P. D., Howanitz, E., Parrella, M., White, L., Davidson, M., Mohs, R. C., … Davis, K. L. (1998). Symptoms, cognitive functioning, and adaptive skills in geriatric patients with lifelong schizophrenia: a comparison across treatment sites. *American Journal of Psychiatry*, *155*(8), 1080-1086.

Harvey, P. D., & Keefe, R. S. E. (2001). Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *American Journal of Psychiatry*, *158*(2), 176-184.

Harvey, P. D., Lombardi, J., Leibman, M., White, L., Parrella, M., Powchik, P., … Davidson, M. (1996). Performance of chronic schizophrenic patients on cognitive neuropsychological measures sensitive to dementia. *International Journal of Geriatric Psychiatry*, *11*(7), 621-627.

Harvey, P. D., Silverman, J. M., Mohs, R. C., Parrella, M., White, L., Powchik, P., … Davis, K. L. (1999). Cognitive decline in late-life schizophrenia: a longitudinal study of geriatric chronically hospitalized patients. *Biological Psychiatry*, *45*(1), 32-40.

Hasson-Ohayon, I., Roe, D., Kravetz, S., Levy-Frank, I., & Meir, T. (2011). The relationship between consumer insight and provider-consumer agreement regarding consumer's quality of life. *Community Mental Health Journal*, *47*(5), 607-612.

Hazlett, E. A., Buchsbaum, M. S., Jeu, L. A., Nenadic, I., Fleischman, M. B., Shihabuddin, L., … Harvey, P. D. (2000). Hypofrontality in unmedicated schizophrenia patients studied with PET during performance of a serial verbal learning task. *Schizophrenia Research*, *43*(1), 33-46.

Heaton, R. K., Gladsjo, J. A., Palmer, B. W., Kuck, J., Marcotte, T. D., & Jeste, D. V. (2001). Stability and course of neuropsychological deficits in schizophrenia. *Archives of General Psychiatry*, *58*(1), 24-32.

Hegarty, J. D., Baldessarini, R. J., Tohen, M., Waternaux, C., & Oepen, G. (1994). One hundred years of schizophrenia: a meta-analysis of the outcome literature. *American Journal of Psychiatry*, *151*(10), 1409-1416.

Hegelstad, W. T., Larsen, T. K., Auestad, B., Evensen, J., Haahr, U., Joa, I., … McGlashan, T. (2012). Long-term follow-up of the TIPS early detection in psychosis study: effects on 10-year outcome. *American Journal of Psychiatry*, *169*(4), 374-380.

Ho, B-C., Andreasen, N. C., Flaum, M., Nopoulos, P., & Miller, D. (2000). Untreated initial psychosis: its relation to quality of life and symptom remission in first-episode schizophrenia. *American Journal of Psychiatry*, *157*(5), 808-815.

Hoenig, J. (1983). The concept of schizophrenia. Kraepelin-Bleuler-Schneider. *British Journal of Psychiatry*, *142*, 547-556.

Hoff, A. L., Sakuma, M., Wieneke, M., Horon, R., Kushner, & M., Delisi, L.E. (1999). Longitudinal neuropsychological follow-up study of patients with first-episode schizophrenia. *American Journal of Psychiatry*, *156*(9), 1336-1341.

Hoff, A. L., Svetina, C., Shields, G., Stewart, J., & Delisi, L. E. (2005). Ten year longitudinal study of neuropsychological functioning subsequent to a first episode of schizophrenia. *Schizophrenia Research*, *78*(1), 27-34.

Holmén, A., Juuhl-Langseth, M., Thormodsen, R., Melle, I., & Rund, B. R. (2010). Neuropsychological profile in early-onset schizophrenia-spectrum disorders: measured with MATRICS battery. *Schizophrenia Bulletin*, *36*(4), 852-859.

Horan, W. P., Foti, D., Hajcak, G., Wynn, J. K., & Green, M. F. (2012). Intact motivated attention in schizophrenia: evidence from event-related potentials. *Schizophrenia Research*, *135*(1-3), 95-99.

Hulsfoff Pol, H. E., & Kahn, R. S. (2008). What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophrenia Bulletin*, *34*(2), 354-366.

Jääskeläinen, E., Juola, P., Hirvonen, N., McGrath, J. J., Saha, S., Isohanni, M., … Miettunen, J. (2013). A systematic review and meta-analysis of recovery in schizophrenia. *Schizophrenia Bulletin*, *39*(6), 1296-1306.

Jahshan, C., Heaton, R. K., Golshan, S., & Cadenhead, K. S. (2010). Course of neurocognitive deficits in the prodrome and first episode of schizophrenia. *Neuropsychology*, *24*(1), 109-120.

Jenkins, J. H., & Carpenter-Song, E. (2005). The new paradigm of recovery from schizophrenia: cultural conundrums of improvement without cure. *Culture, Medicine, and Psychiatry*, *29*(4), 379-413.

Jeste, S. D., Patterson, T. L., Palmer, B. W., Dolder, C. R., Goldman, S., & Jeste, D. V. (2003). Cognitive predictors of medication adherence among middle-aged and older outpatients with schizophrenia. *Schizophrenia Research*, *63*(1-2), 49-58.

Jonides, J., & Nee, D. E. (2005). Assessing dysfunction using refined cognitive methods. *Schizophrenia Bulletin*, *31*(4), 823-829.

Juuhl-Langseth, M., Holmén, A., Thormodsen, R., Øie, M., Rund, B. R. (2014). Relative stability of neurocognitive deficits in early onset schizophrenia spectrum patients. *Schizophrenia Research*, *156*(2-3), 241-247.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANNS) for schizophrenia. *Schizophrenia Bulletin*, *13*(2), 261-276.

Keefe, R. S. E., Fox, K. H., Harvey, P. D., Cucchiaro, J., Siu, C., & Loebel, A. (2011). Characteristics of the MATRICS consensus cognitive battery in a 29-site antipsychotic schizophrenia clinical trial. *Schizophrenia Research*, *125*(2-3), 161-168.

Keefe, R. S. E., Bilder, R. M., Davis, S. M., Harvey, P. D., Palmer, B. W., Gold, J. M., ... Lieberman, J. A. (2007). Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. *Archives of General Psychiatry*, *64*(6), 633-647.

Keefe, R. S. E., Perkins, D. O., Gu, H., Zipursky, R. B., Christensen, B. K., & Lieberman, J. A. (2006). A longitudinal study of neurocognitive function in individuals at-risk for psychosis. *Schizophrenia Research*, *88*(1-3), 26-35.

Keefe, R. S. E., Sweeney, J. A., Gu, H., Hamer, R. M., Perkins, D. O., McEvoy, J. P., & Lieberman, J. A. (2007). Effects of olanzapine, quetiapine, and risperiode on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. *American Journal of Psychiatry*, *164*(7), 1061-1071.

Kern, R. S., Hartzell, A. M., Izaguirre, B., & Hamilton, A. H. (2010). Declarative and nondeclarative memory in schizophrenia: what is impaired? What is spared? *Journal of Clinical and Experimental Neuropsychology*, *32*(9), 1017-1027.

Keshavan, M. S., & Schooler, N. R. (1992). First-episode studies in schizophrenia: criteria and characterization. *Schizophrenia Bulletin*, *18*(3), 491-513.

Kravetz, S., Faust, M., & Dasberg, I. (2002). A comparison of care consumer and care provider perspectives on the quality of life of persons with persistent and severe psychiatric disabilities. *Psychiatric Rehabilitation Journal*, *25*(4), 388-397.

Lally, J., Ajnakina, O., Stubbs, B., Cullinane, M., Murphy, K. C., Gaughran, F., & Murray, R. M. (2017). Remission and recovery from first-episode psychoses in adults: systematic review and meta-analysis of long-term outcome studies. *The British Journal of Psychiatry*, *211*(6), 350-358.

Lally, J., & MacCabe, J. H. (2015). Antipsychotic medication in schizophrenia: a review. *British Medical Bulletin*, *114*(1). 169-179.

Lee, J., Kern, R. S., Harvey, P.-O., Horan, W. P., Kee, K. S., Ochsner, K., … Green, M. F. (2013). An intact social cognitive process in schizophrenia: situational context effects on perception of facial affect. *Schizophrenia Bulletin*, *39*(3), 640-647.

Lees, J., Applegate, E., Emsley, R., Lewis, S., Michalopoulou, P., Collier, T., … Drake, R. J. (2015). Calibration and cross-validation of MCCB and CogState in schizophrenia. *Psychopharmacology*, *232*(21-22), 3873-3882.

Lehman, A. F., Lieberman, J. A., Dixon, L. B., McGlashan, T. H., Miller, A. L., Perkins, D. O., & Kreyenbuhl, J. (2004). Practice guidelines for the treatment of patients with schizophrenia, second edition. *American Journal of Psychiatry*, *161*, 1-56.

Leifker, F. R., Patterson, T. L., Heaton, R. K., & Harvey, P. D. (2011). Validating measures of real-world outcome: the results of the VALERO expert survey and RAND panel. *Schizophrenia Bulletin*, *37*(2), 334-343.

Leonhardt, B. L., Huling, K., Hamm, J. A., Roe, D., Hasson-Ohayon, I., McLeod, H. J., & Lysaker, P. H. (2017). Recovery and serious mental illness: a review of current clinical and research paradigms and future directions. *Expert Review of Neurotherapeutics*, *17*(11), 1117-1130.

Leucht, S., Arbter, D., Engel, R. R., Kissling, W., & Davis, J. M. (2009). How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry*, *14*(4), 429-447.

Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Örey, D., Richter, F., … Davis, J. M. (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *The Lancet*, *382*(9896), 951-962.

Leucht, S., & Lasser, R. (2006). The concepts of remission and recovery in schizophrenia. *Pharmacopsychiatry*, *39*(5), 161-170.

Leucht, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Salanti, G., & Davies, J. M. (2012). Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *The Lancet*, *379*(9831), 2063-2071.

Lezak, M. D., Howieson, D. B., Loring, D. W., Hannay, H. J., & Fischer, J. S. (2004). *Neuropsychological assessment* (Fourth ed.). New York: Oxford University Press.

Liberman, R.P., & Kopelowicz, A. (2002). Recovery from schizophrenia: a challenge for the 21st century. *International Review of Psychiatry*, *14*, 245-255.

Liberman, R. P., & Kopelowicz, A. (2005). Recovery from schizophrenia: a concept in search of research. *Psychiatric Services*, *56*(6), 735-742.

Liberman, R. P., Kopelowicz, A., Ventura, J., & Gutkind, D. (2002). Operational criteria and factors related to recovery in schizophrenia. *International Review of Psychiatry*, *14*, 256-272.

Lysaker, P. H., Clements, C. A., Plascak-Hallberg, C. D., Knipscheer, S. J., & Wright, D. E. (2002). Insight and personal narratives of illness in schizophrenia. *Psychiatry*, *65*(3), 197-206.

Lysaker, P. H., Damaggio, G., Buck, K. D., Carcione, A., & Nicolo, G. (2007). Metacognition within narratives of schizophrenia. Associations with multiple domains of neurocognition. *Schizophrenia research*, *93*(1-3), 278-287.

Lysaker, P. H., Ringer, J., Maxwell, C., McGuire A., & Lecomte, T. (2010). Personal narratives and recovery from schizophrenia. *Schizophrenia Research*, *121*(1-3), 271-276.

Malla, A. K., Norman, R. M. G., Manchanda, R., Ahmed, M. R., Scholton, D., Harricharan, R., … Takhar, J. (2002). One year outcome in first episode psychosis: influence of DUP and other predictors. *Schizophrenia Research*, *54*(3), 231-242.

Malla, A., & Payne, J. (2005). First-episode psychosis: psychopathology, quality of life, and functional outcome. *Schizophrenia Bulletin*, *31*(3), 650-671.

Manu, P., Dima, L., Shulman, M., Vancampfort, D., De Hert, M., & Correll C. U. (2015). Weight gain and obesity in schizophrenia: epidemiology, pathobiology, and management. *Acta Psychiatrica Scandinavica*, *132*(2), 97-108.

Mason, P., Harrison, G., Glazebrook C., Medley, I., Dalkin, T., & Croudace, T. (1995). Characteristics of outcome in schizophrenia at 13 years. *British Journal of Psychiatry, 167*(5), 596-603.

Masten, A. S. (2006). Developmental psychopathology: pathways to the future. *International Journal of Behavioral Development*, *30*(1), 47-54.

McGlashan, T. H. (1984). The Chestnut Lodge follow-up study. II Long-term outcome of schizophrenia and the affective disorders. *Archives of General Psychiatry*, *41*(6), 586-601.

McGorry, P., Alvarez-Jimenez, M., & Killackey, E. (2013). Antipsychotic medication during the critical period following remission from first-episode psychosis. Less is more. *JAMA Psychiatry*, *70*(9), 898-900.

McGurk, S. R., Twamley, E. W., Sitzer, D. I., McHugo, G. J., & Mueser, K. T. (2007). A meta-analysis of cognitive remediation in schizophrenia. *American Journal of Psychiatry*, *164*(12), 1791-1802.

Menezes, N. M., Arenovich, T., & Zipursky, R. B. (2006). A systematic review of longitudinal outcome studies of first-episode psychosis. *Psychological Medicine*, *36*(10), 1349-1362.

Mesholam-Gately, R. J., Guiliano, A. J., Goff, K. P., Faraone, S. V., & Seidman, L. J. (2009). Neurocognition in first-episode schizophrenia: a meta-analytic review. *Neuropsychology*, *23*(3), 315-336.

Milev, P., Ho, B. C., Arndt, S., & Andreasen, N. C. (2005). Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *American Journal of Psychiatry*, *162*(3), 495-506.

Miller, M. B., Chapman, J. P., Chapman, L. J., & Collins, J. (1995). Task difficulty and cognitive deficits in schizophrenia. *Journal of Abnormal Psychology*, *104*(2), 251-258.

Mohn, C., Sundet, K., & Rund, B. R. (2012). The Norwegian standardization of the MATRICS (measurement and treatment research to improve cognition in schizophrenia) consensus cognitive battery. *Journal of Clinical and Experimental Neuropsychology*, *34*(6), 667-677.

Moilanen, J., Haapea, M., Miettunen, J., Jääskeläinen, E., Veijola, J., Isohanni, M., & Koponen, H. (2013). Characteristics of subjects with schizophrenia spectrum disorder with and without antipsychotic medication – a 10-year follow-up of the northern Finland 1966 birth cohort study. *European Psychiatry*, *28*(1), 53-58.

Morrison, A. P., Hutton, P., Shiers, D., & Turkington, D. (2012). Antipsychotics: is it time to introduce patient choice? *The British Journal of Psychiatry*, *201*, 83-84.

Mueser, K. T., & McGurk, S. R. (2004). Schizophrenia. *The Lancet*, *363*, 2063-2072.

Novick, D., Haro, J. M., Suarez, D., Perez, V., Dittmann, R. W., & Haddad, P. M. (2009). Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. *Psychiatry Research*, *176*(2-3), 109-113.

Nuechterlein, K. H., Barch, D. M., Gold, J. M., Goldberg, T. E., Green, M. F., & Heaton, R.K., 2004. Identification of separable cognitive factors in schizophrenia. *Schizophrenia Research*, *72*(1), 29-39.

Nuechterlein, K. H., Green, M. F., Kern, R. S., Baade, L. E., Barch, D. M., Cohen, J. D., … Marder, S. R. (2008). The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. *American Journal of Psychiatry*, *165*(2), 203-213.

Nuectherlein, K. H., Subotnik, K. L., Green, M. F., Ventura, J., Asarnow, R. F., Gitlin, M. J., … Mintz, J. (2011). Neurocognitive predictors of work outcome in recent-onset schizophrenia. *Schizophrenia Bulletin*, *37*(2), S33-S40.

Palmer, B. W., Heaton, R. K., Paulsen, J. S., Kuck, J., Braff, D., Harris, M. J., … Jeste, D. V. (1997). Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology*, *11*(3), 437-446.

Pantelis, C., Yücel, M., Wood, S. J., Velakoulis, D., Sun, D., Berger, G., … McGorry, P. D. (2005). Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophrenia Bulletin*, *31*(3), 672-696.

Peralta, V., & Cuesta, M. J. (1994). Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. *Psychiatry Research*, *53*(1), 31-40.

Peugh, J. L. (2010). A practical guide to multilevel modeling. *Journal of School Psychology*, *48*(1), 85-112.

Peugh, J. L., & Enders, C. K. (2004). Missing data in educational research: a review of reporting practices and suggestions for improvement. *Review of Educational Research*, *74*(4), 525-556.

Quené, H., & van den Bergh, H. (2004). On multi-level modeling of data from repeated measures designs: a tutorial. *Speech Communication*, *43*(1), 103-121.

Resnick, S. G., Rosenheck, R. A., & Lehman, A. F. (2004). An exploratory analysis of correlates of recovery. *Psychiatric Services*, *55*(5), 540-547.

Robinson, D., Woerner, M. G., Alvir, J. M. J., Bilder, R., Goldman, R., Geisler, S., ... Lieberman, J. A. (1999). Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Archives of General Psychiatry*, *56*(3), 241-247.

Robinson, D., Woerner, M. G., McMeniman, M., Mendelowitz, A., & Bilder, R. M. (2004). Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. *American Journal of Psychiatry*, *161*(3), 473-479.

Rodríguez-Sánchez, J. M., Pérez-Iglesias, R., González-Blanch, C., Pelayo-Terán, J. M., Mata, I., Martínez, O., … Crespo-Facorro, B. (2008). 1-year follow-up study of cognitive function in first-episode non-affective psychosis. *Schizophrenia Research*, *104*(1-3), 165-174.

Roe, D., & Davidson, L. (2005). Self and narrative in schizophrenia: time to author a new story. *Medical Humanities*, *31*(2), 89-94.

Roe, D., Lereya, J., & Fennig, S. (2001). Comparing patients' and staff members' attitudes: does patients' competence to disagree mean they are not competent? *The Journal of Nervous and Mental Disease*, *189*(5), 307-310.

Roe, D., Mashiach-Eizenberg, M., & Lysaker, P. H. (2011). The relation between objective and subjective domains of recovery among persons with schizophrenia-related disorders. *Schizophrenia Research*, *131*(1-3), 133-138.

Rapoport, J. L., Giedd, J. N., & Gogtay, N. (2012). Neurodevelopmental model of schizophrenia: update 2012. *Molecular Psychiatry*, *17*(12), 1228-1238.

Rund, B. R. (2009). Is schizophrenia a neurodegenerative disorder? *Nordic Journal of Psychiatry*, *63*(3), 196-201.

Rund, B. R. (2018). The research evidence for schizophrenia as a neurodevelopmental disorder. *Scandinavian Journal of Psychology*, *59*(1), 49-58.

Rund, B. R., Barder, H. E., Evensen, J., Haahr, U., ten Velden Hegelstad, W., Joa, I., ... Friis, S. (2016). Neurocognition and duration of psychosis: a 10-year follow-up of first-episode patients. *Schizophrenia Bulletin*, *42*(1), 87-95.

Rund, B. R., Sundet, K., Asbjørnsen, A., Egeland, J., Landrø, N. I., Lund, A., ... Hugdahl, K. (2006). Neuropsychological test profiles in schizophrenia and non-psychotic depression. *Acta Psychiatrica Scandinavica*, *113*(4), 350-359.

Saavedra, J., Cubero, M., & Crawford, P. (2009). Incomprehensibility in the narratives of individuals with a diagnosis of schizophrenia. *Qualitative Health Research*, *19*(11), 1548-1558.

Schaefer, J., Giangrande, E., Weinberger, D. R., & Dickinson, D. (2013). The global cognitive impairment in schizophrenia: consistent over decades and around the world. *Schizophrenia Research*, *150*(1), 42-50.

Schmidt, S. J., Mueller, D. R., & Roder, V. (2011). Social cognition as a mediator variable between neurocognition and functional outcome in schizophrenia: empirical review and new results by structural equation modeling. *Schizophrenia Bulletin*, *37*(suppl.2), S41-S54.

Seidman, L. J., Kremen, W. S., Koren, D., Faraone, S. V., Goldstein, J. M., & Tsuang, M. T. (2002). A comparative profile analysis of neuropsychological functioning in patients with schizophrenia and bipolar psychoses. *Schizophrenia Research*, *53*(1-2), 31-44.

Shapiro, R., & Shader, R. (1979). Selective review of results of previous follow-up studies of schizophrenia and other psychoses. In *Schizophrenia: An international follow-up study*. World Health Organization. New York: John Wiley & Sons.

Shenton, M. E., Dickey, C. C., Frumin, M., & McCarley, R. W. (2001). A review of MRI findings in schizophrenia. *Schizophrenia Research*, *49*(1-2), 1-52.

Shrivastava, A., Shah, N., Johnston, M., Stitt, L., & Thakar, M. (2010). Predictors of long-term outcome of first-episode schizophrenia: a ten-year follow-up study. *Indian Journal of Psychiatry*, *52*(4), 320-326.

Silver, H., Feldman, P., Bilker, W., & Gur, R. C. (2003). Working memory deficit as a core neuropsychological dysfunction in schizophrenia. *American Journal of Psychiatry*, *160*(10), 1809-1816.

Silverstein, S. M., & Bellack, A. S. (2008). A scientific agenda for the concept of recovery as it applies to schizophrenia. *Clinical Psychology Review*, *28*(7), 1108-1124.

Simon, G. E., Coleman, K. J., Yarborough, B. J., Operskalski, B., Stewart, C., Hunkeler, E., ... Beck, A. Incidence and presentation of first-episode psychosis in a population-based sample. *Psychiatric Services*, *68*(5), 456-461.

Sohler, N., Adams, B. G., Barnes, D. M., Cohen, G. H., Prins, S. J., & Schwartz, S. (2016). Weighing the evidence for harm from long-term treatment with antipsychotic medications, a systematic review. *American Journal of Orthopsychiatry*, *86*(5), 477-485.

Sterling, J., White, C., Lewis, S., Hopkins, R., Tantam, D., Huddy, A., & Montague, L. (2003). Neurocognitive function and outcome in first-episode schizophrenia: a 10-year follow-up of an epidemiological cohort. *Schizophrenia Research*, *65*(2-3), 75-86.

Strauss, J. S., & Carpenter, W. T. (1972). The prediction of outcome in schizophrenia. I. Characteristics of outcome. *Archives of General Psychiatry*, *27*(6), 739-746.

Swartz, M. S., Perkins, D. O., Stroup, T. S., Davis, S. M., Capuano, G., Rosenheck, R. A., … Keefe, R. S. E. (2007). Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study. *American Journal of Psychiatry*, *164*(3), 428-436.

Szöke, A., Trandafir, A., Dupont, M.-E., Méary, A., Schürhoff, F., & Leboyer, M. (2008). Longitudinal studies of cognition in schizophrenia: meta-analysis. *British Journal of Psychiatry*, *192*(4), 248-257.

Tandberg, M., Ueland, T., Sundet, K., Haahr, U., Joa, I., Johannessen, J. O., ... McGlashan, T. (2011). Neurocognition and occupational functioning in patients with first-episode psychosis: a 2-year follow-up study. *Psychiatry Research*, *188*(3), 334-342.

Tandon, R., Gaebel, W., Barch, D. M., Bustillo, J., Gur, R.E., Heckers, S., … Carpenter, W. (2013). Definition and description of schizophrenia in the DSM-5. *Schizophrenia Research*, *150*(1), 3-10.

Torgalsbøen, A.-K. (2005). What is recovery in schizophrenia? In: Davidson L., Harding, C., Spaniol, L. (Ed.), *Recovery from severe mental illnesses: Research evidence and implication for practice. 1.* Boston: Boston University.

Torgalsbøen, A.-K. (2012). Sustaining full recovery in schizophrenia after 15 years: does resilience matter? *Clinical Schizophrenia & Related Psychoses*, *5*(4), 193-200.

Torgalsbøen, A.-K., Fu, S., & Czajkowski, N. (2018). Resilience trajectories to full recovery in first-episode schizophrenia. *European Psychiatry*, *52*, 54-60.

Torgalsbøen, A.-K., Mohn, C., Czajkowski, N., & Rund, B. R. (2015). Relationship between neurocognition and functional recovery in first-episode schizophrenia: results from the second year of the Oslo multi-follow-up study. *Psychiatry Research*, *227*(2-3), 185-191.

Torgalsbøen, A.-K., Mohn, C., & Rund, B. R. (2014). Neurocognitive predictors of remission of symptoms and social and role functioning in the early course of first-episode schizophrenia. *Psychiatry Research*, *216*(1), 1-5.

Torgalsbøen, A.-K., & Rund, B. R. (2010). Maintenance of recovery from schizophrenia at 20-year follow-up: what happend? *Psychiatry Interpersonal & Biological Processes*, *73*(1), 70-83.

Tsuang, M. T., Woolson, R. F., & Fleming, J. A. (1979). Long-tern outcome of major psychoses. I Schizophrenia and affective disorders compared with psychiatrically symptom-free surgical conditions. *Archives of General Psychiatry*, *36*(12), 1295-1301.

Ücok, A., Polat, A., Cakir, S., & Genc, A. (2006). One year outcome in first episode schizophrenia. Predictors of relapse. *European Archives of Psychiatry and Clinical Neuroscience*, *256*(1), 37-43.

van der Gaag, M., Cuijpers, A., Hoffman, T., Remijsen, M., Hijman, R., de Haan, L., … Wiersma, D. (2006). The five-factor model of the positive and negative syndrome scale I: confirmatory factor analysis fails to confirm 25 published five-factor solutions. *Schizophrenia Research*, *85*(1-3), 273-279.

Vaskinn, A., Sundet, K., Friis, S., Simonsen, C., Birkenaes, A. B., Jónsdóttir, H., … Andreassen, O. A. (2008). Emotion perception and learning potential: mediators between neurocognition and social problem-solving in schizophrenia? *Journal of the International Neuropsychological Society*, *14*(2), 279-288.

Velligan, D. I., Mahurin, R. K., Diamond, P. L., Hazleton, B. C., Eckert, S. L., & Miller, A. L. (1997). The functional significance of symptomatology and cognitive function in schizophrenia. *Schizophrenia Research*, *25*(1), 21-31.

Ventura, J., Hellemann, G. S., Thames, A. D., Koellner, V., & Nuechterlein, K. H. (2009). Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. *Schizophrenia Research*, *113*(2-3), 189-199.

Verma, S., Subramaniam, M., Abdin, E., Poon, L. Y., & Chong, S. A. (2012). Symptomatic and functional remission in patients with first-episode psychosis. *Acta Psychiatrica Scandinavica*, *126*(4), 282-289.

Whitaker, R. (2004). The case against antipsychotic drugs: a 50-year record of doing more harm than good. *Medical Hypotheses*, *62*(1), 5-13.

Wils, R. S., Gotfredsen, D. R., Hjorthøj, C., Austin, S. F., Albert, N., Secher, R. G., … Nordentoft, M. (2017). Antipsychotic medication and remission of psychotic symptoms 10 years after first-episode psychosis. *Schizophrenia Research*, *182*, 42-48.

Woodward, N. D., Purdon, S. E., Meltzer, H. Y., & Zald, D. H. (2005). A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. *International Journal of Neuropsychopharmacology*, *8*(3), 457-472.

Wunderink, L. (2018). Who needs antipsychotic maintenance treatment and who does not? Our need to profile and personalize the treatment of first episode psychosis. *Schizophrenia Research*, *197*, 65-66.

Wunderink, L., Nieboer, R. M., Wiersma, D., Sytema, S., & Nienhuis, F. J. (2013). Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/

discontinuation or maintenance treatment strategy. Long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry*, *70*(9), 913-920.

Wunderink, L., Nienhuis, F. J., Sytema, S., Slooff, C. J., Knegtering, R., & Wiersma, D. (2007). Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *Journal of Clinical Psychiatry*, *68*(5), 654-661.

Wunderink, L., Sytema, S., Nienhuis, F. J., & Wiersma, D. (2009). Clinical recovery in first-episode psychosis. *Schizophrenia Bulletin*, *35*(2), 362-369.

Wyatt, R. J., Damiani, L. M., & Henter, I. D. (1998). First-episode schizophrenia. Early intervention and medication discontinuation in the context of course and treatment. *British Journal of Psychiatry. Supplement*, *172*(33), 77-83.

Wykes, T., Huddy, V., Cellard, C., McGurk, S. R., & Czobor, P. (2011). A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *American Journal of Psychiatry*, *168*(5), 472-485.

Yanos, P. T., Roe, D., Markus, K., & Lysaker, P. H. (2008). Pathways between internalized stigma and outcomes related to recovery in schizophrenia spectrum disorders. *Psychiatric Services*, *59*(12), 1437-1442.

Zipursky, R. B., Menezes, N. M., & Streiner, D. L. (2014). Risk of symptom recurrence with medication discontinuation in first-episode psychosis: a systematic review. *Schizophrenia Research*, *152*(2-3), 408-414.

Øie, M., Sundet, K., & Rund, B. R. (2008). Neurocognitive decline in early-onset schizophrenia compared with ADHD and normal controls: evidence from a 13-year follow-up study. *Schizophrenia Bulletin*, *36*(3), 557-565.

I

Schizophrenia Research 190 (2017) 144–149

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The relationship between level of cognitive impairments and functional outcome trajectories in first-episode schizophrenia

Susie Fu [a,b], Nikolai Czajkowski [a,c], Bjørn Rishovd Rund [a,b,*], Anne-Kari Torgalsbøen [a]

[a] Department of Psychology, University of Oslo, PO Box 1094, 0373 Oslo, Norway
[b] Vestre Viken Hospital Trust, PO Box 800, 3004 Drammen, Norway
[c] Division of Mental Health, Norwegian Institute of Public Health, PO Box 4404, 0403 Oslo, Norway

ARTICLE INFO

Article history:
Received 18 August 2016
Received in revised form 21 February 2017
Accepted 2 March 2017
Available online 14 March 2017

Keywords:
Psychosis
Longitudinal
Cognition
Functional outcome
Recovery

ABSTRACT

Although cognitive impairments are consistently linked to functional outcome in chronic schizophrenia, the relationship remains unclear for patients with first-episode schizophrenia. The objective of this present study was to determine whether there are distinct developmental trajectories for functional outcome in patients with different levels of baseline cognition. The present study has a multi-follow-up design, and includes data from six follow-ups over four years. Assessments were conducted yearly, apart from the first year where assessments were conducted every six months. A total of 28 patients with first-episode schizophrenia participated in the study, with 79% of patients retained at the 4-year follow-up. Cognition was assessed with MATRICS Consensus Cognitive Battery. Functional outcomes were obtained through Global functioning: Social and Global functioning: Role. Data were analyzed with linear multilevel models. Results suggest steady improvements in social and role functioning among the patients across the four year period. Baseline attention, verbal learning, and verbal working memory were significantly associated with social outcome. Role functioning was significantly associated with attention, verbal working memory, and reasoning/problem solving. Furthermore, the rate of change in social outcome varies among patients depending on their baseline level of attention and verbal working memory, with the lowest scoring group showing the least improvement over the years. The subgroup of patients with the largest cognitive impairments at the onset of the disorder shows limited improvements in social functioning compared to higher functioning groups.

1. Introduction

Impaired cognition is considered a fundamental deficit in patients with schizophrenia (Kahn and Keefe, 2013). A number of studies have found cognition to be one of the most robust predictors of functional outcome (Green and Harvey, 2014). There is a growing interest in examining the relationship between cognition and functional outcome, as cognitive rehabilitation is recognized as a possible target in the treatment of the disorder. With the emerging knowledge of the existence of subgroups of schizophrenia patients, recent reports emphasize the importance of personalized schizophrenia treatment. An important goal is to understand the unique characteristics of a patient and how this affects individual risk of illness onset and treatment response (Insel, 2010; Ozomaro et al., 2013), thereby providing interventions that increase the chances of recovery.

In recent years, a large number of studies have examined the relationship between cognition and functional outcomes. For instance, better global cognition at stabilization is associated with full recovery, indicating symptom remission and adequate social and vocational functioning (Robinson et al., 2004). In a review of cross-sectional studies, Green et al. (2000) identified attention, along with executive functions and verbal memory, as promising neurocognitive domains that are consistently associated with functional outcome. When considering longitudinal studies, Green et al. (2004) concluded that there is convincing evidence for an association between cognition and functional outcome in chronic schizophrenia. However, when considering first-episode schizophrenia (FES), the longitudinal effects of cognition on functional outcome are not as well-established (Nuechterlein et al., 2011), even though the cognitive deficits in chronic patients and FES-patients are found to be comparable in magnitude and pattern (Mesholam-Gately et al., 2009). One reason is the scarcity of longitudinal studies which include cohorts of FES-patients (Milev et al., 2005). Furthermore, it is difficult to make direct comparisons across studies due to large differences in methodology (Allott et al., 2011).

Regarding the relationship between cognition and functional outcomes in FES, several longitudinal studies have attempted to identify

* Corresponding author at: Department of Psychology, University of Oslo, PO Box 1094, Blindern, 0317 Oslo, Norway.
E-mail addresses: susie.fu@psykologi.uio.no (S. Fu), n.o.czajkowski@psykologi.uio.no (N. Czajkowski), b.r.rund@psykologi.uio.no (B.R. Rund), a.k.torgalsboen@psykologi.uio.no (A.-K. Torgalsbøen).

http://dx.doi.org/10.1016/j.schres.2017.03.002
0920-9964/

specificity by exploring how various cognitive domains are differently linked to or predictive of outcome. For instance, Milev et al. (2005) found that attention and processing speed were related to the degree of work impairment in an average follow-up period of seven years. On the other hand, only verbal memory predicted the degree of relationship impairment. A study by Nuechterlein et al. (2011) found that three cognitive factors (attention and perceptual processing; working memory; verbal memory and processing speed), accounted for 52% of the variance in the rate of returning to work within a 9-month period. Another studies found that attention at baseline predicted work outcome at 2 year follow-up (Tandberg et al., 2011). When considering predictive factors of social outcome, studies have consistently found an association between attention and social outcome (Torgalsbøen et al., 2015), which is in accordance with findings on chronic schizophrenia (Addington and Addington, 2000; Velligan et al., 2000). However, a review by Allott et al. (2011) reported a predominance of negative findings in previous studies of FES, partially due to heterogeneous measurements of cognition and functional outcome. It has been suggested that these negative findings might not be attributable to FES, but instead to specific features of the individual studies (Nuechterlein et al., 2011).

Longitudinal studies on neurocognition in schizophrenia are rare, and many include only two measurement occasions. Multi-follow-up studies provide opportunities to discover long-term changes in neurocognition and fluctuations in illness trajectories. A recent multi-follow-up study of processing speed showed impairment in patients with schizophrenia compared to other diagnostic groups. Impairment in processing speed was most pronounced following the acute psychotic phase, and with the patients subsequently demonstrating improvements followed by stability (Bonner-Jackson et al., 2010). The current literature lacks studies that include both measures of neurocognitive variables and functional outcome, which is unfortunate given the value of long term multi-follow-up studies. Moreover, current multi-follow-up studies include assessment points many years apart, thereby being less sensitive to changes that occur in between the assessment points. Another issue pertaining to current studies is that they often examine the patient sample as a single group. However, since patients with schizophrenia experience varying degrees of neurocognitive deficits, it seems likely that the recovery processes will differ for different subgroups of patients. A recent multi-follow-up study by Rund et al. (2016) compared the cognitive trajectories of three subgroups of patients over 10 years. They found that patients with stable remissions in the first year improved in cognition compared to patients who experienced relapses and patients in continuous psychosis. Still, this study did not include measures of functional outcome.

In the Oslo schizophrenia recovery study, FES-patients are assessed annually over ten years with measures of cognition and functional outcomes. This procedure enables us to study the recovery process in greater detail than previous studies.

The present study addresses two research questions: Which cognitive domains at baseline predict later functional outcome? Are there distinct developmental trajectories for functional outcome in patients with different levels of baseline cognition?

2. Methods

2.1. Participants

A total of 28 patients with first-episode schizophrenia were recruited from mental health service institutions in the Oslo area. The patients were referred to the study by their treating clinicians, and were screened using the following inclusion criteria: age ≥ 18 years; the first episode of mental illness was within the spectrum of schizophrenia and psychosis according to DSM-IV (American Psychiatric Association, 1994); IQ > 70; presented no evidence of affective disorders, head trauma, and primary diagnosis of substance abuse; and referred to the study within five months of their first contact with mental health service institutions. Demographic and clinical characteristics of the participants are presented in Table 1.

In the follow-up period, patients were provided treatment by their local mental health service institutions, through medication, psychoeducation and case management. All patients could read and write Norwegian fluently, and written informed consent was obtained from all participants. The study was approved by the Regional Committee for Research Ethics (REK).

Here we present data from six follow-ups over four years: baseline, after six months and after a year. Thereafter, they were measured every year for three consecutive years. All patients were retained during the first three follow-ups, while three participants left the study during the 2-year follow-up and an additional three dropped out during the 3-year follow-up. On every measurement occasion, the patients completed all the assessments as described below.

2.2. Clinical instruments

The clinical interviews and tests of the participants were conducted within the first five months of their admission to a hospital or outpatient clinic, and were carried out by an experienced clinical psychologist. Diagnoses were established using the Structural Clinical Instrument of Diagnosis for DSM-IV Axis I disorders (SCID-I), modules A-D. Furthermore, a semi-structured interview was used, and based on this information a score of social and role functioning was given according to the Global Functioning: Social (GF:Social) and the Global Functioning: Role (GF: Role) (Cornblatt et al., 2007). A score ranging 1–10 was given. A higher score indicates better functioning.

2.3. Neurocognitive measures

Cognition was measured with the MATRICS Consensus Cognitive Battery (MCCB), which is a standardized test battery for use with adults with schizophrenia and related disorders (Nuechterlein and Green, 2006). The assessments were carried out by graduate students of clinical psychology trained in neuropsychological assessments, using the Norwegian version of MCCB. Norwegian reference data has been collected and reported (Mohn et al., 2012).

This battery consists of 10 tests measuring 7 different cognitive domains: Speed of processing: *Trail Making Test A (TMT-A)*, *Symbol Coding (Brief Assessment of Cognition in Schizophrenia, BACS)*, *Category Fluency*; Attention/Vigilance: *Continuous Performance Test – Identical Pairs (CPT-IP)*; Working memory: *Spatial Span (Wechsler Memory Scale, SS-WMS)*, *University of Maryland Letter Number Span test (LNS)*; Verbal learning: *The revised Hopkins Verbal Learning Test (HVLT-R)*; Visual learning: *The revised Brief Visuospatial Memory Test (BVMT-R)*; Reasoning/Problem solving: *Reasoning and Problem Solving* (*Neuropsychological*

Table 1
Demographic variables of the participants.

	Patients (n = 28)
Age in years	21.0 (SD 2.6)
Gender	17 (60.7%) men, 11 women
Level of education	
Elementary school	n = 11 (39.3%)
High school	n = 8 (28.6%)
Some college	n = 7 (25.0%)
BA degree or higher	n = 2 (7.2%)
Diagnoses	
Schizophrenia	21 (75.0%)
Schizoaffective disorder	6 (21.4%)
Psychotic disorder NOS	1 (3.6%)
Substance abuse earlier	18 (64.3%)
Substance abuse at baseline	1 (3.6%)
Treatment status	
Hospitalized	16 (57.0%)
Outpatient	12 (43%)

Assessment Battery, NAB); and Social Cognition: *The Managing Emotions part of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT)*. The tests were scored using American norms (Mohn et al., 2012).

2.4. Data analyses

IBM SPSS Statistics version 22.0 was used for all statistical analyses. The data consist of two hierarchical levels: time (measurement waves) represents level 1, and are nested within individuals (level 2). Since multilevel models can handle missing data flexibly (Quené and van den Bergh, 2004), all available data are included in the analyses.

A series of multilevel growth curve models were fitted for social functioning and role functioning to estimate initial level and changes in functioning over time. We started with a growth model with a random intercept, then allowed for variations in both individuals' initial level of functioning (the intercept) and change in functioning over time (the slope). Lastly, a quadratic effect of time was added to the model.

Next, we conducted separate analyses for each cognitive domain, for which an interaction between baseline T-scores and time was introduced into the existing model. Lastly, in order to examine whether a stratification of the patients group would further improve our model, the participants were divided into three approximately equally large groups based on T-scores at baseline for each of the significant cognitive domains in the last model, e.g. low attention, medium attention, and high attention. Multilevel analyses were conducted for social functioning and role functioning to examine group-by-time interactions.

All models were fitted using maximum likelihood and an unstructured covariance structure. Sex and level of education at baseline were entered as covariates in the various multilevel models in forward stepping procedures. The covariates were removed from the final model if they were not significant. Education and cognition scores were grand-mean centered to facilitate the interpretation of the results. AIC was used to determine the best fitting models (Akaike, 1974), as well as the likelihood ratio test using maximum likelihood.

3. Results

3.1. Trajectories of social functioning and role functioning

The best fitting model included a fixed linear time effect, a random intercept, and a random slope. For social functioning the mean value at baseline was $\beta = 6.11$ (SE = 0.22), and the increase in the expected score per year was $\beta = 0.20$ (SE = 0.08) (Table 2 (Model 1)). For role functioning the mean value at baseline was $\beta = 4.11$ (SE = 0.31) (Table 3 (Model 1)), and the increase in the expected score was $\beta = 0.75$ (SE = 0.13). A quadratic effect of time was not significant for social functioning, $F(1, 96.09) = 1.22$, $p = 0.27$, but it was significant for role functioning, $F(1, 102.79.) = 8.13$, $p = 0.01$. These results indicate that there was a significant constant linear increase in the predicted mean level of social functioning, and a significant quadratic effect of time in the predicted mean level of role functioning over the six measurement waves.

3.2. Association between baseline cognition and social functioning and role functioning

When a time × baseline interaction was included into the existing model, social functioning was significantly predicted by attention ($\beta = 0.03$, $p \leq 0.001$), verbal learning ($\beta = 0.02$, $p = 0.03$), and verbal working memory ($\beta = 0.03$, $p = 0.003$). Role functioning was significantly predicted by attention ($\beta = 0.03$, $p = 0.001$), verbal working memory ($\beta = 0.03$, $p = 0.001$), and reasoning/problem solving ($\beta = 0.02$, $p = 0.01$). The other cognitive domains did not significantly predict functional outcome. Of the other demographic covariates added to the model, only education level at baseline was significantly associated

Table 2
The best fitting models (model 1–3) for social functioning.

	Model 1		Model 2						Model 3					
			Attention		Verbal working memory		Verbal learning		Attention		Verbal working memory		Verbal learning	
	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p
Fixed effects														
Intercept	6.111 (0.215)	<0.001	6.804 (0.293)	<0.001	6.568 (0.328)	<0.001	6.417 (0.342)	<0.001	6.479 (0.338)	<0.001	6.294 (0.367)	<0.001	6.217 (0.370)	<0.001
Time	0.202 (0.080)	0.021	0.212 (0.077)	0.012	0.216 (0.081)	0.015	0.202 (0.082)	0.023	0.388 (0.111)	0.003	0.367 (0.123)	0.008	0.359 (0.137)	0.018
Low			−1.694 (0.355)	<0.001	−1.322 (0.414)	0.004	−0.763 (0.461)	0.110	−0.998 (0.466)	0.041	−0.528 (0.512)	0.317	−0.462 (0.524)	0.385
Moderate			−0.287 (0.363)	0.436	−0.094 (0.404)	0.817	−0.168 (0.448)	0.711	−0.039 (0.478)	0.935	−0.025 (0.505)	0.960	−0.126 (0.509)	0.807
Low * time									−0.394 (0.156)	0.022	−0.440 (0.173)	0.020	−0.242 (0.202)	0.246
Moderate * time									−0.126 (0.159)	0.437	−0.037 (0.165)	0.826	−0.230 (0.189)	0.239
Random effects														
Residual	0.261 (0.039)	<0.001	0.263 (0.039)	<0.001	0.260 (0.038)	<0.001	0.260 (0.038)	<0.001	0.271 (0.041)	<0.001	0.264 (0.039)	0.001	0.260 (. 038)	<0.001
Intercept	1.169 (0.348)	0.001	1.021 (0.318)	0.001	1.239 (0.388)	0.001	1.129 (0.344)	0.001	0.907 (0.278)	0.001	1.087 (0.327)	0.001	1.114 (0.334)	0.001
Slope	0.135 (0.054)	0.012	0.125 (0.048)	0.010	0.144 (0.056)	0.011	0.141 (0.057)	0.013	0.079 (0.038)	0.035	0.092 (0.042)	0.028	0.133 (0.054)	0.014
Model fit[a]														
-2 log likelihood	355.313		338.456		346.834		352.596		333.199		339.924		350.696	
AIC	367.313		354.456		362.834		368.596		353.199		359.924		370.696	

Abbreviations: Low = low baseline group, Moderate = moderate baseline group.
[a] The model fit index presented here is the -2 log likelihood and AIC.

Table 3
The best fitting models (model 1-3) for role functioning.

	Model 1		Model 2						Model 3					
			Attention		Verbal working memory		Reasoning/ problemsoving		Attention		Verbal working memory		Reasoning/ problemsoving	
	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p
Fixed effects														
Intercept	3.866 (0.317)	<0.001	4.205 (0.410)	<0.001	4.407 (0.403)	<0.001	4.670 (0.378)	<.001	3.721 (0.560)	<0.001	3.969 (0.558)	<0.001	4.692 (0.485)	<0.001
Time	1.302 (0.232)	<0.001	1.297 (0.229)	<0.001	1.326 (0.230)	<0.001	1.296 (0.230)	<.001	1.507 (0.282)	<0.001	1.529 (0.290)	<0.001	1.295 (0.274)	0.001
Time*time	-0.145 (0.051)	0.005	-0.144 (0.050)	0.005	-0.151 (0.050)	0.003	-0.146 (0.050)	0.005	-0.146 (0.050)	0.005	-0.154 (0.050)	0.003	-0.147 (0.051)	0.004
Low			-1.203 (0.408)	0.007	-1.470 (0.399)	0.001	-1.378 (0.392)	0.002	-0.239 (0.766)	0.758	-0.519 (0.780)	0.511	-0.830 (0.694)	0.242
Moderate			0.287 (0.418)	0.498	-0.198 (0.379)	0.606	-1.118 (0.384)	0.007	0.721 (0.782)	0.364	0.171 (0.760)	0.824	-1.734 (0.694)	0.019
Low*time									-0.421 (0.280)	0.145	-0.431 (0.304)	0.167	-0.286 (0.282)	0.319
Moderate*time									-0.175 (0.285)	0.544	-0.165 (0.291)	0.577	0.299 (0.278)	0.292
Education			0.251 (0.089)	0.009	0.242 (0.081)	0.006	0.227 (0.082)	0.010	0.261 (0.089)	0.007	0.239 (0.081)	0.006	0.213 (0.082)	0.015
Random effects														
Residual	0.849 (0.122)	<0.001	0.851 (0.121)	<0.001	0.844 (0.120)	<0.001	0.846 (0.120)	<0.001	0.852 (0.122)	<0.001	0.845 (0.120)	<0.001	0.852 (0.122)	<0.001
Intercept	2.215 (0.698)	0.001	2.401 (0.781)	0.002	2.500 (0.802)	0.002	2.142 (0.720)	0.003	2.258 (0.730)	0.002	2.348 (0.750)	0.002	1.893 (0.634)	0.003
Slope	0.344 (0.122)	0.005	0.309 (0.107)	0.004	0.339 (0.117)	0.004	0.330 (0.114)	0.004	0.275 (0.099)	0.006	0.309 (0.109)	0.004	0.272 (0.099)	0.006
Model fit[a]														
-2 log likelihood	499.874		482.235		482.688		483.051		480.077		480.713		479.390	
AIC	513.874		502.235		502.688		503.051		504.077		504.713		503.390	

Abbreviations: Low = low baseline group, Moderate = moderate baseline group.
[a] The model fit index presented here is the -2 log likelihood and AIC.

with role functioning.

AIC showed that compared to Model 1, this model provided a better fit for social functioning and role functioning when a baseline × time interaction was included.

3.3. Social functioning and role functioning for groups with varying baseline cognition

In the subsequent set of analyses the sample was divided into three different groups for each of the cognitive domains that were significant in the previous models.

For social functioning, a time × baseline attention interaction was found to be significant (Table 2 (Model 3)). All groups showed an increase in social functioning over time. However, the gain in social functioning was significantly lower for the low attention group compared to the high attention group ($\beta = -0.39$, SE = 0.16, $p < 0.05$). There were no differences in social functioning score between the medium attention and high attention groups ($\beta = -0.13$, SE = 0.16, $p > 0.05$). A time × baseline verbal working memory was also found significant. The gain in social functioning over time was again significantly lower for the low working memory group compared to the high working memory group ($\beta = -0.44$, SE = 0.17, $p < 0.05$). A time × baseline verbal learning interaction was not significant. The other covariates, sex and education level, did not significantly predict social functioning. Fig. 1 shows the mean levels of social functioning across the six measurement waves for the three groups.

For role functioning, analyses based on a stratification of the patient group did not provide any significant results (Table 3 (Model 3)).

Compared to the two previous models (Table 2 (Model 1–2)), model 3 provided a better fit for social functioning with AIC comparison.

4. Discussion

The purpose of the present study was to identify cognitive predictors of functional outcome. Differences in social functioning were seen among the patients. A subgroup of patients who scored the lowest on baseline cognitive measures of attention and verbal working memory, displayed a significantly smaller rate of change in social functioning compared to patients with a higher cognitive level. Although the patient group as a whole displayed a steady improvement in social and role functioning, a subgroup of patients only had a limited improvement in functional outcomes over three years. When examining their social functioning score, this patient group is more socially secluded, and has fewer steady friendships and intimate relationships compared to other patients. Their social relationships are characterized by more conflicts with peers and less involvement with family members. Our statistical models were indeed enhanced when we divided the patient group into subgroups, supporting the idea of schizophrenia being a heterogeneous disorder with many possible trajectories to recovery. Although functional outcome is a major focus in schizophrenia research, specific predictors of different outcome domains have not yet been established (Green et al., 2015). In this study, attention and verbal working memory predicted social functioning.

We found an association between cognition and role functioning which is consistent with previous studies. The differences in role functioning within the patient group were not significant. One possible explanation for the lack of differences may be explained by the extensive support Norwegian health institutions provide to patients, in order for them to get back to work after mental illness. Probably this subgroup of patients experiences more difficulties with simultaneously maintaining a satisfying work and social life; being able to master work, but struggling in the personal arena.

Cognitive impairments may influence everyday functioning directly, but also indirectly influence how well a person responds to rehabilitation. It has been suggested that the relationship between cognition and function is not just a matter of cause and effect. Consistent with

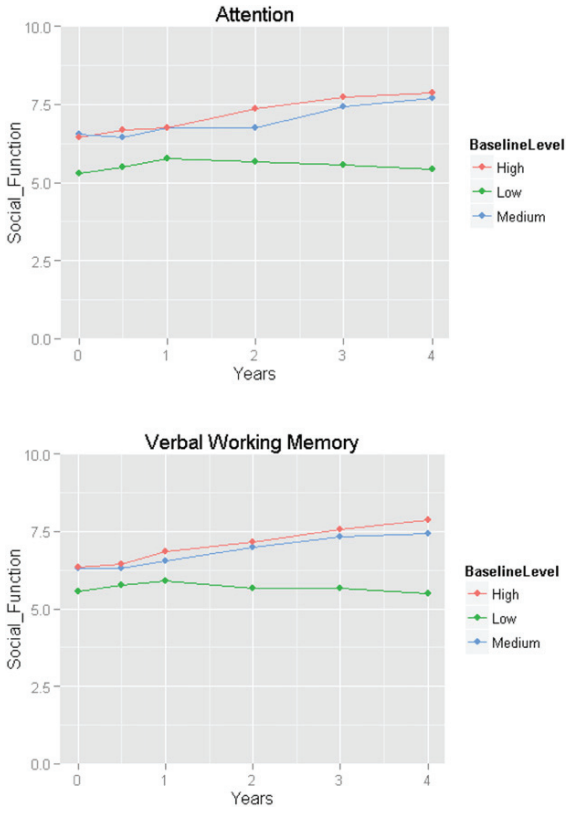

Fig. 1. Mean levels of social functioning across six measurement waves. Values are raw scores. The participants are divided into three groups based on attention and verbal memory baseline T-scores.

this view, earlier studies of cognitive rehabilitation in schizophrenia have shown limited effects of cognitive training on clinical measures (Benedict et al., 1994; Pilling et al., 2002). By examining studies that provided cognitive remediation in conjunction with other psychiatric rehabilitation, some studies have found a stronger positive association between cognitive remediation and functional outcome (McGurk et al., 2007; Wykes et al., 2011). We argue that the group with the lowest score on baseline cognition in the current study represents a more severely ill group with the least resources in daily life, thus responding less effectively to rehabilitation. Since these differences between subgroups of patients increase with time, it is important to identify patients with poorer outcomes as early as possible and provide suitable interventions. Our findings indicate that with FES, it is possible to identify this subgroup of patients within the first five months of hospitalization. This may have important implications for clinical practice.

Previous findings are conflicting concerning which cognitive domains predict functional outcome in FES (Allott et al., 2011). Nevertheless, the majority of recent studies have found significant relationships between cognition and functional outcome, thereby strengthening the importance of cognition in the recovery from schizophrenia. Consistent with previous findings (González-Blanch et al., 2010; Mesholam-Gately et al., 2009; Nuechterlein et al., 2011), baseline levels of attention and verbal working memory predicted functional outcome.

By including multiple assessments and stratifying the patient group in our analyses, we identified a poor outcome group early in the course of illness, as well as fluctuations and stability in functioning over time. Our findings support the notion that schizophrenia is a heterogeneous disease with different recovery processes, and that the subgroup of patients with the largest cognitive impairments at the onset of the disorder may have special rehabilitation needs in order to recover and improve their quality of life.

So far many research groups have studied cognition as a continuous predictor of functional outcome, and some consistent findings have emerged. By creating subgroups we have been able to explore this relationship even further. We are aware that there are a small number of patients in each group, but even so we were able to discover a significant effect of cognition on social functioning trajectory. Future studies with larger sample sizes may apply more sophisticated methods to create subgroups.

The study's strengths are the high retention rate, yearly measurement occasions, and the inclusion of the same assessment instruments in each follow-up, making it possible to examine the trajectory of social and role functioning over time. The main limitation is the small sample size. Yet, a large sample may be hard to attain for longitudinal studies with many repeated measurements. It has been suggested that more reliable estimates of growth models can be obtained by increasing the number of measurement waves (Quené and van den Bergh, 2004). Moreover, the aim of this study is exploratory in nature and replication is therefore needed with larger sample sizes. Another potential limitation is the possibility of medication effects on cognition. However, we did not find any significant correlations between daily doses of medication and cognitive scores (Torgalsbøen et al., 2015; Torgalsbøen et al., 2014). Therefore, we argue that there is no direct relationship between medication dose and test performance.

Role of the funding source

This study is internally funded by the Department of Psychology, University of Oslo. This funding source had no role in the design of this study, nor during its execution, analyses, interpretation of the data, and decision to submit results.

Author disclosure

Fu and Torgalsbøen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Torgalsbøen designed the study and wrote the protocol. Fu and Czajkowski undertook the statistical analysis. Fu wrote the first draft of the manuscript, and all authors provided valuable feedback. All authors contributed to and have approved the final manuscript. This work was supported by the Department of Psychology, University of Oslo.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgements

This work was supported by the Department of Psychology, University of Oslo.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.03.002.

References

Addington, J., Addington, D., 2000. Neurocognitive and social functioning in schizophrenia: a 2.5 year follow-up study. Schizophr. Res. 44 (1), 47–56.
Akaike, H., 1974. A new look at the statistical model identification. IEEE Trans. Autom. Control 19 (6), 716–723.
Allott, K., Liu, P., Proffitt, T.M., Killackey, E., 2011. Cognition at illness onset as a predictor of later functional outcome in early psychosis: systematic review and methodological critique. Schizophr. Res. 125 (2–3), 221–235.
American Psychiatric Association, 1994. Diagnostic and statistical manual for mental disorders. fourth ed. American Psychiatric Association, Washington, DC revised.
Benedict, R.H.B., Harris, A.E., Markow, T., McCormick, J.A., Neuchterlein, K.H., Asarnow, R.F., 1994. Effects of attention training on information processing in schizophrenia. Schizophr. Bull. 20 (3), 537–546.

Bonner-Jackson, A., Grossman, L.S., Harrow, M., Rosen, C., 2010. Neurocognition in schizophrenia: a 20-year multi-follow-up of the course of processing speed and stored knowledge. Compr. Psychiatry 51 (5), 471–479.
Cornblatt, B.A., Auther, A.M., Niendam, T., Smith, C.W., Zinberg, J., Bearden, C.E., Cannon, T.D., 2007. Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. Schizophr. Bull. 33 (3), 688–702.
González-Blanch, C., Perez-Iglesias, R., Pardo-García, G., Rodríguez-Sánchez, J.M., Martínez-García, O., Vázquez-Barquero, J.L., Crespo-Facorro, B., 2010. Prognostic value of cognitive functioning for global functional recovery in first-episode schizophrenia. Psychol. Med. 40 (6), 935–944.
Green, M.F., Harvey, P.D., 2014. Cognition in schizophrenia: past, present, and future. Schizophr. Res. Cogn. 1 (1), e1–e9.
Green, M.F., Kern, R.S., Braff, D.L., Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr. Bull. 26 (1), 119–136.
Green, M.F., Kern, R.S., Heaton, R.K., 2004. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr. Res. 72 (1), 41–51.
Green, M.F., Llerena, K., Kern, R.S., 2015. The "right stuff" revisited: what have we learned about the determinants of daily functioning in schizophrenia? Schizophr. Bull. 41 (4), 781–785.
Insel, T.R., 2010. Rethinking schizophrenia. Nature 468 (11), 187–193.
Kahn, R.S., Keefe, R.S.E., 2013. Schizophrenia is a cognitive illness. Time for a change in focus. JAMA Psychiat. 70 (10), 1107–1112.
McGurk, S.R., Twamley, E.W., Sitzer, D.I., McHugo, G.J., Mueser, K.T., 2007. A meta-analysis of cognitive remediation in schizophrenia. Am. J. Psychiatry 164 (12), 1791–1802.
Mesholam-Gately, R.J., Guiliano, A.J., Goff, K.P., Faraone, S.V., Seidman, L.J., 2009. Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology 23 (3), 315–336.
Milev, P., Ho, B.C., Arndt, S., Andreasen, N.C., 2005. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. Am. J. Psychiatry 162 (3), 495–506.
Mohn, C., Sundet, K., Rund, B.R., 2012. The Norwegian standardization of the MATRICS (measurement and treatment research to improve cognition in schizophrenia) consensus cognitive battery. J. Clin. Exp. Neuropsychol. 34 (6), 667–677.
Nuechterlein, K.H., Green, M.F., 2006. MATRICS Consensus Cognitive Battery. Manual. MATRICS Assessment Inc., Los Angeles, CA.
Nuectherlein, K.H., Subotnik, K.L., Green, M.F., Ventura, J., Asarnow, R.F., Gitlin, M.J., Yee, C.M., Gretchen-Doorly, D., Mintz, J., 2011. Neurocognitive predictors of work outcome in recent-onset schizophrenia. Schizophr. Bull. 37 (2), S33–S40.
Ozomaro, U., Wahlestedt, C., Nemeroff, C.B., 2013. Personalized medicine in psychiatry: problems and promises. BMC Med. 11 (1):132. http://dx.doi.org/10.1186/1741-7015-11-132.
Pilling, S., Bebbington, P., Kuipers, E., Garety, P., Geddes, J., Martindale, B., Orbach, G., Morgan, C., 2002. Psychological treatments in schizophrenia: II. Meta-analyses of randomized controlled trials of social skills training and cognitive remediation. Psychol. Med. 32 (5), 783–791.
Quené, H., van den Bergh, H., 2004. On multi-level modeling of data from repeated measures designs: a tutorial. Speech Comm. 43 (1), 103–121.
Robinson, D.G., Woerner, M.G., McMeniman, M., Mendelowitz, A., Bilder, R.M., 2004. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. Am. J. Psychiatry 161 (3), 473–479.
Rund, B.R., Barder, H.E., Evensen, J., Haahr, U., ten Velden Hegelstad, W., Joa, I., Johannessen, J.O., Langeveld, J., Larsen, T.K., Melle, I., Opjordsmoen, S., Røssberg, J.I., Simonsen, E., Sundet, K., Vaglum, P., McGlashan, T., Friis, S., 2016. Neurocognition and duration of psychosis: a 10-year follow-up of first-episode patients. Schizophr. Bull. 42 (1), 87–95.
Tandberg, M., Ueland, T., Sundet, K., Haahr, U., Joa, I., Johannessen, J.O., Larsen, T.K., Opjordsmoen, S., Rund, B.R., Røssberg, J.I., Simonsen, E., Vaglum, P., Melle, I., Friis, S., McGlashan, T., 2011. Neurocognition and occupational functioning in patients with first-episode psychosis: a 2-year follow-up study. Psychiatry Res. 188 (3), 334–342.
Torgalsbøen, A.K., Mohn, C., Rund, B.R., 2014. Neurocognitive predictors of remission of symptoms and social and role functioning in the early course of first-episode schizophrenia. Psychiatry Res. 216 (1), 1–5.
Torgalsbøen, A.K., Mohn, C., Czajkowski, N., Rund, B.R., 2015. Relationship between neurocognition and functional recovery in first-episode schizophrenia: results from the second year of the Oslo multi-follow-up study. Psychiatry Res. 227 (2–3), 185–191.
Velligan, D.I., Bow-Thomas, C.C., Mahurin, R.K., Miller, A.L., Halgunseth, L.C., 2000. Do specific neurocognitive deficits predict specific domains of community function in schizophrenia? J. Nerv. Ment. Dis. 188 (8), 518–524.
Wykes, T., Huddy, V., Cellard, C., McGurk, S.R., Czobor, P., 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am. J. Psychiatry 168 (5), 472–485.

II

Psychiatry Research 267 (2018) 319–326

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Cognitive improvement in first-episode schizophrenia and healthy controls: A 6-year multi-assessment follow-up study

Susie Fu[a,b,*], Nikolai Czajkowski[a,c], Anne-Kari Torgalsbøen[a]

[a] Department of Psychology, University of Oslo, PO Box 1094, Oslo 0373, Norway
[b] Vestre Viken Hospital Trust, PO Box 800, Drammen 3004, Norway
[c] Division of Mental Health, Norwegian Institute of Public Health, PO Box 4404, Oslo 0403, Norway

ARTICLE INFO

Keywords:
Psychosis
Longitudinal
Cognition
Full recovery

ABSTRACT

The development of individual cognitive domains over time is not yet fully examined in first-episode schizophrenia (FES). This study's objective was to explore the cognitive trajectories of FES-patients (n = 28) and compare them to a pairwise matched healthy control group (n = 28, total n = 56). This study has a multi-assessment design, and includes patient data from seven assessments over six years. Healthy controls were assessed at baseline, after two years and after six years. Cognition was assessed with the MATRICS Consensus Cognitive Battery. Data were analyzed with linear multilevel models. FES-patients scored significantly lower than the control group across all cognitive domains at baseline. Over six years, improvements were seen in attention, verbal learning, processing speed, reasoning/ problem solving, working memory and social cognition. The overall trend points toward a similar cognitive change in both groups. The patient group's improvement in reasoning/ problem solving was significantly larger that the control group, but improvement in working memory was smaller. Cognitive improvements were seen under and after the initial psychosis episode and throughout the recovery process with 45.5% of the patients fully recovered by 6-year follow-up. Cognitive improvements were seen in almost every cognitive domain that is consistently impaired in FES.

1. Introduction

Cognitive impairment is a core deficit in schizophrenia. Compared to healthy individuals, patients with schizophrenia show impaired cognitive functioning across a broad array of cognitive domains including attention, executive functioning, processing speed and verbal learning (Schaefer et al., 2013). These findings are consistent both in first-episode schizophrenia (FES) (Mesholam-Gately et al., 2009) and in individuals with prolonged illness (Heinrichs and Zakzanis, 1998).

Less is known about the longitudinal development of cognition over the course of illness. Studies of psychosis prodrome showed that cognitive impairments are already present in at-risk individuals (Niendam et al., 2006), although to a lesser degree than in FES (Keefe et al., 2006). The cognitive performance of at-risk individuals who later progress to psychosis show no further cognitive decline from pre- to post-psychosis onset (Carrión et al., 2018; Keefe et al., 2006), suggesting that cognitive deficits are established before the prodromal phase (Becker et al., 2010; Bora and Murray, 2014). After psychosis onset the cognitive composite performance in FES-patients remains stable over time (Rund et al., 2016), which is in line with the idea that schizophrenia is a static encephalopathy disorder (Rund, 1998).

There is a knowledge gap regarding the changes in individual cognitive domains over the course of illness. In their meta-analysis Bora and Murray (2014) found significant improvements in all cognitive domains except from working memory. Bozikas and Andreou (2011) also found stability in most cognitive domains with the possible exceptions of verbal learning and executive functioning, where the evidence of change remains inconclusive. Most of the reported studies have follow-up intervals of two to five years. Three studies of FES-patients reported a follow-up length of ten years (Hoff et al., 2005; Rund et al., 2016; Sterling et al., 2003), but these either did not include a healthy control group or the control group was not matched to the patient group. Barder et al. (2013) reported stability in most cognitive domains apart from motor speed which declined in a follow-up period of five years, but again this study did not include healthy controls. The lack of a healthy control group renders it difficult to conclude that the cognitive changes were genuine improvements (Szöke et al., 2008). A recent meta-analytic review report that the degree of overall cognitive change can be expected to be similar in FES and controls (Bora and Murray, 2014), but yet again the follow-up intervals were mostly two

* Corresponding author at: Department of Psychology, University of Oslo, PO Box 1094, Blindern, Oslo 0317, Norway
E-mail addresses: susie.fu@psykologi.uio.no (S. Fu), n.o.czajkowski@psykologi.uio.no (N. Czajkowski), a.k.torgalsboen@psykologi.uio.no (A.-K. Torgalsbøen).

https://doi.org/10.1016/j.psychres.2018.06.016
Received 2 February 2018; Received in revised form 29 May 2018; Accepted 7 June 2018
Available online 18 June 2018

years or less. As described by Bozikas and Andreou (2011), the current literature has a few limitations that affect the interpretability of results: lack of control group or different attrition rates in healthy and control groups; differences in how patients are recruited; differences in the timing of baseline cognition assessments; differences in cognitive measurements and various durations between follow-ups.

Studies of cognitive development in FES are important because cognition seems to be related to functional outcomes. For instance, stability or improvement in cognition are respectively associated with stability/decline or improvement in social functioning (Niendam et al., 2007). While the relationship between symptoms and global cognitive dysfunction has been debated, recent findings by Rund et al. (2016) showed an association between improved cognitive trajectories and symptom remission during the first year of illness.

In the Oslo schizophrenia recovery study, we seek to further clarify the cognitive trajectories in FES while remedying some of the limitations mentioned above. FES-patients were assessed annually over six years with the MATRICS Consensus Cognitive Battery (MCCB), which is considered to be the gold standard for the assessment of cognition in schizophrenia clinical trials (Buchanan et al., 2011). This cognitive battery covers the seven cognitive domains that are found to be persistently impaired in schizophrenia (Neuchterlein et al., 2004). Earlier longitudinal studies varied in the number of cognitive domains that were assessed, and there was no clear consensus in how to measure these cognitive domains (Mesholam-Gately et al., 2009). Cognitive domains were hence assessed with a vast array of different cognitive measures, hampering the comparableness of studies. So far few studies have investigated the longitudinal development of different cognitive domains using the MCCB with multiple yearly assessments. Juuhl-Langseth et al. (2014) found cognitive improvements in most cognitive domains assessed with the MCCB, but the follow-up period was only two years and the patient group consisted of individuals with early onset schizophrenia (EOS).

Earlier longitudinal studies have mostly included two or three assessment points, but by including yearly cognitive assessments we are able to examine the cognitive trajectories more closely. Bonner-Jackson et al. (2010) assessed individuals with schizophrenia seven times over a time span of 20 years. They found that processing speed and verbal knowledge were most impaired during the acute phase, followed by improvements at 2-year follow-up and stability throughout the 20-year time period. However, their study did not include any other cognitive domains, nor did they include a healthy control group. In one of our previous papers that reported data from the 2-year follow-up, we saw a statistically significant decline in verbal learning and improvements in reasoning/problem solving and social cognition in FES compared to healthy controls (Torgalsbøen et al., 2015), indicating differentiated trajectories for different cognitive domains. Yet, two years is a short amount of time in the clinical course of schizophrenia, and these cognitive trajectories need to be reexamined in order to determine the cognitive development beyond the first episode of schizophrenia.

To our knowledge this is the first study where the patient group is matched pairwise with a healthy control group to examine the differences in cognitive development over time using the MCCB. The two groups remain matched over the current research period of six years.

The present study addresses the following research question:

Do the cognitive domains develop similarly in FES and healthy controls over a six year interval?

2. Methods

2.1. Participants

A total of 31 patients with first-episode schizophrenia were referred to the study from mental health service institutions in the Oslo area by their treating clinicians. The patients were screened using the following inclusion criteria: age ≥ 18 years; the first episode of mental illness was within the spectrum of schizophrenia and psychosis according to DSM-IV (American Psychiatric Association, 1994); IQ > 70; presented no evidence of affective disorders, head trauma, and primary diagnosis of substance abuse; and referred to the study within five months of their first contact with mental health service institutions. 28 patients fulfilled the criteria and were included in the study. In the follow-up period, the patient group were provided treatment by their local mental health service institutions, through medication, psychoeducation and case management.

A healthy control group with 28 participants was matched pairwise with the patient group on gender, age and education level (± one year). The youngest participants in the control group were recruited through inquiries at junior and senior high schools in and around the Oslo metropolitan area. The older participants were recruited through electronic advertisements on the Vestre Viken Hospital Trust (VVHF) homepage. The VVHF provides state funded healthcare to the south-eastern part of Norway and consists of rural areas as well as city centers. Exclusion criteria were a history of schizophrenia or other severe mental disorders; mental retardation; a history of neurological disease; head injury and/or loss of consciousness for more than 10 minutes; current psychotropic medication; chronic somatic illness inducing significant fatigue or pain; current narcotics for pain; a history of alcohol or substance abuse; dyslexia or other significant learning difficulties; inability to understand spoken and written Norwegian sufficiently to comprehend testing instructions. Demographic and clinical characteristics of the participants are presented in Table 1.

All participants could read and write Norwegian fluently, and written informed consent was obtained from all participants. The study was approved by the Regional Committee for Research Ethics (REK).

Here we present data from seven assessment points over six years. The patient group was assessed on baseline, after six months and after a year. Thereafter, they were assessed every year for four consecutive years. Beginning from the 5-year follow-up the patient group was assessed every other year. All patients were retained during the first three assessments, while three participants left the study during the 2-year follow-up and an additional three dropped out during the 3-year follow-up. The healthy control group was assessed on baseline, after two years and after six years. Three participants were unable to participate on the 2-year follow-up only. On every measurement occasion, the

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

	Patients (n = 28)	Controls (n = 28)
Age in years	21.0 (SD 2.6)	21.1 (SD 2.7)
Gender	17 (60.7%) men, 11 women	17 (60.7%) men, 11 women
Level of education		
Elementary school	n = 11 (39.3%)	n = 9 (32.1%)
High school	n = 8 (28.6%)	n = 16 (57.1%)
Some college	n = 7 (25.0%)	n = 2 (7.1%)
BA degree or higher	n = 2 (7.1%)	n = 1 (3.6%)
Diagnoses		
Schizophrenia	21 (75.0%)	
Schizoaffective disorder	6 (21.4%)	
Psychotic disorder NOS	1 (3.6%)	
Substance abuse earlier	18 (64.3%)	
Substance abuse at baseline	1 (3.6%)	
Treatment status		
Hospitalized	16 (57.0%)	
Outpatient	12 (43%)	
Duration of untreated psychosis (months)	15.9 (SD 15.4)	
Drug-naïve at baseline	2 (7.1%)	
Fully recovered on year 6	10 (45.5%)	

participants completed the neurocognitive test battery as described below.

2.2. Clinical instruments

The clinical interviews and tests of the patients were conducted within the first five months of their admission to a hospital or out-patient clinic, and were carried out by an experienced clinical psychologist. Diagnoses were established using the Structural Clinical Instrument of Diagnosis for DSM-IV Axis I disorders (SCID-I), modules A–D.

2.3. Neurocognitive measures

Cognition was measured with the MCCB, which is a standardized test battery for use with adults with schizophrenia and related disorders (Nuechterlein and Green, 2006). The assessments were carried out by graduate students of clinical psychology trained in neuropsychological assessments, using the Norwegian version of MCCB. Norwegian reference data has been collected and reported, and it concludes that US norms may be employed for the Norwegian population (Mohn et al., 2012).

This battery consists of 10 tests measuring 7 different cognitive domains: Speed of processing: *Trail Making Test A (TMT-A), Symbol Coding (Brief Assessment of Cognition in Schizophrenia, BACS), Category Fluency*; Attention/Vigilance: *Continuous Performance Test – Identical Pairs (CPT-IP)*; Working memory: *Spatial Span (Wechsler Memory Scale, SS-WMS), University of Maryland Letter Number Span test (LNS)*; Verbal learning: *The revised Hopkins Verbal Learning Test (HVLT-R)*; Visual learning: *The revised Brief Visuospatial Memory Test (BVMT-R)*; Reasoning/ Problem solving: *Reasoning and Problem Solving* (*Neuropsychological Assessment Battery, NAB)*; and Social Cognition: *The Managing Emotions part of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT)*. The tests were scored using American norms.

2.4. Data analyses

IBM SPSS Statistics version 22.0 was used for all statistical analyses. The data consist of two hierarchical levels: measurement waves represents level 1, and are nested within individuals (level 2). Since multilevel models can handle missing data flexibly (Quené and van den Bergh, 2004), all available data are included in the analyses.

A series of multilevel growth curve models were fitted for each neurocognitive domain to estimate initial level and changes in cognitive functions over time. We started with a random intercept model, then allowed for variations in both individuals' baseline cognition (the intercept) and change in cognition over time (the slope).

Next, in order to further improve our base models, we introduced group effect as a parameter. Lastly, an interaction between baseline *T*-scores and time was introduced into the existing model to examine group-by-time interactions.

All models were fitted using maximum likelihood and an unstructured covariance structure. Sex and level of education at baseline were entered as covariates one at a time to test for inclusion in the models. The covariates were removed from the final model if they were not significant. Akaike information criterion (AIC) was used to determine the best fitting models (Akaike, 1974).

3. Results

The best fitting models (model 1–3) all included a fixed linear time effect, a random intercept, and a random slope. The final models are shown in Table 2.

3.1. Cognitive trajectories for all participants (model 1) and baseline differences between FES- patients and healthy controls (model 2)

Analyses with all participants showed a significant linear increase in cognition across all cognitive domains over six years (model 1) with the exception of visual learning. Compared to healthy controls, the FES patients scored significantly lower on all cognitive domains at baseline except for social cognition (model 2). Also, AIC comparisons showed that model 2 had a better fit than model 1 for all cognitive domains except social cognition. We therefore included all cognitive domains in the final multilevel model to examine whether an added interaction parameter would further improve the fit of these models. The effects of sex and level of education were insignificant and were subsequently removed from the final models.

3.2. Cognitive trajectories of FES-patients compared to healthy controls (model 3)

Model 3 included a group*time interaction parameter. Regarding model 2, where insignificant group effects were shown for social cognition, the added interaction parameter did not improve the model fit for social cognition according to AIC comparisons. Nor did the model fit improve for processing speed, verbal learning and visual learning. AIC comparisons showed that model 3 had a better model fit than model 2 for attention, working memory and reasoning/ problem solving.

There was a significant difference in slope between patients and healthy controls in working memory and reasoning/ problem solving. Both groups showed an increase in cognitive scores over time, but the increase in working memory was significantly lower for the patient group compared to the control group ($\beta = -0.84$, $SE = 0.42$, $p < 0.05$). Meanwhile, the increase in reasoning/ problem solving was significantly higher for the patient group than the control group ($\beta = 1.03$, $SE = 0.41$, $p < 0.05$). For the rest of the cognitive domains, no significant interaction effects were found. Moreover, the analyses did not achieve convergence for processing speed, attention and visual learning. Another set of analyses were therefore performed for these cognitive domains where time was removed as a random effect in order to simplify the model and facilitate convergence. The group*time interaction remained insignificant, although the *p*-value for attention was close to being significant ($\beta = 0.56$, $SE = 0.29$, $p < 0.051$). Fig. 1 shows the mean levels of different cognitive domains across the 7 measurement waves.

4. Discussion

The purpose of the present study was to examine the cognitive development in FES-patients over six years, and compare their cognitive domain trajectories to those of healthy controls.

Compared to the healthy control group, the patient group performed worse on baseline on all cognitive domains. This was to be expected given the large amount of evidence indicating generalized cognitive impairments in schizophrenia compared to healthy controls (Fioravanti et al., 2012). When compared over time however, some interesting findings emerged in the present study.

Firstly, the analyses comparing cognitive trajectories between patients and healthy controls yielded mostly insignificant results. A comparable improvement in both groups was seen in processing speed. As for attention, verbal learning and social cognition, the cognitive trajectories suggested a larger improvement for the patient group than for the control group over time. However, the difference between the groups were not statistically significant and remained non-significant with a simpler model, although attention was significant on a trend level. There is a possibility that we were unable to discern the differences due to a small sample size, but another explanation is that the cognitive change is of comparable magnitude in the two groups. In their longitudinal study on first-episode schizophrenia, Hoff et al. (1999)

Table 2
The best fitting models for the cognitive domains.

	Attention		Processing speed		Working memory		Verbal learning		Visual learning		Reasoning/ problem solving		Social cognition	
	Estimate (SE)	*p*	Estimate (SE)	*p*	Estimate (SE)	*p*	Estimate (SE)	*p*	Estimate (SE)	*p*	Estimate (SE)	*p*	Estimate (SE)	*p*
Model 1														
Fixed effects														
Intercept	40.349 (1.218)	< 0.001	42.893 (1.508)	< 0.001	44.658 (1.344)	< 0.001	44.087 (1.212)	< 0.001	44.368 (1.256)	< 0.001	45.900 (1.268)	< 0.001	45.590 (1.369)	< 0.001
Time	1.068 (0.148)	< 0.001	1.399 (0.180)	< 0.001	0.710 (0.217)	0.002	0.528 (0.243)	0.034	0.265 (0.200)	0.186	1.350 (0.214)	< 0.001	0.757 (0.242)	0.003
Random effects														
Residual	24.967 (2.858)	< 0.001	35.013 (3.616)	< 0.001	44.754 (5.158)	< 0.001	46.771 (5.372)	< 0.001	48.915 (4.920)	< 0.001	45.802 (5.246)	< 0.001	49.506 (5.636)	< 0.001
Intercept	69.230 (15.623)	< 0.001	108.301 (24.036)	< 0.001	76.515 (19.166)	< 0.001	56.531 (15.972)	0.001	61.528 (15.636)	< 0.001	64.279 (17.219)	< 0.001	77.560 (19.819)	< 0.001
Slope	0.008 (0.229)	0.720	0.198 (0.000)		0.532 (0.503)	0.291	1.074 (0.582)	0.065	0.065 (0.000)		0.438 (0.468)	0.350	0.951 (0.604)	0.115
Model fit														
AIC	1684.932		1785.798		1821.982		1822.677		1811.442		1801.324		1841.603	
Model 2														
Fixed effects														
Intercept	45.638 (1.470)	< 0.001	50.945 (1.658)	< 0.001	49.336 (1.756)	< 0.001	47.422 (1.570)	< 0.001	48.679 (1.481)	< 0.001	48.302 (1.651)	< 0.001	47.026 (1.839)	< 0.001
Time	1.028 (0.149)	< 0.001	1.326 (0.201)	< 0.001	0.716 (0.216)	0.002	0.498 (0.243)	0.045	0.267 (0.197)	0.178	1.334 (0.214)	< 0.001	0.745 (0.242)	0.003
Group	−10.192 (2.014)	< 0.001	−15.327 (2.240)	< 0.001	−8.955 (2.257)	< 0.001	−6.189 (2.007)	0.003	−8.123 (1.828)	< 0.001	−4.535 (2.125)	0.037	−2.706 (2.364)	0.257
Random effects														
Residual	24.709 (2.801)	< 0.001	35.908 (3.940)	< 0.001	44.530 (5.098)	< 0.001	46.741 (5.364)	< 0.001	48.408 (4.796)	< 0.001	45.815 (5.250)	< 0.001	49.501 (5.632)	< 0.001
Intercept	43.056 (10.451)	< 0.001	50.354 (13.048)	< 0.001	68.195 (17.611)	< 0.001	44.446 (13.607)	0.001	40.729 (11.609)	< 0.001	53.282 (15.345)	0.001	73.426 (19.086)	< 0.001
Slope	0.104 (0.231)	0.451	0.573 (0.000)		0.552 (0.502)	0.271	1.074 (0.581)	0.064	0.038 (0.000)		0.430 (0.467)	0.357	0.930 (0.598)	0.119
Model fit														
AIC	1666.592		1757.289		1810.689		1815.970		1797.425		1799.393		1842.357	
Model 3														
Fixed effects														
Intercept	45.940 (1.481)	< 0.001	50.943 (1.658)	< 0.001	47.962 (1.877)	< 0.001	47.894 (1.681)	< 0.001	49.531 (1.653)	< 0.001	49.871 (1.769)	< 0.001	48.031 (1.983)	< 0.001
Time	0.734 (0.223)	0.001	1.264 (0.299)	< 0.001	1.173 (0.313)	< 0.001	0.292 (0.357)	0.416	−0.006 (0.307)	0.986	0.755 (0.312)	0.018	0.387 (0.355)	0.279
Group	−10.516 (2.023)	< 0.001	−15.273 (2.248)	< 0.001	−6.561 (2.549)	0.013	−6.993 (2.254)	0.003	−9.555 (2.207)	< 0.001	−7.136 (2.378)	0.004	−4.458 (2.693)	0.103
Group*time	0.523 (0.296)	0.083	0.114 (0.404)	0.777	−0.843 (0.416)	0.048	0.385 (0.486)	0.432	0.465 (0.400)	0.246	1.026 (0.413)	0.016	0.659 (0.480)	0.175
Random effects														
Residual	24.328 (2.722)	< 0.001	35.906 (3.940)	< 0.001	44.425 (5.077)	< 0.001	46.732 (5.360)	< 0.001	48.095 (4.767)	< 0.001	45.497 (5.181)	< 0.001	49.391 (5.609)	< 0.001
Intercept	43.367 (10.432)	< 0.001	50.371 (13.048)	< 0.001	65.664 (16.956)	< 0.001	44.518 (13.588)	0.001	40.868 (11.485)	< 0.001	52.681 (14.897)	< 0.001	73.445 (18.930)	< 0.001
Slope	0.089 (0.228)	0.696	0.571 (0.000)		0.347 (0.460)	0.451	1.048 (0.575)	0.068	0.047 (0.000)		0.240 (0.418)	0.567	0.879 (0.583)	0.132
Model fit														
AIC	1665.534		1759.187		1808.871		1817.348		1798.262		1795.475		1842.499	

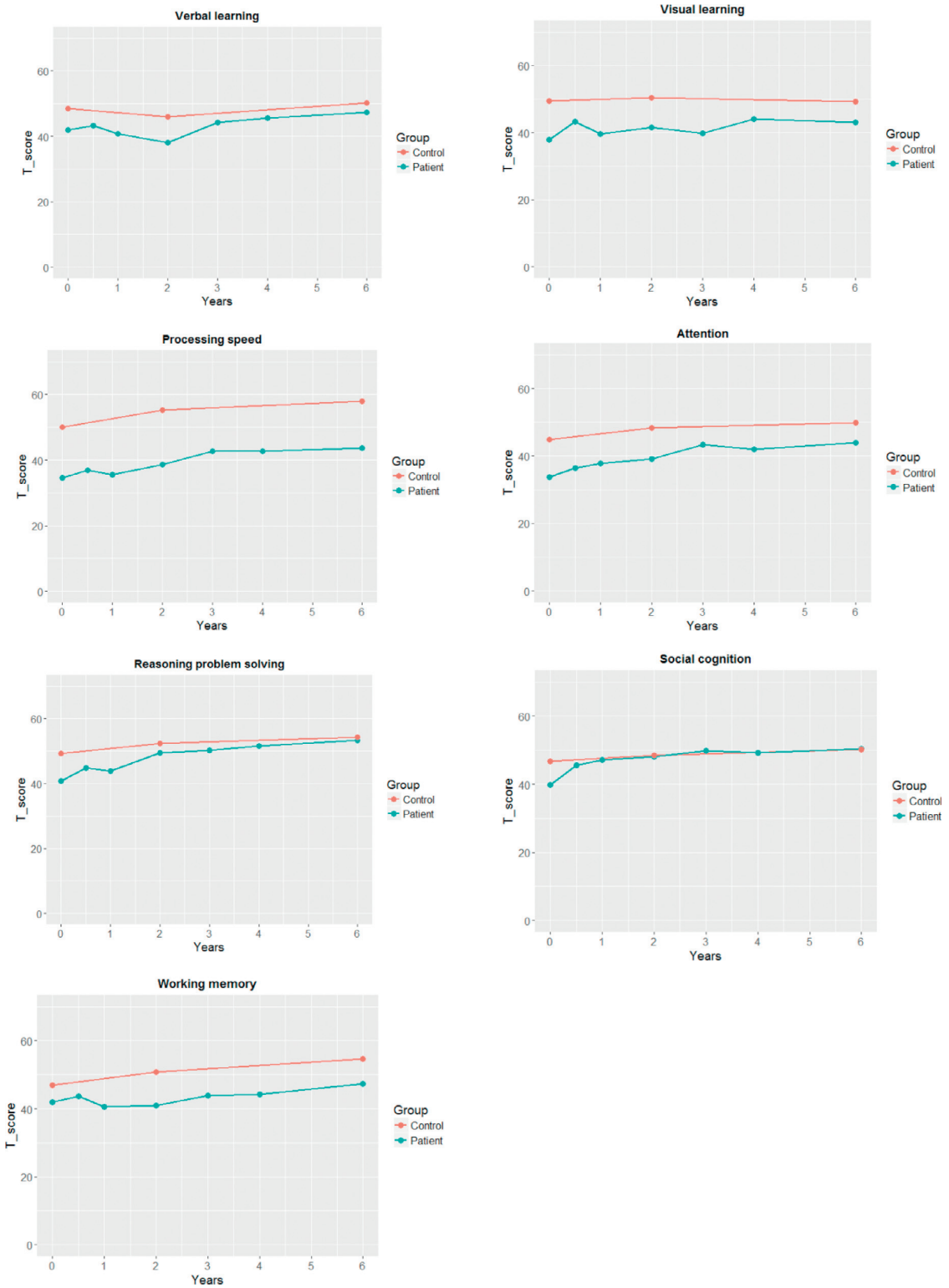

Fig. 1. Mean levels of cognitive domains across 7 measurement waves. *X*-axis represents time measured in years. *Y*-axis is cognitive scores reported as *t*-scores.

have demonstrated that patients scored below controls on all cognitive domains on baseline, and although many cognitive domains improved over time, the cognitive deficits remained 1 to 2 standard deviations below controls throughout a five-year period. Other studies have reported domain specific differences between patients and controls, but the overall trend points toward a similar cognitive change in both groups with the possible exception of executive functions and verbal learning (Bozikas and Andreou, 2011).

Studies of patients with EOS have reported a lack of improvement and even decline in cognition over time (Øie et al., 2011). Many EOS

and FES-patients are often of similar age when they first receive treatment. However, the prospect of cognitive improvement seems to be different for the two groups, as our results show stability or improvement in all cognitive domains, supporting the view of EOS being more severe than first-episode schizophrenia (Raji et al., 2009; Øie et al., 2011).

When comparing the current results with our paper on the 2-year follow-up (Torgalsbøen et al., 2015), we made an interesting finding. In that paper, the patient group showed decline on verbal learning and improvement on reasoning/ problem solving and social cognition compared to healthy controls. However, analyses of the six-year follow-up suggest that these cognitive changes are only temporary. Verbal learning improves after two years, while social cognition stabilizes. Only reasoning/ problem solving continues to improve over time. This points to the importance of assessing cognitive development over many years with multiple assessments when exploring cognitive impairments in schizophrenia. It has been reported that the evidences of change in verbal learning remain inconclusive (Bozikas and Andreou, 2011). However, this may be due to short follow-up periods, as most of the earlier studies had only a follow-up period of two years, and the studies with a longer follow-up period had only two or three assessments in total (Rund et al., 2016). According to the figures, social cognition seems to stabilize over time, and the cognitive trajectories of patients and healthy controls seem to be on the same level after one year. This is interesting as social cognition is increasingly recognized as a potential mediator in the relationship between cognition and functioning (Green et al., 2015). The initial improvement in social cognition may be due to psychoeducation and/or psychotherapy provided to the patients. As symptoms decreases and their illnesses stabilizes, the patients may not attend psychotherapy as frequently anymore, and maybe this is reflected in a stable social cognition score. Holmén et al. (2010) found no difference in social cognition between patients with EOS and healthy controls as measured with the MCCB. They suggested that patients with schizophrenia may have no problems with knowing how to act in social situations, but still have problems performing these actions in real life. They also noted that both patients and controls were younger and performed poorer than the lowest age group in the American norms, suggesting that the test may not be suitable for adolescents. Our populations consisted of older individuals, and neither patients or controls underperformed on the tests. However, it still remains to be determined whether the MSCEIT subtest would yield the same results as role-play tests.

The second interesting finding in our study was that two cognitive domain trajectories were significantly different between control group and FES-patients. Compared to the control group, the patient group showed a larger improvement in reasoning/ problem solving over time, whereas the improvement in working memory was smaller than the control group. There is some evidence of domain specific differences between FES-patients and healthy controls, although the findings remain inconclusive due to heterogeneous measurements and study designs. Most studies have a follow-up period of one to two years, and the comparative groups are seldom matched. These studies have reported differences in cognitive change between patients and controls, for instance in verbal and non-verbal recall and inhibitory processes (Hoff et al., 2005); visual memory and executive function (Crespo-Facorro et al., 2009); verbal fluency and verbal memory (Albus et al., 2006). Studies regarding verbal memory show varied results indicating smaller differences, no differences or larger changes in FES-patients than healthy controls. In the current study where the two groups are matched, we found no differences in verbal memory development as discussed earlier. A larger improvement in reasoning/ problem solving in the patient group was found, suggesting that patients are able to use more flexible problem solving techniques when symptoms subside. On the other hand, patients showed smaller improvements in working memory compared to controls. Working memory is one of the core cognitive deficits in first-episode schizophrenia, and baseline working memory is associated with later social functioning (Fu et al., 2017) and role functioning (Torgalsbøen et al., 2014). This result indicates that the gap in performance seen between the two groups on baseline will only grow larger over time. The current results support our earlier findings (Torgalsbøen et al., 2015) that there are different trajectories for different cognitive domains. From a clinical perspective, this may speak in favor of a targeted rehabilitation of different cognitive domains, such as working memory. Further research into how long-term cognitive development affects functioning is needed.

By including annual assessments over six years we aim to elucidate the cognitive trajectories of patients both under and after the initial psychosis episode and throughout the recovery process. Since we have more frequent assessment points in the early stages of illness, we can see in the figures that improvements are already discernable after 6 months following illness outbreak. Moreover, these improvements continue up to six years and are seen in almost every cognitive domain that are consistently impaired in FES. Studies have consistently shown an association between cognitive functions and functional outcome (Green et al., 2015; Green and Harvey, 2014). However, full recovery from schizophrenia is a lengthy process where clinical symptoms may fluctuate over time. For instance, cognitive improvements have been found to disappear when symptoms are controlled for, suggesting a common origin or a moderating effect (Mayoral et al., 2008). In the present study, most cognitive functions in FES-patients improved in the same rate as healthy individuals, also when symptoms stabilized and patients regained their roles in society. One characteristic with the current study is that 45.5% of the patients are fully recovered by 6-year follow-up (Table 1), with some patients showing signs of partial recovery as early as the first two years. Full recovery is defined as working or studying, having symptoms that are stably mild or absent for two years or more, having contact with friends and/or dating, participating in leisure activities and living independently (Liberman and Kopelowicz, 2005). This may explain why most of the cognitive trajectories start to improve within the first year of illness as seen in the figures. The high recovery rate may also indicate that the cognitive impairments are less manifested in our patient sample, thus we see continued improvements over many years. As the rate of fully recovered patients reported in our study is somewhat higher than what has been reported in other studies, it might be another reason for why our results did not match earlier reports that showed stability in cognitive functioning. In a study by Kopelowicz et al. (2005), it was reported that recovered subjects scored significantly better than non-recovered subjects on executive function, verbal learning, verbal working memory and verbal fluency.

The study's strengths are a healthy control group that is matched pairwise to the patient group, high retention rate in both groups, complete assessments with the MCCB at each assessment point, and multiple measurement occasions across 6 years, which is substantial.

The study's main limitations are a small sample size and uneven assessment points for the two research groups. A small sample size limits the generalizability of our results. However, the drop-out rates from both groups were low, and we were able to analyze all available data with multi-level analyses, thus strengthening our findings. Out of the 56 participants, 84% completed every assessment over the six-year period. Regarding practice effects, we are aware that there is uncertainty regarding whether the changes are due to genuine improvements in cognition or to practice effects, especially when the groups were assessed a different number of times. It has been argued that in samples of patients with schizophrenia, improvements in cognition are mostly accounted for by practice effects (Szöke et al., 2008). However, these studies did not use a consensus based cognitive battery. MCCB has shown small practice effects in validation studies with a test-retest periods as brief as 15 days (Buchanan et al., 2011; Keefe et al., 2011; Nuechterlein et al., 2008). Goldberg et al. (2010) found that practice effects are largest between the initial and second assessments, with smaller increases with subsequent follow-ups. The practice effects are

also comparable between patients and healthy controls. Although it is likely that improvements in both groups are partly due to practice effects, the magnitude of the improvements are comparable in both groups and we argue that no deterioration in FES-patients has been masked by practice effects. Since our patient sample consists of many individuals that are either partially or fully recovered, we also find it likely that the improvements in cognition reflect the improvements in clinical status. Another potential limitation is the possibility of medication effects on cognition. Husa et al. (2014) reported that the cumulative use of antipsychotics affected cognitive functioning negatively, while Takeuchi et al. (2013) found improved cognitive performances following antipsychotics dose reduction. However, the populations in these studies were not FES-patients. We did not find any significant correlations between daily doses of medication and cognitive scores (Torgalsbøen et al., 2014, 2015). Therefore, we argue that there is no direct relationship between medication dose and test performance in our sample. Finally, we did not examine the effects of IQ, which may be associated with cognitive performance at baseline and cognitive change over time.

Conflict of interest

None.

Role of the funding source

This study is internally funded by the Department of Psycholgy, University of Oslo. This funding source had no role in the design of this study, nor during its execution, analyses, interpretation of the data, and decision to submit results.

Acknowledgement

This work was supported by the Department of Psychology, University of Oslo.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: 10.1016/j.psychres.2018.06.016.

References

Akaike, H., 1974. A new look at the statistical model identification. IEEE Trans. Autom. Control. 19 (6), 716–723.
Albus, M., Hubmann, W., Mohr, F., Hecht, S., Hinterberger-Weber, P., Seitz, NN., et al., 2006. Neurocognitive functioning in patients with first-episode schizophrenia. Results of a prospective 5-year follow-up study. Eur. Arch. Psychiatry Clin. Neurosci 256 (7), 442–451.
American Psychiatric Association, 1994. Diagnostic and Statistical Manual for Mental Disorders, fourth ed. Revised. Author, Washington, DC.
Barder, H.E., Sundet, K., Rund, B.R., Evensen, J., Haahr, U., Ten Velden Hegelstad, W., et al., 2013. Neurocognitive development in first episode psychosis 5 years follow-up: associations between illness severity and cognitive course. Schizophr. Res 149 (1-3), 63–69.
Becker, H.E., Nieman, D.H., Wiltink, D., Dingemans, P.M., van de Fliert, J.R., Velthorst, E., et al., 2010. Neurocognitive functioning before and after the first psychotic episode: does psychosis result in cognitive deterioration? Psychol. Med. 40 (10), 1599–1606.
Bora, E., Murray, R.M., 2014. Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: do the cognitive deficits progress over, or after, the onset of psychosis? Schizophr. Bull 40 (4), 744–755.
Bonner-Jackson, A., Grossman, L.S., Harrow, M., Rosen, C., 2010. Neurocognition in schizophrenia: a 20-year multi-follow-up of the course of processing speed and stored knowledge. Compr. Psychiatry 51 (5), 471–479.
Bozikas, V.P., Andreou, C., 2011. Longitudinal studies of cognition in first episode psychosis: a systematic review of the literature. Aust. N. Z. J. Psychiatry 45 (2), 93–108.
Buchanan, R.W., Keefe, R.S.E., Umbricht, D., Green, M.F., Laughren, T., Marder, S.R., 2011. The FDA-NIMH-MATRICS guidelines for clinical trial design of cognitive-enhancing drugs: what do we know 5 years later? Schizophr. Bull 37 (6), 1209–1217.
Carrión, R.E., Walder, D.J., Auther, A.M., McLaughlin, D., Zyla, H.O., Adelsheim, S., et al., 2018. From the psychosis prodrome to the first-episode of psychosis: no evidence of a cognitive decline. J Psychiatr. Res. 96, 231–238.
Crespo-Facorro, B., Rodríguez-Sánchez, J.M., Pérez-Iglesias, R., Mata, I., Ayesa, R., Ramirez-Bonilla, ML., et al., 2009. Neurocognitive effectiveness of haloperidol, risperidone, and olanzapine in first-episode psychosis: a randomized, controlled 1-year follow-up comparison. J. Clin. Psychiatry 70 (5), 717–729.
Fioravanti, M., Bianchi, V., Cinti, M.E., 2012. Cognitive deficits in schizophrenia: an updated metaanalysis of the scientific evidence. BMC Psychiatry 12 (64). http://dx.doi.org/10.1186/1471-244X-12-64.
Fu, S., Czajkowski, N., Rund, B.R., Torgalsbøen, A.K., 2017. The relationship between level of cognitive impairments and functional outcome trajectories in first-episode schizophrenia. Schizophr. Res. 190, 144–149.
Goldberg, T.E., Keefe, R.S.E., Goldman, R.S., Robinson, D.G., Harvey, P.D., 2010. Circumstances under which practice does not make perfect: a review of the practice effect literature in schizophrenia and its relevance to clinical treatment studies. Neuropsychopharmacology 35 (5), 1053–1062.
Green, M.F., Harvey, P.D., 2014. Cognition in schizophrenia: past, present, and future. Schizophr. Res. 1 (1), e1–e9.
Green, M.F., Llerena, K., Kern, R.S., 2015. The “right stuff” revisited: what have we learned about the determinants of daily functioning in schizophrenia? Schizophr. Bull 41 (4), 781–785.
Heinrichs, R.W., Zakzanis, K.K., 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12 (3), 426–445.
Hoff, A.L., Sakuma, M., Wieneke, M., Horon, R., Kushner, M., Delisi, L.E., 1999. Longitudinal neuropsychological follo-up study of patients with first-episode schizophrenia. Am. J. Psychiatry 156 (9), 1336–1341.
Hoff, A.L., Svetina, C., Shields, G., Stewart, J., Delisi, L.E., 2005. Ten year longitudinal study of neuropsychological functioning subsequent to a first episode of schizophrenia. Schizophr. Res. 78 (1), 27–34.
Holmén, A., Juuhl-Langseth, M., Thormodsen, R., Melle, I., Rund, B.R., 2010. Neuropsychological profile in early-onset schizophrenia-spectrum disorders: measured with MATRICS battery. Schizophr. Bull. 36 (4), 852–859.
Husa, A.P., Rannikko, I., Moilanen, J., Haapea, M., Murray, G.K., Barnett, J., et al., 2014. Lifetime use of antipsychotic medication and its relation to change of verbal learning and memory in midlife schizophrenia – an observational 9-year follow-up study. Schizophr. Res 158 (1-3), 134–141.
Juuhl-Langseth, M., Holmén, A., Thormodsen, R., Øie, M., Rund, B.R., 2014. Relative stability of neurocognitive deficits in early onset schizophrenia spectrum patients. Schizophr. Res. 156 (2-3), 241–247.
Keefe, R.S.E., Perkins, D.O., Gu, H., Zipursky, R.B., Christensen, B.K., Lieberman, J.A., 2006. A longitudinal study of neurocognitive function in individuals at-risk for psychosis. Schizophr. Res. 88 (1-3), 26–35.
Keefe, R.S.E., Fox, K.H., Harvey, P.D., Cucchiaro, J., Siu, C., Loebel, A., 2011. Characteristics of the MATRICS consensus cognitive battery in a 29-site antipsychotic schizophrenia clinical trial. Schizophr. Res. 125 (2-3), 161–168.
Kopelowicz, A., Libermanm, R.P., Ventura, J., Zarate, R, Mintz, J., 2005. Neurocognitive correlates of recovery from schizophrenia. Psychol. Med. 35 (8), 1165–1173.
Liberman, R.P., Kopelowicz, A., 2005. Recovery from schizophrenia: a concept in search of research. Psychiatr. Serv. 56 (6), 735–742.
Mayoral, M., Zabala, A., Robles, O., Bombín, I., Andrés, P., Parellada, M., et al., 2008. Neuropsychological functioning in adolescents with first episode psychosis: a two-year follow-up study. Eur. Psychiatry 23 (5), 375–383.
Mesholam-Gately, R.J., Guiliano, A.J., Goff, K.P., Faraone, S.V., Seidman, L.J., 2009. Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology 23 (3), 315–336.
Mohn, C., Sundet, K., Rund, B.R., 2012. The Norwegian standardization of the MATRICS (measurement and treatment research to improve cognition in schizophrenia) consensus cognitive battery. J. Clin. Exp. Neuropsychol. 34 (6), 667–677.
Niendam, T.A., Bearden, C.E., Johnson, J.K., McKinley, M., Loewy, R., O'Brien, M., et al., 2006. Neurocognitive performance and functional disability in the psychosis prodrome. Schizophr. Res. 84 (1), 100–111.
Niendam, T.A., Bearden, C.E., Zinberg, J., Johnson, J.K., O'Brien, M., Cannon, T.D., 2007. The course of neurocognition and social functioning in individuals at ultra high risk for psychosis. Schizophr. Bull. 33 (3), 772–781.
Nuechterlein, K.H., Barch, D.M., Gold, J.M., Goldberg, T.E., Green, M.F., Heaton, R.K., 2004. Identification of separable cognitive factors in schizophrenia. Schizophr. Res. 72 (1), 29–39.
Nuechterlein, K.H., Green, M.F., 2006. MATRICS Consensus Cognitive Battery. MATRICS Assessment Inc, Los Angeles, CA Manual.
Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., et al., 2008. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. Am. J. Psychiatry 165 (2), 203–213.
Quené, H., van den Bergh, H., 2004. On multi-level modeling of data from repeated measures designs: a tutorial. Speech Commun. 43 (1), 103–121.
Raji, T.K., Ismail, Z., Mulsant, B.H., 2009. Age at onset and cognition in schizophrenia: a meta-analysis. Br. J. Psychiatry. 195 (4), 286–293.
Rund, B.R., 1998. A review of longitudinal studies of cognitive functions in schizophrenia patients. Schizophr. Bull. 24 (3), 425–435.
Rund, B.R., Barder, H.E., Evensen, J., Haahr, U., ten Velden Hegelstad, W., Joa, I., et al., 2016. Neurocognition and duration of psychosis: a 10-year follow-up of first-episode patients. Schizophr. Bull. 42 (1), 87–95.
Schaefer, J., Giangrande, E., Weinberger, D.R., Dickinson, D., 2013. The global cognitive impairment in schizophrenia: consistent over decades and around the world. Schizophr. Res. 150 (1), 42–50.
Sterling, J., White, C., Lewis, S., Hopkins, R., Tantam, D., Huddy, A., et al., 2003. Neurocognitive function and outcome in first-episode schizophrenia: a 10-year follow-up of an epidemiological cohort. Schizophr. Res 65 (2-3), 75–86.

Szöke, A., Trandafir, A., Dupont, M.-E., Méary, A., Schürhoff, F., Leboyer, M., 2008. Longitudinal studies of cognition in schizophrenia: meta-analysis. Br. J. Psychiatry. 192 (4), 248–257.
Takeuchi, H., Suzuki, T., Remington, G., Bies, R.R., Abe, T., Graff-Guerro, A., et al., 2013. Effects of risperidone and olanzapine dose reduction on cognitive function in stable patients with schizophrenia: an open-label, randomized, controlled, pilot study. Schizophr. Bull 39 (5), 993–998.
Torgalsbøen, A.K., Mohn, C., Czajkowski, N., Rund, B.R., 2015. Relationship between neurocognition and functional recovery in first-episode schizophrenia: results from the second year of the Oslo multi-follow-up study. Psychiatry Res 227 (2-3), 185–191.
Torgalsbøen, A.K., Mohn, C., Rund, B.R., 2014. Neurocognitive predictors of remission of symptoms and social and role functioning in the early course of first-episode schizophrenia. Psychiatry Res 216 (1), 1–5.
Øie, M., Sundet, K., Ueland, T., 2011. Neurocognition and functional outcome in early-onset schizophrenia and attention-deficit/hyperactivity disorder: a 13-year follow-up. Neuropsychology 25 (1), 25–35.

III

Psychiatry

Interpersonal and Biological Processes

ISSN: 0033-2747 (Print) 1943-281X (Online) Journal homepage: https://www.tandfonline.com/loi/upsy20

Cognitive, Work, and Social Outcomes in Fully Recovered First-Episode Schizophrenia: On and off Antipsychotic Medication

Susie Fu, Nikolai Czajkowski & Anne-Kari Torgalsbøen

To cite this article: Susie Fu, Nikolai Czajkowski & Anne-Kari Torgalsbøen (2019): Cognitive, Work, and Social Outcomes in Fully Recovered First-Episode Schizophrenia: On and off Antipsychotic Medication, Psychiatry, DOI: 10.1080/00332747.2018.1550735

To link to this article: https://doi.org/10.1080/00332747.2018.1550735

Published online: 04 Jan 2019.