Cognitive change in psychosis

Liss G Anda

UNIVERSITY OF BERGEN

Cognitive change in psychosis

Liss G Anda

Thesis for the degree of Philosophiae Doctor (PhD)
at the University of Bergen

Date of defense: 23.10.2020

Year: 2020
Title: Cognitive change in psychosis

Name: Liss G Anda
Print: Skipnes Kommunikasjon / University of Bergen

Scientific environment

This thesis has been written under the auspices of the Research department, Psychiatric division, Haukeland University Hospital, Bergen, Norway, where I was employed 2013-2017, funded by grants from the Liaison Committee of Helse-Vest. I was sited with TIPS at the Centre for Clinical Research in Psychosis, Stavanger University Hospital, Norway while completing my PhD studies at the International Graduate School in Integrated Neuroscience (IGSIN) at the University of Bergen.

My project has investigated cognitive impairment and change during various stages of psychosis, ranging from prodromal ultrahigh risk groups to established illness requiring medication. It has been a sub-project of the Bergen psychosis project (BPP) and the Bergen Psychosis Project 2 (BP2), which compared the effect of four and three antipsychotic drugs in patients with psychotic disorders, respectively.

My main supervisor, Professor Else-Marie Løberg, was the BP2 co-principal investigator. During the project she was affiliated with the Institutes of Clinical as well as Biological and Medical Psychology at the University of Bergen. Co-supervisor Dr Erik Johnsen (PhD) was affiliated to the Department of Clinical Medicine, University of Bergen. Both are also affiliated with the Division of psychiatry, Helse Bergen, in addition to the Department of Addiction medicine for Løberg. Co-supervisor Professor Astri Lundervold is also affiliated with the Department of Biological and Medical Psychology, University of Bergen. Finally, co-supervisor Professor Kolbjørn K Brønnick is affiliated with the Department of Public Health, University of Stavanger, and the Centre for Age-Related Medicine - SESAM, Helse Stavanger.

This thesis is based on collaborative data from several research sites. The first paper used data from the BPP from the Bergen Psychosis Research Group at Haukeland University Hospital. The second paper includes data from the Prevention of Psychosis Project (POP) at the Centre for Clinical Research in Psychosis, Stavanger University Hospital, Norway as well as from the BP2 project. The third paper is based entirely on BP2 data.

Acknowledgements

A great thank you to study participants who made this thesis possible by giving their time to the POP, BP2 and BPP projects. I am especially grateful to the BP2 Stavanger site participants whom I followed up: I feel privileged to have been invited into your lives and even in some cases, your homes.

I would also like to thank my main supervisor Professor Else-Marie Løberg and co-supervisor Dr Erik Johnsen for giving me the opportunity to do this PhD. They have both demonstrated faith in its eventual completion, and Løberg taught me to never lose faith in my ideas. Thanks also to my co-supervisor Kolbjørn Brønnick for originally pointing me to the BP2 project, and for practical, literary, and social support throughout. Last, but not least, I am grateful to my wise co-supervisor Astrid Lundervold for never being too busy to lend an ear at very short notice, and for psychological support in times of need.

I would like to thank PhD colleagues and the whole TIPS group in Stavanger for providing a stimulating work environment throughout my thesis work. The detection team at TIPS Stavanger have provided invaluable practical and psychological support throughout my work. Special mention to Inge Joa who helped throughout the process, more times than could strictly be expected. Thanks also to the remaining co-authors whom I have had the pleasure of collaborating with. I am also grateful to clinical staff helped me reach participants, and to nurses at Stavanger Helseforskning for their practical support.

I would also like to thank psychologist Rolf Gjestad, who was incredibly patient with my second paper statistics, and statistician Christoffer Bartz-Johannessen for providing excellent statistical and psychological support for the third paper.

Finally, I am grateful to my friends and family for diversion and support in equal measure. My husband Bjørn-Are Ågotnes deserves special mention for putting up with a third entity in our relationship for over half of its duration, however you look at it. And I apologise to the kids for all the times I've said "no, Mummy has to work!" From now on: 24/7 Minecraft, I promise.

Abbreviations

General

ANOVA: Analysis of Variance

BPP: Bergen Psychosis Project

BP2: Bergen Psychosis Project 2

CI: Confidence interval

CBT: Cognitive-behavioural therapy

DDD: Defined daily doses

DSM-IV: Diagnostic and Statistical Manual for Mental Disorders, 4th edition

DSM-5: Diagnostic and Statistical Manual for Mental Disorders, 5th edition

D2: Dopamine 2 receptor

fMRI: Functional magnetic resonance imaging

ICD: International Statistical Classification of Diseases

IGSIN: International Graduate School in Integrated Neuroscience

ITT: Intention to treat

PANSS: Positive and Negative Syndrome Scale for Schizophrenia

POP: Prevention of psychosis study

PP: Per protocol

SCID-I: Structured Clinical Interview for DSM-IV Axis disorders

SD: Standard deviation

SIPS: Structured Interview for Prodromal Symptoms

SZ: Schizophrenia

SPSS: Statistical Package for the Social Sciences

TIPS-II: Early Treatment and Intervention in Psychosis study

UHR: Ultra High Risk for psychosis

Neurocognitive tests

CVLT-II: California Verbal Learning Test II

CWIT: Colour-Word Interference test

D-KEFS: Delis-Kaplan Executive Function System

DL: Dichotic listening test

FAS: Verbal fluency test

HVLT-R: Hopkins Verbal Learning Test – Revised

RBANS: The Repeatable Battery for the Assessment of Neuropsychological Status

TMA: Trail Making Test A

TMB: Trail Making Test B

WAIS-III: Wechsler Adult Intelligence Scale -Third Edition

WAIS-IV: Wechsler Adult Intelligence Scale –Fourth Edition

WMS: Wechsler Memory Scales

Abstract

Background
Cognitive functioning is impaired in schizophrenia spectrum disorders, with cognitive symptoms a core part of schizophrenia. Cognitive impairment is associated with poorer daily life functioning and prognosis, making it an important treatment goal. As opposed to positive symptoms, cognitive symptoms have proven quite resistant to antipsychotic drug treatment. It is also unclear how cognitive functioning changes throughout the course of psychosis, from the prodromal stage, during acute psychosis and after the onset of medical treatment. The aim of this thesis was to investigate cognitive impairment and change during these three important stages of illness.

Paper I aimed to investigate the relation between cognitive and symptomatic change in patients with psychotic disorders (n=84) during the early acute phase of illness. Psychotic symptoms in the sample were due to schizophrenia spectrum disorders (F20-29), psychoactive substance use (F12-19), and affective disorders with psychosis (F31-33). We administered the tests of the Repeateble Battery for the Assessment of Neuropsychological Status (RBANS) on admission and again at acute ward discharge (mean time 4.1 weeks, SD 1.86 weeks), using the Positive and Negative Syndrome Scale (PANSS) to assess symptomatic change. We found cognitive impairment (t < 35) in 28.6% of participants at baseline and 13.1% at follow-up. PANSS negative symptoms change significantly predicted total RBANS performance improvement (beta = -.307, p = .016). There was no significant difference in cognitive change between subjects with schizophrenia and those with other psychotic disorders. Findings thus indicated that the proportion of subjects with mild to moderate impairment in cognitive test performance is reduced across the acute phase of psychosis, and that improvement is related to amelioration of negative symptoms.

Paper II compared the cognitive functioning and profile of subjects deemed at ultra high risk for psychotic disorder (UHR, n=51) to a sample with schizophrenia (F20), split into two groups based on duration of illness (n=19 and 22). Comparisons were

made using coordinated norms based on healthy controls (n=61) reflecting the younger UHR age spectrum. A comprehensive neurocognitive test battery aiming to measure speed of processing, working memory, verbal learning, reasoning, and problem solving, as well as visual problem solving were used. UHR subjects showed impaired speed of processing (p<.001), working memory (p=.042) and verbal learning, reasoning and problem solving (p=.007) as compared to the control group. Visual problem-solving skills appeared unimpaired. UHR subjects significantly outperformed the schizophrenia group with duration of illness >3 years for speed of processing and working memory (both p<.001). There were no significant differences in performance between the UHR group and the group with duration of schizophrenia < 3 years. It can be concluded that cognitive performance is impaired in UHR subjects and should thus be monitored by clinicians. If spatial skills are less impaired, this could be useful to know when facilitating academic and work participation for this group.

Paper III compared cognitive change in three groups of participants with schizophrenia spectrum disorder (F20-F29) receiving amisulpride (n=33), aripiprazole (n=32), and olanzapine (n=39) over 12 months. A short neurocognitive test battery was administered at baseline and again at 6, 26 and 52 weeks. Sample average cognitive test t-scores improved from 42.20 to 46.39 over the year, rising significantly to 6 (Δ2.0; p= .002), 26 (Δ3.4; p< .001) and 52 (Δ4.2; p< .001) weeks, corresponding to a medium effect size Cohen's d of .53. There were no significant between-drug changes in the amount of improvement. Nor were there any significant differences in change between subjects with schizophrenia and those with other psychotic disorders. Our findings thus indicate that despite significant improvements in cognitive test performance, there were no significant between-drug differences in cognitive change in the 12 months following onset of a new course of treatment.

Conclusion

The findings from the present thesis suggest that cognitive impairment in psychosis is present before the appearance of positive symptoms, with a similar but less severe profile of impairment than in established psychotic disorders. Cognitive impairment

appears to fluctuate alongside the course of psychosis, with improvement seen during the first weeks of treatment in acute psychosis, and further improvement with the onset of medical treatment.

List of Publications

1. Anda, L., Brønnick, K. S., Johnsen, E., Kroken, R. A., Jørgensen, H., & Løberg, E.-M. (2016). The course of neurocognitive changes in acute psychosis: relation to symptomatic improvement. *PloS one*, *11*(12), e0167390.
2. Anda, L., Brønnick, K. S., Johnsen, E., Kroken, R. A., Johannessen, J.O., Joa, I., & Løberg, E.-M. (2019). Cognitive profile in ultra-high risk for psychosis and schizophrenia: A comparison using coordinated norms. *Frontiers in Psychiatry*, *10*, 695.
3. Anda, L., Johnsen, E., Kroken, R. A., Joa, I., Rettenbacher, M., Løberg, E.-M. (Ready for publication). Cognitive change and antipsychotic medications: Results from a pragmatic rater-blind RCT.

Contents

14

1. Introduction

1.1 Psychosis

The phenomenon of psychosis encompasses a diverse set of disturbances to perception, cognition, emotions, and behaviour, where a person develops inappropriate interpretations of their environment and sense of self and falls out of touch with reality. Adverse life events and psychosocial stressors may trigger a psychotic episode, but symptoms may also arise spontaneously. It may form part of a primary psychotic disorder of which psychosis is the most prominent expression, with schizophrenia considered the most severe form. Psychosis may also occur as part of an affective disorder (e.g. depression or bipolar disorders), or in relation to psychoactive substance use or somatic health issues. Gathering good quality longitudinal data about psychosis is difficult due to the fluctuating nature of psychotic disorders, as well as the challenging life circumstances of many subjects. Despite research efforts across several decades, the pathway or pathways to psychosis remains unclear. Outcomes of schizophrenia and psychotic disorders are heterogeneous (Lepage, Bodnar, & Bowie, 2014), and the expected progression or treatment response of each person is often uncertain at the point of diagnosis.

1.1.1 Symptom dimensions in psychosis

Symptoms associated with psychosis are often categorised as positive, negative, affective, disorganised, and cognitive (Shevlin, McElroy, Bentall, Reininghaus, & Murphy, 2016). A psychotic episode may entail symptoms falling under some or all of these symptom dimensions, yielding a clinically diverse population. The comprehensive and heterogenous symptomatology leaves psychosis a complicated phenomenon to study. For the purposes of paper II on symptomatic change and cognition, this thesis used a five-factor symptomatic model with affective symptoms split into depressive and excitatory symptoms (Wallwork, Fortgang, Hashimoto, Weinberger, & Dickinson, 2012).

Positive symptoms occur in addition to normal behaviour. They commonly manifest as delusions and / or hallucinations. Delusions are firmly held beliefs which are upheld contrary to conflicting evidence, and which cannot be explained by a person's cultural or religious background. Bizarre delusions in particular were identified as one of Schneider's first-rank schizophrenia symptoms in the 50s. A bizarre delusion according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) entails something which is "clearly implausible" (American Psychiatric Association, 2000), e.g. believing one's brain is missing and stored in the fridge. Such delusions were previously considered to satisfy on their own the diagnostic A-criteria for schizophrenia until being downplayed in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM5) (American Psychiatric Association, 2013). Delusions about external control, thought insertion or theft are common in schizophrenia. Other common delusions have grandiose or paranoid content, often with self-referencing aspects, e.g. believing that objects in the environment are placed to express a "secret message". Hallucinations are perceptual disturbances where the person perceives e.g. sound or images in lieu of external stimuli. The third-generation dopamine theory of schizophrenia by Howes and Kapur (Howes & Kapur, 2009; Howes & Nour, 2016) describe positive symptoms as arising from abnormal mesostriatal dopamine functioning. Excess dopaminergic activity in the mesolimbic pathway, which regulates reward responses in the brain, causes otherwise innocuous stimuli to gain aberrant salience. The person thus falsely perceives these stimuli as having "special meaning". Similarly, internal stimuli may gain sensory properties, giving rise to e.g. hearing non-existent voices. Given that antipsychotic drugs all rely on dopamine 2 (D2) receptor antagonism, positive symptoms respond better to medication than the other symptom dimensions (Miyamoto, Duncan, Marx, & Lieberman, 2005).

Negative symptoms involve a loss of normal behaviour and motivation including social withdrawal, diminished emotional expression and avolition (Foussias & Remington, 2008). Negative symptoms are thought to arise partly due to low levels of dopamine in the prefrontal cortex, dopamine D1 receptor dysfunction and reduced

mesocortical pathway activity (Howes & Kapur, 2009; Lally & MacCabe, 2015), but the biological underpinnings remain only partly clarified. Negative symptoms were previously thought to appear and worsen as illness progressed, but current research indicates that they are present already at the prodromal stage (Piskulic et al., 2012). They in fact fluctuate less throughout the course of illness than do positive symptoms (Austin et al., 2015). Negative symptoms are more strongly correlated with poor functional outcome than are positive symptoms (Fervaha, Foussias, Agid, & Remington, 2014) and respond poorly to antipsychotic treatment (Fusar-Poli et al., 2014).

Affective symptoms are similar to those seen in both depressive and maniform affective disorders, e.g. feelings of guilt, anxiety, tension and poor impulse control (Wallwork et al., 2012). Some have also noted that anxious symptoms may form a meaningful separate dimension (Emsley, Rabinowitz, & Torreman, 2003), illustrating perhaps a non-categorical partition between affective and non-affective psychosis. The Kraepelinian model of mental illness stipulates a schism between affective disorders and psychotic disorder. Still, about one third of patients with schizophrenia spectrum disorders may suffer from depressive symptoms (Conley, Ascher-Svanum, Zhu, Faries, & Kinon, 2007), although reviewed findings have varied widely from 7% to 75% . Symptoms of anxiety and depression are also common during the prodromal stage of psychosis (Falkenberg et al., 2015). Depressive symptoms in schizophrenia are associated with risk of suicidality, poorer functional outcomes, more frequent relapse and lower quality of life (Conley et al., 2007; Hor & Taylor, 2010).

Disorganized symptoms may in extreme cases result in bizarre behaviour, but are more commonly expressed as problems organising conversation and actions, partly due to conceptual disorganization (Wallwork et al., 2012). Formal thought disorder entails impairments in the capacity to sustain coherent discourse, expressed through disturbed organization of written or spoken language. Formal thought disorder may be seen as a positive symptom, but is classed as disorganized because it affects the organization of thoughts rather than their content, which sets it apart from e.g.

delusions. Certain expressions like poverty of speech and interrupted thoughts may also be seen as related to negative symptoms. During acute psychosis, some display so-called word salad, a severe breakdown of syntactic or semantic language content and use of neologisms. Milder forms of disorganization may be expressed in a loosening of associations or difficulties in maintaining targeted conversation, either veering off or return constantly to the same point. One study linked disorganized symptoms to reduced dorsolateral prefrontal grey matter, which in turn was associated with childhood neglect (Cancel et al., 2015). The association was stronger in the psychosis group than in healthy controls, illustrating an aspect of the stress-vulnerability hypothesis of psychosis whereby childhood stressors have a greater impact in those with a genetic predisposition for psychosis. Disorganization is closely tied to neurocognitive processes, possibly more so than any other symptom dimension (Minor & Lysaker, 2014).

Cognitive symptoms, on which this thesis is written, are expressed as impaired cognitive functioning in many people with schizophrenia and other psychotic disorders (Kahn & Keefe, 2013). Problems with verbal abilities, processing speed and working memory are particularly common. In the International Statistical Classification of Diseases, 11th edition (ICD-11), cognitive symptoms are explicitly coded for in primary psychotic disorders, including a severity qualifier (World Health Organization, 2018a). This symptom dimension is described in more detail in section 1.9.

1.2 Schizophrenia spectrum disorders

Schizophrenia has been described as a "global" condition, which is true both geographically and physiologically. It affects more than 21 million people worldwide, with an estimated lifetime prevalence of about 1% (World Health Organization, 2018b). Schizophrenia likely represents the tail end of a spectrum of disorders. The DSM/5 reflects this, having renamed the DSM-IV heading "Schizophrenia and other psychotic disorders" to "Schizophrenia Spectrum and Other Psychotic Disorders" (American Psychiatric Association, 2000, 2013). Schizophrenia spectrum disorders

may entail positive, negative, disorganized and cognitive symptoms alongside impaired psychomotor functions (World Health Organization, 2018a). Affective symptoms including poor emotional rapport and disharmony are common but not considered a primary aspect of schizophrenia spectrum disorders.

The ICD and DSM systems both classify schizophrenia spectrum disorders as distinct from psychosis related to substance use and affective disorders (American Psychiatric Association, 2000, 2013; World Health Organization, 2009, 2018a). The schizophrenia spectrum (F20 – F29) includes schizophrenia itself as well as related disorders like acute and transient schizophrenia-like psychosis (F23), delusional disorder (F22), schizotypal disorder (F21) and schizoaffective disorders (F25). Diagnostic criteria of SSD are based on the primary symptomatic criteria for schizophrenia, with duration and severity varying. Historically, psychosis research, including that on cognition, has often focused rather narrowly on schizophrenia or schizophrenia spectrum disorders alone (Hagger et al., 1993; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009; Rajji, Miranda, & Mulsant, 2014; Riedel, Schennach-Wolff, et al., 2010). This in part because of the severity and great personal and societal impact of schizophrenia, but also because the stringent diagnostic criteria make for more homogenous and comparable groups of subjects. In line with this, Paper II I compared cognitive performance in a group of youth at ultra high risk for psychotic illness (UHR) to that of a group with schizophrenia.

Schizophrenia (F20) is set apart in the main diagnostic manuals by its longer duration, greater symptom load and more severe functional loss. Positive symptoms often appear in the late teens and early 20s. For some, full or partial recovery is possible, while others have a more chronic course. Schizophrenia is associated with anomalies in large neurotransmitter systems, brain physiology and connectivity, which again are linked to positive, negative and cognitive symptoms (Schaefer, Giangrande, Weinberger, & Dickinson, 2013). Affected individuals also have a higher odds ratio for a wide range of physiological conditions including metabolic syndrome, diabetes, heart disease and Alzheimer's disease (Hjorthøj, Stürup, McGrath, & Nordentoft, 2017). A link to chronic inflammation has also been suggested, as inflammation is both a state and trait phenomenon in schizophrenia

(Kirkpatrick & Miller, 2013). The link between somatic issues and schizophrenia may be due to a combination of lifestyle issues, shared genetic risk factors (Dieset, Andreassen, & Haukvik, 2016), side effects of psychotropic drug use (Huhn et al., 2019) as well as challenges in accessing adequate somatic health care (Swildens, Termorshuizen, de Ridder, Smeets, & Engelhard, 2016). The suicide rate is also high with 5% a conservative measure, and some reviews finding a rate of up to 13% (Popovic et al., 2014), up to tenfold that of the general population (Chesney, Goodwin, & Fazel, 2014). Added together these factors all contribute to shortened life expectancy: A Nordic study estimated life expectancy of patients with schizophrenia to be from 15.6 to 16.9 years shorter than that of the general population (Laursen, Nordentoft, & Mortensen, 2014).

1.3 Other psychosis: Affective and substance incuded psychotic disorders

Psychotic disorders as a whole have a worldwide prevalence of about 3% (Bonnett, Varese, Smith, Flores, & Yung, 2019). Schizophrenia spectrum disorders make up only part of these. Our developing understanding of psychosis might however benefit from a broader conceptualisation also encompassing psychotic symptoms due to psychoactive substance use (F12-19) and affective disorders with psychotic symptoms (F31-33). This thesis therefore chose to include participants with substance induced psychosis in the sample for Paper I. Inclusion in the schizophrenia spectrum disorders group required a primary ICD-10 diagnosis of F20, F23.0 or F23.2, with SIP and affective disorders with psychotic symptoms (F31-33), grouped as other psychotic disorders.

The Kraepelinian affective/non-affective distinction is reflected in the description of ICD-10 diagnoses F20-F29 as the "non-affective psychoses". This created a need for a diagnosis to describe cases straddling the affective and psychotic symptom dimensions, and this task fell to schizoaffective disorder (F25). Where the ICD-10 which asks for symptoms insufficient to "justify a diagnosis of either schizophrenia or a depressive episode", the DSM/5 outlines that schizoaffective disorder be used

where A-criteria for schizophrenia *are* met. The DSM-IV-TR conceded that schizoaffective disorder "unfortunately does not do its job very well" and struggles with low reliability and poor temporal stability and clinical stability (Malaspina et al., 2013). High affective symptom scores are also common in non-affective diagnoses (van Os et al., 2000), and the two disorder spectrums share genetic factors (Kavanagh, Tansey, O'Donovan, & Owen, 2015). This thesis therefore included participants with affective disorder and psychotic symptoms (F31-33) in the sample of papers I, aiming of giving a broader and more clinically representative view of cognition during acute psychosis. Similarly, in paper III, inclusion of affective psychosis gives a more representative view of the group actually receiving antipsychotic drugs in clinical settings.

Substance induced psychosis diagnoses (F11-19 with signifier x.x5) are used when psychotic symptoms are thought to be triggered by psychoactive substance use, although not as a direct effect of intoxication. Importantly, to differentiate from primary psychosis disorders like F20-29, symptoms should subside within a certain timeframe. This time is set at "about a month" for the DSM/5 and for the ICD-10, partial remission within a month and full remission within six months. During the acute phase of psychosis, it is difficult to clinically differentiate between the symptom profiles of substance induced psychosis and psychosis with comorbid substance use, and the validity of this distinction has been questioned. About 25% of substance induced psychosis diagnoses are re-assigned as primary psychosis after one year (Caton et al., 2007) rising to 50% after two years (Alderson et al., 2017). Initial diagnoses of these disorders thus appear to drift towards schizophrenia spectrum diagnoses over time (Niemi-Pynttari et al., 2013). Due to this diagnostic instability, patients with substance induced psychosis were included in paper I where inclusion happened during the acute phase of illness.

Diagnostic instability in general has long presented a major challenge to clinical schizophrenia research, with each update to new diagnostic manuals introducing new imperfections in categorical overlap (Rund, 1998). A core aim of DSM editions, including the DSM-5, has thus been to create reliable diagnostic criteria. However,

controversy remains over how to categorise psychotic illness, and whether these categories are sound. The diagnostic criteria of ICD-10, ICD11 and DSM-5 also allow for a great deal of heterogeneity in the diagnosing of psychotic disorders, meaning that even persons diagnosed with the same illness may differ considerably from one another. The Kraepelinian divide and the concept of schizophrenia itself have also been subject to criticism (Bentall, 2004; Boyle, 2014). An in-depth discussion of this important debate falls outside the scope of this thesis. However, a shift away from a singular focus on schizophrenia may more closely reflect a clinical reality where schizophrenia forms only a small and shifting, although significant, part of the puzzle of psychosis. Cognitive symptoms also exist across the psychotic spectrum, and not just in schizophrenia (Bora, Yucel, & Pantelis, 2009; Simonsen et al., 2009). This thesis has therefore aimed to investigate both schizophrenia spectrum psychosis as well as high risk youth and the wider range of psychotic disorders presented in acute clinical settings.

1.4 Disability and the societal impact of schizophrenia

Despite the prevalence of only 1%, schizophrenia is one of the costliest mental health disorders. Worldwide, schizophrenia is among the 20 leading causes of disability, with 0.5% of disability-adjusted life years attributed to it in 2017 (Institute for Health Metrics and Evaluation, 2019). Disability arises not only from psychotic symptoms including cognitive impairment, but also from somatic conditions associated with it (Hjorthøj et al., 2017). In Norway alone, the cost p.a. of schizophrenia has been estimated to USD 890m, including USD19.5m spent on antipsychotic medication (Evensen et al., 2015). In addition, expenses include medical and psychosocial treatment, hospital admissions and social support. Schizophrenia also contributed to about 12.7 million years lived with disability measured globally in 2017 (James et al., 2018), illustrating the great impact of this disorder on each person's life. Only about 10% of this patient group in Norway is in ordinary paid employment (Evensen et al., 2015), and up to 85% of worldwide costs related to schizophrenia may be attributed to such indirect sources (Chong et al., 2016).

Progress in attaining functional recovery in schizophrenia has not kept pace with the alleviation of positive symptoms by antipsychotic drugs, perhaps because neither negative nor cognitive symptoms have responded well to drug treatment (Foussias & Remington, 2008). Cognitive deficits are likely responsible for a considerable part of lingering functional impairment. Cognitive functioning is a better predictor of outcome than either positive and negative symptoms (Green & Harvey, 2014; Lepage et al., 2014). In first-episode psychosis, working memory, attention, and speed of processing performance appears to predict over half of longitudinal variance in school or work participation (Nuechterlein et al., 2011). Working memory and attention may be especially important to work skills (Bowie et al., 2008). However, other factors including the number and duration of psychotic episodes, any residual positive and negative symptoms, as well as the gradual erosion of academic and social opportunities most likely also compound effects of cognitive problems on functioning. Better knowledge about these symptoms and how to facilitate improved functioning would reduce both societal and personal costs of psychotic illness.

1.5 Modelling psychosis: A continuum and stages

Psychotic disorders and schizophrenia appear to represent the severe end of an experiential continuum, and psychosis-like symptoms may occur in about 5% of the general population (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009) The majority of people experiencing these phenomena do not however come to the attention of mental health care services (Løberg, Gjestad, Posserud, Kompus, & Lundervold, 2019). However, experience of psychosis-like symptoms may be associated with increased risk of later psychotic disorder (van Os & Reininghaus, 2016). Phenomena like the 6% of healthy people reporting non-distressing hallucinatory experiences (Linscott & van Os, 2013) are difficult to contain within traditional and categorical models of psychopathology as represented by the ICD and DSM diagnostic systems. This has motivated the development of an alternative model of psychosis as a range of experiences of varying severity and intensity. The continuum would range from sub-clinical phenomena to full-blown psychosis with

functional impairment and high levels of distress (Yung et al., 2012), perhaps based on an extended psychosis phenotype (Howes & Kapur, 2009). Psychosis may thus be described as a highly heterogenous phenomenon which may vary hugely not just in presentation but also in severity and course.

Schizophrenia has shifted from historically being a "grim diagnosis with a poor prognosis" to currently being one which offers hopes of remission and recovery (Green & Harvey, 2014). This shift necessitated a more complex model of illness course, and motivated the development of the current staged model of psychotic illness. Full-blown psychosis is regularly preceded by a prodrome in which attenuated positive symptoms or self-disturbance are accompanied by cognitive deficits and often functional decline (Møller & Husby, 2000; Yung & McGorry, 1996). For some individuals, this prodromal state develops into acute psychosis, characterised by florid positive symptoms. First episode psychosis has been a particular topic of research interest, especially for efforts to ameliorate illness course by early intervention (González-Blanch et al., 2010; McGorry, Killackey, & Yung, 2008; ten Velden Hegelstad et al., 2012). Although the vast majority of first episode psychosis patients achieve symptomatic remission over a year, over 50% are likely to relapse and have another acute episode within three years, rising to 80% over five year (Alvarez-Jimenez et al., 2012).Whereas chronic psychotic disorder and schizophrenia were previously thought to be superseded by a progressive deterioration of negative symptomatology, functioning and cognition (Bilder et al., 1992; McGlashan & Fenton, 1993) a more optimistic view now prevails of fluctuating but not deteriorating symptomatology in those who experience multiple psychotic episodes of acute psychosis (Crumlish et al., 2009).

1.5.1 The psychosis prodrome and ultra high risk groups

In medical terms, a prodrome describes the phenomenon of signs and symptoms preceding acute or fully developed illness (Yung & McGorry, 1996). The word itself originated from the Latin prodromus, which describes a written work preliminary to another larger work (OED, n.d.-b). For psychotic disorders more specifically, the prodrome encompasses the time between a notable change in behaviour from

baseline, to the development of full-blown psychotic symptoms (Beiser, Erickson, Fleming, & Iacono, 1993). The idea of a prodrome has been described as part of the phenomenon of schizophrenia since the time of Bleuler (Yung & McGorry, 1996).

The late 1990s saw renewed interest in the prodromal phase of psychotic disorder. Research and clinical efforts aiming at providing early interventions for first episode psychosis patients noted that many first episode psychosis patients had experienced lengthy periods of subclinical disturbances before falling ill (Joa, Gisselgård, Brønnick, McGlashan, & Johannessen, 2015). In addition, it was discovered that early intervention services in first-episode psychosis might shorten the duration of untreated psychosis and thereby ameliorate the course psychotic disorders (Larsen et al., 2011). By extension, being able to intervene before the development of de facto symptoms might prove useful.

Having identified a prodromal phase in psychosis, work began on to identify risk factors for prediction of so-called "conversion" to full-blown psychotic disorders. This led to the conceptualisation of a state of Ultra High Risk for psychosis (UHR) (Yung & McGorry, 1996), which may be screened for in much the same way as first-episode psychosis. This state is currently conceptualised encompassing sub-clinical or attenuated positive symptoms, which may be less pronounced, more infrequent or of briefer duration than the diagnostic cut-offs, as well as a related decline in social, academic or professional functioning (T. J. Miller et al., 2003). Research has also focused on so-called basic symptoms of the prodromal phase, i.e. subjective deficits in stress reactivity, perception and cognition (Hambrecht, Lammertink, Klosterkötter, Matuschek, & Pukrop, 2002). Known risk factors include genetic risk combined with functional decline, attenuated psychosis symptoms like unusual thought content and suspiciousness, poor social functioning, anhedonia and substance abuse, with the addition of neurocognitive measures further improving predictions (Fusar-Poli, Borgwardt, Bechdolf, & et al., 2013).

Despite work to map out risk factors, accurately identifying those at risk of imminent psychotic illness has proved challenging, with only about 25% of identified UHR individuals actually developing psychotic illness (Simon et al., 2011). It has been

suggested that this is due to UHR selection often focusing on attenuated positive symptoms rather than state deficits causing social withdrawal and anhedonia, which may be a less distinct but more permanent indicator of psychosis risk (Simon & Umbricht, 2010). Still, it should be noted that UHR individuals often struggles with mental health and functional issues outside that of psychotic disorder, and still require from follow-up even if they do not develop psychotic symptoms (Falkenberg et al., 2015; Ruhrmann et al., 2008).

1.5.2 First-episode psychosis

First-episode psychosis usually refers to the first time a person experiences clinically significant positive symptom. Early first episode psychosis research suggested that this phase was a critical period in which treatment and treatment response might determine long-term prognosis (Birchwood, Todd, & Jackson, 1998). More recent reviews and research support the efficiency of targeted first episode psychosis programs aiming to reduce DUI and the risk of relapse (Álvarez-Jiménez, Parker, Hetrick, McGorry, & Gleeson, 2009; Crumlish et al., 2009; ten Velden Hegelstad et al., 2012). Longer duration of untreated psychosis is associated with poorer clinical and functional outcomes (Penttilä, Jääskeläinen, Hirvonen, Isohanni, & Miettunen, 2014). For the purposes of Paper III of this thesis we have compared first episode psychosis to non-first episode psychosis subjects in terms of cognitive response to medication. Another meaningful distinction may be made between groups with recent onset and more distant onset schizophrenia (Sponheim et al., 2010), which formed the basis of group comparisons in paper II.

1.6 Aetiology and risk factors in schizophrenia

The idea of a biological basis for schizophrenia or madness may have been with us since prehistoric times. The discovery of ancient human skulls with trepanations have been hypothesized to represent crude surgery to alleviate spirits plaguing the brain (Faria, 2013). However, centuries later, we still do not fully understand the mechanisms or aetiology of psychosis.

Twin studies have indicated schizophrenia to have a high heritability of nearly 80% (Hilker et al., 2018). No causative genes for schizophrenia have been isolated, suggesting both polygenic inheritance and genetic heterogeneity (Greenwood, Braff, Light, & et al., 2007). There is significant genetic overlap between schizophrenia and other mental health problems, e.g. bipolar disorder and autism spectrum disorders (Carroll & Owen, 2009). Schizophrenia is also more common in populations with general learning disabilities, and overrepresented in groups with childhood learning disabilities (Welch, Lawrie, Muir, & Johnstone, 2011). It should however be noted that learning disabilities in themselves are not indicative of ultra-high risk for psychosis.

The broad range of symptoms has allowed investigators to focus on one part of the elephant while ignoring others, with schizophrenia famously being deemed in the 70s "the graveyard of neuropathologists" (Plum, 1972). However, pharmacological and technological progress have since motivated massive research efforts. Later in the 70s, early computed tomography imaging studies found enlarged lateral ventricles in chronic schizophrenia (Johnstone, Frith, Crow, Husband, & Kreel, 1976; Weinberger, Torrey, Neophytides, & Wyatt, 1979). However, enlarged ventricles also exist in mood disorder (Elkis, Friedman, Wise, & Meltzer, 1995) and came to be seen as indicative of an underlying risk factor rather than a cause (Chua & McKenna, 1995). The advent of magnetic resonance imaging in the 80s led to abnormalities being identified in temporal structures including the amygdala, hippocampus, and the temporal neocortex as well as in prefrontal grey matter, the orbitofrontal cortex, and subcortical areas including the basal ganglia and cavum septi pellucidi (Shenton, Dickey, Frumin, & McCarley, 2001). Again, the specificity of magnetic resonance imaging findings to schizophrenia was unclear.

More recently, diffusion tensor imaging and functional magnetic resonance imaging (fMRI) technology made possible detailed studies of white matter integrity as well as brain connectivity patterns in schizophrenia. Studies using fMRI have found impairments in both task related and resting state brain network connectivity in first-episode illness (Mwansisya et al., 2017). UHR fMRI studies have similarly found

differences in resting state connectivity (Shim et al., 2010) and white matter integrity (Karlsgodt, Niendam, Bearden, & Cannon, 2009; Rigucci et al., 2016), with authors suggesting links to functional outcome and the appearance of hallucinations. Studies combining fMRI with diffusion tensor imaging indicate dysconnectivity especially in frontal and temporal regions, with findings more consistent for chronically ill groups (Fitzsimmons, Kubicki, & Shenton, 2013). Although a specific underlying neurobiological white matter deficit for psychosis has yet to be identified (Samartzis, Dima, Fusar-Poli, & Kyriakopoulos, 2014), symptoms have been suggested to arise from brain dysconnectivity and dysregulation (S. Li et al., 2019).

Positive symptoms have long been linked to neurotransmitter abnormalities. The chance discovery of dopamine antagonistic antipsychotic drugs in the 1950s motivated intense theoretical and research efforts aimed at exploring the role of dopamine in psychosis (Lally & MacCabe, 2015; Snyder, 1976). It also became clear that certain dopaminergic stimulants, e.g. amphetamine, could induce psychosis-like symptoms. The current third-generation dopamine hypothesis still places aberrant salience driven by dopaminergic dysfunction at the core of psychotic symptoms (Howes & Kapur, 2009). A meta-analysis of positron emission tomographystudies found strong evidence for elevated presynaptic dopamine synthesis in schizophrenia, including in drug-naïve subjects (Howes et al., 2012) Synaptic dopamine levels and dopamine release was also found to be elevated. Although the reason for this dysfunction remains unknown, decreased prefrontal dopaminergic neurotransmission (Fusar-Poli et al., 2010; Meyer-Lindenberg et al., 2002) and glutamatergic dysfunction (West, Floresco, Charara, Rosenkranz, & Grace, 2003) have both been suggested as potential causal mechanisms (Stone et al., 2010).

Neuroinflammation and immunology in psychosis are currently subject to intense research efforts (Dickerson et al., 2015; Orlovska-Waast et al., 2019). Certain maternal infections during the prenatal phase increase risk of later psychosis (Brown & Derkits, 2010). Inflammation affecting foetal brain development was suggested as a common mediator of this effect, motivating further explorations of immunological abnormalities as an endophenotype of schizophrenia. (B. J. Miller, Culpepper,

Rapaport, & Buckley, 2013). Microglia activation and release of cytokines may for instance be causing dopaminergic and glutamatergic dysregulation by causing damage to glial cells, though post mortem findings of such damage in schizophrenia are equivocal (Trépanier, Hopperton, Mizrahi, Mechawar, & Bazinet, 2016). Schizophrenia is also linked to autoimmune disease and immune related genetic markers (Khandaker et al., 2015). Inflammation thus provides a potential unifying mechanism for previous findings of both genetic, structural and neurotransmitter abnormalities. It may also potentially provide a bridging between physiological findings and known environmental risk factors for psychosis, e.g. childhood adversity (Mondelli et al., 2011). However, these mechanisms remain poorly understood.

The two-hit model of schizophrenia, a version of which was suggested already in the 60s by Mednick and McNeil (1968) suggests that genetic risk factors are compounded by subsequent stressors to produce psychotic symptoms (van Os, Kenis, & Rutten, 2010). Twin studies support the existence of a considerable environmental component, with a risk of 33% in monozygotic twins (Hilker et al., 2018). Although evidence is somewhat equivocal, childhood adversity is likely a major risk factor especially for positive symptoms and also for being at UHR for psychosis (Kraan, Velthorst, Smit, de Haan, & van der Gaag, 2015). Urbanicity and ethnic minority status also contribute to increased risk, with authors suggesting that these factors impact the brain during sensitive periods of development (van Os et al., 2010). Use of recreational drugs, especially cannabis (Volkow et al., 2016) and amphetamine (Niemi-Pynttäri et al., 2013) also increases risk although the exact mechanisms remain unclear. Cannabis abuse or addiction may also increase the risk of conversion to psychosis in UHR groups (Kraan et al., 2016). Effects of drug use are likely compounded by genetic vulnerabilities (Misiak et al., 2017) to produce psychosis.

1.7 Treatment of psychotic disorders

1.7.1 Antipsychotic drug treatment

Medical treatment in psychotic disorders aims to reduce symptoms in the acute phase, while maintaining this improvement through the recovery phase. Preventing or reversing functional loss is also central to attaining the best quality of life possible. Antipsychotic drugs were discovered in the 50s and have since been a mainstay of psychosis treatment according to clinical guidelines (NICE, 2014; Norwegian Directorate of Health, 2013). First-generation antipsychotics had sedative effects as well as dampening positive symptoms like hallucinations and delusions, and were a big improvement to existing treatments, which were mainly based on containment or heavy sedation of the patient. The advent in the late 80s of clozapine (Kane, Honigfeld, Singer, & Meltzer, 1988) and subsequently a wider range of second-generation or atypical antipsychotic drugs brought more tolerable drugs promising fewer extrapyramidal side effects, which was a problem with First-generation antipsychotic drugs (Leucht et al., 2009). However, extrapyramidal side effects remain an issue (Divac, Prostran, Jakovcevski, & Cerovac, 2014; Rummel-Kluge et al., 2012). Although current Norwegian national guidelines stipulate that patients be offered non-pharmacological interventions if they wish (Norwegian Directorate of Health, 2013), antipsychotics remain the cornerstone of first-line treatment of acute psychosis, as well as for the maintenance phase (APA, 2006; Kreyenbuhl, Buchanan, Dickerson, & Dixon, 2010; NICE, 2014; Sohler et al., 2016). Due to the symptomatic complexity and severity in this patient group, many will also receive other psychotropic drugs including mood stabilizers, anxiolytics, sedatives, or antidepressants.

Antipsychotic treatment is often continued for several years after an acute episode in order to minimise risk of relapse, and guidelines recommend continuing medication for 1-2 years after a first episode, or up to 5 years after a relapse (NICE, 2014; Norwegian Directorate of Health, 2013). Still, discontinuation of drugs or poor compliance is common in psychotic disorders: as symptoms improve, disadvantages like weight gain and metabolic syndrome may seem to outweigh benefits (Sendt,

Tracy, & Bhattacharyya, 2015), even though discontinuation increases the risk of relapse. Although some studies also show that dose reduction or cessation of antipsychotics is associated with higher rates of functional recovery (Wunderink, Nieboer, Wiersma, Sytema, & Nienhuis, 2013) it is difficult in general to untangle whether this is due to the drug, or due to the fact that dose reduction in itself is a symptom of a budding recovery process.

Despite existing guidelines, the ideal length of antipsychotic treatment for each individual cannot easily be determined based on current knowledge (Bjornestad et al., 2017). Atypical antipsychotic drugs are quite effective for the treatment of acute positive symptoms, with about 50-80% of recipients experiencing improvement in positive symptom load, as compared to 5-40% of groups receiving placebo treatment (Buchanan et al., 2010; Dixon, Lehman, & Levine, 1995; Leucht et al., 2012). However, for patients requiring the trial of a second antipsychotic due to non-response, the response rate may fall to below 20% (Agid et al., 2011). Although on a group level, several factors including female gender, drug naivety and shorter DUP appear to predict a better response (Zhu et al., 2017), it is still uncertain on an individual level why certain patients respond well to antipsychotics while others do not. Despite large metastudies indicating that some AA are more effective than others (Leucht et al., 2013), we also do not know how to predict individual responses to individual drugs. The Bergen Psychosis Project 2 aimed amongst other things to investigate factors which might affect individual drug responses.

1.7.2 Psychosocial treatment

Non-pharmacological and psychosocial interventions are an important part of psychosis treatment, and physical exercise, social contact, art and music therapy are recommended by guidelines (Norwegian Directorate of Health, 2013). Talking therapies are important tools in reducing symptom load, but unlike medication they may also build life skills and support the person and their social surroundings to understand and cope with the disorder.

The main recommended psychotherapeutic approach for psychotic disorders is cognitive behavioural therapy (NICE, 2014; Norwegian Directorate of Health, 2013)

Although these recommendations have been criticized (Jauhar et al., 2014), cognitive-behavioural therapy (CBT) has shown consistently positive effects on positive symptoms of schizophrenia spectrum disorders (Zimmermann, Favrod, Trieu, & Pomini, 2005) and may also reduce the risk of developing psychosis in high-risk groups (Hutton & Taylor, 2014). CBT primarily aims to reduce symptom load and distress, but also to improve general functioning. Other approaches include metacognitive narrative therapy, which aims to ameliorate impairments in the ability to organize information about self, others and the world into complex ideas, allowing the person to build intrinsic and personal motivation for recovery (Lysaker & Dimaggio, 2014). Mindfulness based interventions are a third-wave cognitive therapy which encourage presence in the moment, acceptance, detachment, and compassion in placement of reactivity, struggling and judgement, aiming to alleviate distress arising from stressful attempts at controlling psychotic symptoms (Khoury, Lecomte, Gaudiano, & Paquin, 2013). Psychoeducative family based interventions have been successful in reducing relapse rates through the reduction of expressed emotion (McFarlane, 2016), in addition to building coping skills in both the patient and their next of kin (Onwumere, Bebbington, & Kuipers, 2011). Multiple-family groups have been found superior to single family groups, indicating a positive effect of social interaction between families (McFarlane, 2016). Psychosocial treatments may also improve drug compliance by reducing paranoid though patterns and building therapeutic relations and illness insight (Higashi et al., 2013).

Despite decades of intense efforts, the aetiology and pathogenesis of psychosis remains unclear, which impedes the development of treatment for schizophrenia. However, new non-medical treatments are continually being developed, partly in response to scientific and technological advancement. Non-invasive transcranial magnetic stimulation may have a moderate effect on negative symptoms (Aleman, Enriquez-Geppert, Knegtering, & Dlabac-de Lange, 2018) and may potentially also ameliorate cognitive impairment, although previously reported effects on auditory hallucinations have been limited (Slotema, Blom, van Lutterveld, Hoek, & Sommer, 2014). Avatar based virtual reality treatment and other digitally delivered interventions are also an interesting and promising addition to available treatments

(Rus-Calafell & Schneider, 2020). Cognitive remediation interventions have also shown promising results and is described in more detail in section 1.8.7.

1.8 Current views of psychosis -a more optimistic path

Despite the number of important jigsaw pieces still to be placed in the puzzle of psychosis, the former view of psychotic disorders as synonymous with a life spent medicated or with debilitating residual symptoms has fortunately shifted in a more optimistic direction. Also, the continued presence of early intervention and information services may help destigmatize psychotic disorders. The singular focus on remission of symptoms alone has shifted to a broader view of recovery and coping. This has left more space for subjective experiences of psychosis and treatment to be heard (Read & Sacia, 2020), while paving the way for interventions aiming to strengthen coping skills and social and professional participation despite any residual symptoms. For instance, programs of individual placement and support have shown promising results (Killackey et al., 2017). Studies have found the majority of first episode psychosis participants to remain in paid employment at the end of follow-up, although authors warn that follow-up ideally should be open-ended in order to maintain positive outcomes over time (Hegelstad, Joa, Heitmann, Johannessen, & Langeveld, 2019). This shift is in line with first episode psychosis groups and user perspectives reporting that functional recovery is their most valued treatment outcome (Iyer, Mangala, Anitha, Thara, & Malla, 2011), which underscores the importance of learning more about the key factor of cognitive impairment.

1.9 Cognitive impairment in psychosis

1.9.1 What is cognition and cognitive impairment

The English expression cognition comes from the Latin word cognoscere, meaning to get to know in-depth or to investigate. Cognition entails "the action or faculty of knowing taken in its widest sense, including sensation, perception, conception, etc., as distinguished from feeling and volition" (OED, n.d.-a). In psychology, cognition is

widely used to mean the processing of information as well as the application of information and knowledge in tasks requiring conscious thought activity. Cognition is thus a multifaceted concept, tangential to or including a range of conscious mental functioning, deliberation and capability, for instance intelligence, attention, learning, memory, perception, decision making and planning, as well as aspects of social interaction dependent on understanding the intentions and actions of others.

Cognition arises from neurological activity, both at the neuronal and system level (Lezak, Howieson, Loring, & Fischer, 2004). Any significant disturbance of brain activity, be it on a structural or neurotransmitter level, is thus likely to affect cognitive functioning. Cognitive neuropsychology is concerned with understanding how brain functioning relates to psychological processes or deficits. The most widely used form of assessment is neurocognitive testing.

What constitutes cognitive impairment

Neurocognitive impairment may be conceptualised and measured either as underperformance in relation to a given population norm, or as an individual loss of functioning over time, e.g. as seen in someone with traumatic brain injury following a car accident. Variability in both cut-offs and measuring instruments means that the proportion of individuals in a group deemed to show signs of cognitive impairment may vary from study to study. For the purposes of this thesis, cognitive impairment has been set to scoring 1.5 SD below the healthy population mean in accordance with Heaton, Grant, and Matthews (1991).

1.9.2 Cognition in schizophrenia

Regardless of whether one believes that Shakespeare used cognitive disorganization in his portrayal of a schizophrenia-like malingerer in King Lear (Bark, 1985), cognitive impairment has been central to the idea of schizophrenia since its invention as an explicit entity. Kraepelin's text on dementia praecox (1919) described in a form of precocious cognitive disintegration (Falkai et al., 2015). Bleuler suggested the existence of "fundamental" symptoms in schizophrenia, including disturbances in association and attention (Green & Harvey, 2014). He tested word association in a way resembling contemporary neurocognitive assessment, taking note of response

times as well as the actual associations (Moskowitz & Heim, 2011). In their retrospective on cognition and schizophrenia, Green and Harvey (2014) describe the post-World War II period as focusing on assessing and measuring cognitive impairments, drawing on models of healthy cognition as well as clinical neuropsychology.

The last decades of the 1900s saw a flourishing of studies targeting cognition in schizophrenia in a much more integrated way. This came partially as a response to technological developments in brain imaging and findings of ventricular enlargement hinting at underlying physiological factors contributing to psychosis (Palmer, Dawes, & Heaton, 2009; Tandon, Nasrallah, & Keshavan, 2009). Also, it arose from a recognition that level of cognitive impairment predicts functional outcomes (Green, 1996; Green, Kern, & Heaton, 2004; Heaton & Pendleton, 1981). An early metanalysis of cognitive deficits in schizophrenia was published in 1998 (Heinrichs & Zakzanis) and found schizophrenia as entailing general cognitive impairment as well as deficits across tested subdomains. Cognitive impairment is currently considered a core aspect of schizophrenia (Kahn & Keefe, 2013), and is also seen to a lesser extent in other disorders with psychosis, e.g. bipolar disorder (Bortolato, Miskowiak, Köhler, Vieta, & Carvalho, 2015).

Despite individual heterogeneity, schizophrenia groups appear to perform at about 1 SD below the expected population mean (Tandon et al., 2009), with an estimated premorbid IQ of about 0.5 SD below the mean (Woodberry, Giuliano, & Seidman, 2008). However, although some with schizophrenia perform at the population norm (Reichenberg et al., 2008), some argue such subjects still perform worse than would be expected from their reading scores and parental education levels (Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000), with one study finding that about 95% of a group with schizophrenia showed signs of cognitive underperformance when measured in this way (Keefe, Eesley, & Poe, 2005). Surfing on the rise of vast genetic cohort studies, cognition studies have also become more international, with schizophrenia being linked to general cognitive ability (Lencz et al., 2014), although cognitive impairment in itself is not specific to psychotic disorders (Millan et al., 2012). However, the firm consensus that cognitive impairment exists ahead of and in

schizophrenia is matched by a corresponding disagreement on the nature and course of this impairment.

1.9.3 Cognitive impairment in UHR

Cognitive underperformance is one of the earliest identifiable signs of psychosis risk, as indicated by large longitudinal cohort studies such as the Dunedin study, which found cognitive deficits at the age of 7 and stable through the age of 13 in individuals later diagnosed with schizophrenia (Reichenberg et al., 2010). These early cognitive deficits have been argued to be behavioural expressions of developmental abnormalities increasing the risk of developing psychosis (Bora, 2015). Cognitive performance in UHR groups falls below that of healthy controls but is better than in groups with both first episode psychosis (Hou et al., 2016) and schizophrenia (Giuliano et al., 2012). Falling behind academically or socially due to cognitive impairment is a considerable stressor for this group. Poorer baseline scores (Giuliano et al., 2012) as well as poorer attention and working memory abilities as well as problems with language skills and declarative memory have been found to indicate higher risk of conversion to full psychosis (Koutsouleris et al., 2011; Seidman et al., 2016). Knowledge of cognitive functioning in groups at risk of psychosis is thus important both as an indicator of prognosis and as a tool for implementing tailored support for UHR youth (Hartmann et al., 2019).

1.9.4 Assessment of cognitive performance in psychosis

Studies have used a vast array of tests to assess cognition in psychosis, spanning both established test batteries (Hagger et al., 1993; Johnstone et al., 1976) and purposely designed composite batteries (Davidson et al., 2009; Keefe et al., 2003). Like the main diagnostic manuals, commonly used neuropsychological measures have also undergone regular major revisions, e.g. WAIS III to IV (Wechsler, 1997a, 2008). In addition, views evolve over time of what tests are seen as optimal for investigating cognitive changes in psychosis. The great variety in tests used has complicated comparison of results across tests. In response to this, Nuechterlein and Green (2006) presented the MATRICS Consensus Cognitive Battery into which a working group of field experts selected sub-tests based on reliability, validity and feasibility for clinical

trials, including suitability for repeated measurement, potential sensitivity to pharmacological effects, relationship to functional measures as well as tolerability. With this they aimed to unify neuropsychological research by making single study test results more comparable.

1.9.5 Impairment in specific cognitive domains

The majority of studies looking at impairment in specific cognitive domains have focused on groups with established schizophrenia. Detangling specific impairments from each other is a challenge for all neurocognitive research. For instance, psychosis groups perform especially poorly for processing speed, particularly digit symbol coding tasks, which most likely contributes to the general deficit seen (Dickinson, Ramsey, & Gold, 2007). Digit-symbol coding tasks in turn place demands on several processes including motor speed, attention, working memory motor speed and to some extent executive functions for strategic planning, all of which also been found to be impaired in this patient (Heinrichs & Zakzanis, 1998; Tandon et al., 2009). Working memory is in itself a complex process relying on various processes like attention, encoding, representation and maintenance (Baddeley, 2002). Impairment in schizophrenia is especially evident in tests of processing speed, working memory, executive functioning and language abilities (Schaefer et al., 2013), although deficits have been found across a wide range of domains (Mesholam-Gately et al., 2009).

1.9.6 What affects cognitive functioning in psychosis

Genetic factors and IQ

The heritability of adult IQ is at least 60%, perhaps as much as 80% (Plomin & Deary, 2015). Low adult IQ is an established risk factor for schizophrenia (Barnett, Salmond, Jones, & Sahakian, 2006; Khandaker, Barnett, White, & Jones, 2011). There is a genetic overlap between schizophrenia and general IQ (Lencz et al., 2014) and cognitive impairment has also been found in healthy first-degree relatives of people with schizophrenia (Snitz, MacDonald III, & Carter, 2006). More specifically, studies of endophenotypes indicate heritability estimates of up to 55% for performance in groups with schizophrenia on various cognitive tests including word recall, letter number sequencing task and spatial skills (Greenwood et al., 2007).

Better cognitive reserve may be a protective factor (Khandaker et al., 2011). Given the genetic overlap found between psychotic disorders and other mental health conditions (Carroll & Owen, 2009), the phenotype for cognitive impairment in psychosis is likely to be at least in part shared across conditions. However, premorbid deficits may be more specific to schizophrenia (Mollon & Reichenberg, 2018).

Brain physiology

Global cognitive impairment has been associated with reduced volume of the dorsolateral prefrontal cortex, inferior frontal gyrus, hippocampus, and white matter in both schizophrenia groups and healthy individuals (Jirsaraie, Sheffield, & Barch, 2018). This study also found reduced hippocampal volume in the schizophrenia group, suggesting that cognition relying on this structure may be particularly affected. A review also concluded that abnormal connectivity between resting state and task networks appear to be linked to impaired attention, working memory and executive functioning, with abnormal pathways between the prefrontal cortex, thalamus and striatum additionally related to deficits in processing speed (Sheffield & Barch, 2016). However, the neural correlates of cognitive impairment in psychosis remain poorly understood.

Positive and negative symptom dimensions

A major systematic review concluded in 2009 that neither positive nor depressive symptom dimensions were associated with neurocognitive measures (de Gracia Dominguez, Viechtbauer, Simons, van Os, & Krabbendam, 2009). However, negative and disorganized symptoms were moderately correlated with cognitive impairment. This pattern held true across cognitive domains, independently of age, gender, and duration of illness. Negative symptoms were associated in particular with poor verbal fluency while disorganized symptoms were related to reasoning and problem solving, attention/vigilance. The review authors suggested that differential brain mechanisms drive positive and affective symptoms vs. disorganized and negative symptoms, and that neurocognitive symptoms are somehow related to the latter.

Both negative and cognitive symptoms commonly occur ahead of development of positive symptoms, and are similarly associated with prognosis (van Os et al., 2010).

They may arise from common structural and functional brain abnormalities. Hypofrontality in schizophrenia is linked to impaired cognitive task performance (Ortiz-Gil et al., 2011; Samartzis et al., 2014). Negative symptoms have also been associated with reduced dorsolateral prefrontal grey matter (Bergé et al., 2011) and prefrontal white matter (Carletti et al., 2012). Both cognitive and negative symptoms also respond to antipsychotic treatment to a lesser extent than do positive symptoms (Foussias & Remington, 2008). Cognitive impairment might also take longer to respond to medication (Désaméricq et al., 2014). Cognitive impairment and negative symptoms thus appear to be related although separate constructs.

Psychosocial and environmental factors

Cognitive reserve and the ability to compensate for any impairment are affected by socioeconomic status and access to education, lifestyle, nutrition and physical activity, as these in turn influence neuroplasticity (Vance, Roberson, McGuinness, & Fazeli, 2010). Multiple types of childhood trauma may affect cognitive change in psychosis (Mørkved, 2020). A complex relationship exists between cognition and recreational drug use. Cannabis users with psychotic disorders may in fact be outperforming non-drug using psychosis groups, with review authors suggesting that this demonstrates that the former group enters psychosis via an alternative cannabis triggered pathway (Løberg & Hugdahl, 2009).

1.9.7 Treatment of cognitive impairment

Antipsychotic drug treatment

It has been argued that studies of first-generation antipsychotic drug effects on cognition served mostly to demonstrate the treatment resistant nature of these symptoms (Keefe, Bollini, & Silva, 1999). When so-called second generation or atypical antipsychotics were launched on the market in the 80s, they were purported to positively affect cognitive functioning (Gallhofer, Bauer, Lis, Krieger, & Gruppe, 1996; Meltzer & McGurk, 1999). Clozapine was found to both improve cognitive performance as well as reducing negative symptoms (Kane et al., 1988; Sharma & Mockler, 1998). Early studies of atypical antipsychotics even searched for positive effects of specific drugs within specific cognitive domains, e.g. olanzapine for verbal

fluency (Meltzer & McGurk, 1999) or effects of clozapine on attention (Sharma & Mockler, 1998). The serotonin receptor antagonism and stimulation associated with some atypical antipsychotics s were also thought to potentially improve cognition (Meltzer, 1999). Recent reviews however note that early findings on atypical antipsychotics effects might have been related to participants changing from high doses of cognition impairing first-generation antipsychotics, and that although atypical antipsychotics s outperform first-generation antipsychotics for cognitive symptoms, effects sizes have been small (Désaméricq et al., 2014).

Even with the advent of atypical antipsychotics s, functional striatal dopamine D2 antagonism remains the main pharmacological mechanism of all antipsychotic drugs. Interaction between prefrontal areas and dopaminergic circuits supports cognitive problem solving strategies, and any impairment would thus affect e.g. verbal and working memory (Barch & Ceaser, 2012). Atypical antipsychotics s however differ in their pharmacological profiles and might plausibly have differential positive and negative effects on cognition (Steen et al., 2017). Partial D2 agonists, e.g. aripiprazole, may simultaneously reduce striatal hyperdopaminergia and boost prefrontal hypodopaminergia, thus targeting both aspects of the third generation dopamine hypothesis (Howes & Kapur, 2009). This sets these drugs apart from strict D2 blockers, e.g. amisulpride and olanzapine, which only target striatal hyperdopaminergia, and improved prefrontal dopaminergic function has been found in animal models using aripiprazole (Z. Li, Ichikawa, Dai, & Meltzer, 2004). While amisulpride has a narrow affinity profile limited to dopamine, olanzapine also affects 5-hydroxytryptamine, adrenergic, muscarinic acetylcholine and Histamine1 receptors, which may cause impaired psychomotor speed and memory (Chew et al., 2006; Van Ruitenbeek, Vermeeren, & Riedel, 2010). It would therefore still be useful to further examine between-drug differences for cognition.

A considerable proportion of atypical antipsychotics drug studies, including projects looking at cognitive impairment, have been funded by the pharmaceutical industry, e.g. (Kern et al., 2006; Riedel, Spellmann, et al., 2010). Industry funded research is more likely to be commercially motivated, favouring drugs still within their patent

period. Investigations of existing expired patent drugs like amisulpride are comparably scarce. Industry studies are also often based on small, selective samples of schizophrenia patients with chronic phase disorder, which fails to accurately reflect clinical drug use. Treatment algorithms in Norway and elsewhere indicate antipsychotic drug treatment during acute psychosis, when an exact diagnosis often cannot be determined e.g. due to diagnostic criteria related to duration. Industry studies also frequently have short follow-up periods, e.g. two months (Riedel, Spellmann, et al., 2010). This fails to reflect recommendations that antipsychotic drugs be used for at least a year in clinical settings.

Independently funded, updated knowledge on differential atypical antipsychotics' effects on cognition would be useful. Sampling and follow-up duration should be as close to treatment as usual as possible. A longer-term head-to-head drug comparison for cognitive effects of atypical antipsychotic drugs would also have a better chance of separating acute phase spontaneous cognitive recovery from drug-specific effects. Examining between-drug differences might thus yield clinically important knowledge in the search for individually tailored treatment of psychotic disorders.

Cognitive remediation training

Given the inadequacies of antipsychotic drug treatment for cognitive impairment, non-pharmacological interventions are of particular importance. One promising avenue to amelioration of cognitive symptoms is cognitive remediation, i.e. nonpharmacological interventions aimed at improving neurocognitive functioning (Galletly and Rigby, 2013). Based on behavioural training, cognitive remediation interventions often aim at improving specific cognitive processes like memory, social cognition, or metacognition, with the ultimate aim to generalize any learning to other real-life situations. Approaches can aim at restitution or repair of damaged neural pathways, or teaching new skills to compensate for existing impairment (Medalia & Saperstein, 2013). Treatment effects are moderate for both neurocognitive functioning (.41-.45) and functional outcome (.36) as well as for negative symptoms (.36) (Morin & Franck, 2017). Effects are compounded by implementation of other rehabilitative interventions.

1.10 Cognitive change in psychosis

For almost as long as cognitive impairment has been studied in psychotic disorder, disagreement has existed about the nature of psychosis related cognitive change. A main controversy is whether cognitive impairment is present from birth or early childhood or arises shortly before the onset of psychotic illness. A second question is whether cognitive functioning remains relatively stable, fluctuates, or deteriorates in chronic illness. Some authors have argued that psychosis in itself is neurotoxic and damaging to cognitive processing, whilst others have found deficits to be relatively stable from first episode psychosis onwards (Bozikas & Andreou, 2011). Psychosis has thus been modelled as arising from either neurodevelopmental or neurodegenerative processes.

The neurodegenerative view of psychosis was founded in part on early brain imaging studies showing progressive ventricular enlargement in psychosis patients (Shenton et al., 2001), but also from cross-sectional comparisons between first episode psychosis and chronic schizophrenia groups (Lieberman, 1999) . Also, functional decline during the prodrome and first episode of psychosis is common, with functional loss associated with poorer prognosis (Addington, van Mastrigt, & Addington, 2003; Keshavan, DeLisi, & Seidman, 2011). In addition, some have found multiple psychotic episodes to be associated with lower levels of cognitive functioning (Heaton et al., 1994). Comparison between medicated and non-medicated trajectories of schizophrenia led some to argue that active psychosis in itself is neurotoxic (Wyatt, 1991).

However, the relative stability of cognitive deficits after the onset of psychosis, identified during the upsurge of cognitive testing studies from the 80s onward has drawn criticism to the neurodegenerative model (Rund, 1998). The presence of cognitive impairment before the advent of positive symptoms is also an argument against the view of neurotoxicity of untreated psychosis (McGlashan, 2006). Also, any decline across the course of illness may also be related to factors other than neurodegeneration, e.g. psychoactive substance or antipsychotic use. Illustrating this, dose reduction and controlled discontinuation of atypical antipsychotics is potentially

associated with cognitive improvement outside the acute phase (Takeuchi et al., 2013).

Any exacerbation in deficits may also result from genetically driven changes in cognition which may manifest at multiple points along the developmental trajectory (Mollon & Reichenberg, 2018). Early abnormalities or delays in the development of basic cognitive skills will also affect the subsequent development of more complex cognitive operations, especially as tested against healthy population norms (Bora, 2015). Prodromal deficits and any later impairment may thus both result from developmental lag, not the loss of previously acquired skills. This argument fits well with McGlashan's (2006) suggestion the brain process underlying loss of cognitive capacity would be one of dysconnectivity in the form of "disuse atrophy".

This alternative neurodevelopmental view thus conceptualizes cognitive impairment as an expression of aberrant neurodevelopment in childhood and early adulthood (Bora, 2015). Further support for this model is found e.g. in a large 10-year follow up study finding no significant long-term decline (Barder et al., 2013) and other studies finding no change beyond normal ageing (Sponheim et al., 2010). A large meta-analysis recently concluded that longitudinal data overall do not firmly support progressive decline, with the possibility that function may even improve within certain domains after the onset of illness (Bortolato et al., 2015). The neurodevelopmental model leaves greater room for the fluctuations and change seen throughout the course of psychotic illness.

2. STUDY AIMS

This PhD aimed to investigate cognitive changes in psychosis, from the prodromal stage through acute phase psychosis to established psychotic disorders. A central aim was to investigate whether cognitive impairment is static or fluctuates across the course, stages, and treatment of psychosis.

2.1 Research questions

1. What characterises the neurocognitive profile in the ultra-high risk for psychosis state? (Paper II)
2. How does cognitive functioning change during the acute phase of psychotic disorder? (Paper I)
3. Do different second-generation antipsychotic medications differentially affect cognitive performance in psychotic disorders? (Paper III)
4. Does cognitive change differ between groups with schizophrenia and those with other psychotic disorders? (Papers I, II and III)

3. METHODS

3.1 RESEARCH PROJECTS/SETTING

This PhD was based on data from three different projects: The Bergen Psychosis project (BPP), the Prevention of Psychosis Project (POP) and the Bergen Psychosis project 2 (BP2) including the BestIntro antipsychotic drug trial, of which the PhD work formally formed a part.

3.1.1 Bergen Psychosis Project

Study design

The Bergen Psychosis Project (BPP) was a pragmatically randomized, rater-blinded comparison of the four first-line second-generation antipsychotics quetiapine, olanzapine, risperidone, and ziprasidone.

Recruiting centres

Participants were consecutively invited to participate from the acute psychiatric emergency ward of Haukeland University Hospital, Bergen, Norway (n=226). The Regional Committee for Medical Research Ethics allowed inclusion of eligible patients ahead of informed consent, in order to give a clinically relevant representation of patients with acute psychosis. Participants were asked for their written informed at first follow-up before being enrolled in the full 24-month project follow-up programme. Participants involved in the current project were included between March 2004 and January 2009.

Inclusion and exclusion criteria

Participants were required to be aged ≥ 18, to present with acute psychotic symptoms and to understand Norwegian language. For the sub-study forming part of this thesis they also had to have a completed Positive and Negative Syndrome Scale (PANSS) interview and neurocognitive testing both at baseline and at first follow-up.

Diagnostic process

Active psychosis was defined by a PANSS (Kay, Fiszbein, & Opler, 1987) score of ≥ 4 on the items for either Delusions, Hallucinatory behaviour, Grandiosity, Suspiciousness/persecution, or Unusual thought content. Diagnoses were assessed by trained clinicians, with study data gathered from participants' medical records at the time of discharge.

Exclusion criteria

Ineligibility for oral antipsychotics, organic brain disease, manic psychosis, substance-induced psychosis resolving within a few days of admission, inability to cooperate reliably during investigations, indication for electroconvulsive therapy, or being medicated with clozapine on admittance.

Withdrawal criteria

The participant was able to withdraw from further follow-up at any time. Other withdrawal criteria included serious somatic events requiring non-protocol follow-up, as well as pregnancy. Regular concomitant use of multiple antipsychotic drugs also led to exclusion. However, any change in antipsychotics for reasons of efficacy, safety or side effects was not a reason for exclusion, in line with the study pragmatic design. Details related to such changes were however considered important information.

3.1.2 Prevention of Psychosis project

Study design

The Prevention of Psychosis (POP) project was a detection and intervention study aiming to reduce incidence of psychotic disorders in high-risk youth through appropriate early support. Details can be found in its published study protocol (Joa et al., 2015) Building on the existing infrastructure of the TIPS early intervention in psychosis programme (Joa, Johannessen, Larsen, & McGlashan, 2008), POP used information campaigns and assessment by early intervention teams to detect high-risk participants.

Recruiting centres

Participants were recruited from Stavanger University Hospital.

Inclusion and exclusion criteria

Eligible candidates were invited to participate if they were aged 13–65 years, with IQ ≥ 70 and ability to speak / understand Norwegian as well as to understand and sign an informed consent / assent for minors document.

Diagnostic and symptom assessment

Participants were required to meet prodromal syndrome diagnostic criteria according to the Structured Interview For Prodromal Syndromes (SIPS) (T. J. Miller et al., 2003) with either 1) *brief, intermittent positive symptoms* of psychosis scoring ≥ 6 on the Scale of Prodromal Symptms, 2) *attenuated positive symptoms* scored 3–5 on the P1–P5 SOPS scales or (3) *genetic risk and deterioration syndrome* with a first-degree family history of nonaffective psychotic disorder and ≥ 30% functional loss over the past 12 months, as measured by the Global Assessment of Functioning scale.

Diagnostic interviews were performed after inclusion, with Kiddie Schredule for Affective Disorders and Schizophrenia (Kaufman et al., 1997) or Structured Clinical Interview for the DSM-IV (SCID) (Spitzer, Williams, Gibbon, & First, 1992) assessment being administered by trained clinicians or researchers.

Exclusion criteria

Current or lifetime psychotic disorder or symptoms better accounted for by neurological, endocrine, axis I, II, or substance use disorders. The exception was schizotypal personality disorder, which was not an exclusion criterion. Participants were also required never to have used antipsychotic medication for more than 4 weeks in a lifetime perspective.

3.1.3 Bergen Psychosis Project 2/ Bergen-Stavanger-Innsbruck-Trondheim study

Study design

Bergen Psychosis Project 2/ Bergen-Stavanger-Innsbruck-Trondheim (BP2/ Best Intro) study was a pragmatically randomized, rater-blinded head-to-head comparison of amisulpride, aripiprazole and olanzapine. Participants were followed-up for 12 months, with assessment at baseline, 1, 3 and 6 weeks and then 3, 6, 9 and 12 months.

Study population

Participants were included if they had been diagnosed with a current psychotic episode with clinical indications for oral antipsychotic treatment.

Recruiting centers

BP2/ Best Intro participants were consecutively recruited from Haukeland University Hospital, Bergen (n=75), Stavanger University Hospital, Stavanger (n=14), Medizinische Universität Innsbruck, Innsbruck (n=15). Numbers given are for those included in the current thesis. St. Olav's University Hospital, Trondheim recruited participants but did not perform cognitive testing. A comparison group receiving treatment as usual was also recruited in Bergen, and contributed data to Paper I.

Inclusion and exclusion criteria

Participants were invited to participate if they were aged ≥ 18 and eligible for oral antipsychotic drug treatment as determined by their attending clinician, with symptoms indicating non-affective psychotic disorder according to the ICD-10 (F20-29) (World Health Organization, 2007) or DSM-IV (American Psychiatric Association, 2000) and ability to provide informed written consent. They were also required to speak and write the site language.

Diagnostic process

Trained clinicians or researchers administered the Structured Clinical Interview for the DSM-IV (SCID)(First, Spitzer, Gibbon, & Williams, 1997). The SCID was performed as early as possible after inclusion.

Exclusion criteria

Exclusion criteria were inability to use oral antipsychotics, being medicated with clozapine on admission, inability to cooperate reliably during investigations, indication for electroconvulsive therapy, organic brain disorder causing the psychotic symptoms, pregnancy or breastfeeding or hypersensitivity to study drug substances. Participants were also excluded from the study if the SCID interview indicated that their symptoms were due to mania with psychosis or other diagnoses not compatible with the inclusion criteria range of disorders.

Withdrawal criteria

In line with the pragmatic study design, change of antipsychotic medication for whatever reason was considered important information though not grounds for withdrawal. However, serious somatic events indicating follow-up outside the study protocol or use of concomitant use of antipsychotic drugs would cause a person to be excluded from further follow-ups. Pregnancy would cause withdrawal from the study.

3.2 Treatment

BPP & BP2/ Best Intro: Participants received oral tablets based on randomization. Study drug dosage, the further treatment trajectory with any changes to other antipsychotic drugs or use of non-antipsychotic concomitant drugs was at the attending clinician's discretion in order to closely resemble treatment as usual. In line with Norwegian treatment guidelines, antipsychotic polypharmacy was however not permitted except for in the case of cross-titration at antipsychotic drug switching.

POP: Participants were given the opportunity to participate in one or more of the interventions: monthly comprehensive independent clinical assessments, case

management support with psychosocial needs including familial and vocational issues, omega-3 fatty acids (12-week daily dose of 2g fish oil capsules), 26 sessions of individual cognitive behavioural therapy over 6 months, single-family psycho-education, and anxiolytics and antidepressants if indicated by symptom load. Antipsychotic medication was to be administered open-label if a person either entered the study or was rated during follow-up to have a SIPS positive symptom score of ≥5. However, none of the participants included in the current thesis received antipsychotic medication.

3.3 Data and variables

3.3.1 Clinical variables

Psychotic symptoms: For the BPP and BP2/ Best Intro, trained clinicians and research staff administered the Structured Clinical Interview: Positive and Negative Syndrome Scale (Opler, Kay, Lindenmayer, & Fiszbein, 1999) to assess psychotic symptoms at each follow up. For POP, the SIPS (T. J. Miller et al., 2003) was used to assess attenuated psychotic symptoms.

Drugs and alcohol use: The BPP and BP2/ Best Intro used the Clinical Drug and Alcohol Use Scales (Mueser et al., 1995) to assess drug and alcohol use during the follow-up period. The Alcohol Use Disorders Identification Test (AUDIT) (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998) and Drug Use Disorders Identification Test (DUDIT) (Berman, Palmstierna, Källmén, & Bergman, 2007) were also administered at baseline. BP2/ Best Intro also used this instrument again at 6 weeks, 26 weeks, and 52 weeks. POP used AUDIT and DUDIT.

Functioning and symptom severity: The Global Assessment of Functioning-Split Version, Functions scale (American Psychiatric Association, 2000) was scored at every follow-up for all three projects, yielding a subscale score for function and symptom severity.

3.3.2 Cognitive performance and change

The BPP used the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Gold, Queern, Iannone, & Buchanan, 1999; Randolph, 1998), administered by trained and experienced raters at baseline and follow-up. The battery can be completed in 30 minutes and yields a total score as well as subscales for immediate and delayed memory, visuospatial skills, language, and attention. Subtests are word list learning and recall, story memory and recall, figure copying and recall, line orientation, picture naming, semantic fluency, digit span and coding.

The BP2/ Best Intro project used both a brief and a comprehensive neurocognitive test battery. *The brief battery* formed the basis of Paper III of this thesis. It aimed to assess working memory, processing speed and verbal ability and was designed to withstand learning effects. It comprised Dichotic Listening, Trail Making A (TMA) and Trail Making B (TMB) from the Halsted-Reitan test set (Reitan, 1958), The Hopkins Verbal Learning Test (HVLT-R) (Benedict, Schretlen, Groninger, & Brandt, 1998), WAIS-IV letter number sequencing (Wechsler, 1997a), and the Delis-Kaplan Executive Function System (D-KEFS) verbal fluency tests (FAS) and Symbol Coding (Delis, Kramer, Kaplan, & Holdnack, 2004), administered in that order. Trained staff administered this assessment at baseline, 6 weeks, 6 and 12 months.

The comprehensive battery lasted approximately 2-3 hours and was given at the three-month follow-up. This test battery provided data for Paper II of this thesis and consisted of Dichotic Listening and TMA and TMB from the Halsted Reitan test set (Reitan, 1958), the California Verbal Learning test (CVLT) (Delis, Kramer, Kaplan, & Ober, 2000), WAIS-III tests for vocabulary, similarities, number span, letter number sequencing, vocabulary, digit-symbol coding and block design (Wechsler, 1997a), WMS spatial span (Wechsler, 1997b), the Grooved Pegboard Test (Bryden & Roy, 2005), D-KEFS Color Word Interference Test (CWIT) and FAS (Delis et al., 2004), Rey Osterrieth Complex Figure Test (Shin, Park, Park, Seol, & Kwon, 2006), Digital vigilance test, the California Computerized Assessment Package Continuous performance test (E. Miller, 1990), and Wisconsin Card Sorting test (McGrath, 2011).

The POP project used a comprehensive cognitive test battery administered at baseline and consisting of Dichotic listening, Halsted-Reitan's TMA and TMB, the CVLT, WAIS III tests for number span, letter number sequencing, vocabulary, and block design, WMS spatial span and the D-KEFS CWIT, and FAS verbal fluency tests. This battery was designed in order to be compatible with the BP2/Best Intro project test battery in terms of comparison. Data from this battery was used for Paper II of this project.

3.4 Statistical analysis

Statistical methods are described in detail in their respective papers. Following is a short summary of statistical procedures for each paper.

SPSS was used to conduct descriptive analyses of clinical and demographic baseline characteristics in each paper. SPSS was also used for the main analyses in papers I and II. Categorical variables (e.g. gender) were compared between groups using χ^2, while one-way ANOVAs were used for continuous variables (e.g. age). In the event of ANOVAS indicating significant between-group differences, independent samples T-tests were applied to further explore the nature of these differences.

3.4.1 Paper I

Variables predicting cognitive change were assessed using sequential multiple linear regression analyses. We used two blocks with RBANS change scores as the dependent variable to assess the contribution of PANSS composites symptom load change. Block one consisted of gender, age, and baseline RBANS total and PANSS composite variable scores (Positive, Negative, Depressive, Excitatory and Disorganized) while in the second block, PANSS composite variable change scores were entered using forward stepwise selection (Criterion for inclusion: $p < .05$; criterion for exclusion: $p < .1$). Equivalent models were also made to assess change in each RBANS sub scale.

We also calculated the percentage of participants falling below the cut-off for cognitive impairment set at total RBANS score of $t < 35$, i.e. > 1.5 SD below population mean, corresponding impairment as conceptualised by Heaton et al. (1991). We compared cognitive scores at baseline and follow-up using two-tailed, paired t-tests. Pearson correlations between cognitive scores and PANSS scores at baseline were also calculated. We also compared cognitive change between the schizophrenia spectrum disorders group and other participants using a repeated measures ANOVA. The grouping variable was constructed by dividing the patients into a Schizophrenia spectrum disorders group (F20, F23.0 or F23.2, i.e. fulfilling the core symptomatic criteria for F20, but not necessarily the duration criteria) vs. a group with other psychotic disorders. We used the Greenhouse-Geisser correction for violations of the assumption of sphericity.

3.4.2 Paper II

We compared UHR cognitive performance with recent onset and longer onset schizophrenia groups by way of coordinated norms. Raw test scores were normalized by calculating z values relative to healthy control group baseline performance. Negative z-scores would indicate performance below controls. Using z-scores allowed cross-domain comparisons and also ensured our norms were appropriate for the young age UHR group for whom standardised test norms do not exist. We calculated a four-domain cognitive profile by grouping tests according to literature and neuropsychological conventions (46), with mean domain z-score based on for the tests comprising each domain. Domains used were speed of processing (TMA, WAIS digit symbol coding, CWIT colour and word reading conditions), working memory (TMB, WAIS number span and letter number sequencing, inhibition, and inhibition and switching conditions from D-KEFS CWIT), verbal learning, reasoning, and problem solving (D-KEFS FAS, WAIS vocabulary, and CVLT), and spatial reasoning (WAIS block design and WMS spatial span). Subscale z-scores were compared between groups using one-way ANOVAs. Post-hoc pairwise t-tests were used to assess significant between-group differences. We also calculated Pearson correlations between cognitive subscales and symptom scores, and antipsychotics

defined daily doses (DDD) and duration of illness for the F20 groups. We applied the Siddaq correction for multiple comparisons where applicable.

3.4.3 Paper III

The main analysis looked at cognitive change in intention-to-treat (ITT) randomization groups. ITT analysis entails analysis of trial participants in the group to which they were randomized (The Cochrane Collaboration, 2011). Supporting analyses were based on per-protocol (PP) groups based on the drug actually initiated for each participant. In both cases, analysis was done by way of linear mixed effects models (LME) (Pinheiro & Bates, 2000) using R software (R Core Team, 2013). LME was chosen for its ability to use all available data even when participants had completed different numbers of visits, as well as due to its ability to handle non-ignorable missing data (Hedden et al., 2009).

3.5 Funding, approvals and ethical considerations

All three contributing projects (BPP, POP and BP2/ Best Intro) were conducted according to the World Medical Association Declaration of Helsinki (World Medical Association, 2013)*,* and approved by the Regional Committee for Medical Research Ethics West-Norway and Norwegian Social Science Data Services.

In addition, BP2/ Best Intro was also approved by the Norwegian Medicines Agency in Norway, Etikkommission der Medizinische Universität Innsbruck, and the Austrian Federal Office for Safety in Health Care in Austria. The project was monitored according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Guideline for Good Clinical Practice,(2016). In Norway, the Department of Research and Development, Haukeland University Hospital provided monitoring services, while the Clinical Trial Centre at the Medical University Innsbruck provided these services for the Austria site. The BP2/ Best Intro study was conducted in line with the Norwegian Health Research Act (Helse- og omsorgsdepartementet, 2008).

BPP enrollment procedure

The Regional Committee for Medical Research Ethics allowed eligible participants for BPP to be included ahead of providing their informed consent, in order to maximise clinical representativeness. The project was divided into two phases: Phase one did not require informed consent as it ran from acute ward admission to discharge or up to 6 weeks, and included only measurements already a part of routine clinical practice. In order to enter the second phase, which included non-standard measurements and follow-up at 3, 6, 12 and 24 months after admission, participants were required to sign an informed consent form at discharge or 6 weeks at the latest.

4. RESULTS

4.1 Paper I: Cognitive change during acute phase psychotic disorder

4.1.1 Regression model of symptoms (PANSS) and cognitive change (RBANS)

The mean time from baseline to follow-up was 4.1 weeks (SD = 1.9 weeks). Change
in PANSS negative symptoms was the only PANSS change score to significantly
predict improved overall RBANS performance (beta = -.307, p < .016). Changes in
RBANS and PANSS are displayed in Figure 1.

Figure 1: RBANS total and PANSS composite scores change baseline to follow-up.
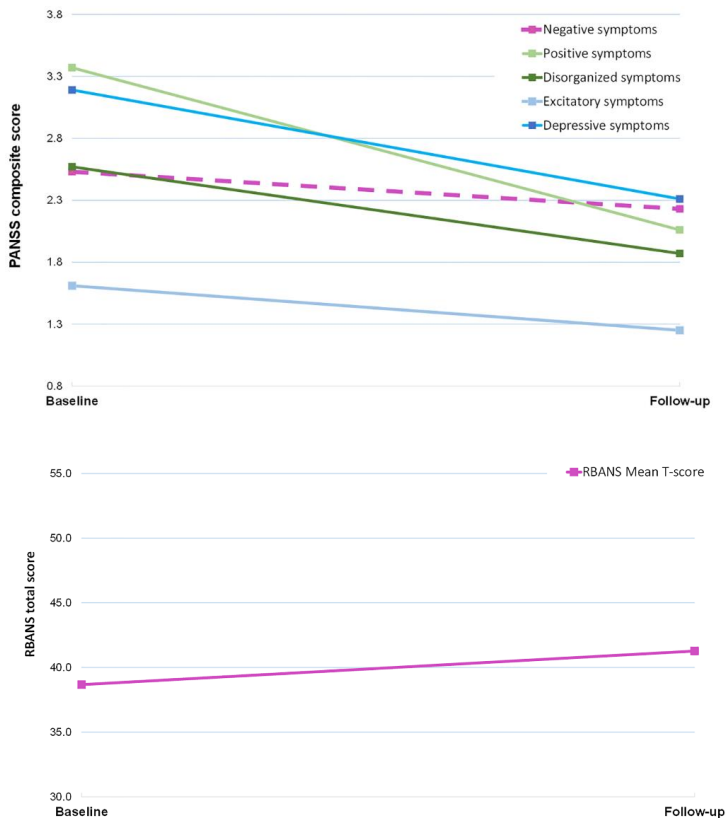
4.1.2 Correlation between PANSS and RBANS scores

The only significant symptom-RBANS correlation was between PANSS disorganized scores and RBANS total mean (r = -.515, p < .001). Attention was also significantly correlated with PANSS disorganization, but not after applying a Bonferroni corrected alpha level of .002 (r = -.296, p = .006).

4.1.3 Rate of cognitive impairment

The proportion of participants performing below an RBANS t-score of 35 fell from 28.6% (24/84) at baseline to 13.1% (11/84) at the point of follow-up. Mean total RBANS scores improved from 38.67 at baseline to 41.27 at follow-up (p < .001, d = .35). Mean attention scores similarly increased from 39.9 to 45.95 (p < .001, d = .75) while verbal scores went up from 30.32 to 33.93 (p < .001, d = -.39). Participants performed significantly below the norm average overall and for every RBANS subscale (all p < .001).

4.1.4 Comparing schizophrenia spectrum disorders to other psychotic disorders

There was no significant interaction between having a diagnosis of schizophrenia, and cognitive change over time as analysed by a repeated measures ANOVA including age and gender.

4.2 Paper II: Neurocognitive profile in UHR

The group with UHR scored significantly lower for cognitive performance in most domains than did healthy controls, as did both the group with recent-onset schizophrenia and the group with longer duration of illness.

A one-way ANOVA of z-scores found significant between-group differences for speed of processing [F(3) = 18.24, p < 0.001], working memory [F(3) = 13.71, p < 0.001) as well as for verbal learning, reasoning, and problem solving [F(3) = 4.94, p = 0.003). The groups did not perform significantly differently for visual problem solving [F(3) = 1.16, p = 0.327]. Fig. 2 shows group cognitive profiles.

Pairwise t-tests indicated that healthy controls outperformed the UHR group for speed of processing ($p < 0.001$), working memory ($p = 0.042$), and verbal learning, reasoning, and problem solving ($p = 0.007$). The UHR group in turn outperformed the longer duration of illness schizophrenia group for speed of processing and working memory (both $p < 0.001$). However, the UHR group and the recent onset schizophrenia group performance did not significantly differ in any domain.

No correlation between symptom scores or DDD and cognitive performance remained significant upon a Bonferroni correction for any of the groups.

Figure 2: Cognitive profiles in UHR and groups with recent onset and longer duration schizophrenia.
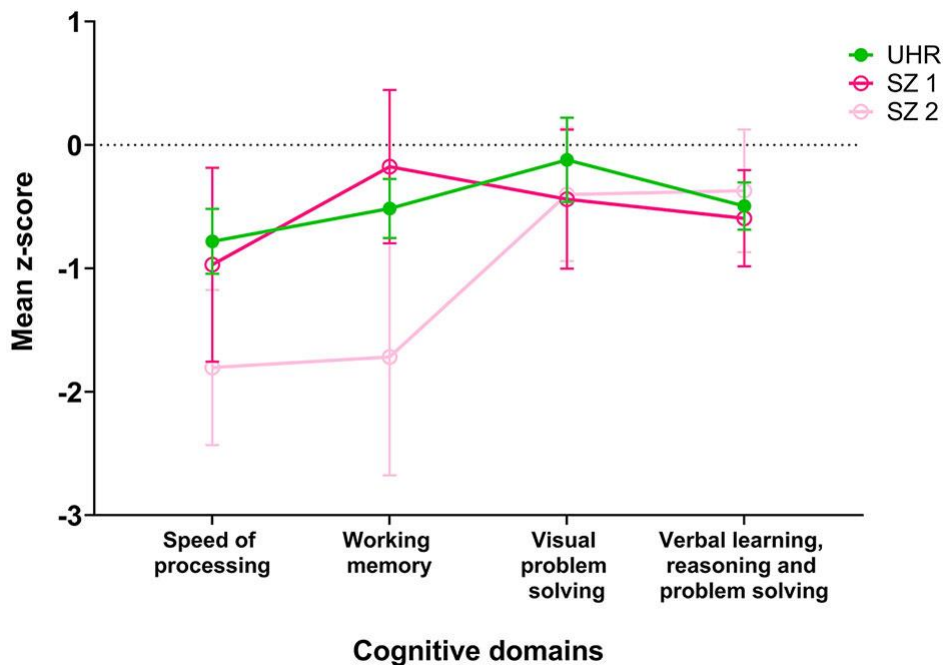
Note: UHR, ultra-high risk group; SZ1, group with recent onset schizophrenia (< 3); SZ2, group with remote onset schizophrenia (> 3 years). Error bars show 95% CI.

4.3 Paper III: The effect of atypical antipsychotic medication on cognitive performance over a 12-month period

4.3.1 Study drug acceptance, dosage and additional antipsychotics

A Chi square test found no significant between-group differences in acceptance of first study drug offered (X^2=5.26, df=2, p=.074), nor any differences in Defined Daily Doses (DDD) to any follow-ups. There were no ITT group differences in medication naivety, with 42.3% of the overall group AP naïve at baseline. There were no ITT group differences in additional APs for any visit.

4.3.2 Primary outcome: Cognitive change per medication group over time

No significant differences were found between ITT groups in terms of overall cognitive change. According to the LME model, overall t-scores for the amisulpride group increased by 6.7% (2.9 points) on average over 12 months, with corresponding increases of 12.6 (5.0 points) and 12.2% (5.3 points) for aripiprazole and olanzapine respectively. Per-protocol (PP) analyses also failed to identify significant between-group differences. Fig. 3 shows cognitive change over time, comparing amisulpride to aripiprazole and olanzapine.

Figure 3: Change in cognitive performance t-scores over 52 weeks per ITT group
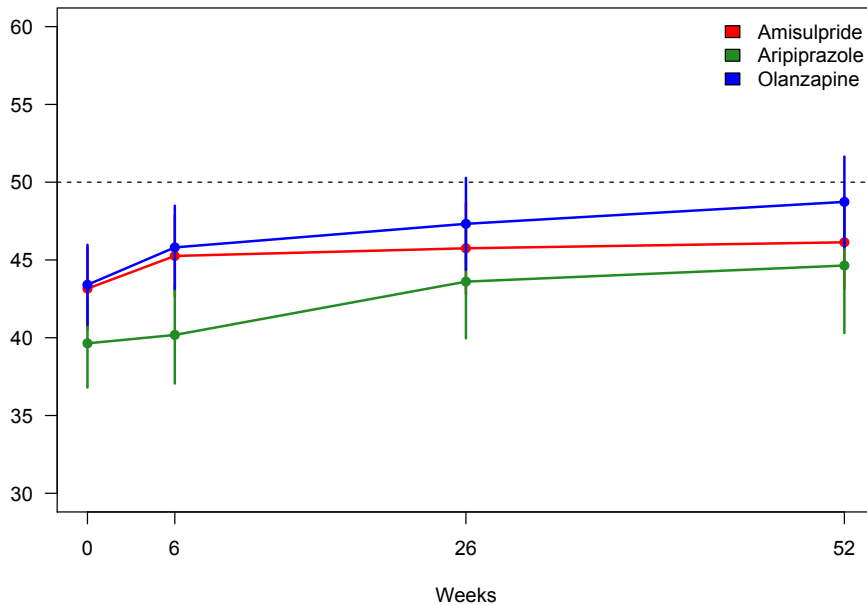
Note: Dashed line at 50 shows general population mean

4.3.3 Cognitive performance and change scores

Mean cognitive performance t-score improved from 46.39 at baseline to 47.53 at 52 weeks. The total sample mean t-scores improved significantly to 6 (Δ*2.0; p= .002*), 26 (Δ3.4; *p*< .001) and 52 (Δ4.2; *p*< .001) weeks, corresponding to a medium effect size (Cohen's d=.53). The percentage showing cognitive impairment (defined as scoring at t<35) was 27.9% (n=29) at baseline, improving to 17.0% at 52 weeks.

4.3.4 Schizophrenia vs. other psychoses

Out of the F20 group, 33.3% had t-score below the cut-off for cognitive impairment, compared to 20.5% among the other participants. However, this difference was not significant (X^2=2.094, df=1, p=.15). There were no significant differences in cognitive change between participants with schizophrenia and those with other psychotic disorders.

5. DISCUSSION

5.1 Short summary of main findings

5.1.1 Paper I: Cognitive change happens in acute phase psychosis

This study found that significant cognitive improvement can happen early in the course of acute psychosis treatment. Participants RBANS score increased significantly during the follow-up period, with the proportion of cognitively impaired subjects reducing from 28.6% to 13.1%. Neurocognitive improvement over the four-week follow-up period was associated with a reduction of negative symptoms, but with no other symptom changes. The improvement, rather than baseline severity, appeared to be key to cognitive improvement, indicating a close relationship between cognition and negative symptoms.

As far as we know this was the first study to show a correlation between acute phase improvement in negative symptoms and cognitive functioning in a sample not consisting exclusively of first episode psychosis participants. Our findings indicate that positive cognitive change is not limited to homogenous first episode psychosis samples. The schizophrenia subgroup did not differ from other participants in terms of cognitive change.

5.1.2 Paper II: UHR group performs between healthy controls and established schizophrenia

For overall test results, the UHR group significantly outperformed the group with longer duration schizophrenia, while underperforming compared to healthy controls. There were no significant differences between the UHR group and the recent onset schizophrenia group. This is in line with previous findings (Fusar-Poli et al., 2012; Giuliano et al., 2012) that cognitive performance is impaired in UHR groups but less so than in established schizophrenia.

In terms of cognitive subscales, UHR scores were significantly worse than healthy controls for speed of processing and cognitive flexibility as well as for verbal skills. However, the UHR group had better processing speed and working memory

performance than the longer duration schizophrenia group. There were no significant subscale differences between UHR and recent onset schizophrenia group performances. Interestingly, neither of the clinical groups differed significantly from healthy controls in spatial abilities. Our findings support previous findings that UHR and psychosis groups show impaired speed of processing, working memory, and verbal ability (Tandon et al., 2009).

5.1.3 Paper III: Atypical antipsychotics do not differentially affect cognitive change

Total sample cognitive test scores improved significantly to each of the three follow-ups at 6 weeks, 6 and 12 months, from the baseline level about one SD below the population mean. The majority of this improvement happened during the first six weeks. There were however no significant differences in cognitive change over 12 months between our study groups for amisulpride, aripiprazole and olanzapine for neither ITT nor PP analyses. The subsample with schizophrenia also performed significantly better across the 12-month follow-up, with no significant differences in change from other participants.

5.2 General findings

5.2.1 Cognitive impairment exists across the course of illness, but it is subject to positive change

A central finding of this thesis is that cognitive impairment is in flux throughout the course of illness. This is contrary to models of cognitive impairment as a static trait in psychotic disorders (Patel et al., 2010; Tyson, Laws, Roberts, & Mortimer, 2004). Despite impairment being present in the UHR group, the onset of treatment is associated with improved cognitive functioning, both through the acute phase (Paper I) and over the first year after starting antipsychotic treatment (Paper III). Although the onset of psychosis has been associated with a deterioration in cognitive functioning, there appears to be potential for positively influencing cognitive performance through follow- up and treatment. This is an important message to give to service users whom often strongly wish to participate in work and educational

activities (Iyer et al., 2011). In line with existing literature this thesis found that cognitive impairment exists across all stages of psychotic illness from UHR youth (Paper II), through the acute phase (Paper I) to groups of participants with a diagnosis of severe psychotic disorder like schizophrenia (Papers II and III). Impairment appears to be more severe in cases of well-established illness than in recent onset schizophrenia (Paper III). This confirms the view of cognitive impairment as a core aspect of schizophrenia in particular and primary psychotic disorders in general (Bora, 2015; Kahn & Keefe, 2013).

In their comprehensive review of the field, Fusar-Poli et al. (2013) ask whether the intermediate cognitive impairment seen in UHR groups represents state risk factors likely to deteriorate as illness progresses, or whether group level UHR impairments are milder due to the presence of false positives. Our findings of an association between longer duration of schizophrenia and worse cognitive performance could be seen as supporting the first model of gradually worsening impairment in line with a neurodegenerative view of psychosis (Lieberman, 1999). However, although our cross-sectional data cannot fully illuminate this, it is more likely in my point of view that the worse performance in our Paper II chronic SZ group instead reflects the second scenario suggested by Fusar-Poli et al. (2013): A greater neurological variation in UHR and early schizophrenia groups as compared to chronic groups. The Paper II UHR group contains some "false positives" who will not develop psychotic disorder. Alongside these are found participants who will see persistent, multi-episode illness, as well as an intermediate group who will develop psychosis but recover relatively quickly. Our UHR group is thus likely to include a greater range of neurological susceptibility and variation. This will be especially evident as compared to the longer duration SZ group which consists almost exclusively of multi-episode participants, the vast majority of whom are known to show a decrement in cognitive functioning (Tandon et al., 2009). This may explain why the longer duration schizophrenia group has more severe impairments across the subscales tested for.

Although the results from this thesis are partly cross-sectional and unable to conclude definitively, the collective findings may be seen as supporting existing literature (Seidman, Giuliano, & Meyer, 2010) that poor cognitive functioning at the UHR

stage is a marker for poor prognosis, thus explaining the worse performance seen in the chronic schizophrenia group in Paper II. Showing weaker improvement after acute episodes may also be such an indicator, though this could only be explored by a longitudinal setup closely following participants through the early acute phase. Further large-sample longitudinal work should study individual paths in UHR youth, to reveal any correlations between individual or group patterns of cognitive change. Better cognitive functioning in an UHR individual may also potentially modify the course of illness by enabling the person to make better use of available support. This may hold true once symptoms of schizophrenia are established, with the recent onset group from Paper III including a group of individuals more able to adhere to treatment, increasing their possibilities for a quicker recovery. Only longitudinal studies from UHR to persistent psychotic disorder may however illuminate these ideas further.

5.2.2 Which cognitive domains are impaired?

All three papers found impaired overall cognitive performance in the groups with established psychosis of about one standard deviation below the population mean at baseline. The Paper II group with UHR performed about half a standard deviation below the control group mean.

Impaired processing speed and working memory

Tasks requiring speed and cognitive manipulation of information appeared to present challenges for both UHR and psychosis groups, with Paper II finding that healthy controls outperformed the UHR for both processing speed and cognitive flexibility as well as for verbal skills. However, the UHR group in turn outperformed the longer duration schizophrenia group for both processing speed and working memory. Our findings are in line with research indicating that psychosis is associated with impairment especially in processing speed, working memory and verbal abilities (Schaefer et al., 2013).

Unimpaired spatial skills in UHR

One of the most interesting results from this thesis was that the Paper II UHR group performed almost on par with the healthy control group in spatial abilities measured by WAIS block design and WMS spatial span scores. Another recent study similarly found unimpaired visual skills in a clinical high-risk group, as opposed to in all other domains (Carrión et al., 2018). The seminal review of Heinrichs and Zakzanis (1998) interestingly also mentions block design as one of the tests with the smallest difference between schizophrenia groups and healthy controls.

We suggest that the strong results in spatial abilities in our sample might in part be due to the use of tests involving use or manipulation of physical test objects. In contrast to these, many commonly used spatial skills tests are non-tactile and screen based, e.g. the delayed response task. Such tests are more abstract and most likely place heavier demands on the working memory and visuospatial sketchpad aspect of spatial task solving. Our findings indicate that support by physical objects may aid cognitive performance in this group. A useful avenue for future research might be to directly compare these two aspects of visuospatial functioning in both UHR and established psychosis groups. Better visual learning has been found to distinguish those of schizophrenia groups who are in regular employment (Kern et al., 2011), highlighting the potential clinical importance of this domain.

5.2.3 No differential effects found between antipsychotic drugs

The comparison of olanzapine, aripiprazole and amisulpride in Paper III of this thesis found no significant differences between these drugs in terms of effect on cognitive improvement. This was surprising especially for olanzapine, which has previously been found to outperform amisulpride for effect on cognition (Désaméricq et al., 2014). Aripiprazole as a partial D2 agonist might also be expected to have a particularly beneficial effect on PFC dopamine and thus cognitive performance (Z. Li et al., 2004; Riedel, Spellmann, et al., 2010). However, Paper III findings are also supported by two major atypical antipsychotics comparison studies, CATIE and EUFEST, which found no differences for effect on neurocognitive functioning (Davidson et al., 2009; Keefe, Bilder, Davis, & et al., 2007).

A notable though non-significant trend across every follow-up was that the aripiprazole group underperformed the others. The difference was more notable during the first six weeks but remained through the year. It was mostly driven by lower performance speed, which is interesting in light of previous findings of motor coordination disturbances in animal models of aripiprazole (Burda et al., 2011). Also, although sometimes used to manage agitation, aripiprazole may also *trigger* aggression and activation, especially at the onset of treatment (Lea, Stoner, & LaFollette, 2007; Takeuchi & Remington, 2013). The partial D2 agonist action of this drug could potentially cause excessive dopaminergic activity in people who have upregulated levels of dopamine receptors due to previous use of receptor blocking drugs, which may in turn plausibly affect attention and cognitive test performance. The favourable trend for olanzapine and amisulpride may thus not exclusively reflect positive drug effects as much as detrimental side effects of aripiprazole. This angle should be further investigated with data including subjective and observed side effect ratings.

Another possibility is that despite our best randomization efforts, the aripiprazole group differed in some way from the other groups. Although differences were not significant, this group had a younger mean age, had an earlier age of onset, less education (this perhaps due to age), and more frequent alcohol abuse. In this regard, the status of aripiprazole as the primary choice of drug for younger subjects in many clinical settings may be relevant. Site clinicians may harbour a bias for picking aripiprazole for younger participants. Although any such bias was not pronounced enough to create significant between group differences in acceptance of allocated study drugs, it may have contributed to our findings of the aripiprazole group performing differently.

An important note is that despite the lack of between-drug differences, Paper III participants as a complete group improved significantly across the year. Although no placebo or healthy control group was used for this study, making it difficult to disentangle effects of atypical antipsychotic from those of time alone or even learning

effects, this is an important indicator of the potential for cognitive change after a psychotic episode.

5.2.4 The relationship between cognition and other symptom dimensions

In Paper I, acute phase changes in cognition were unrelated to both baseline positive symptoms as well as changes in these, despite the considerable reduction in positive symptom scores to follow-up. This is perhaps surprising as one might imagine e.g. voice hearing to interfere with verbal abilities. Cognitive improvement alongside general symptomatic recovery thus does not appear to merely reflect e.g. a reduction in positive symptoms that might have previously disturbed cognitive test performance. Our findings fit a two-pathway model of psychosis, where negative and disorganized symptom dimensions are associated with phenotypic neurocognitive impairment, less related to positive and affective symptom dimensions (de Gracia Dominguez et al., 2009).

The link found in Paper I between impaired cognitive performance and negative symptoms might be explained by reduced drive, an integral part of the negative symptom dimension (Foussias & Remington, 2008). Reduced drive is associated with impaired motivation, which in turn negatively affects efforts made to complete or "do well" at a task. Brain reward responses are attenuated in schizophrenia (Waltz et al., 2008), providing a possible explanation for this phenomenon. Low effort and amotivation might in fact account for up to a third of cognitive test result variance in schizophrenia (Foussias et al., 2015; Strauss, Morra, Sullivan, & Gold, 2015). Although in our sample, negative symptoms change only accounted for a limited amount of the variance in cognitive change, future research would benefit from trying to assess amotivation alongside other symptom dimensions.

Change scores for the PANSS disorganized subscale failed to significantly explain cognitive change in Paper I. This was despite baseline disorganized symptoms and RBANS scores being significantly correlated, and the considerable mean improvement in disorganized symptoms. The inclusion of PANSS items for abstract thinking and poor attention in the disorganized composite score may go some way to

explain the high baseline correlation, though this would not account for the lack of covariation between disorganized and cognitive symptoms, often seen as closely related symptom dimensions (Minor & Lysaker, 2014).

5.2.5 Cognition in schizophrenia vs. other psychosis

Across the papers of this thesis, the subgroups with schizophrenia were not found to perform significantly worse than groups with other psychotic disorders. In Paper II we also found that performance for the recent onset schizophrenia group equalled that of the UHR group. This is in line with a metanalysis which concluded that neuropsychological studies overall do not support categorical differences between schizophrenia and other groups with psychosis (Bora et al., 2009). However, this same analysis suggested that more severe cognitive impairment in a subgroup of those with schizophrenia may be related to more severe negative symptoms, which resonates with the findings of Paper I that change in negative symptoms is key in predicting cognitive change.

An alternative interpretation of the findings pertaining to schizophrenia groups in this thesis is that the similar potential for cognitive change across SZ and non-SZ psychosis groups might indicate problems with diagnostic validity. Might the distinction between schizophrenia and "other psychotic disorders" be a false one? An illness model based e.g. on total and general symptom load or symptom dimensions rather than narrow F20 criteria might go some way to remedy this, although the association between fulfilled F20 criteria and higher symptom load is likely high. It may also be argued that although the SZ-non SZ between-group differences were not statistically significant for Paper III, our samples were small, and the finding might still represent a clinically meaningful distinction in potential for cognitive change.

The relatively small SZ sample sizes throughout this thesis means all interpretations should be read with caution. In Paper II however, UHR and recent onset SZ groups significantly outperformed longer duration SZ. Again, a neurodegenerative model of schizophrenia could account for this. In Paper III, the SZ subgroup also improved their cognitive performance score across the follow-up period with no significant difference to the group with other psychotic disorders in terms of change. It is of

course possible that the majority of change happened in the recent onset segment of this group, as the Paper III SZ group encompassed both first episode psychosis and more chronically ill participants. However, I think the most important message to take from these findings is that positive cognitive change exists and happens across diagnostic groups, even in severe disorders like schizophrenia.

5.3 Clinical implications

The main clinical message of this thesis is one of hope. With treatment, positive cognitive change can and does happen after a psychotic episode, even in persons fulfilling diagnostic criteria for schizophrenia, where the symptom load is high. Cognitive impairment lacks specificity for diagnostic purposes, but impairment e.g. in speed of processing and working memory is more common in psychotic disorders, and this should inform clinicians in their work with patients who experience psychosis. Our findings also underscore the importance of assessing cognitive problems when working with UHR youth. The existence of cognitive impairment in this group lends support to the need for targeted interventions and support for cognitive challenges in e.g., academic settings in order to avoid further functional loss. Targeted interventions like psychoeducation about cognitive challenges, cognitive training, and physical exercise, may form part of this. Knowledge about patterns of cognitive impairment in psychosis and UHR enables clinicians to give accurate psychoeducation as well as conveying an understanding that cognitive functioning may fluctuate and improve across the course of illness.

The lack of concurrence between drugs reducing positive symptom load and those aiding cognitive function complicates tailored treatment with antipsychotic drugs. This study underscores the importance of considering non-medication avenues like cognitive remediation training or physical exercise. Even small improvements in cognitive functioning might contribute to reducing both societal and personal costs of psychotic illness.

When to test?

Clinicians and researchers alike commonly postpone neuropsychological testing for several months, waiting for the clinical picture to stabilise. While gathering data for this thesis I found that testing is indeed possible in the first few weeks after the onset of an acute episode. This is in line with findings that psychotic symptoms do not appear to affect the reliability of neuropsychological assessment (Heaton et al., 2001).

Although cognition changes on a group level during the time after the onset of treatment for psychosis, many patients fall out of treatment quite shortly after being discharged from hospital. They thus end up not being neurocognitively assessed at all, and thus miss out on a valuable assessment of their cognitive strengths and weaknesses which might have been vital to assisting them to participation in work and education settings. Given the lack of correlation between cognitive performance and positive symptoms, I therefore believe that on suspicion of cognitive impairment in psychosis, testing should be done as soon as the person is willing and able to participate, despite any positive symptoms.

In addition, our findings underscore the fact that cognitive performance fluctuates throughout the course of illness, and testing procedures should reflect this, perhaps by testing repeatedly during different phases and states in order to be able to inform the patient about her current condition.

6. METHODOLOGICAL CONSIDERATIONS

6.1 Trial designs

For the POP project, an important strength is the existence of a solid framework for recruitment of participants, in the form of Stavanger's well established early intervention team for psychotic disorders. The recruitment of an age and gender matched control group is also a significant advantage. This aspect was particularly important to this thesis as the control group also completed neuropsychological assessment, allowing us to create age appropriate norms for our young UHR participants. A weakness pertaining to the sample contributing to Paper II of this thesis is the relatively small sample size. It might also be argued that a longitudinal design would have yielded better information about the Paper II research question of UHR cognitive profile compared with that in established schizophrenia.

The open randomization design is a major strength of both the BPP and BP2/ Best Intro projects. This most likely made participation in the trials more tolerable to both patients and clinicians who might not have wished to participate in a closed randomization trial. This is especially pertinent given the high prevalence of paranoid symptoms in the target population, and may have strengthened generalizability the findings of this thesis.

The lack of a placebo control group in BP2/ Best Intro meant that Paper III did not allow for distinguishing between atypical antipsychotic effects on cognition, and effects from treatment as usual (including both other drugs and psychosocial interventions / talking therapies) or the natural course of illness in itself. A double-blinded placebo-controlled trial remains the gold standard of drug trials and might have minimized any existing bias. However, it was decided that the advantages of a pragmatic design outweighed the drawbacks. In addition, the considerable financial costs of double-blinded trials preclude most independent trials from implementing such designs.

As for Paper I, an important weakness is the variability in time to retest. Although the paper was able to conclude that cognitive change happens during the acute phase of psychosis, it would have been preferable to have a stricter window for re-testing. However, setting this at e.g. four or six weeks would most likely have exacerbated the amount of missing data as many subjects are hard to reach after hospital discharge. This may in turn have limited the generalizability of data.

Especially for Paper III which followed participants over a full year, it would have been desirable to have more knowledge of non-medical interventions received across the follow-up period, e.g. family and individual psychotherapy or work participation programmes, as this may also have affected cognitive change. However, the randomisation procedure aimed to ensure any such effects were equally distributed between groups.

All three projects were funded by industry independent sources, which is a considerable strength given findings that 90% of sponsored trials of antipsychotic drugs find in favour of the sponsor drug (Heres et al., 2006). Our independent funding meant the entire research process from design through inclusion and data collection, analyses and conclusions could be independently made with a clinically representative setting in mind. Both BPP and BP2/ Best Intro were designed where possible to resemble treatment as usual in order to strengthen ecological validity.

6.1.1 Clinical inclusion criteria

Determining symptom thresholds

Inclusion in the POP study was based on SIPS interview scores of ≥3 on the SOPS scale or familial risk combined with recently developed functional impairment. Although these criteria have been validated and are widely used in UHR research, selection of participants remains a major challenge. Alternative paradigms exist for delimiting groups more likely to develop psychosis, e.g. basic symptoms (Schultze-Lutter & Theodoridou, 2017). This complicates direct comparisons between studies and is a general challenge for studies of psychosis risk. Also, regardless of selection process UHR samples typically include a majority of "false positives", i.e. youth who will not go on to develop psychotic disorders. This is problematic when trying to

extrapolate findings to "true" UHR subjects who do convert. However, the POP youth are help seeking and often in significant clinical distress, and POP findings may therefore be of clinical relevance outwith the scope of psychotic disorders.

Inclusion based on psychotic symptoms screened with the PANSS, as done by the BPP and BP2/ Best Intro, may be considered the gold standard in studies of psychosis. The ≥ 4 points threshold is widely used in both drug trials and studies of cognitive functioning in psychosis.

Diagnostic assessment

Diagnosing patients presenting with psychotic symptoms remains challenging in part due to the nature of psychosis itself, which sometimes precludes the person from describing their inner state. In BP2/ Best Intro and also in POP, all participants were subjected to a SCID interview (or in the case of younger subjects, the K-SADS), ensuring a homogenous diagnostic process. In BPP, however, a range of diagnostic instruments including the SCID and Mini Plus were used as part of regular clinical practise. Although this gives a closer resemblance to how diagnoses are often determined in clinical practice, it means the process was less uniform and reliable, even for the diagnostic categorization for the current thesis which included only F20 participants.

The wide diagnostic inclusion range of the BPP and BP2/ Best Intro studies have the advantage of involving a more clinically relevant selection of people with psychosis. Drug induced psychosis, although often excluded from studies of cognition, was included given that many of these patients are known to be diagnosed with other psychotic disorders at a later stage (Whitty et al., 2005). The projects excluded only those whose condition resolved within a few days, in order to eliminate cases of acute intoxication as outlined by the ICD-10. Drug induced psychosis subjects made up about 18% of the Paper I BPP sample for this thesis.

6.1.2 Follow-up time windows

For BPP, the mean time to follow-up was 1.4 weeks with an SD of 1.9 weeks. Follow-up happened at discharge or at 6 weeks at the latest, giving a relatively wide

window. This wide range might have affected both symptomatic and cognitive change data. In hindsight, a narrower window would have been preferable, although the intention was to test as many patients as possible before hospital discharge.

Based on experiences from the BPP, the BP2/ Best Intro follow-up windows were much stricter, allowing a maximum of 48h of deviation from the set time points. This means much of the bias introduced in BPP by the wide window was less problematic for BP2/ Best Intro data, even though more follow-ups were used from BP2/ Best Intro than from BPP in the current thesis.

The time windows for POP follow-ups were more pragmatic. The baseline comprehensive neuropsychological assessment was at three months, but allowed for some flexible scheduling due to most subjects being in full-time education. This was done in order to maximise the number of subjects able to participate in assessment and is unlikely to have affected the results of this thesis.

6.1.3 Consent procedures

The BPP inclusion procedure with ethical approval for inclusion ahead of informed consent probably contributed to BPP s high attrition rates, as people dropped out before providing consent for the second phase of the project. The high attrition rate limits the generalizability of findings and might also be problematic when interpreting data as we do not know whether the followed-up group is representative of the baseline population. One way to combat this problem might have been to conduct targeted drop-out data gathering. Unfortunately this was not permitted in this project. However, the only significant baseline differences between drop-outs and those who completed the follow-up was that dropouts had higher baseline PANSS negative scores. Given that the change in negative symptoms was a significant predictor of cognitive change, if anything, participants with a higher PANSS negative score at baseline might have contributed to making this association stronger.

6.2 The patient sample

Enrolment in POP started in 2009 and still continues. Tailored screening logs unfortunately do not exist as screening was done as a part of the standard early intervention detection, with recruitment of those potentially eligible for POP happening after the initial assessment. Enrolment in BPP ran from March 2003 until June 2008. Due to lack of detail in the BPP screening logs in the period 2003-2006, the percentage included from all those screened and eligible is uncertain. Although the inclusion criteria for BPP were very wide, this means representativity is somewhat uncertain. For BP2, logs show that 40.1% of screened participants (n=144) were eligible and accepted randomization. Out of these, 104 completed neuropsychological assessment at baseline. Reasons given for not completing testing was known cognitive problems (e.g. cerebral palsy with cognitive impairment, or mental retardation), or not speaking / understanding the site language. This of course means any findings should not be generalized to such subgroups. No information has been systematically recorded about POP participant reasons for not completing cognitive testing, though not wanting to miss school and finding test situations uncomfortable were known reasons. It is therefore difficult to know how this might have affected data.

Norway's health care system is public, universal, and affordable. The early intervention services recruiting for the POP study forms a part of this public mental health care system. Although private mental health care facilities exist, they are mostly non-profit and catering to publicly funded patients. The vast majority of acutely ill people, as recruited by BPP and BP2/ Best Intro, will be referred via their GP or emergency room to a local and public psychiatric treatment facility. Thus, the participant sample is likely to be representative of the catchment area population. However, as all centres were urban areas, results may be less generalizable to rural settings.

6.2.1 Selection bias and representativeness

Selection bias may arise in any study not employing random selection for recruitment. Further bias may arise because the decision to decline participation among eligible / approached potential participants is rarely random. For instance, macro- or micro cultural factors like views of the mental health care system or medication may systematically affect someone's decision to participate. For Paper III, any selection bias affecting results may reasonably be assumed to be at least in part compensated for by the randomization procedure. However, representativeness in terms of important demographic variables of age, gender and ethnicity remains a challenge, in addition to the obvious selection bias due to the inability to grant informed consent among the eligible participants with the highest symptom loads.

Gender

Participants from the POP project for the sub study included in this thesis were 61.2% female. For BPP and BP2/ Best Intro on the other hand, respective percentages of females were 40.1% (Paper II) and 37.5% (Paper III) female. The overrepresentation of males is actually less than some former antipsychotic drug trials (Keefe et al., 2007) but comparable to others (Davidson et al., 2009), and reflects the higher number of male patients in psychiatric care for psychotic disorders. It is interesting to note the overrepresentation of females in the UHR sample vs. their underrepresentation in acute psychotic populations, though the reasons for this cannot be ascertained.

Age

The mean age of participants from POP was 17 years while participants from BPP and BP2/ Best Intro were older at about 30 years on average. The POP project had a maximum age limit of 65, while the BPP and BP2 projects had none at all. POP eligible patients would at any rate be rare given the young average age of onset in psychotic disorders, but the low rate of older participants in BPP and BP2/ Best Intro is notable. Cognition in elderly patients with psychosis remains underexplored, and our data cannot necessarily be generalized to this age group.

Diagnostic diversity

The BPP sample for Paper I was diagnostically highly diverse, with 23.8% fulfilling the diagnostic criteria for schizophrenia. This sample was recruited from a single acute psychiatric unit in Bergen. From the BP2/ Best Intro sample for Papers II and III, only data from participants with schizophrenia were included. Still, recruitment for this project tapped into both inpatients and outpatients from multiple sites, providing a different kind of diversity. This variability between projects presents some challenges in comparing results from the different papers, but samples aimed to be representative of their respective populations, i.e. acutely admitted inpatients with psychosis, and the more general population of people with psychosis starting a new course of treatment.

Concomitant drug and alcohol use

Further strengthening the clinical representativeness of all three contributing projects is that none of them excluded participants using drugs or alcohol, although for the POP project these could not form the primary cause for attenuated symptoms. Due to a singular focus on schizophrenia, drug efficacy trials in particular often exclude participants with drug- or alcohol disorders. Clinically, these make up a considerable proportion of patients, e.g. 17.9% in the BPP sample in Paper I. Given that underreporting of drug use as well as concomitant drug abuse is common in schizophrenia and related disorders, openly including these patients might give a more representative sample.

Ethnic diversity

Ethnic minorities were not widely represented in any of the samples in this project. To illustrate, in BP2/ Best Intro, the ethnic minority percentage was 6.7%, and included people identifying as African, Latin American, Asian, and mixed. In projects including neuropsychological testing, strict language requirements may have contributed to this. The percentage is also not far off the proportion of non-European ethnicities living in Stavanger (8.8%), Bergen (7.0%) and Trondheim (6.2%) (Statistisk Sentralbyrå, 2019). Although the rate may be representative, it is still problematic as it may limit the generalizability of results but more so because cultural

factors or the stress of having an ethnic minority status may both affect the trajectory of cognition in psychotic disorders. Without more closely exploring data from ethnic minority populations it may be difficult to adjust individual care programs to such factors.

All POP participants were drug naïve as per project inclusion criteria. BPP and BP2/ Best Intro samples included 51.2% and 57.7% non-naïve participants respectively. However, the considerable proportion these samples with longer-standing illness (schizophrenia diagnosis with onset > 5 years ago) still means thesis findings are not directly comparable to first episode psychosis studies.

Recruitment structure

POP participants were recruited through the low-threshold early intervention services of TIPS in Stavanger University Hospital. The use of an experienced screening team might have strengthened reliability in recruiting eligible participants. The reasons for eligible youth to decline participation after initial TIPS assessment were not systematically assessed. However, this recruitment approach could also be seen as problematic, as recruitment exclusively from help-seeking populations is a known source of sampling bias (Fusar-Poli et al., 2016). A broader approach e.g. including direct recruitment from high schools and primary health care might have yielded a different and more representative sample. Reversely, youth with e.g. high levels of social withdrawal, anxiety and paranoia might have refused getting in touch with TIPS in the first place, either directly or through an attending clinician. The number of POP participants was at any rate far lower than the number expected to experience relevant symptoms in the catchment area. It is therefore difficult to assess the degree to which POP participants are representative of the UHR population in general. Bias arising from need for informed consent

Participants in POP and BP2 had to be well enough to provide informed consent. The selection bias resulting from this is unavoidable in studies where consent is necessary. However, the most unwell participants are at great risk of being excluded. The exclusion of those in need of depot or clozapine treatment further exacerbates this trend, as these are often treatment resistant or poorly patients. In psychotic

disorder research this is exacerbated by the fact that poorer condition is likely to be accompanied with paranoia, further reducing the likelihood that these people will agree to participate in research. This is a problem in all research relying on direct data collection and active participation from subjects. However, the BPP and BP2/ Best Intro participants studied in this thesis were all required to report a high symptom load above the cut-off for active psychosis. The very similar mean PANSS positive symptoms subscale score at baseline were 20.5 and 20.7 for Paper I and III respectively. These relatively high scores mean findings might still be relevant to the severely ill group which could not be included.

Potential bias of neuropsychological results

In addition to excluding those with the highest symptom load, research into neuropsychological variables in particular will further risk excluding those with the poorest cognitive functioning. All three projects excluded participants with known mental retardation. This is common in such studies and means we know very little about cognitive change in people with both mental retardation and psychotic disorder, despite the higher occurrence of e.g. schizophrenia in conditions like Downs syndrome (Dykens et al., 2015).

It should also be noted that neuropsychological performance was a secondary outcome in all three projects, neither of which were designed to primarily target cognitive functioning. This is likely to have had a negative effect on statistical power, as projects were designed to detect phenomena with different thresholds from cognitive impairment. A more specific design would for also be better suited to gather data on premorbid academic and cognitive functioning which may be helpful when interpreting findings.

The three contributing projects to this thesis did not systematically assess reasons for participants not completing cognitive testing. Notes from testing staff reveals that for POP, time was an important consideration given that many participants were still in school. At the Bergen site for BP2/ Best Intro, two people were excluded from testing due to known intellectual impairment, seven were excluded due to insufficient language comprehension. In addition, two were excluded due to questionable validity

of test results. For BPP and BP2/ Best Intro, a commonly recorded note was that general poor level of functioning precluded assessment. If poor functioning affected a larger fraction of those not tested, this might cause artificially strong test results in the remaining sample. This is a problem affecting every project looking at cognitive functioning, especially in psychosis and other severe mental health disorders. It is difficult to get a completely representative sample within the boundaries of sound ethical research conduct, and it is also possible normal instruments may never give an accurate picture given that they require a certain level of functioning for completion.

6.2.2 Dropout

Like most longitudinal studies of psychotic disorders in general, antipsychotic drug trials in particular, both BPP and BP2 had high attrition rates. This however did not greatly affect Paper I of this thesis, as the follow-up time was relatively short (average 4.2 weeks), when many participants were still inpatients and thus available to follow-up.

Dropout was more problematic in the BP2/ Best Intro data for Paper III due to the longer follow-up period. The overall BP2/ Best Intro study designs attempted to discourage drop-out by allowing for flexible dosing and by not using a placebo group, as a strict RCT design might exacerbate drop-out (Kemmler, Hummer, Widschwendter, & Fleischhacker, 2005). Also, the opportunity to contact and remind participants ahead of each follow-up was intended to increase attendance. For the Stavanger site and my own work in particular I also found that having the opportunity to complete all assessments except blood samples for each participant made it easier to support participants to keep contributing to all follow-ups. This seemed like an advantage of running a smaller study site. However, lack of insight, cognitive impairment and disorganized symptoms remain challenges to attendance even despite every effort made.

Reasons for dropout
Like refusal to participate, dropout of subjects is a potential source of bias especially those with extreme scores on clinical or neurocognitive variables may especially have affected results. Reasons for drop-out from antipsychotic drug trials are diverse and

may be illness related such as an increase in paranoia. Drop-out might also be motivated by changing life circumstances not directly related to psychotic symptoms. To illustrate, stated reasons for dropout from the Stavanger site of BP2/ Best Intro included moving abroad, becoming asymptomatic and wishing to not be reminded of prior illness, as well as re-starting illicit drug use.

6.3 Assessment

6.3.1 Clinical assessment

In terms of symptom rating for inclusion and follow-up, in BP2/ Best Intro, all participating raters passed PANSS reliability training and testing by the PANSS Institute (panss.org). For BPP, PANSS ratings were done by experienced clinicians. POP raters received SIPS training. They were able to discuss any rating questions at weekly consensus meetings. However, SIPS / SOPS interrater reliability rates are known to improve significantly with targeted training (T. J. Miller et al., 2003). The gold standard for both POP and BPP would have been similar to the BP2 procedure with formal reliability testing,

For diagnostic assessment, in BPP this was left to the attending clinician's discretion. Both MINI plus (Sheehan et al., 1998) and SCID (First et al., 1997) were used, both of which yield DSM-IV diagnoses. MINI has the advantage of being short and requiring no training for administration. However, SCID assesses in particular psychotic symptoms more thoroughly and is more commonly used in international research. It covers the interviewee's subjective patient's own account of events as well as symptoms, medical records, and co-lateral information. It also to a large extent avoids the risk with MINI of allocating an artificially high number of diagnoses. The lack of systematic use of the same diagnostic instrument in BPP might have limited diagnostic reliability. This realization motivated the strict use of SCID for diagnostic purposes in the BP2/ Best Intro design. These were carried out by experienced clinicians tied to the research group. For similar reasons, the POP project also strictly used SCID for diagnostic purposes, with challenging cases being discussed among researchers at the consensus meeting.

Gathering of data on drug and alcohol use was retrospective and based on self-report, which is inherently prone to recollection bias. However, AUDIT and DUDIT are well-established instruments known to have good reliability and validity, including for the Norwegian language version and for use with psychotic disorders (Berman, Bergman, Palmstierna, & Schlyter, 2005; Gundersen, Gundersen, Mordal, Berman, & Bramness, 2013; Hildebrand & Noteborn, 2015).

6.3.2 Neurocognitive assessment

The BPP used the established RBANS battery. This was selected for the brevity and ease of administration necessary for testing the acute phase patients in the BPP, as well as for its resistance to retest effects. BP2/ Best Intro and POP both used custom batteries described in detail in section 3.3.2. BP2/ Best Intro used both a brief test battery repeated four times (baseline, 6, 26 and 52 weeks) and designed to withstand retest effects, as well as a comprehensive battery administered only once. The long BP2/ Best Intro battery was developed to capture a more general neuropsychological profile of clinical value for everyday functioning, and more relevant for a comparison between UHR and established psychosis. In line with this, POP used only a comprehensive battery, designed to be comparable to the BP2/ Best Intro battery and repeated twice but at longer intervals (12 and 24 months). The short BP2/ Best Intro battery was designed specifically to target the effort-demanding processes hypothesised to be more likely to be influenced by antipsychotic medication, both psychologically and due to dopaminergic effects on the brain. In the case of BP2/ Best Intro and POP batteries, all tests were commonly used in research, well established and reliable.

In retrospect, it might have been beneficial to use a consensus battery for BP2/ Best Intro, as the MATRICS battery (Nuechterlein & Green, 2006) was available by this stage. This would have eased comparison between our findings and those of future studies. Another possible improvement to Papers I and III would have been to repeat a comprehensive test rather than the brief ones used. However, this might have exacerbated any learning effects as alternative versions of certain tests are difficult to find (e.g. the Ray complex figure test or Block design). Also, repeated use of longer

tests is likely to have led to greater drop-out as they are less tolerable to participants. It should also be noted that RBANS results have been valid when compared to comprehensive test battery results (Loberg, Langeland, & Jorgensen, 2006).

No reliability training or testing was done for neurocognitive assessment in any of the contributing studies. This might have affected the reliability of the main outcomes of this thesis. However, all neurocognitive batteries were designed with strict instructions, and administered by experienced testers, which would have strengthened reliability.

Retest-effects for cognitive testing

Papers I and III both rely on retesting for cognitive change assessment. This may clearly influence results as previous completion of tests may affect later scores due to learning effects. Apparent improvement like that seen in papers I and III may thus be resulting from prior knowledge of tests rather than clinically based change. However, both the RBANS and BP2/ Best Intro brief battery were chosen for their ability to withstand retest effects. The tests we used including HVLT-R, trail making, coding and letter-number sequencing were recently found to withstand learning effects relatively well (Rodriguez-Toscano et al., 2019). Still, a better way to distinguish learning effects from actual cognitive improvement would have been to use a control group. For Paper III, learning effects are also unlikely to have affected the main outcome of between-drugs difference as any such effects are likely to be evenly distributed between groups.

6.3.3 Rater blindness in BPP and BP2.

A double-blinded design remains the gold standard especially for medication research, and a rater blinded design as used by the BPP and BP2/ Best Intro will inevitably leave greater room for interpretation bias despite every care taken to ensure raters remained blinded. For instance, at the Stavanger site where I personally performed most of the recruitment and follow-up work, I would leave the room when blood samples were being labelled, and a separate member of staff was in charge of recording medication doses and blood sample results for each participant. This member of staff would also answer any questions pertaining to study medication to

ensure I remained blinded. One way to assess the impact of rater blindness would have been to survey raters regularly or at the end of data collection for potential problems with blinding. Use of entirely independent raters might also have been a better way to ensure blindness. Interestingly, few studies to my knowledge have carried out an extensive comparison of potential bias in fully-blinded and rater-blinded studies of psychosis, perhaps because rater-blinded studies are less common.

However, even a fully blinded design cannot preclude participants, clinicians and raters from speculating and possibly also guessing which drug has been allocated, especially in cases where the pharmacological profiles of study drugs differ. For instance olanzapine is known to lead to more fatigue and weight gain than other drugs (Ratzoni et al., 2002). It is also notable that the majority of double-blinded studies fail to report methods or success indicators of concealment (Leucht et al., 2013). A double-blind design would also have negated the pragmatic design intended to give better clinical validity and better information about efficacy.

6.4 Antipsychotic treatment

The naturalistic design of BPP and BP2/ Best Intro meant that both the length of cross-taper periods and any wash-out periods before randomization were left to the discretion of the attending clinician. Although these variables might be confounding factors, the randomization procedure would serve to evenly distribute them among the study drug groups.

The study design as a head-to-head comparison of atypical antipsychotic only, with no placebo control, means that our data are not directly comparable to results from first-generation antipsychotic studies. However, a placebo controlled study would be unlikely to pass the Norwegian requirements for ethics in research, given the known efficacy of atypical antipsychotic in psychosis. Although an first-generation antipsychotics group might have added value to the results, this would have required a much larger sample, and costs of setting up a sufficiently powered trial would have been prohibitive.

For the purposes of cognition, a healthy control group was set up, but due to attrition in this group data from these participants were only used for Paper II in this thesis.

It should be noted that the change in cognitive functioning described in Paper III happened at the same time as patients tended to come off benzodiazepines. Long-term use of benzodiazepines are known to impact cognitive functioning, with impairment abating upon discontinuation of these drugs (Stewart, 2005). This should be considered when ascertaining how much of the overall cognitive change may be ascribed to atypical antipsychotics alone. However, any effects of stopping benzodiazepines could be expected to be evenly distributed between ITT and PP study medication groups, as there were no between-group differences in use of benzodiazepines.

6.5 Statistical considerations

Paper I used sequential multiple linear regression analyses to investigate cognitive change in acute psychosis. Multiple regression analysis allows for the examination of several predictors, and may thus reveal associations which might be masked by a series of simple regression models. The use of forwards stepwise selection was intended to create the most parsimonious model possible while still achieving a good fit to the data. This method is vulnerable to outliers (Slinker & Glantz, 2008), which might reasonably be expected to occur in cognitive scores from acutely ill participants. However, visual inspection of data indicated this was not an issue with our data set.

Paper II created coordinated norms to compare UHR cognitive test performance to scores from two groups with schizophrenia. Z-score based norms were created based on a healthy control group, to allow for cross-domain comparison and age appropriateness for the young UHR group, for whom standardised norms do not exist for many tests. This was seen as a better alternative to using tests aimed at children, e.g. the Wechsler intelligence scale for children, which would have complicated comparison to adult groups. Between-group analyses were done using one-way ANOVAs. Although there was a greater than ideal difference in standard deviations

for scores between our groups, we believe this still to have been a robust choice of analysis.

Paper III used linear mixed effects models (LME) which is commonly used in drug trials due to its robust handling of missing data and their ability to account for dependencies in the data due to repeated measurements from the same individuals. Although no longitudinal data were imputed in our model for dropped-out subjects, all their data up to drop-out were included in the model, and hence this strengthen the LME model compared to simpler models that require listwise deletion (i.e. patients without a complete set of observations are removed). However, LME has its own inherent limitations. It is more complex than more standardized models, and might therefore be considered less transparent and intuitive compared with the ANOVAs used in Paper II or multiple linear modelling as in Paper I. Still, given the high attrition to be expected from a drug trial with follow-up over 12 months, the ability of LME models to better handle missing data was considered paramount. The BP2 attrition meant that information was clearly lost to the later follow-ups, making slopes of the LME analysis less certain towards the end of follow-up. However, attrition rates were similar across medication groups, and not related to known baseline characteristics.

The advantage of LME models is their ability to handle both data where we have observations missing completely at random (MCAR) and missing at random (MAR). All model types and imputation techniques have problems if we have observations that are missing not at random (MNAR). The missing at random (MAR) assumption is difficult to verify without follow-up of the drop-outs. The uncertainty introduced by not collecting drop-out data would affect all types of analysis, and would best have been avoided by gathering data from those who did not complete the study.

6.6 Ethical considerations

6.6.1 Stigma and overtreatment for UHR groups

The POP project was created in order to target psychotic disorders before the appearance of above-threshold positive symptoms, hoping ultimately to reduce the regional incidence of illness. Given the challenges in assessing risk for psychosis, UHR interventions inevitably end up targeting a majority of false positives. Some have criticized pre-psychosis intervention projects for potentially stigmatizing participants, as well as for possibly over-treating their mental health problems (Raven, Stuart, & Jureidini, 2012).

Most UHR groups including the POP participants are help-seeking youth, often with a high symptom load regardless of conversion status, which we believe justify the interventions delivered, especially given the stepped approach where antipsychotic drug treatment is a rare last resort (McGorry & Mei, 2018). The experienced clinical team assessing potential POP participants is also able to signpost youth to wide range of mental health service providers, not just those targeting psychosis. In some cases, they are able to rule out serious mental illness and return the person to the community or low-threshold care. At the other end of the spectrum they may fast-track a severely ill person into specialized treatment. Somewhere in between these two extremes the average POP participants can be found: In most cases also able to get on with their daily lives, but in order to maintain function, it is paramount that they get appropriate support. The consequences of waiting for a further loss of function and potentially serious psychotic disorder are severe. We believe this justifies ultra-early intervention for this group. Although any clinical intervention will pose some interruption to a person's life. However, interventions like family groups and CBT have few negative side effects and are also helpful for POP participants who "only" end up struggling with less severe mental health challenges than psychosis.

Despite active work to reduce stigma attached to severe mental illness, schizophrenia remains associated with high levels of experienced stigma, alienation and shame (Gerlinger et al., 2013). However, we believe that the route to stigma reduction is

through informational work, psychosocial support, and openness rather than avoiding identification of youth in psychosis risk states. By providing excellent early intervention services we also hope to reduce the incidence of severe, untreated illness which is at the core of what makes schizophrenia so stigmatizing. Stigma and poor outcome may be related, as self-stigma is associated with lower adherence to treatment (Fung, Tsang, & Corrigan, 2008). A better way to achieve stigma reduction is to shift the public understanding of schizophrenia as associated with uniformly poor prognosis and an inability to meaningfully participate in society (Perkins, Raines, Tschopp, & Warner, 2008), which is exactly what we try to achieve by aiming to identify youth at risk.

6.6.2 Inclusion before or after informed consent

The BP2 / Bestintro and POP projects both required participants to give their informed consent before enrolling in the study. Informed consent poses a challenge for all research into severe psychotic disorder, given that psychosis affects a person's ability to make qualified decisions based on objective information. Informed consent requires the participant to understand both the nature of the research project and what their participation entails. On top of symptoms such as delusions and disorganized thinking, the cognitive symptoms with which this thesis is concerned pose an additional obstacle to ensuring a mutual understanding of participation. The baseline part of the Bergen Psychosis project on the other hand was designed by our research group as a clinical site quality assurance project, and thus able to study results from assessments which formed part of routine hospital treatment and records for inpatients with psychosis. Informed consent was obtained before including participants in part II of the project, a research design following up patients over time.

These contrasting approaches both have their advantages and disadvantages. Psychosis research requiring informed consent by nature excludes the most severely ill participants as these are unable to grant consent. At the same time this is a group for which more knowledge about how to help them is absolutely vital. However, the inclusion procedure of BPP might arguably be ethically problematic as data is gathered from participants without their agreement.

7. CONCLUSION

Cognitive improvement may be identified in groups at high risk of psychosis, though at an attenuated level compared to groups with established schizophrenia (Paper II), Cognitive performance improves during early recovery from acute phase psychosis (Paper I). Improvement is unrelated to both baseline positive symptom load and change, and thus does not appear to merely reflect a reduction in potentially distracting other symptoms. Paper III replicated the finding of early acute phase improvement, and also found that this improvement continues at a slower pace throughout the first year after the initiation of antipsychotic treatment. However, the three antipsychotic drugs trialled in this thesis appeared to have similar associations with cognitive change, with no drug significantly outperforming the others.

Seen together, this indicates that cognitive impairment is not a stable or uniform trait within each individual. Fluctuations and improvement in cognitive functioning happens not only in early psychotic disorder but also in established schizophrenia (Paper III). However, the existence of cognitive impairment in UHR indicates that impairment is not a temporary related to full-blown psychotic episodes. It should also be noted that in Paper III, 17% of participants still scored at least 1.5SD below the population mean at the ultimate follow-up 12 months, thus fulfilling our criteria for cognitive impairment. Although positive change does happen during recovery, this indicates that normal functioning may not be achievable for all.

A possible way to reconcile the findings of cognitive impairment in psychosis as pervasive yet changing, is to assume that different trajectories exist between various aspects of cognition. They may develop differently, with some more affected by periods of active psychosis, and others more stable throughout. Although a decrement in functioning remains for many well past the acute phase, the majority of participants in Paper III (73%) scored above our cut-off for cognitive impairment 12 months after inclusion in the study. In other words, many people with psychosis do recover towards the population norm, even if we do not know if they still showed a decrement relative to earlier individual functioning. This knowledge should inform a

message of hope to patients, and also encourage the development of targeted interventions for cognitive impairment in psychosis. These may in turn strengthen a person's ability to understand, adhere to and benefit from other interventions and treatment options.

8.   FUTURE PERSPECTIVES

I have noticed while working on this thesis that qualitative studies of cognition in schizophrenia are very scarce. Given that this is such a central aspect of psychotic disorders in general and schizophrenia in particular, we need to know more about how people with psychosis experience their cognitive functioning with its strengths and weaknesses. Such knowledge could perhaps in turn inform the improvement of targeted interventions aiming to relieve subjective distress associated with cognitive issues.

Another issue pertaining to perspectives on cognitive impairment is that despite notable exceptions, the field suffers from a relative lack of non-Western studies. The WHO estimates that at least 69% of those with schizophrenia receive appropriate care (Lora et al., 2012). Out of those that do not, 90% live in low- to middle- income countries where access to mental health services may be poor (WHO, 2020). The vast majority of schizophrenia research has studied the minority of people who access care, especially those who live in wealthy, Western societies. We need to investigate whether our truths about schizophrenia are representative of the large proportion of people not included in this relatively privileged group. Low- and middle- income countries have established promising primary health care services for psychotic disorders, where life and social skills training forms an important part of a recovery-oriented approach. Knowledge about cognitive impairment and its importance to recovery is cheap to disseminate and might bolster the success rate of such programmes. Cognitive remediation interventions aiming to improve social cognition skills may be one avenue to explore.

Also of interest would be further longitudinal explorations of potentially different individual trajectories of cognitive functioning from the UHR stage through acute psychosis and beyond, to look at what identifies whether subgroups of individuals improve, worsen, or remain stable in their cognitive impairment. One interesting angle would be the connection between emotion regulation and cognitive skills, and how it affects functioning. Closely related to this would be an exploration of how

early life trauma affects both emotion regulation, stress reactivity and cognition in psychosis.

As for specific aspects of psychosis and cognition, cognition and motivation have often been studied separately. However, although motivation is linked to avolition and is an integral part of negative symptoms as they are currently conceptualized, it may be more closely associated with cognitive impairment than hitherto thought. The possibility of dopaminergic dysfunction affecting both of these phenomena is clear, and this overlap or interaction deserves research attention (Green & Harvey, 2014). A criticism levelled 20 years ago at research looking at cognitive impairment in psychosis was that it was too atheoretical (Green, Kern, Braff, & Mintz, 2000). To some extent this is still the case. However, the opportunity to view cognitive impairment to a greater extent in the light of more recent neurological, genetic, and psychological knowledge may pave the way for a more integrated approach.

9. REFERENCES

Addington, J., van Mastrigt, S., & Addington, D. (2003). Patterns of premorbid functioning in first-episode psychosis: initial presentation. *Schizophrenia Research, 62*(1), 23-30. doi:https://doi.org/10.1016/S0920-9964(02)00408-5

Agid, O., Arenovich, T., Sajeev, G., Zipursky, R. B., Kapur, S., Foussias, G., & Remington, G. (2011). An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. *The Journal of clinical psychiatry, 72*(11), 1439-1444. doi:10.4088/jcp.09m05785yel

Alderson, H. L., Semple, D. M., Blayney, C., Queirazza, F., Chekuri, V., & Lawrie, S. M. (2017). Risk of transition to schizophrenia following first admission with substance-induced psychotic disorder: a population-based longitudinal cohort study. *Psychological medicine, 47*(14), 2548-2555. doi:10.1017/S0033291717001118

Aleman, A., Enriquez-Geppert, S., Knegtering, H., & Dlabac-de Lange, J. J. (2018). Moderate effects of noninvasive brain stimulation of the frontal cortex for improving negative symptoms in schizophrenia: Meta-analysis of controlled trials. *Neuroscience & Biobehavioral Reviews, 89*, 111-118. doi:https://doi.org/10.1016/j.neubiorev.2018.02.009

Álvarez-Jiménez, M., Parker, A. G., Hetrick, S. E., McGorry, P. D., & Gleeson, J. F. (2009). Preventing the Second Episode: A Systematic Review and Meta-analysis of Psychosocial and Pharmacological Trials in First-Episode psychosis. *Schizophrenia Bulletin, 37*(3), 619-630. doi:10.1093/schbul/sbp129

Alvarez-Jimenez, M., Priede, A., Hetrick, S. E., Bendall, S., Killackey, E., Parker, A. G., . . . Gleeson, J. F. (2012). Risk factors for relapse following treatment for first episode psychosis: A systematic review and meta-analysis of longitudinal studies. *Schizophrenia Research, 139*(1), 116-128. doi:https://doi.org/10.1016/j.schres.2012.05.007

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*. Washington, DC, USA.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders : DSM-5*.

APA. (2006). *American Psychiatric Association Practice Guidelines for the treatment of psychiatric disorders: Compendium*: American Psychiatric Pub.

Austin, S. F., Mors, O., Budtz-Jørgensen, E., Secher, R. G., Hjorthøj, C. R., Bertelsen, M., . . . Nordentoft, M. (2015). Long-term trajectories of positive and negative symptoms in first episode psychosis: A 10year follow-up study in the OPUS cohort. *Schizophrenia Research, 168*(1), 84-91. doi:https://doi.org/10.1016/j.schres.2015.07.021

Baddeley, A. D. (2002). Is working memory still working? *European psychologist, 7*(2), 85.

Barch, D. M., & Ceaser, A. (2012). Cognition in schizophrenia: core psychological and neural mechanisms. *Trends in Cognitive Sciences, 16*(1), 27-34. doi:https://doi.org/10.1016/j.tics.2011.11.015

Barder, H. E., Sundet, K., Rund, B. R., Evensen, J., Haahr, U., Ten Velden Hegelstad, W., . . . Friis, S. (2013). Ten year neurocognitive trajectories in first-episode psychosis. *Frontiers in human neuroscience, 7*, 643-643. doi:10.3389/fnhum.2013.00643

Bark, N. M. (1985). Did Shakespeare know Schizophrenia?: The Case of Poor Mad Tom in King Lear. *British Journal of Psychiatry, 146*(4), 436-438. doi:10.1192/bjp.146.4.436

Barnett, J. H., Salmond, C. H., Jones, P. B., & Sahakian, B. J. (2006). Cognitive reserve in neuropsychiatry. *Psychological medicine, 36*(8), 1053-1064. doi:10.1017/S0033291706007501

Beiser, M., Erickson, D., Fleming, J., & Iacono, W. G. (1993). Establishing the onset of psychotic illness. *American Journal ofPsychiatry, 150*, 1349-1354.

Benedict, R. H., Schretlen, D., Groninger, L., & Brandt, J. (1998). Hopkins Verbal Learning Test–Revised: Normative data and analysis of inter-form and test-retest reliability. *The Clinical Neuropsychologist, 12*(1), 43-55.

Bentall, R. P. (2004). *Madness explained: Psychosis and human nature*: Penguin UK.

Bergé, D., Carmona, S., Rovira, M., Bulbena, A., Salgado, P., & Vilarroya, O. (2011). Gray matter volume deficits and correlation with insight and negative symptoms in first-psychotic-episode subjects. *Acta Psychiatrica Scandinavica, 123*(6), 431-439.

Berman, A. H., Bergman, H., Palmstierna, T., & Schlyter, F. (2005). Evaluation of the Drug Use Disorders Identification Test (DUDIT) in criminal justice and detoxification settings and in a Swedish population sample. *European addiction research, 11*(1), 22-31.

Berman, A. H., Palmstierna, T., Källmén, H., & Bergman, H. (2007). The self-report drug use disorders identification test—extended (DUDIT-E): reliability, validity, and motivational index. *Journal of Substance Abuse Treatment, 32*(4), 357-369.

Bilder, R. M., Lipschutz-Broch, L., Reiter, G., Geisler, S. H., Mayerhoff, D. I., & Lieberman, J. A. (1992). Intellectual Deficits in First-Episode Schizophrenia: Evidence for Progressive Deterioration. *Schizophrenia Bulletin, 18*(3), 437-448. doi:10.1093/schbul/18.3.437

Birchwood, M., Todd, P., & Jackson, C. (1998). Early intervention in psychosis. The critical period hypothesis. *Br J Psychiatry Suppl, 172*(33), 53-59. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9764127

Bjornestad, J., Davidson, L., Joa, I., Larsen, T. K., Hegelstad, W. t. V., Langeveld, J., . . . Bronnick, K. (2017). Antipsychotic treatment: experiences of fully recovered service users. *Journal of Mental Health, 26*(3), 264-270. doi:10.1080/09638237.2017.1294735

Bonnett, L. J., Varese, F., Smith, C. T., Flores, A., & Yung, A. R. (2019). Individualised prediction of psychosis in individuals meeting at-risk mental state (ARMS) criteria: protocol for a systematic review of clinical prediction models. *Diagnostic and Prognostic Research, 3*(1), 21. doi:10.1186/s41512-019-0066-5

Bora, E. (2015). Neurodevelopmental origin of cognitive impairment in schizophrenia. *Psychological medicine, 45*(1), 1-9. doi:10.1017/S0033291714001263

Bora, E., Yucel, M., & Pantelis, C. (2009). Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: meta-analytic study. *British Journal of Psychiatry, 195*(6), 475-482. doi:10.1192/bjp.bp.108.055731

Bortolato, B., Miskowiak, K. W., Köhler, C. A., Vieta, E., & Carvalho, A. F. (2015). Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses. *Neuropsychiatric disease and treatment, 11*, 3111-3125. doi:10.2147/NDT.S76700

Bowie, C. R., Leung, W. W., Reichenberg, A., McClure, M. M., Patterson, T. L., Heaton, R. K., & Harvey, P. D. (2008). Predicting Schizophrenia Patients' Real-World Behavior with Specific Neuropsychological and Functional Capacity Measures. *Biological Psychiatry, 63*(5), 505-511. doi:https://doi.org/10.1016/j.biopsych.2007.05.022

Boyle, M. (2014). *Schizophrenia: A scientific delusion?* : Routledge.

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. doi:10.3109/00048674.2010.541418

Brown, A. S., & Derkits, E. J. (2010). Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. *American Journal of Psychiatry, 167*(3), 261-280.

Bryden, P. J., & Roy, E. A. (2005). A new method of administering the Grooved Pegboard Test: Performance as a function of handedness and sex. *Brain and Cognition, 58*(3), 258-268. doi:http://dx.doi.org/10.1016/j.bandc.2004.12.004

Buchanan, R. W., Kreyenbuhl, J., Kelly, D. L., Noel, J. M., Boggs, D. L., Fischer, B. A., . . . Schizophrenia Patient Outcomes Research, T. (2010). The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull, 36*(1), 71-93. doi:10.1093/schbul/sbp116

Burda, K., Czubak, A., Kus, K., Nowakowska, E., Ratajczak, P., & Zin, J. (2011). Influence of aripiprazole on the antidepressant, anxiolytic and cognitive functions of rats. *Pharmacological Reports, 63*(4), 898-907. doi:10.1016/S1734-1140(11)70605-3

Bush, K., Kivlahan, D. R., McDonell, M. B., Fihn, S. D., & Bradley, K. A. (1998). The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. *Archives of Internal Medicine, 158*(16), 1789-1795.

Cancel, A., Comte, M., Truillet, R., Boukezzi, S., Rousseau, P.-F., Zendjidjian, X. Y., . . . Fakra, E. (2015). Childhood neglect predicts disorganization in schizophrenia through grey matter decrease in dorsolateral prefrontal cortex. *Acta Psychiatrica Scandinavica, 132*(4), 244-256. doi:10.1111/acps.12455

Carletti, F., Woolley, J. B., Bhattacharyya, S., Perez-Iglesias, R., Fusar Poli, P., Valmaggia, L., . . . McGuire, P. K. (2012). Alterations in white matter evident before the onset of psychosis. *Schizophr Bull, 38*(6), 1170-1179. doi:10.1093/schbul/sbs053

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. doi:https://doi.org/10.1016/j.jpsychires.2017.10.014

Carroll, L. S., & Owen, M. J. (2009). Genetic overlap between autism, schizophrenia and bipolar disorder. *Genome medicine, 1*(10), 102.

Caton, C. L., Hasin, D. S., Shrout, P. E., Drake, R. E., Dominguez, B., First, M. B., . . . Schanzer, B. (2007). Stability of early-phase primary psychotic disorders with concurrent substance use and substance-induced psychosis. *The British Journal of Psychiatry, 190*(2), 105-111.

Chesney, E., Goodwin, G. M., & Fazel, S. (2014). Risks of all-cause and suicide mortality in mental disorders: a meta-review. *World Psychiatry, 13*(2), 153-160. doi:10.1002/wps.20128

Chew, M. L., Mulsant, B. H., Pollock, B. G., Lehman, M. E., Greenspan, A., Kirshner, M. A., . . . Gharabawi, G. (2006). A model of anticholinergic activity of atypical antipsychotic medications. *Schizophrenia Research, 88*(1), 63-72. doi:https://doi.org/10.1016/j.schres.2006.07.011

Chong, H. Y., Teoh, S. L., Wu, D. B.-C., Kotirum, S., Chiou, C.-F., & Chaiyakunapruk, N. (2016). Global economic burden of schizophrenia: a systematic review. *Neuropsychiatric disease and treatment, 12*, 357.

Chua, S. E., & McKenna, P. J. (1995). Schizophrenia--a brain disease? A critical review of structural and functional cerebral abnormality in the disorder. *Br J Psychiatry, 166*(5), 563-582. doi:10.1192/bjp.166.5.563

Conley, R. R., Ascher-Svanum, H., Zhu, B., Faries, D. E., & Kinon, B. J. (2007). The burden of depressive symptoms in the long-term treatment of patients with schizophrenia. *Schizophrenia Research, 90*(1), 186-197. doi:https://doi.org/10.1016/j.schres.2006.09.027

Crumlish, N., Whitty, P., Clarke, M., Browne, S., Kamali, M., Gervin, M., . . . Larkin, C. (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, M., Galderisi, S., Weiser, M., Werbeloff, N., Fleischhacker, W. W., Keefe, R. S. E., . . . Rybakowski, J. K. (2009). Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). *American Journal of Psychiatry, 166*(6), 675-682.

de Gracia Dominguez, M., Viechtbauer, W., Simons, C. J., van Os, J., & Krabbendam, L. (2009). Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. *Psychological Bulletin, 135*(1), 157.

Delis, D., Kramer, J., Kaplan, E., & Ober, B. (2000). CVLT-II. *The Psychological Corporation*.

Delis, D., Kramer, J. H., Kaplan, E., & Holdnack, J. (2004). Reliability and validity of the Delis-Kaplan Executive Function System: an update. *Journal of the International Neuropsychological Society, 10*(2), 301-303.

Désáméricq, G., Schurhoff, F., Meary, A., Szöke, A., Macquin-Mavier, I., Bachoud-Lévi, A., & Maison, P. (2014). Long-term neurocognitive effects of antipsychotics in schizophrenia: a network meta-analysis. *European journal of clinical pharmacology, 70*(2), 127-134.

Dickerson, F., Stallings, C., Origoni, A., Schroeder, J., Katsafanas, E., Schweinfurth, L., . . . Yolken, R. (2015). Inflammatory Markers in Recent Onset Psychosis and Chronic Schizophrenia. *Schizophrenia Bulletin, 42*(1), 134-141. doi:10.1093/schbul/sbv108

Dickinson, D., Ramsey, M. E., & Gold, J. M. (2007). Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Arch Gen Psychiatry, 64*(5), 532-542. doi:10.1001/archpsyc.64.5.532

Dieset, I., Andreassen, O. A., & Haukvik, U. K. (2016). Somatic Comorbidity in Schizophrenia: Some Possible Biological Mechanisms Across the Life Span. *Schizophrenia Bulletin, 42*(6), 1316-1319. doi:10.1093/schbul/sbw028

Divac, N., Prostran, M., Jakovcevski, I., & Cerovac, N. (2014). Second-generation antipsychotics and extrapyramidal adverse effects. *BioMed research international, 2014*.

Dixon, L. B., Lehman, A. F., & Levine, J. (1995). Conventional antipsychotic medications for schizophrenia. *Schizophr Bull, 21*(4), 567-577. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8749885

Dykens, E. M., Shah, B., Davis, B., Baker, C., Fife, T., & Fitzpatrick, J. (2015). Psychiatric disorders in adolescents and young adults with Down syndrome and other intellectual disabilities. *Journal of neurodevelopmental disorders, 7*(1), 9.

Elkis, H., Friedman, L., Wise, A., & Meltzer, H. Y. (1995). Meta-analyses of Studies of Ventricular Enlargement and Cortical Sulcal Prominence in Mood Disorders: Comparisons With Controls or Patients With Schizophrenia. *Archives of General Psychiatry, 52*(9), 735-746. doi:10.1001/archpsyc.1995.03950210029008

Emsley, R., Rabinowitz, J., & Torreman, M. (2003). The factor structure for the Positive and Negative Syndrome Scale (PANSS) in recent-onset psychosis. *Schizophrenia Research, 61*(1), 47-57. doi:https://doi.org/10.1016/S0920-9964(02)00302-X

Evensen, S., Wisløff, T., Lystad, J. U., Bull, H., Ueland, T., & Falkum, E. (2015). Prevalence, employment rate, and cost of schizophrenia in a high-income welfare society: a population-based study using comprehensive health and welfare registers. *Schizophrenia Bulletin, 42*(2), 476-483.

Falkai, P., Rossner, M. J., Schulze, T., Hasan, A., Brzózka, M. M., Malchow, B., . . . Schmitt, A. (2015). Kraepelin revisited: schizophrenia from degeneration to failed regeneration. *Molecular psychiatry, 20*(6), 671.

Falkenberg, I., Valmaggia, L., Byrnes, M., Frascarelli, M., Jones, C., Rocchetti, M., . . . Fusar-Poli, P. (2015). Why are help-seeking subjects at ultra-high risk for psychosis help-seeking? *Psychiatry research, 228*(3), 808-815. doi:http://dx.doi.org/10.1016/j.psychres.2015.05.018

Faria, M. A., Jr. (2013). Violence, mental illness, and the brain - A brief history of psychosurgery: Part 1 - From trephination to lobotomy. *Surgical neurology international, 4*, 49-49. doi:10.4103/2152-7806.110146

Fervaha, G., Foussias, G., Agid, O., & Remington, G. (2014). Impact of primary negative symptoms on functional outcomes in schizophrenia. *European Psychiatry, 29*(7), 449-455. doi:https://doi.org/10.1016/j.eurpsy.2014.01.007

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (1997). *User's guide for the Structured clinical interview for DSM-IV axis I disorders SCID-I: clinician version*: American Psychiatric Pub.

Fitzsimmons, J., Kubicki, M., & Shenton, M. E. (2013). Review of functional and anatomical brain connectivity findings in schizophrenia. *Current opinion in psychiatry, 26*(2), 172-187. doi:10.1097/YCO.0b013e32835d9e6a

Foussias, G., & Remington, G. (2008). Negative symptoms in schizophrenia: avolition and Occam's razor. *Schizophrenia Bulletin, 36*(2), 359-369.

Foussias, G., Siddiqui, I., Fervaha, G., Mann, S., McDonald, K., Agid, O., . . . Remington, G. (2015). Motivated to do well: An examination of the relationships between motivation, effort, and cognitive performance in schizophrenia. *Schizophrenia Research, 166*(1–3), 276-282. doi:http://dx.doi.org/10.1016/j.schres.2015.05.019

Fung, K. M. T., Tsang, H. W. H., & Corrigan, P. W. (2008). Self-stigma of people with schizophrenia as predictor of their adherence to psychosocial treatment. *Psychiatric Rehabilitation Journal, 32*(2), 95-104. doi:10.2975/32.2.2008.95.104

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., & et al. (2013). The psychosis high-risk state: A comprehensive state-of-the-art review. *JAMA Psychiatry, 70*(1), 107-120. doi:10.1001/jamapsychiatry.2013.269

Fusar-Poli, P., Deste, G., Smieskova, R., Barlati, S., Yung, A. R., Howes, O., . . . Borgwardt, S. (2012). Cognitive functioning in prodromal psychosis: a meta-analysis. *Archives of General Psychiatry, 69*(6), 562-571. Retrieved from http://archpsyc.jamanetwork.com/pdfaccess.ashx?url=/data/journals/psych/23651/yma110002_562_571.pdf

Fusar-Poli, P., Howes, O. D., Allen, P., Broome, M., Valli, I., Asselin, M. C., . . . McGuire, P. K. (2010). Abnormal frontostriatal interactions in people with prodromal signs of psychosis: a multimodal imaging study. *Arch Gen Psychiatry, 67*(7), 683-691. doi:10.1001/archgenpsychiatry.2010.77

Fusar-Poli, P., Papanastasiou, E., Stahl, D., Rocchetti, M., Carpenter, W., Shergill, S., & McGuire, P. (2014). Treatments of Negative Symptoms in Schizophrenia: Meta-Analysis of 168 Randomized Placebo-Controlled Trials. *Schizophrenia Bulletin, 41*(4), 892-899. doi:10.1093/schbul/sbu170

Fusar-Poli, P., Schultze-Lutter, F., Cappucciati, M., Rutigliano, G., Bonoldi, I., Stahl, D., . . . Perkins, D. O. (2016). The dark side of the moon: meta-analytical impact of recruitment strategies on risk enrichment in the clinical high risk state for psychosis. *Schizophrenia Bulletin, 42*(3), 732-743.

Gallhofer, B., Bauer, U., Lis, S., Krieger, S., & Gruppe, H. (1996). Cognitive dysfunction in schizophrenia: comparison of treatment with atypical antipsychotic agents and conventional neuroleptic drugs. *European*

Neuropsychopharmacology, 6, 13-20. doi:https://doi.org/10.1016/0924-977X(96)00010-7

Gerlinger, G., Hauser, M., De Hert, M., Lacluyse, K., Wampers, M., & Correll, C. U. (2013). Personal stigma in schizophrenia spectrum disorders: a systematic review of prevalence rates, correlates, impact and interventions. *World Psychiatry, 12*(2), 155-164. doi:10.1002/wps.20040

Giuliano, A. J., Li, H., I. Mesholam-Gately, R., M. Sorenson, S., A. Woodberry, K., & J. Seidman, L. (2012). Neurocognition in the Psychosis Risk Syndrome: A Quantitative and Qualitative Review. *Current pharmaceutical design, 18*(4), 399-415. doi:10.2174/138161212799316019

Gold, J. M., Queern, C., Iannone, V. N., & Buchanan, R. W. (1999). Repeatable battery for the assessment of neuropsychological status as a screening test in schizophrenia I: sensitivity, reliability, and validity. *Am J Psychiatry, 156*(12), 1944-1950. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10588409

González-Blanch, C., Perez-Iglesias, R., Pardo-García, G., Rodríguez-Sánchez, J., Martínez-García, O., Vázquez-Barquero, J., & Crespo-Facorro, B. (2010). Prognostic value of cognitive functioning for global functional recovery in first-episode schizophrenia. *Psychological medicine, 40*(06), 935-944.

Green, M. F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *The American journal of psychiatry*.

Green, M. F., & Harvey, P. D. (2014). Cognition in schizophrenia: Past, present, and future. *Schizophrenia Research: Cognition, 1*(1), e1-e9. doi:https://doi.org/10.1016/j.scog.2014.02.001

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. doi:10.1093/oxfordjournals.schbul.a033430

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.

Greenwood, T. A., Braff, D. L., Light, G. A., & et al. (2007). Initial heritability analyses of endophenotypic measures for schizophrenia: The consortium on the genetics of schizophrenia. *Archives of General Psychiatry, 64*(11), 1242-1250. doi:10.1001/archpsyc.64.11.1242

Gundersen, Ø. H., Gundersen, Ø. H., Mordal, J., Berman, A. H., & Bramness, J. G. (2013). Evaluation of the Alcohol Use Disorders Identification Test and the Drug Use Disorders Identification Test among Patients at a Norwegian Psychiatric Emergency Ward. *European addiction research, 19*(5), 252-260. doi:10.1159/000343485

Hagger, C., Buckley, P., Kenny, J. T., Friedman, L., Ubogy, D., & Meltzer, H. Y. (1993). Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. *Biological Psychiatry, 34*(10), 702-712.

Hambrecht, M., Lammertink, M., Klosterkötter, J., Matuschek, E., & Pukrop, R. (2002). Subjective and objective neuropsychological abnormalities in a

psychosis prodrome clinic. *British Journal of Psychiatry, 181*(S43), s30-s37. doi:10.1192/bjp.181.43.s30

Hartmann, J. A., Schmidt, S. J., McGorry, P. D., Berger, M. E., Berger, G. E., Chen, E. Y. H., . . . Nelson, B. (2019). Trajectories of symptom severity and functioning over a three-year period in a psychosis high-risk sample: A secondary analysis of the Neurapro trial. *Behaviour research and therapy*, 103527. doi:https://doi.org/10.1016/j.brat.2019.103527

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.

Heaton, R. K., Grant, I., & Matthews, C. G. (1991). *Comprehensive norms for an expanded Halstead-Reitan battery: demographic corrections, research findings, and clinical applications; with a supplement for the Wechsler Adult Intelligence Scale-Revised (WAIS-R)*: Psychological Assessment Resources.

Heaton, R. K., Paulsen, J. S., McAdams, L. A., Kuck, J., Zisook, S., Braff, D., . . . Jeste, D. V. (1994). Neuropsychological Deficits in Schizophrenics: Relationship to Age, Chronicity, and Dementia. *Archives of General Psychiatry, 51*(6), 469-476. doi:10.1001/archpsyc.1994.03950060033003

Heaton, R. K., & Pendleton, M. G. (1981). Use of Neuropsychological tests to predict adult patients' everyday functioning. *Journal of consulting and clinical psychology, 49*(6), 807.

Hedden, S. L., Woolson, R. F., Carter, R. E., Palesch, Y., Upadhyaya, H. P., & Malcolm, R. J. (2009). The impact of loss to follow-up on hypothesis tests of the treatment effect for several statistical methods in substance abuse clinical trials. *J Subst Abuse Treat, 37*(1), 54-63. doi:S0740-5472(08)00159-1 [pii]

10.1016/j.jsat.2008.09.011

Hegelstad, W. t. V., Joa, I., Heitmann, L., Johannessen, J. O., & Langeveld, J. (2019). Job- and schoolprescription: A local adaptation to individual placement and support for first episode psychosis. *Early intervention in psychiatry, 13*(4), 859-866. doi:10.1111/eip.12686

Heinrichs, R. W., & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology, 12*(3), 426-445.

Heres, S., Davis, J., Maino, K., Jetzinger, E., Kissling, W., & Leucht, S. (2006). Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. *American Journal of Psychiatry, 163*(2), 185-194.

Higashi, K., Medic, G., Littlewood, K. J., Diez, T., Granström, O., & De Hert, M. (2013). Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. *Therapeutic Advances in Psychopharmacology, 3*(4), 200-218. doi:10.1177/2045125312474019

Hildebrand, M., & Noteborn, M. G. C. (2015). Exploration of the (Interrater) Reliability and Latent Factor Structure of the Alcohol Use Disorders Identification Test (AUDIT) and the Drug Use Disorders Identification Test

(DUDIT) in a Sample of Dutch Probationers. *Substance Use & Misuse,*
50(10), 1294-1306. doi:10.3109/10826084.2014.998238

Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T. M., . .
. Glenthøj, B. (2018). Heritability of Schizophrenia and Schizophrenia
Spectrum Based on the Nationwide Danish Twin Register. *Biological*
Psychiatry, 83(6), 492-498. doi:10.1016/j.biopsych.2017.08.017

Hjorthøj, C., Stürup, A. E., McGrath, J. J., & Nordentoft, M. (2017). Years of
potential life lost and life expectancy in schizophrenia: a systematic review
and meta-analysis. *The Lancet Psychiatry, 4*(4), 295-301.
doi:https://doi.org/10.1016/S2215-0366(17)30078-0

Hor, K., & Taylor, M. (2010). Review: Suicide and schizophrenia: a systematic
review of rates and risk factors. *Journal of Psychopharmacology, 24*(4_suppl),
81-90. doi:10.1177/1359786810385490

Hou, C.-L., Xiang, Y.-T., Wang, Z.-L., Everall, I., Tang, Y., Yang, C., . . . Jia, F.-J.
(2016). Cognitive functioning in individuals at ultra-high risk for psychosis,
first-degree relatives of patients with psychosis and patients with first-episode
schizophrenia. *Schizophrenia Research, 174*(1-3), 71-76.

Howes, O. D., Kambeitz, J., Kim, E., Stahl, D., Slifstein, M., Abi-Dargham, A., &
Kapur, S. (2012). The nature of dopamine dysfunction in schizophrenia and
what this means for treatment. *Arch Gen Psychiatry, 69*(8), 776-786.
doi:10.1001/archgenpsychiatry.2012.169

Howes, O. D., & Kapur, S. (2009). The Dopamine Hypothesis of Schizophrenia:
Version III—The Final Common Pathway. *Schizophrenia Bulletin, 35*(3), 549-
562. doi:10.1093/schbul/sbp006

Howes, O. D., & Nour, M. M. (2016). Dopamine and the aberrant salience hypothesis
of schizophrenia. *World Psychiatry, 15*(1), 3.

Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter,
N., . . . Cipriani, A. (2019). Comparative efficacy and tolerability of 32 oral
antipsychotics for the acute treatment of adults with multi-episode
schizophrenia: a systematic review and network meta-analysis. *The Lancet,*
394(10202), 939-951.

Hutton, P., & Taylor, P. J. (2014). Cognitive behavioural therapy for psychosis
prevention: a systematic review and meta-analysis. *Psychological medicine,*
44(3), 449-468. doi:10.1017/S0033291713000354

Institute for Health Metrics and Evaluation. (2019). Global Burden of Disease Tool.
Retrieved from http://ghdx.healthdata.org/gbd-results-tool

Iyer, S. N., Mangala, R., Anitha, J., Thara, R., & Malla, A. K. (2011). An
examination of patient-identified goals for treatment in a first-episode
programme in Chennai, India. *Early intervention in psychiatry, 5*(4), 360-365.

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., . . .
Murray, C. J. L. (2018). Global, regional, and national incidence, prevalence,
and years lived with disability for 354 diseases and injuries for 195 countries
and territories, 1990–2017: a systematic analysis for the Global Burden of
Disease Study 2017. *The Lancet, 392*(10159), 1789-1858.
doi:https://doi.org/10.1016/S0140-6736(18)32279-7

Jauhar, S., McKenna, P. J., Radua, J., Fung, E., Salvador, R., & Laws, K. R. (2014). Cognitive–behavioural therapy for the symptoms of schizophrenia: systematic review and meta-analysis with examination of potential bias. *British Journal of Psychiatry, 204*(1), 20-29. doi:10.1192/bjp.bp.112.116285

Jirsaraie, R. J., Sheffield, J. M., & Barch, D. M. (2018). Neural correlates of global and specific cognitive deficits in schizophrenia. *Schizophrenia Research, 201*, 237-242. doi:https://doi.org/10.1016/j.schres.2018.06.017

Joa, I., Gisselgård, J., Brønnick, K., McGlashan, T. H., & Johannessen, J. O. (2015). Primary prevention of psychosis through interventions in the symptomatic prodromal phase, a pragmatic Norwegian Ultra High Risk study. *BMC psychiatry, 15*(1), 89.

Joa, I., Johannessen, J. O., Larsen, T. K., & McGlashan, T. H. (2008). Information campaigns: 10 years of experience in the Early Treatment and Intervention in Psychosis (TIPS) study. *Psychiatric Annals, 38*(8).

Johnstone, E., Frith, C., Crow, T., Husband, J., & Kreel, L. (1976). Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *The Lancet, 308*(7992), 924-926.

Kahn, R. S., & Keefe, R. S. E. (2013). Schizophrenia is a cognitive illness: time for a change in focus. *JAMA Psychiatry, 70*(10), 1107-1112.

Kane, J., Honigfeld, G., Singer, J., & Meltzer, H. (1988). Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Archives of General Psychiatry, 45*(9), 789-796.

Karlsgodt, K. H., Niendam, T. A., Bearden, C. E., & Cannon, T. D. (2009). White Matter Integrity and Prediction of Social and Role Functioning in Subjects at Ultra-High Risk for Psychosis. *Biological Psychiatry, 66*(6), 562-569. doi:https://doi.org/10.1016/j.biopsych.2009.03.013

Kaufman, J., Birmaher, B., Brent, D., Rao, U. M. A., Flynn, C., Moreci, P., . . . Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial Reliability and Validity Data. *Journal of the American Academy of Child & Adolescent Psychiatry, 36*(7), 980-988. doi:https://doi.org/10.1097/00004583-199707000-00021

Kavanagh, D. H., Tansey, K. E., O'Donovan, M. C., & Owen, M. J. (2015). Schizophrenia genetics: emerging themes for a complex disorder. *Mol Psychiatry, 20*(1), 72-76. doi:10.1038/mp.2014.148

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophrenia Bulletin, 13*(2), 261-276. doi:10.1093/schbul/13.2.261

Keefe, R. S. E., Bilder, R. M., Davis, S. M., & et al. (2007). Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. *Archives of General Psychiatry, 64*(6), 633-647. doi:10.1001/archpsyc.64.6.633

Keefe, R. S. E., Bollini, A. M., & Silva, S. G. (1999). Do novel antipsychotics improve cognition? A report of a meta-analysis. *Psychiatric Annals, 29*(11), 623-629.

Keefe, R. S. E., Eesley, C. E., & Poe, M. P. (2005). Defining a cognitive function decrement in schizophrenia. *Biological Psychiatry, 57*(6), 688-691.

Keefe, R. S. E., Mohs, R. C., Bilder, R. M., Harvey, P. D., Green, M. F., Meltzer, H. Y., . . . Sano, M. (2003). Neurocognitive Assessment in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Project Schizophrenia Trial: Development, Methodology, and Rationale. *Schizophrenia Bulletin, 29*(1), 45-55. doi:10.1093/oxfordjournals.schbul.a006990

Kemmler, G., Hummer, M., Widschwendter, C., & Fleischhacker, W. W. (2005). Dropout Rates in Placebo-Controlled and Active-Control Clinical Trials of Antipsychotic Drugs: A Meta-analysis. *Archives of General Psychiatry, 62*(12), 1305-1312. doi:10.1001/archpsyc.62.12.1305

Kern, R. S., Gold, J. M., Dickinson, D., Green, M. F., Nuechterlein, K. H., Baade, L. E., . . . Marder, S. R. (2011). The MCCB impairment profile for schizophrenia outpatients: Results from the MATRICS psychometric and standardization study. *Schizophrenia Research, 126*(1), 124-131. doi:https://doi.org/10.1016/j.schres.2010.11.008

Kern, R. S., Green, M. F., Cornblatt, B. A., Owen, J. R., McQuade, R. D., Carson, W. H., . . . Marcus, R. (2006). The neurocognitive effects of aripiprazole: an open-label comparison with olanzapine. *Psychopharmacology, 187*(3), 312-320. doi:10.1007/s00213-006-0428-x

Keshavan, M. S., DeLisi, L. E., & Seidman, L. J. (2011). Early and broadly defined psychosis risk mental states. *Schizophrenia Research, 126*(1), 1-10. doi:https://doi.org/10.1016/j.schres.2010.10.006

Khandaker, G. M., Barnett, J. H., White, I. R., & Jones, P. B. (2011). A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. *Schizophrenia Research, 132*(2), 220-227. doi:https://doi.org/10.1016/j.schres.2011.06.017

Khandaker, G. M., Cousins, L., Deakin, J., Lennox, B. R., Yolken, R., & Jones, P. B. (2015). Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. *The Lancet Psychiatry, 2*(3), 258-270. doi:https://doi.org/10.1016/S2215-0366(14)00122-9

Khoury, B., Lecomte, T., Gaudiano, B. A., & Paquin, K. (2013). Mindfulness interventions for psychosis: A meta-analysis. *Schizophrenia Research, 150*(1), 176-184. doi:https://doi.org/10.1016/j.schres.2013.07.055

Killackey, E., Allott, K., Woodhead, G., Connor, S., Dragon, S., & Ring, J. (2017). Individual placement and support, supported education in young people with mental illness: an exploratory feasibility study. *Early intervention in psychiatry, 11*(6), 526-531. doi:10.1111/eip.12344

Kirkpatrick, B., & Miller, B. J. (2013). Inflammation and Schizophrenia. *Schizophrenia Bulletin, 39*(6), 1174-1179. doi:10.1093/schbul/sbt141

Koutsouleris, N., Davatzikos, C., Bottlender, R., Patschurek-Kliche, K., Scheuerecker, J., Decker, P., . . . Meisenzahl, E. M. (2011). Early recognition and disease prediction in the at-risk mental states for psychosis using neurocognitive pattern classification. *Schizophrenia Bulletin, 38*(6), 1200-1215.

Kraan, T., Velthorst, E., Koenders, L., Zwaart, K., Ising, H. K., van den Berg, D., . . . van der Gaag, M. (2016). Cannabis use and transition to psychosis in individuals at ultra-high risk: review and meta-analysis. *Psychological medicine, 46*(4), 673-681. doi:10.1017/S0033291715002329

Kraan, T., Velthorst, E., Smit, F., de Haan, L., & van der Gaag, M. (2015). Trauma and recent life events in individuals at ultra high risk for psychosis: Review and meta-analysis. *Schizophrenia Research, 161*(2), 143-149. doi:https://doi.org/10.1016/j.schres.2014.11.026

Kraepelin, E. (1919). Dementia praecox and paraphrenia (RM Barclay, Trans.). *Huntingdon, NY: Krieger*.

Kremen, W. S., Seidman, L. J., Faraone, S. V., Toomey, R., & Tsuang, M. T. (2000). The paradox of normal neuropsychological function in schizophrenia. *Journal of Abnormal Psychology, 109*(4), 743.

Kreyenbuhl, J., Buchanan, R. W., Dickerson, F. B., & Dixon, L. B. (2010). The schizophrenia patient outcomes research team (PORT): updated treatment recommendations 2009. *Schizophrenia bulletin, 36*(1), 94-103.

Lally, J., & MacCabe, J. H. (2015). Antipsychotic medication in schizophrenia: a review. *British Medical Bulletin, 114*(1), 169-179. doi:10.1093/bmb/ldv017

Larsen, T. K., Melle, I., Auestad, B., Haahr, U., Joa, I., Johannessen, J. O., . . . Simonsen, E. (2011). Early detection of psychosis: positive effects on 5-year outcome. *Psychological medicine, 41*(7), 1461-1469.

Laursen, T. M., Nordentoft, M., & Mortensen, P. B. (2014). Excess Early Mortality in Schizophrenia. *Annual review of clinical psychology, 10*(1), 425-448. doi:10.1146/annurev-clinpsy-032813-153657

Lea, J. W., Stoner, S. C., & LaFollette, J. (2007). Agitation Associated with Aripiprazole Initiation. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 27*(9), 1339-1342. doi:10.1592/phco.27.9.1339

Lencz, T., Knowles, E., Davies, G., Guha, S., Liewald, D. C., Starr, J. M., . . . Malhotra, A. K. (2014). Molecular genetic evidence for overlap between general cognitive ability and risk for schizophrenia: a report from the Cognitive Genomics consorTium (COGENT). *Molecular psychiatry, 19*(2), 168-174. doi:10.1038/mp.2013.166

Lepage, M., Bodnar, M., & Bowie, C. R. (2014). Neurocognition: clinical and functional outcomes in schizophrenia. *The Canadian Journal of Psychiatry, 59*(1), 5-12.

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. doi:https://doi.org/10.1016/S0140-6736(13)60733-3

Leucht, S., Corves, C., Arbter, D., Engel, R. R., Li, C., & Davis, J. M. (2009). Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *The Lancet, 373*(9657), 31-41. doi:https://doi.org/10.1016/S0140-6736(08)61764-X

Leucht, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Salanti, G., & Davis, 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., & Fischer, J. S. (2004). *Neuropsychological assessment*: Oxford University Press, USA.

Li, S., Hu, N., Zhang, W., Tao, B., Dai, J., Gong, Y., . . . Lui, S. (2019). Dysconnectivity of Multiple Brain Networks in Schizophrenia: A Meta-Analysis of Resting-State Functional Connectivity. *Frontiers in Psychiatry, 10*(482). doi:10.3389/fpsyt.2019.00482

Li, Z., Ichikawa, J., Dai, J., & Meltzer, H. Y. (2004). Aripiprazole, a novel antipsychotic drug, preferentially increases dopamine release in the prefrontal cortex and hippocampus in rat brain. *European journal of pharmacology, 493*(1-3), 75-83.

Lieberman, J. A. (1999). Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. *Biological Psychiatry, 46*(6), 729-739.

Linscott, R. J., & van Os, J. (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological medicine, 43*(6), 1133-1149. doi:10.1017/S0033291712001626

Løberg, E.-M., Gjestad, R., Posserud, M.-B., Kompus, K., & Lundervold, A. J. (2019). Psychosocial characteristics differentiate non-distressing and distressing voices in 10,346 adolescents. *European child & adolescent psychiatry, 28*(10), 1353-1363. doi:10.1007/s00787-019-01292-x

Løberg, E.-M., & Hugdahl, K. (2009). Cannabis use and cognition in schizophrenia. *Frontiers in human neuroscience, 3*(53). doi:10.3389/neuro.09.053.2009

Loberg, E., Langeland, M., & Jorgensen, H. (2006). Reliability and validity of a Norwegian translation of the repeatable battery for the assessment of neuropsychological status in patients with psychosis. *Nevropsykologi, 9*, 36.

Lora, A., Kohn, R., Levav, I., McBain, R., Morris, J., & Saxena, S. (2012). Service availability and utilization and treatment gap for schizophrenic disorders: a survey in 50 low- and middle-income countries. *Bull World Health Organ, 90*(1), 47-54, 54a-54b. doi:10.2471/blt.11.089284

Lysaker, P. H., & Dimaggio, G. (2014). Metacognitive capacities for reflection in schizophrenia: implications for developing treatments. *Schizophrenia Bulletin, 40*(3), 487-491.

Malaspina, D., Owen, M. J., Heckers, S., Tandon, R., Bustillo, J., Schultz, S., . . . Carpenter, W. (2013). Schizoaffective Disorder in the DSM-5. *Schizophrenia Research, 150*(1), 21-25. doi:https://doi.org/10.1016/j.schres.2013.04.026

McFarlane, W. R. (2016). Family Interventions for Schizophrenia and the Psychoses: A Review. *Family Process, 55*(3), 460-482. doi:10.1111/famp.12235

McGlashan, T. H. (2006). Schizophrenia in Translation: Is Active Psychosis Neurotoxic? *Schizophrenia Bulletin, 32*(4), 609-613. doi:10.1093/schbul/sbl032

McGlashan, T. H., & Fenton, W. S. (1993). Subtype progression and pathophysiologic deterioration in early schizophrenia. *Schizophrenia Bulletin, 19*(1), 71-84.

McGorry, P. D., Killackey, E., & Yung, A. (2008). Early intervention in psychosis: concepts, evidence and future directions. *World Psychiatry, 7*(3), 148-156.

McGorry, P. D., & Mei, C. (2018). Ultra-high-risk paradigm: lessons learnt and new directions. *Evidence Based Mental Health, 21*(4), 131-133. doi:10.1136/ebmental-2018-300061

McGrath, M. C. (2011). Wisconsin Card Sorting Test. In S. Goldstein & J. A. Naglieri (Eds.), *Encyclopedia of Child Behavior and Development* (pp. 1571-1572). Boston, MA: Springer US.

Medalia, A., & Saperstein, A. M. (2013). Does cognitive remediation for schizophrenia improve functional outcomes? *Current opinion in psychiatry, 26*(2), 151-157.

Mednick, S. A., & McNeil, T. F. (1968). Current methodology in research on the etiology of schizophrenia: Serious difficulties which suggest the use of the high-risk-group method. *Psychological Bulletin, 70*(6, Pt.1), 681-693. doi:10.1037/h0026836

Meltzer, H. Y. (1999). The Role of Serotonin in Antipsychotic Drug Action. *Neuropsychopharmacology, 21*(1), 106-115. doi:10.1016/S0893-133X(99)00046-9

Meltzer, H. Y., & McGurk, S. R. (1999). The Effects of Clozapine, Risperidone, and Olanzapine on Cognitive Function in Schizophrenia. *Schizophrenia Bulletin, 25*(2), 233-256. doi:10.1093/oxfordjournals.schbul.a033376

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

Meyer-Lindenberg, A., Miletich, R. S., Kohn, P. D., Esposito, G., Carson, R. E., Quarantelli, M., . . . Berman, K. F. (2002). Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. *Nat Neurosci, 5*(3), 267-271. doi:10.1038/nn804

Millan, M. J., Agid, Y., Brüne, M., Bullmore, E. T., Carter, C. S., Clayton, N. S., . . . Young, L. J. (2012). Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nature Reviews Drug Discovery, 11*(2), 141-168. doi:10.1038/nrd3628

Miller, B. J., Culpepper, N., Rapaport, M. H., & Buckley, P. (2013). Prenatal inflammation and neurodevelopment in schizophrenia: A review of human studies. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 42*, 92-100. doi:https://doi.org/10.1016/j.pnpbp.2012.03.010

Miller, E. (1990). California computerized assessment package. *Los Angeles: Norland Software*.

Miller, T. J., McGlashan, T. H., Rosen, J. L., Cadenhead, K., Cannon, T., Ventura, J., . . . Woods, S. W. (2003). Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophrenia Bulletin, 29*(4), 703-715.

Minor, K. S., & Lysaker, P. H. (2014). Necessary, but not sufficient: Links between neurocognition, social cognition, and metacognition in schizophrenia are

moderated by disorganized symptoms. *Schizophrenia Research, 159*(1), 198-204. doi:https://doi.org/10.1016/j.schres.2014.08.005

Misiak, B., Krefft, M., Bielawski, T., Moustafa, A. A., Sąsiadek, M. M., & Frydecka, D. (2017). Toward a unified theory of childhood trauma and psychosis: A comprehensive review of epidemiological, clinical, neuropsychological and biological findings. *Neuroscience & Biobehavioral Reviews, 75*, 393-406. doi:https://doi.org/10.1016/j.neubiorev.2017.02.015

Miyamoto, S., Duncan, G. E., Marx, C. E., & Lieberman, J. A. (2005). Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Molecular psychiatry, 10*(1), 79-104. doi:10.1038/sj.mp.4001556

Møller, P., & Husby, R. (2000). The initial prodrome in schizophrenia: searching for naturalistic core dimensions of experience and behavior. *Schizophrenia Bulletin, 26*(1), 217.

Mollon, J., & Reichenberg, A. (2018). Cognitive development prior to onset of psychosis. *Psychological medicine, 48*(3), 392-403. doi:10.1017/S0033291717001970

Mondelli, V., Cattaneo, A., Murri, M. B., Di Forti, M., Handley, R., Hepgul, N., . . . Aitchison, K. J. (2011). Stress and inflammation reduce BDNF expression in first-episode psychosis: a pathway to smaller hippocampal volume. *The Journal of clinical psychiatry, 72*(12), 1677.

Morin, L., & Franck, N. (2017). Rehabilitation Interventions to Promote Recovery from Schizophrenia: A Systematic Review. *Frontiers in Psychiatry, 8*(100). doi:10.3389/fpsyt.2017.00100

Mørkved, N. J., E; Kroken, RA; Gjestad, R; Winje, D; Thimm, J; Fathian, F; Rettenbacher, M; Anda, LG; Løberg, EM. (2020). Does childhood trauma influence cognitive functioning in schizophrenia? The association of childhood trauma and cognition in schizophrenia spectrum disorders. *Schizophrenia Research: Cognition, 21*, 100179.

Moskowitz, A., & Heim, G. (2011). Eugen Bleuler's Dementia Praecox or the Group of Schizophrenias (1911): A Centenary Appreciation and Reconsideration. *Schizophrenia Bulletin, 37*(3), 471-479. doi:10.1093/schbul/sbr016

Mueser, K. T., Drake, R. E., Clark, R. E., McHugo, G. J., Mercer-McFadden, C., & Ackerson, T. H. (1995). *Toolkit for evaluating substance abuse in persons with severe mental illness*. Cambridge, M: Evaluation Center, Human Services Research Institute.

Mwansisya, T. E., Hu, A., Li, Y., Chen, X., Wu, G., Huang, X., . . . Liu, Z. (2017). Task and resting-state fMRI studies in first-episode schizophrenia: A systematic review. *Schizophrenia Research, 189*, 9-18. doi:https://doi.org/10.1016/j.schres.2017.02.026

NICE. (2014). *Psychosis and schizophrenia in adults*. National Collaborating Centre for Mental Health

Niemi-Pynttäri, J. A., Sund, R., Putkonen, H., Vorma, H., Wahlbeck, K., & Pirkola, S. P. (2013). Substance-induced psychoses converting into schizophrenia: a register-based study of 18,478 Finnish inpatient cases. *The Journal of clinical psychiatry, 74*(1), e94-99.

Norwegian Directorate of Health. (2013). *Nasjonal faglig retningslinje for psykoselidelser*. Retrieved from https://www.helsedirektoratet.no/retningslinjer/psykoselidelser

Nuechterlein, K. H., & Green, M. F. (2006). MATRICS consensus cognitive battery manual. *Los Angeles, CA: MATRICS Assessment Inc*.

Nuechterlein, 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*(Suppl 2), S33-S40. doi:10.1093/schbul/sbr084

OED. (Ed.) (n.d.-a) Oxford English Dictionary. Oxford, UK: Oxford University Press.

OED. (Ed.) (n.d.-b) Oxford English Dictionary. Oxford, UK: Oxford University Press.

Onwumere, J., Bebbington, P., & Kuipers, E. (2011). Family interventions in early psychosis: specificity and effectiveness. *Epidemiology and psychiatric sciences, 20*(2), 113-119.

Opler, L. A., Kay, S. R., Lindenmayer, J. P., & Fiszbein, A. (1999) *Structured clinical interview: The positive and negative syndrome scale (SCI-PANSS)*. Multi-Health Systems, North Tonawanda, NY.

Orlovska-Waast, S., Köhler-Forsberg, O., Brix, S. W., Nordentoft, M., Kondziella, D., Krogh, J., & Benros, M. E. (2019). Cerebrospinal fluid markers of inflammation and infections in schizophrenia and affective disorders: a systematic review and meta-analysis. *Molecular psychiatry, 24*(6), 869-887. doi:10.1038/s41380-018-0220-4

Ortiz-Gil, J., Pomarol-Clotet, E., Salvador, R., Canales-Rodríguez, E. J., Sarro, S., Gomar, J. J., . . . Junque, C. (2011). Neural correlates of cognitive impairment in schizophrenia. *The British Journal of Psychiatry, 199*(3), 202-210.

Palmer, B. W., Dawes, S. E., & Heaton, R. K. (2009). What do we know about neuropsychological aspects of schizophrenia? *Neuropsychology Review, 19*(3), 365-384.

Patel, D., Laws, K., Padhi, A., Farrow, J., Mukhopadhaya, K., Krishnaiah, R., & Fineberg, N. (2010). The neuropsychology of the schizo-obsessive subtype of schizophrenia: a new analysis. *Psychological medicine, 40*(06), 921-933.

Penttilä, M., Jääskeläinen, E., Hirvonen, N., Isohanni, M., & Miettunen, J. (2014). Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *The British Journal of Psychiatry, 205*(2), 88-94.

Perkins, D. V., Raines, J. A., Tschopp, M. K., & Warner, T. C. (2008). Gainful Employment Reduces Stigma Toward People Recovering from Schizophrenia. *Community Mental Health Journal, 45*(3), 158. doi:10.1007/s10597-008-9158-3

Pinheiro, C., & Bates, D. (2000). *Mixed effects models in S and S-plus*. New York: Springer.

Piskulic, D., Addington, J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Heinssen, R., . . . McGlashan, T. H. (2012). Negative symptoms in individuals

at clinical high risk of psychosis. *Psychiatry research, 196*(2), 220-224. doi:https://doi.org/10.1016/j.psychres.2012.02.018

Plomin, R., & Deary, I. J. (2015). Genetics and intelligence differences: five special findings. *Molecular psychiatry, 20*(1), 98-108. doi:10.1038/mp.2014.105

Plum, F. (1972). Prospects for research on schizophrenia. 3. Neurophysiology. Neuropathological findings. *Neurosciences Research Program Bulletin, 10*(4), 384-388.

Popovic, D., Benabarre, A., Crespo, J., Goikolea, J., González-Pinto, A., Gutiérrez-Rojas, L., . . . Vieta, E. (2014). Risk factors for suicide in schizophrenia: systematic review and clinical recommendations. *Acta Psychiatrica Scandinavica, 130*(6), 418-426.

R Core Team. (2013). R: A language and environment for statistical computing. Retrieved from http://www.r-project.org/

Rajji, T. K., Miranda, D., & Mulsant, B. H. (2014). Cognition, Function, and Disability in Patients With Schizophrenia: A Review of Longitudinal Studies. *Canadian Journal of Psychiatry, 59*(1), 13.

Randolph, C. (1998). *RBANS Repeatable Battery for the Assessment of Neuropsychological Status. Manual.* . San Antonio: The Psychological Corporation.

Ratzoni, G., Gothelf, D., Brand-Gothelf, A., Reidman, J., Kikinzon, L., Gal, G., . . . Weizman, R. (2002). Weight Gain Associated With Olanzapine and Risperidone in Adolescent Patients: A Comparative Prospective Study. *Journal of the American Academy of Child & Adolescent Psychiatry, 41*(3), 337-343. doi:https://doi.org/10.1097/00004583-200203000-00014

Raven, M., Stuart, G. W., & Jureidini, J. (2012). 'Prodromal' diagnosis of psychosis: Ethical problems in research and clinical practice. *Australian & New Zealand Journal of Psychiatry, 46*(1), 64-65. doi:10.1177/0004867411428917

Read, J., & Sacia, A. (2020). Using Open Questions to Understand 650 People's Experiences With Antipsychotic Drugs. *Schizophrenia Bulletin*. doi:10.1093/schbul/sbaa002

Reichenberg, A., Caspi, A., Harrington, H., Houts, R., Keefe, R. S. E., Murray, R. M., . . . Moffitt, T. E. (2010). Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. *American Journal of Psychiatry*.

Reichenberg, A., Harvey, P. D., Bowie, C. R., Mojtabai, R., Rabinowitz, J., Heaton, R. K., & Bromet, E. (2008). Neuropsychological Function and Dysfunction in Schizophrenia and Psychotic Affective Disorders. *Schizophrenia Bulletin, 35*(5), 1022-1029. doi:10.1093/schbul/sbn044

Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and motor skills, 8*(3), 271-276.

Riedel, M., Schennach-Wolff, R., Musil, R., Dehning, S., Cerovecki, A., Opgen-Rhein, M., . . . Spellmann, I. (2010). Neurocognition and its influencing factors in the treatment of schizophrenia—effects of aripiprazole, olanzapine, quetiapine and risperidone. *Human Psychopharmacology: Clinical and Experimental, 25*(2), 116-125. doi:10.1002/hup.1101

Riedel, M., Spellmann, I., Schennach-Wolff, R., Musil, R., Dehning, S., Cerovecki, A., . . . Möller, H. J. (2010). Effect of Aripiprazole on Cognition in the Treatment of Patients with Schizophrenia. *Pharmacopsychiatry, 43*(02), 50-57. doi:10.1055/s-0029-1239539

Rigucci, S., Santi, G., Corigliano, V., Imola, A., Rossi-Espagnet, C., Mancinelli, I., . . . Comparelli, A. (2016). White matter microstructure in ultra-high risk and first episode schizophrenia: A prospective study. *Psychiatry Research: Neuroimaging, 247*, 42-48. doi:https://doi.org/10.1016/j.pscychresns.2015.11.003

Rodriguez-Toscano, E., López, G., Mayoral, M., Lewis, S., Lees, J., Drake, R., . . . Rapado-Castro, M. (2019). A longitudinal comparison of two neurocognitive test batteries in patients with schizophrenia and healthy volunteers: Time effects on neuropsychological performance and their relation to functional outcome. *Schizophrenia Research*. doi:https://doi.org/10.1016/j.schres.2019.11.018

Ruhrmann, S., Paruch, J., Bechdolf, A., Pukrop, R., Wagner, M., Berning, J., . . . Klosterkötter, J. (2008). Reduced subjective quality of life in persons at risk for psychosis. *Acta Psychiatrica Scandinavica, 117*(5), 357-368. doi:10.1111/j.1600-0447.2008.01152.x

Rummel-Kluge, C., Komossa, K., Schwarz, S., Hunger, H., Schmid, F., Kissling, W., . . . Leucht, S. (2012). Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophrenia Bulletin, 38*(1), 167-177.

Rund, B. R. (1998). A Review of Longitudinal Studies of Cognitive Functions in Schizophrenia Patients. *Schizophrenia Bulletin, 24*(3), 425-435. doi:10.1093/oxfordjournals.schbul.a033337

Rus-Calafell, M., & Schneider, S. (2020). Are we there yet?!-a literature review of recent digital technology advances for the treatment of early psychosis. *mHealth, 6*, 3-3. doi:10.21037/mhealth.2019.09.14

Samartzis, L., Dima, D., Fusar-Poli, P., & Kyriakopoulos, M. (2014). White Matter Alterations in Early Stages of Schizophrenia: A Systematic Review of Diffusion Tensor Imaging Studies. *Journal of Neuroimaging, 24*(2), 101-110. doi:doi:10.1111/j.1552-6569.2012.00779.x

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.

Schultze-Lutter, F., & Theodoridou, A. (2017). The concept of basic symptoms: its scientific and clinical relevance. *World psychiatry : official journal of the World Psychiatric Association (WPA), 16*(1), 104-105. doi:10.1002/wps.20404

Seidman, L. J., Giuliano, A. J., & Meyer, E. C. (2010). Neuropsychology of the prodrome to psychosis in the NAPLS consortium: Relationship to family history and conversion to psychosis. *Archives of General Psychiatry, 67*(6), 578-588. doi:10.1001/archgenpsychiatry.2010.66

Seidman, L. J., Shapiro, D. I., Stone, W. S., Woodberry, K. A., Ronzio, A., Cornblatt, B. A., . . . Cannon, T. D. (2016). Association of neurocognition with transition

to psychosis: baseline functioning in the second phase of the North American prodrome longitudinal study. *JAMA Psychiatry, 73*(12), 1239-1248.

Sendt, K. V., Tracy, D. K., & Bhattacharyya, S. (2015). A systematic review of factors influencing adherence to antipsychotic medication in schizophrenia-spectrum disorders. *Psychiatry Res, 225*(1-2), 14-30. doi:10.1016/j.psychres.2014.11.002

Sharma, T., & Mockler, D. (1998). The Cognitive Efficacy of Atypical Antipsychotics in Schizophrenia. *Journal of Clinical Psychopharmacology, 18*(2), 12S-19S. Retrieved from https://journals.lww.com/psychopharmacology/Fulltext/1998/04001/The_Cognitive_Efficacy_of_Atypical_Antipsychotics.4.aspx

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry, 59 Suppl 20*, 22-33;quiz 34-57. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9881538

Sheffield, J. M., & Barch, D. M. (2016). Cognition and resting-state functional connectivity in schizophrenia. *Neuroscience & Biobehavioral Reviews, 61*, 108-120. doi:https://doi.org/10.1016/j.neubiorev.2015.12.007

Shenton, M. E., Dickey, C. C., Frumin, M., & McCarley, R. W. (2001). A review of MRI findings in schizophrenia. *Schizophrenia Research, 49*(1), 1-52. doi:https://doi.org/10.1016/S0920-9964(01)00163-3

Shevlin, M., McElroy, E., Bentall, R. P., Reininghaus, U., & Murphy, J. (2016). The psychosis continuum: testing a bifactor model of psychosis in a general population sample. *Schizophrenia Bulletin, 43*(1), 133-141.

Shim, G., Oh, J. S., Jung, W. H., Jang, J. H., Choi, C.-H., Kim, E., . . . Kwon, J. S. (2010). Altered resting-state connectivity in subjects at ultra-high risk for psychosis: an fMRI study. *Behavioral and Brain Functions, 6*(1), 58.

Shin, M.-S., Park, S.-Y., Park, S.-R., Seol, S.-H., & Kwon, J. S. (2006). Clinical and empirical applications of the Rey–Osterrieth complex figure test. *Nature protocols, 1*(2), 892-899.

Simon, A. E., & Umbricht, D. (2010). High remission rates from an initial ultra-high risk state for psychosis. *Schizophrenia Research, 116*(2), 168-172. doi:https://doi.org/10.1016/j.schres.2009.10.001

Simon, A. E., Velthorst, E., Nieman, D. H., Linszen, D., Umbricht, D., & de Haan, L. (2011). Ultra high-risk state for psychosis and non-transition: A systematic review. *Schizophrenia Research, 132*(1), 8-17. doi:https://doi.org/10.1016/j.schres.2011.07.002

Simonsen, C., Sundet, K., Vaskinn, A., Birkenaes, A. B., Engh, J. A., Færden, A., . . . Andreassen, O. A. (2009). Neurocognitive Dysfunction in Bipolar and Schizophrenia Spectrum Disorders Depends on History of Psychosis Rather Than Diagnostic Group. *Schizophrenia Bulletin, 37*(1), 73-83. doi:10.1093/schbul/sbp034

Slinker, B. K., & Glantz, S. A. (2008). Multiple Linear Regression. *Circulation, 117*(13), 1732-1737. doi:doi:10.1161/CIRCULATIONAHA.106.654376

Slotema, C. W., Blom, J. D., van Lutterveld, R., Hoek, H. W., & Sommer, I. E. C. (2014). Review of the Efficacy of Transcranial Magnetic Stimulation for Auditory Verbal Hallucinations. *Biological Psychiatry, 76*(2), 101-110. doi:https://doi.org/10.1016/j.biopsych.2013.09.038

Snitz, B. E., MacDonald III, A. W., & Carter, C. S. (2006). Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes.

Snyder, S. H. (1976). The dopamine hypothesis of schizophrenia: focus on the dopamine receptor. *The American journal of psychiatry*.

Sohler, N., Adams, B., Barnes, D., Cohen, G., Prins, S., & Schwartz, S. (2016). Weighing the Evidence for Harm From Long-Term Treatment With Antipsychotic Medications: A Systematic Review. *The American journal of orthopsychiatry, 86*(5), 477-485.

Spitzer, R. L., Williams, J. B., Gibbon, M., & First, M. B. (1992). The structured clinical interview for DSM-III-R (SCID): I: history, rationale, and description. *Archives of General Psychiatry, 49*(8), 624-629.

Sponheim, S. R., Jung, R. E., Seidman, L. J., Mesholam-Gately, R. I., Manoach, D. S., O'Leary, D. S., . . . Schulz, S. C. (2010). Cognitive deficits in recent-onset and chronic schizophrenia. *Journal of psychiatric research, 44*(7), 421-428. doi:https://doi.org/10.1016/j.jpsychires.2009.09.010

Statistisk Sentralbyrå. (2019). 09817: Innvandrere og norskfødte med innvandrerforeldre, etter landbakgrunn, år, statistikkvariabel, innvandringskategori og region - for Stavanger og Bergen og Trondheim. In.

Steen, N. E., Aas, M., Simonsen, C., Dieset, I., Tesli, M., Nerhus, M., . . . Andreassen, O. A. (2017). Serum levels of second-generation antipsychotics are associated with cognitive function in psychotic disorders. *The World Journal of Biological Psychiatry, 18*(6), 471-482. doi:10.1080/15622975.2016.1245441

Stewart, S. A. (2005). The Effects of Benzodiazepines on Cognition. *The Journal of clinical psychiatry, 66*(Suppl2), 9-13.

Stone, J. M., Howes, O. D., Egerton, A., Kambeitz, J., Allen, P., Lythgoe, D. J., . . . McGuire, P. (2010). Altered relationship between hippocampal glutamate levels and striatal dopamine function in subjects at ultra high risk of psychosis. *Biol Psychiatry, 68*(7), 599-602. doi:10.1016/j.biopsych.2010.05.034

Strauss, G. P., Morra, L. F., Sullivan, S. K., & Gold, J. M. (2015). The role of low cognitive effort and negative symptoms in neuropsychological impairment in schizophrenia. *Neuropsychology, 29*(2), 282-291. doi:10.1037/neu0000113

Swildens, W., Termorshuizen, F., de Ridder, A., Smeets, H., & Engelhard, I. M. (2016). Somatic Care with a Psychotic Disorder. Lower Somatic Health Care Utilization of Patients with a Psychotic Disorder Compared to Other Patient Groups and to Controls Without a Psychiatric Diagnosis. *Administration and Policy in Mental Health and Mental Health Services Research, 43*(5), 650-662. doi:10.1007/s10488-015-0679-0

Takeuchi, H., & Remington, G. (2013). A systematic review of reported cases involving psychotic symptoms worsened by aripiprazole in schizophrenia or

schizoaffective disorder. *Psychopharmacology, 228*(2), 175-185. doi:10.1007/s00213-013-3154-1

Takeuchi, H., Suzuki, T., Remington, G., Bies, R. R., Abe, T., Graff-Guerrero, A., . . . Uchida, H. (2013). Effects of Risperidone and Olanzapine Dose Reduction on Cognitive Function in Stable Patients With Schizophrenia: An Open-Label, Randomized, Controlled, Pilot Study. *Schizophrenia Bulletin, 39*(5), 993-998. doi:10.1093/schbul/sbt090

Tandon, R., Nasrallah, H. A., & Keshavan, M. S. (2009). Schizophrenia, "just the facts" 4. Clinical features and conceptualization. *Schizophr Res, 110*(1-3), 1-23. doi:10.1016/j.schres.2009.03.005

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

The Cochrane Collaboration. (2011). Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (updated March 2011). Retrieved from http://www.cochrane.org/training/cochrane-handbook

Trépanier, M. O., Hopperton, K. E., Mizrahi, R., Mechawar, N., & Bazinet, R. P. (2016). Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. *Molecular psychiatry, 21*(8), 1009-1026. doi:http://dx.doi.org/10.1038/mp.2016.90

Tyson, P. J., Laws, K. R., Roberts, K., & Mortimer, A. M. (2004). Stability of set-shifting and planning abilities in patients with schizophrenia. *Psychiatry research, 129*(3), 229-239.

van Os, J., Gilvarry, C., Bale, R., van Horn, E., Tattan, T., White, I., & Murray, R. (2000). Diagnostic value of the DSM and ICD categories of psychosis: an evidence-based approach. UK700 Group. *Soc Psychiatry Psychiatr Epidemiol, 35*(7), 305-311. doi:10.1007/s001270050243

van Os, J., Kenis, G., & Rutten, B. P. (2010). The environment and schizophrenia. *Nature, 468*(7321), 203-212. doi:10.1038/nature09563

van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P., & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. *Psychological medicine, 39*(2), 179-195.

van Os, J., & Reininghaus, U. (2016). Psychosis as a transdiagnostic and extended phenotype in the general population. *World Psychiatry, 15*(2), 118-124.

Van Ruitenbeek, P., Vermeeren, A., & Riedel, W. (2010). Histamine H1 receptor antagonist cetirizine impairs working memory processing speed, but not episodic memory. *British journal of pharmacology, 161*(2), 456-466.

Vance, D. E., Roberson, A. J., McGuinness, T. M., & Fazeli, P. L. (2010). How neuroplasticity and cognitive reserve protect cognitive functioning. *Journal of psychosocial nursing and mental health services, 48*(4), 23-30.

Volkow, N. D., Swanson, J. M., Evins, A. E., DeLisi, L. E., Meier, M. H., Gonzalez, R., . . . Baler, R. (2016). Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review. *JAMA Psychiatry, 73*(3), 292-297. doi:10.1001/jamapsychiatry.2015.3278

Wallwork, R. S., Fortgang, R., Hashimoto, R., Weinberger, D. R., & Dickinson, D. (2012). Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. *Schizophrenia Research, 137*(1-3), 246-250. doi:10.1016/j.schres.2012.01.031

Waltz, J. A., Schweitzer, J. B., Gold, J. M., Kurup, P. K., Ross, T. J., Jo Salmeron, B., . . . Stein, E. A. (2008). Patients with Schizophrenia have a Reduced Neural Response to Both Unpredictable and Predictable Primary Reinforcers. *Neuropsychopharmacology, 34*(6), 1567-1577. doi:http://www.nature.com/npp/journal/v34/n6/suppinfo/npp2008214s1.html

Wechsler, D. (1997a). Wechsler adult intelligence scale-III. In: San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1997b). *Wechsler memory scale (WMS-III)* (Vol. 14): Psychological corporation San Antonio, TX.

Wechsler, D. (2008). Wechsler adult intelligence scale–Fourth Edition (WAIS–IV). *San Antonio, TX: NCS Pearson, 22*(498), 816-827.

Weinberger, D. R., Torrey, E. F., Neophytides, A. N., & Wyatt, R. J. (1979). Lateral cerebral ventricular enlargement in chronic schizophrenia. *Archives of General Psychiatry, 36*(7), 735-739.

Welch, K. A., Lawrie, S. M., Muir, W., & Johnstone, E. C. (2011). Systematic Review of the Clinical Presentation of Schizophrenia in Intellectual Disability. *Journal of Psychopathology and Behavioral Assessment, 33*(2), 246-253. doi:10.1007/s10862-011-9224-y

West, A. R., Floresco, S. B., Charara, A., Rosenkranz, J. A., & Grace, A. A. (2003). Electrophysiological interactions between striatal glutamatergic and dopaminergic systems. *Ann N Y Acad Sci, 1003*, 53-74. Retrieved from https://nyaspubs.onlinelibrary.wiley.com/doi/pdf/10.1196/annals.1300.004

Whitty, P., Clarke, M., McTigue, O., Browne, S., Kamali, M., Larkin, C., & O'Callaghan, E. (2005). Diagnostic stability four years after a first episode of psychosis. *Psychiatric Services, 56*(9), 1084-1088.

WHO. (2020). Schizophrenia. *Newsroom Fact Sheets*. Retrieved from https://www.who.int/news-room/fact-sheets/detail/schizophrenia

Woodberry, K. A., Giuliano, A. J., & Seidman, L. J. (2008). Premorbid IQ in schizophrenia: a meta-analytic review. *American Journal of Psychiatry, 165*(5), 579-587.

World Health Organization. (2007). International Statistical Classification of Diseases and Related Health Problems, 10th Revision. Retrieved from http://apps.who.int/classifications/icd10/browse/2010/en

World Health Organization. (2009). *ICD 10 : international statistical classification of diseases and related health problems*. Geneva: World Health Organization.

World Health Organization. (2018a). *ICD-11 : International Classification of Diseases*. Geneva: World Health Organization.

World Health Organization. (2018b). Schizophrenia. Retrieved from https://www.who.int/news-room/fact-sheets/detail/schizophrenia

World Medical Association. (2013). World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Retrieved from http://www.wma.net/en/30publications/10policies/b3/

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. doi:10.1001/jamapsychiatry.2013.19

Wyatt, R. J. (1991). Neuroleptics and the natural course of schizophrenia. *Schizophrenia Bulletin, 17*(2), 325-351.

Yung, A. R., & McGorry, P. D. (1996). The Prodromal Phase of First-episode Psychosis: Past and Current Conceptualizations. *Schizophrenia Bulletin, 22*(2), 353-370. doi:10.1093/schbul/22.2.353

Yung, A. R., Woods, S. W., Ruhrmann, S., Addington, J., Schultze-Lutter, F., Cornblatt, B. A., . . . Borgwardt, S. (2012). Whither the attenuated psychosis syndrome? *Schizophrenia Bulletin, 38*(6), 1130-1134.

Zhu, Y., Li, C., Huhn, M., Rothe, P., Krause, M., Bighelli, I., . . . Leucht, S. (2017). How well do patients with a first episode of schizophrenia respond to antipsychotics: A systematic review and meta-analysis. *European Neuropsychopharmacology, 27*(9), 835-844. doi:https://doi.org/10.1016/j.euroneuro.2017.06.011

Zimmermann, G., Favrod, J., Trieu, V., & Pomini, V. (2005). The effect of cognitive behavioral treatment on the positive symptoms of schizophrenia spectrum disorders: a meta-analysis. *Schizophrenia Research, 77*(1), 1-9.

10. Papers

10.1 PAPER I

PLOS | ONE

The Course of Neurocognitive Changes in Acute Psychosis: Relation to Symptomatic Improvement

Liss Anda[1,2]*, Kolbjørn S. Brønnick[1,3], Erik Johnsen[4,5], Rune A. Kroken[4,5], Hugo Jørgensen[5], Else-Marie Løberg[4,6,7]

1 TIPS, Division of Psychiatry, Stavanger University Hospital, Stavanger, Norway, 2 Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway, 3 Institute of Health, Faculty of Social Sciences, University of Stavanger, Stavanger, Norway, 4 Division of Psychiatry, Haukeland University Hospital, Bergen, Norway, 5 Department of Clinical Medicine, University of Bergen, Bergen, Norway, 6 Department of Clinical Psychology, University of Bergen, Bergen, Norway, 7 Department of Addiction Medicine, Haukeland University Hospital, Bergen, Norway

* lissgoril@gmail.com

Abstract

Introduction

Cognitive impairment is a core aspect of psychosis, but the course of cognitive functioning during acute psychosis remains poorly understood, as does the association between symptom change and neurocognitive change. Some studies have found cognitive improvement to be related to improvement in negative symptoms, but few have examined cognitive changes in the early acute phase, when clinical improvement mainly happens. This study's aim was to investigate the relation between cognitive and symptomatic change in clinically heterogeneous patients during the early acute phase of psychosis.

Method

Participants (n = 84), including both first-episode and previously ill patients, were recruited from consecutive admissions to the acute psychiatric emergency ward of Haukeland University Hospital, Bergen, Norway, as part of the Bergen Psychosis Project (BPP). The RBANS neurocognitive test battery was administered on admission and again at discharge from the acute ward (mean time 4.1 weeks, SD 1.86 weeks). Symptomatic change was measured by PANSS.

Results

The proportion of subjects with cognitive impairment (t < 35) was 28.6% in the acute phase and 13.1% at follow-up. A sequential multiple linear regression model with RBANS change as the dependent variable found PANSS negative symptoms change to significantly predict total RBANS performance improvement (beta = -.307, p = .016). There was no significant difference between subjects with schizophrenia and those with other psychotic disorders in terms of cognitive change.

Conclusion

The proportion of subjects with mild to moderate impairment in cognitive test performance is
reduced across the acute phase of psychosis, with improvement related to amelioration of
negative symptoms.

Introduction

Cognitive impairment is a core characteristic of schizophrenia and related psychoses [1, 2],
and cognitive functioning is important to successful recovery from psychosis [3, 4]. Cognitive
impairment arises ahead of first episode psychosis, [5] is evident even at primary school age
[6] and further deteriorates into adulthood [7]. Negative and disorganized symptoms have
been associated with neurocognitive impairment [8–12]. However, the trajectory of cognitive
functioning after onset of psychosis remains unclear [3], as does the relation between cogni-
tion and clinical symptoms. Some have found cognitive functioning to remain largely
unchanged after the onset of psychosis [13–17], while others argue that cognitive performance
further declines over time in chronically ill patients, with processing speed, learning and exec-
utive functioning showing particular impairment [3, 7]. In contrast to findings of continued
impairment, a recent comprehensive meta-study also found cognition to improve modestly
with treatment, both in groups deemed at ultra high risk of developing psychotic disorders,
and in first episode psychosis groups [18], an effect also found in non-first episode samples
[19]. It is also possible that different functional dimensions of cognition have different trajecto-
ries, with some static and others dynamic over time [20]

Given that the acute psychotic phase sees the greatest symptom alleviation and early treat-
ment effects, the most pronounced cognitive changes might also take place alongside these
other processes. However, most studies on cognition in psychosis have focused on stabilized
phases of psychotic illness, which is sub-optimal with regard to assessing the relation between
symptomatic change and cognitive dysfunction. As a result, the relation between symptomatic
and cognitive change remains underexplored. One study, looking specifically at changes in
executive functioning during the first four weeks of acute hospital admission for schizophre-
nia, indeed found an improvement in cognitive performance, but unrelated to symptom load
change [21]. A later study, also of acutely admitted subjects, found working memory to
improve over a period of four weeks, related to negative symptom load [22]. However, neither
of these studies directly compared cognitive change with changes in psychotic symptom sever-
ity. A third study with retesting done at six weeks found that amelioration of negative symp-
toms predicted improvement in working and verbal learning scores, while overall
symptomatic improvement predicted better performance in verbal learning [23]. Notably, one
recent study where first-episode psychosis patients were re-tested after 12 weeks, found an
improvement in overall cognition, working memory and verbal learning, with cognitive
improvement mediated by symptom improvement [24]. However, most research looking at
cognitive variables in psychosis has performed cognitive assessment at various times later in
the acute phase, collecting baseline data up to two weeks after admission[25, 26], or even as
late as 3 months [27, 28] or 6 months [6]. This means that the course and nature of cognitive
impairment and its relationship to symptomatic change during the acute phase of psychosis
remains particularly poorly understood.

In addition to focusing on stable phases of illness, studies have mainly investigated homoge-
nous patient groups with schizophrenia (e.g. [13, 20, 29–31]). It has been suggested that

subjects with schizophrenia show more severe neurocognitive impairment and a less favourable trajectory for cognitive change than do subjects with other psychotic disorders [10], meaning that restrictive sampling might limit variability and ecological validity. The present study therefore aims to investigate the course of naturally occurring changes in cognitive performance seen during the early acute phase of psychosis, in a heterogeneous sample of subjects consecutively admitted to an acute mental health ward. We also wished to examine any correlation between cognitive change and changes in symptom load during this stage of illness, as well as effects of diagnostic group.

We hypothesize that 1) overall cognitive performance will be impaired during the acute phase of psychosis, 2) there will be improvement in cognitive performance during the early acute phase of psychosis, which will be related to an improvement in negative symptoms across this time period, and that 3) the cognitive performance of participants with a diagnosis of schizophrenia will show less improvement than that of participants with other psychotic disorders.

Methods

Study design

Participants were recruited from consecutive admissions to the acute psychiatric emergency ward of Haukeland University Hospital, Bergen, Norway, as part of the Bergen Psychosis Project (BPP), a 24-month prospective, rater-blinded, pragmatic, randomized, comparison of first-line second-generation antipsychotics. The project was approved by the Norwegian Social Science Data Services and the Regional Committee for Medical Research Ethics (RCMRE), whom allowed eligible patients to be included before providing informed consent, aiming to achieve a clinically relevant representation of patients with acute psychosis. At first follow-up, all participants were asked for written informed consent to participate in the follow-up project. The BPP was independently funded, and is described in greater detail in Johnsen et al. [32].

Subjects

Inclusion criteria for the BPP were age $\geq$ 18, a score of $\geq$ 4 on one or more of the items Delusions, Hallucinatory behaviour, Grandiosity, Suspiciousness/persecution, or Unusual thought content in the Positive and Negative Syndrome Scale (PANSS) [33], ability to understand Norwegian language, and eligibility for oral antipsychotic drug therapy. Patients met ICD-10 [34] criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic episode, delusional disorder, drug-induced psychosis, and major depressive disorder with psychotic features, as determined by experienced clinicians. Exclusion criteria were ineligibility for oral antipsychotics, organic brain disease, manic psychosis, substance-induced psychosis resolving within a few days of admission, inability to cooperate reliably during investigations, indication for electroconvulsive therapy, or being medicated with clozapine on admittance. Participants involved in the current project were included between March 2004 and January 2009.

Participants from the main BPP study were included in the current sub-study if they had completed both a PANSS interview and neurocognitive testing both at baseline and at first follow-up, yielding a total N = 84, aged on average 33.3 years and including 32.1% females. Sociodemographic variables are displayed in Table 1.

Measures

Baseline assessments were performed immediately after admittance to the acute psychiatric ward. The first follow-up, which formed the basis for comparisons used in the present study, was performed at the time of acute ward discharge or after 6 weeks, which ever came first.

Table 1. Sociodemographic data for the sample (N = 84).

Mean age (SD)	*33.3 (13.3)*
Years education (SD)	12.5 (2.6)
Baseline GAF functioning (SD)	30.5 (4.8)
Females %	32.1
Ethnicity white %	90.5
First hospital admission %	56.5
Previously never used antipsychotics %	51.2

All values reported as mean (standard deviation), except where noted.

doi:10.1371/journal.pone.0167390.t001

Cognitive assessments

Cognitive performance was assessed using the Repeatable Battery for the Assessment of Neu-rocognitive Status (RBANS) [35]. RBANS is sensitive to typical cognitive deficits in schizo-phrenia, and has shown good validity and reliability [36–38]. It measures global performance as well as the sub-domains of Visuospatial/Constructional Ability, Language, Attention, and Immediate as well as Delayed Memory. Administering the RBANS takes only approximately 30 minutes, which makes it feasible to use when testing acutely ill subjects. RBANS exists in two separate forms with norm data adjusted for re-test effects [37], making it suitable for repeated testing with the aim of detecting cognitive change. Follow-up testing was done using the alternate form of RBANS. The overall RBANS score is considered to have good test–retest reliability (Gold et al., 1999 and Wilk et al., 2002). Scores on the Norwegian research version of the RBANS have been shown to be valid when compared to results from a comprehensive test battery [39]. Tests were administered by trained research nurses.

Clinical assessments

Symptoms were assessed at baseline and follow-up using the PANSS [33]. For the purposes of analysis, the five-factor structure of PANSS developed by Wallwork, Fortgang [40] formed the basis of composite symptom scores: positive (items p1, p3, p5, a9), negative (items n1, n2, n3, n4, n6), disorganized (p2, n5, a11), depressive (a2, a3, a6) and excitatory (p4, p7, a8, a14). SCID1 interviews were also performed as part of the standard ward assessment routine, with diagnoses recorded according to ICD-10 criteria as per hospital policy. The PANSS assess-ments were performed by trained psychiatrists, with excellent inter-rater reliability (0.92).

Statistics

Continuous variables were inspected using histograms to assess whether they conformed to the normal distribution. The percentage of participants showing cognitive impairment at base-line and follow-up was calculated, with the cut-off point for impairment being a total RBANS score of $t < 35$, i.e. > 1.5 SD below the mean score, corresponding to the xx impairment as conceptualised by Heaton and colleagues [41]. Univariate comparisons of cognitive scores at baseline and follow-up were done using two-tailed, paired t-tests, and Pearson correlation coefficients were used to analyse the relation between cognitive scores and PANSS scores at baseline. For all univariate analyses we applied Bonferroni-corrected alpha limits according to the number of comparisons or correlations involved, in order to avoid an inflated risk of Type 1 errors. Differences in the cognitive trajectory for subjects with schizophrenia spectrum disor-ders were assessed using repeated measures analysis of variance (ANOVA), with Greenhouse-

Geisser corrections for violations of the assumption of sphericity. The grouping variable was constructed by dividing the patients into a Schizophrenia spectrum disorders group (SD; subjects given a primary diagnosis of F20, F23.0 or F23.2, i.e. fulfilling the core symptomatic criteria for F20, but not necessarily the duration criteria) vs. a group with other psychotic disorders.

Sequential multiple linear regression analyses with two blocks were conducted with RBANS change scores as the dependent variable to assess the contribution of symptom load change as measured by PANSS composite scores. In block one, the confounder variables gender, age, and baseline RBANS total and PANSS composite variable scores (Positive, Negative, Depressive, Excitatory and Disorganized) were entered, and in the second block, PANSS composite variable change scores were entered using forward stepwise selection (Criterion for inclusion: $p < .05$; criterion for exclusion: $p < .1$). Equivalent analyses were performed for change in each of the RBANS sub scales as well as for the RBANS composite score, with a p-value < 0.05 considered significant. Data were checked for multicollinearity, heteroscedasticity and normality of residuals. All analyses were conducted using SPSS 22 [42].

Results

Table 2 shows the clinical and neurocognitive sample characteristics, as well as change in these domains from baseline to follow-up. The mean time from baseline to follow-up was 4.1 weeks (SD = 1.9 weeks). Diagnoses were drug-related psychosis (F12-19.9, n = 15, 17.9%), schizophrenia (F20-20.9, n = 20, 23.8%), schizotypal disorder (F21, n = 1, 1.2%), delusional disorder (F22-22.9, n = 10, 11.9%), acute psychotic disorders with symptoms of schizophrenia (F23.1-F23.2, n = 5), other acute psychotic disorders (without symptoms of schizophrenia) (F23.0, F23.3-F23.9, n = 17), other non-organic psychosis (F28, n = 1, 1.2%), unspecified non-organic psychosis NOS (F29, n = 6, 7.1%), and affective disorders with psychotic symptoms (F31-33.9, n = 9, 10.8%). In three patients, SCID was not performed, and the diagnosis from their discharge journal entry was used for the purposes of this study. There were 25 subjects (29.8%) with schizophrenia spectrum disorders and 59 subjects with other psychotic disorders (70.2%).

Neurocognitive and symptomatic change

Fig 1 shows mean RBANS total and PANSS symptoms at baseline and follow-up. There was a significant correlation (Bonferroni-corrected alpha level = .002) between baseline mean PANSS disorganized scores and RBANS total mean (r = -.515, p < .001), with a trend toward a relationship with Attention (r = -.296, p = .006) scores. No other symptom dimensions were significantly correlated with any RBANS scores.

At baseline, 28.6% (24/84) of patients were cognitively impaired with a total RBANS t-score of < 35, compared to 13.1% (11/84) of patients at the point of follow-up. There was a significant improvement in mean total RBANS scores from the mean of 38.67 at baseline to 41.27 at follow-up (p < .001, d = .35). Similarly, mean attention and verbal scores increased from 39.9 to 45.95 (p < .001, d = .75) and 30.32 to 33.93 (p < .001, d = -.39) respectively. A single-sample t-test showed that patients performed significantly worse than the normative average T-score of 50 both overall and for every RBANS subscale (all p-values < .001).

Regression model of PANSS and RBANS change

The regression analysis, using RBANS composite change scores as the dependent variable, found change in negative symptoms to be the only significant predictor of improved RBANS performance (beta = -.307, p < .016). Details of the model are displayed in Table 3. Equivalent

Table 2. RBANS and PANSS composite scores (n = 84).

	V1		V2		Δ V1 to V2			
	Mean	SD	Mean	SD	Mean	SD	p	E.S.[6]
PANSS Measure *Bonferroni-corrected alpha limit = .006*								
Positive	19.82	4.32	12.43	4.00	-7.39	4.75	< .001	1.78
Negative	18.37	7.07	15.24	6.50	-3.13	6.93	< .001	0.46
General	34.24	6.21	25.68	5.89	-8.56	7.15	< .001	1.41
Total score	72.43	12.72	53.35	13.58	-19.08	14.72	< .001	1.45
Comp. pos.[1]	3.32	.88	2.01	.85	-1.31	-1.31	< .001	1.51
Comp. neg.[2]	2.48	1.19	2.18	1.13	-.30	1.21	= .025	0.26
Comp. dep.[3]	3.14	1.04	2.26	.95	-.88	1.13	< .001	0.88
Comp. excit.[4]	1.56	.58	1.20	.40	-.36	.63	< .001	0.73
Comp. dis.[5]	2.52	1.08	1.82	.69	-.70	.88	< .001	0.79
RBANS[6] Score *Bonferroni-corrected alpha limit = .008*								
Verbal	39.90	8.15	45.95	8.03	6.05	8.34	< .001	0.75
Visuo-spatial	46.25	12.65	47.86	10.97	1.61	10.20	= .152	0.13
Learning	36.58	10.77	38.54	10.72	1.95	9.69	= .068	0.18
Memory	40.29	11.27	40.10	12.38	-.19	11.08	= .875	0.02
Attention	30.32	8.80	33.93	9.57	3.61	7.44	< .001	0.39
RBANS mean	38.67	7.75	41.27	7.30	2.60	5.81	< .001	0.35

[1]. Composite positive symptoms score
[2]. Composite negative score
[3]. Composite depressive score
[4]. Composite excitatory score
[5]. Composite disorganized score
[6]. Repeatable Battery for the Assessment of Neurocognitive Status 6. Effect size (Cohen's d)

analyses were also performed for RBANS subscale change, but PANSS change scores were not a significant predictor of any of these scores.

Comparing schizophrenia spectrum disorders to other psychotic disorders

A repeated measures ANOVA investigating the effect of age, gender and diagnostic group on cognitive change found no significant interaction between having a diagnosis of schizophrenia spectrum disorders, and time. Cognitive change for each group is displayed in Fig 2.

Discussion

In line with our first hypothesis, we found that during the acute phase, 28.6% of patients performed below the normative sample, showing cognitive impairment defined as a T-score < 35, and the average T-score was 38.6, significantly lower than the normative mean of 50. Supporting our second hypothesis, total RBANS score increased significantly and the proportion of cognitively impaired subjects was reduced from 28.6% to 13.1% at the point of follow-up, four weeks later. Further, neurocognitive improvement was related to negative symptom improvement. Our third hypothesis was not supported, as subjects diagnosed with Schizophrenia spectrum disorders did not significantly differ from subjects with other psychotic disorders in terms of cognitive change.
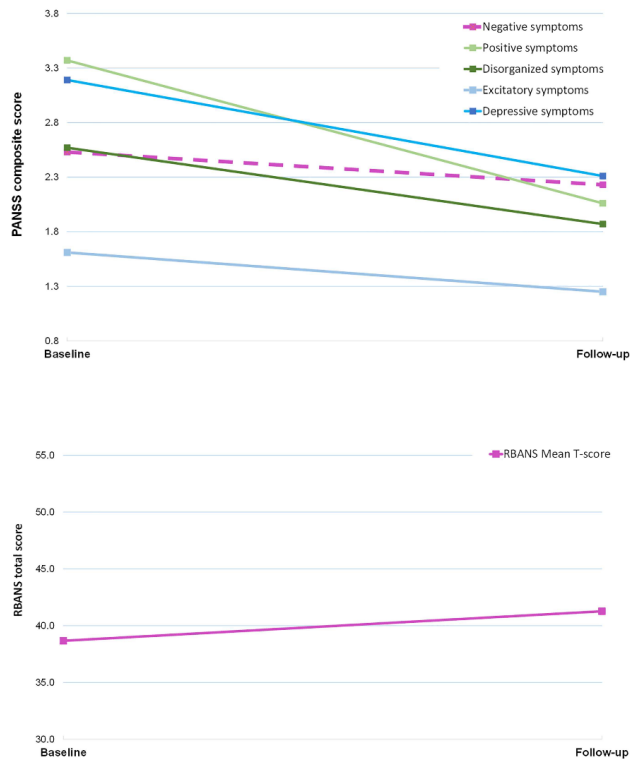
Fig 1. RBANS total and PANSS composite scores change baseline to follow-up.

The current findings indicate that significant improvement in cognitive functioning can take place quite early in the course of acute psychotic episodes. However, although positive symptom load decreased during the follow-up period, the improvement in neuropsychological test performance was in fact related to improvement of negative symptoms, despite these being generally less responsive to antipsychotic treatment than are positive symptoms [43]. The lack of a correlation with positive symptoms may seem counterintuitive, as a high positive symptom load might in itself be expected to be distracting, and thus associated with poor

Cognitive and Symptomatic Changes in Acute Psychosis

Table 3. Regression analysis of PANSS change scores predicting RBANS change total (N = 84).

PANSS composite score	β	p
Positive	.124	.233
Negative	-.307	.016*
Depressive	-.121	.279
Excitatory	-.077	.464
Disorganized	-.060	.654

R^2 = .305 p = .001. Adjusted for gender, age, and baseline PANSS composite variable scores
* Significant at p<.05

doi:10.1371/journal.pone.0167390.t003

performance. Clinicians and researchers alike commonly postpone neuropsychological testing on this assumption, waiting for the clinical picture to stabilise [44].

The link between cognitive performance improvement and negative symptom improvement could be explained by avolition, i.e. decreased drive, which is a core characteristic of negative symptoms [43]. Drive, or the will to initiate goal directed behaviour, is in turn associated with motivation and effort to complete tasks. Impaired effort and amotivation have indeed been found related to negative symptoms, and to account for about a third of variance in cognitive test performance in schizophrenia [31, 45]. Subjects with schizophrenia have been found to show attenuated brain responses to rewards, which may be partly driving impairments in motivation [46]. A proportion of the improved performance seen in our sample could thus be accounted for by improved motivation and effort as a result of receding negative
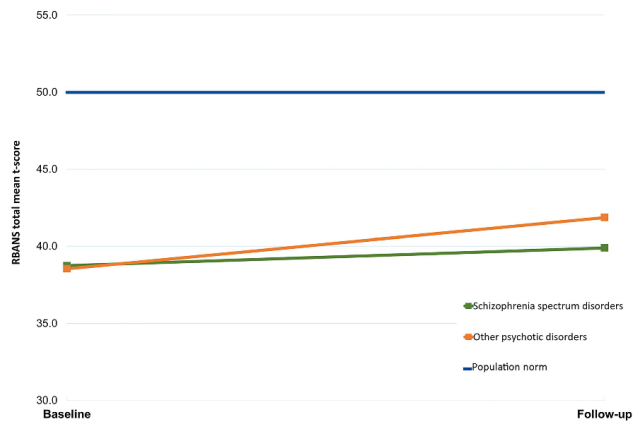
Fig 2. RBANS change from baseline to follow-up for schizophrenia spectrum disorders vs. other psychotic disorders.

doi:10.1371/journal.pone.0167390.g002

symptoms, in line with previous findings showing that 9.1% of subjects with schizophrenia fall below the effort indicator cut-off for RBANS [47].

Neurocognitive impairment in schizophrenia has commonly been understood as a purported trait rather than a state phenomenon [48, 49], with positive symptoms assumed to be related to temporary state impairment. State effects of psychosis, positively correlated with positive symptom load, have been seen for instance in the case of theory of mind [50], and depth perception [51]. The fact that cognitive change in our study was unrelated to both baseline positive symptoms and the alleviation of these indicates however that the change does not simply reflect amelioration of a state effect caused e.g. by intense hallucinations at baseline testing. This means that clinicians should perhaps worry less about positive symptoms being a threat to the validity of neurocognitive assessment, but be more aware of negative symptoms which might affect test performance.

This is to our knowledge the first study to show a correlation between amelioration of negative symptoms during acute psychosis and improved cognitive functioning in a group including patients with psychotic relapse. With cognitive impairment being a central element of psychotic illness, it is possible that cognitive symptoms fluctuate alongside positive, negative and disorganized symptoms, with negative symptoms being the most closely related symptom dimension. Our findings indicate that positive changes in cognitive function are seen in heterogeneous groups of subjects with psychosis, not simply in homogenous FEP samples.

Our findings, with an omnibus total R squared of .305, indicate in line with previous research that negative symptoms account for only a limited proportion of variance in change of cognitive impairment [52]. However, we have found that cognitive impairment does appear to change in parallel over time with negative symptoms. PANSS negative symptoms and RBANS total scores were significantly correlated at baseline, but the absolute change in negative symptoms, rather than baseline severity, appears to be the key factor for improved cognitive performance. Although this does not on its own indicate a causal relationship in either direction, it may be seen as an indication that cognition and negative symptoms are closely associated with each other.

Although they are separate constructs, cognitive impairment and negative symptoms appear linked in that they both occur before the development of positive symptoms, have shared courses and prognostic importance [53]. Neither responds to antipsychotic treatment to the same extent as do positive symptoms [43]. Negative and cognitive symptoms might also be related to structural and functional abnormalities in the same prefrontal areas. Cognitive impairment in schizophrenia has been tied to hypofrontality during task performance, in the form of bilaterally reduced activation in the dorsolateral prefrontal cortex, compared with both cognitively non-impaired individuals and healthy controls [54]. Negative symptoms have been associated with reductions in dorsolateral prefrontal grey matter [55], as well as prefrontal white matter [56]. Our findings could be seen as supporting a two-pathway model of psychosis in which a negative and disorganized dimension is associated with a phenotype of neurocognitive impairment, which in turn is unrelated to positive and affective symptom dimensions [19].

Interestingly, although PANSS disorganized scores were also significantly correlated with RBANS total mean, disorganized symptom change failed to significantly explain changes in performance at follow-up. This was despite average disorganized symptom change having an effect size of .079, compared to .026 for negative symptoms. The correlation between total RBANS scores and disorganized score could possibly be explained by the inclusion of PANSS items n5 (problems with abstract thinking) and a11 (poor attention) in the disorganized composite score. Both of these may to some extent also be measured by neurocognitive assessment.

128

There were no differences in cognitive change between patients with Schizophrenia spectrum disorders and those with other psychotic disorders. This is contrary to previous findings [10] which have looked at change in groups with schizophrenia alone, i.e. having multiple symptoms of psychosis across dimensions, which over a longer period of time have caused functional distress.

Strengths

With baseline neurocognitive testing for the Bergen Psychosis project performed immediately after hospital admission (in most cases within 48 hrs), this study is one of few investigating cognitive change in the very early acute phase of illness, gathering baseline data while subjects were actively psychotic and re-testing them quite shortly after remission began. Our findings thus provide important information about the early time course of cognitive abilities in psychotic episodes, especially given the paucity in this field of data gathered during the early acute phase. The short test-retest interval in the inpatient setting also means this study was less vulnerable to attrition than are studies with a longer retest interval. Finally, the patients were included consecutively, increasing the representativeness of the sample.

Limitations

No control group was included in this study, precluding statistical control of the changes seen in patients with learning effects in healthy individuals. Familiarity with procedures and practice might have affected the results. However, the RBANS neurocognitive battery is designed to withstand such effects. The exclusion of patients unable to cooperate during testing might have made results less representative of subjects with acute psychosis. Most exclusions happened on the basis of patients acting out or being unable to cooperate during assessment, or them being ineligible for oral antipsychotic medication.

Conclusions

In our study, the percentage of cognitively impaired subjects fell from 28.6% during acute phase treatment to 13.1%, at follow-up, demonstrating the potential for positive change in this symptom dimension. Our findings that cognitive improvement is related to improvement in negative symptoms highlight the importance of monitoring the trajectory of negative symptoms across the acute phase of illness. Often less obvious to the clinician than residual positive symptoms, lack of change in negative symptoms might be an important indication of persistent cognitive impairment. Even after the initial deterioration, cognitive recovery is possible and does happen with appropriate treatment and negative symptom remission.

Author Contributions

Conceptualization: HJ EJ RAK.

Data curation: EJ RAK EML.

Formal analysis: KSB LA.

Funding acquisition: HJ EJ RAK EML.

Investigation: HJ EJ RAK EML.

Methodology: HJ EJ RAK EML LA KSB.

Project administration: HJ EJ RAK EML.

Visualization: LA.

Writing – original draft: LA KSB EML.

References

1. Keefe RSE, Harvey PD. Cognitive Impairment in Schizophrenia. In: Geyer MA, Gross G, editors. Novel Antischizophrenia Treatments. Handbook of Experimental Pharmacology. 213: Springer Berlin Heidelberg; 2012. p. 11–37.

2. Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. Schizophrenia research. 2004; 72(1):29–39. doi: 10.1016/j.schres.2004.09.007 PMID: 15531405

3. Kahn RS, Keefe RSE. Schizophrenia is a cognitive illness: time for a change in focus. JAMA psychiatry. 2013; 70(10):1107–12. doi: 10.1001/jamapsychiatry.2013.155 PMID: 23925787

4. Kroken RA, Løberg E-M, Drønen T, Grüner R, Hugdahl K, Kompus K, et al. A Critical Review of Pro-Cognitive Drug Targets in Psychosis: Convergence on Myelination and Inflammation. Frontiers in Psychiatry. 2014; 5:11. doi: 10.3389/fpsyt.2014.00011 PMID: 24550848

5. Cornblatt B, Lencz T, Obuchowski M. The schizophrenia prodrome: treatment and high-risk perspectives. Schizophrenia Research. 2002; 54(1–2):177–86. http://dx.doi.org/10.1016/S0920-9964(01)00365-6. PMID: 11853992

6. Bilder RM, Reiter G, Bates J, Lencz T, Szeszko P, Goldman RS, et al. Cognitive development in schizophrenia: follow-back from the first episode. Journal of Clinical and Experimental Neuropsychology. 2006; 28(2):270–82. doi: 10.1080/13803390500360554 PMID: 16484098

7. Meier MH, Caspi A, Reichenberg A, Keefe RSE, Fisher HL, Harrington H, et al. Neuropsychological decline in schizophrenia from the premorbid to the postonset period: evidence from a population-representative longitudinal study. American Journal of Psychiatry. 2014.

8. de Gracia Dominguez M, Viechtbauer W, Simons CJ, van Os J, Krabbendam L. Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. Psychological bulletin. 2009; 135(1):157. doi: 10.1037/a0014415 PMID: 19210058

9. O'Leary DS, Flaum M, Kesler ML, Flashman LA, Arndt S, Andreasen NC. Cognitive Correlates of the Negative, Disorganized, and Psychotic Symptom Dimensions of Schizophrenia. The Journal of Neuropsychiatry and Clinical Neurosciences. 2000; 12(1):4–15. doi: 10.1176/jnp.12.1.4 PMID: 10678506

10. Zanelli J, Reichenberg A, Morgan K, Fearon P, Kravariti E, Dazzan P, et al. Specific and generalized neuropsychological deficits: a comparison of patients with various first-episode psychosis presentations. The American journal of psychiatry. 2010.

11. Milev P, Ho B-C, Arndt S, Andreasen NC. 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. 2005; 162(3):495–506. doi: 10.1176/appi.ajp.162.3.495 PMID: 15741466

12. Ventura J, Hellemann GS, Thames AD, Koellner V, Nuechterlein KH. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. Schizophrenia research. 2009; 113(2):189–99.

13. Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone SV, Seidman LJ. Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology. 2009; 23(3):315. doi: 10.1037/a0014708 PMID: 19413446

14. Leeson VC, Sharma P, Harrison M, Ron MA, Barnes TR, Joyce EM. IQ trajectory, cognitive reserve, and clinical outcome following a first episode of psychosis: a 3-year longitudinal study. Schizophr Bull. 2011; 37(4):768–77. Epub 2009/11/26. doi: 10.1093/schbul/sbp143 PMID: 19934212

15. Rund BR, Melle I, Friis S, Johannessen JO, Larsen TK, Midbøe LJ, et al. The course of neurocognitive functioning in first-episode psychosis and its relation to premorbid adjustment, duration of untreated psychosis, and relapse. Schizophrenia Research. 2007; 91(1–3):132–40. http://dx.doi.org/10.1016/j.schres.2006.11.030. PMID: 17258891

16. Bozikas VP, Andreou C. Longitudinal studies of cognition in first episode psychosis: a systematic review of the literature. Australian and New Zealand Journal of Psychiatry. 2011; 45(2):93–108. doi: 10.3109/00048674.2010.541418 PMID: 21320033

17. Schaefer J, Giangrande E, Weinberger DR, Dickinson D. The global cognitive impairment in schizophrenia: consistent over decades and around the world. Schizophrenia research. 2013; 150(1):42–50. doi: 10.1016/j.schres.2013.07.009 PMID: 23911259

130

18. Bora E, Murray RM. 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. 2014; 40(4):744–55. doi: 10.1093/schbul/sbt085 PMID: 23770934

19. Riedel M, Schennach-Wolff R, Musil R, Dehning S, Cerovecki A, Opgen-Rhein M, et al. Neurocognition and its influencing factors in the treatment of schizophrenia—effects of aripiprazole, olanzapine, quetiapine and risperidone. Human Psychopharmacology: Clinical and Experimental. 2010; 25(2):116–25.

20. Dickinson D. Zeroing in on early cognitive development in schizophrenia. American Journal of Psychiatry. 2014; 171(1):9–12. doi: 10.1176/appi.ajp.2013.13101303 PMID: 24399421

21. McGrath J, Scheldt S, Welham J, Clair A. Performance on tests sensitive to impaired executive ability in schizophrenia, mania and well controls: acute and subacute phases. Schizophrenia research. 1997; 26(2):127–37.

22. McGrath J, Chapple B, Wright M. Working memory in schizophrenia and mania: correlation with symptoms during the acute and subacute phases. Acta Psychiatrica Scandinavica. 2001; 103(3):181–8. PMID: 11240574

23. Hagger C, Buckley P, Kenny JT, Friedman L, Ubogy D, Meltzer HY. Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. Biological psychiatry. 1993; 34(10):702–12. PMID: 8292674

24. Trampush JW, Lencz T, DeRosse P, John M, Gallego JA, Petrides G, et al. Relationship of Cognition to Clinical Response in First-Episode Schizophrenia Spectrum Disorders. Schizophrenia Bulletin. 2015.

25. Olivier MR, Killian S, Chiliza B, Asmal L, Schoeman R, Oosthuizen PP, et al. Cognitive performance during the first year of treatment in first-episode schizophrenia: a case–control study. Psychological Medicine. 2015; 45(13):2873–83. doi: 10.1017/S0033291715000860 PMID: 25998030

26. Keefe RSE, Seidman LJ, Christensen BK, Hamer RM, Sharma T, Sitskoorn MM, et al. Comparative Effect of Atypical and Conventional Antipsychotic Drugs on Neurocognition in First-Episode Psychosis: A Randomized, Double-Blind Trial of Olanzapine Versus Low Doses of Haloperidol. American Journal of Psychiatry. 2004; 161(6):985–95. doi: 10.1176/appi.ajp.161.6.985 PMID: 15169686

27. Harvey PD, Rabinowitz J, Eerdekens M, Davidson M. Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. American Journal of Psychiatry. 2014.

28. Rund BR, Barder HE, Evensen J, Haahr U, Hegelstad WtV, Joa I, et al. Neurocognition and Duration of Psychosis: A 10-year Follow-up of First-Episode Patients. Schizophrenia Bulletin. 2015.

29. Rajji TK, Miranda D, Mulsant BH. Cognition, Function, and Disability in Patients With Schizophrenia: A Review of Longitudinal Studies. Canadian Journal of Psychiatry. 2014; 59(1):13. PMID: 24444319

30. Reichenberg A, Caspi A, Harrington H, Houts R, Keefe RS, Murray RM, et al. Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. American Journal of Psychiatry. 2010.

31. Foussias G, Siddiqui I, Fervaha G, Mann S, McDonald K, Agid O, et al. Motivated to do well: An examination of the relationships between motivation, effort, and cognitive performance in schizophrenia. Schizophrenia Research. 2015; 166(1–3):276–82. http://dx.doi.org/10.1016/j.schres.2015.05.019. PMID: 26008882

32. Johnsen E, Kroken RA, Wentzel-Larsen T, Jørgensen HA. Effectiveness of second-generation antipsychotics: a naturalistic, randomized comparison of olanzapine, quetiapine, risperidone, and ziprasidone. BMC psychiatry. 2010; 10(1):26.

33. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophrenia Bulletin. 1987; 13(2):261–76. PMID: 3616518

34. World Health Organization. International statistical classification of diseases and related health problems: World Health Organization; 2004.

35. Randolph C. RBANS manual: Repeatable battery for the assessment of neuropsychological status. San Antonio, TX: The Psychological Corporation. 1998.

36. Iverson GL, Brooks BL, Haley GM. Interpretation of the RBANS in inpatient psychiatry: clinical normative data and prevalence of low scores for patients with schizophrenia. Applied neuropsychology. 2009; 16(1):31–41. Epub 2009/02/12. doi: 10.1080/09084280802644128 PMID: 19205946

37. Gold JM, Queern C, Iannone VN, Buchanan RW. Repeatable Battery for the Assessment of Neuropsychological Status as a Screening Test in Schizophrenia, I: Sensitivity, Reliability, and Validity. American Journal of Psychiatry. 1999; 156(12):1944–50. doi: 10.1176/ajp.156.12.1944 PMID: 10588409

38. Wilk CM, Gold JM, Humber K, Dickerson F, Fenton WS, Buchanan RW. Brief cognitive assessment in schizophrenia: normative data for the Repeatable Battery for the Assessment of Neuropsychological Status. Schizophrenia Research. 2004; 70(2–3):175–86. http://dx.doi.org/10.1016/j.schres.2003.10.009. PMID: 15329294

Cognitive and Symptomatic Changes in Acute Psychosis

39. Løberg EM, Langeland M, Jørgensen HA. Reliability and validity of a Norwegian translation of the repeatable battery for the assessment of neuropsychological status in patients with psychosis. 10 year anniversary of the Norwegian neuropsychological association2006.

40. Wallwork RS, Fortgang R, Hashimoto R, Weinberger DR, Dickinson D. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. Schizophrenia Research. 2012; 137(1–3):246–50. doi: 10.1016/j.schres.2012.01.031 PMID: 22356801

41. Heaton RK, Grant I, Matthews CG. Comprehensive norms for an expanded Halstead-Reitan battery: demographic corrections, research findings, and clinical applications; with a supplement for the Wechs-ler Adult Intelligence Scale-Revised (WAIS-R): Psychological Assessment Resources; 1991.

42. IBM Corp. IBM SPSS Statistics for Windows. 22.0 ed. Armonk, NY2013.

43. Foussias G, Remington G. Negative symptoms in schizophrenia: avolition and Occam's razor. Schizo-phrenia Bulletin. 2010; 36(2):359–69. doi: 10.1093/schbul/sbn094 PMID: 18644851

44. González-Blanch C, Perez-Iglesias R, Pardo-Garcia G, Rodríguez-Sánchez J, Martínez-Garcia O, Vázquez-Barquero J, et al. Prognostic value of cognitive functioning for global functional recovery in first-episode schizophrenia. Psychological medicine. 2010; 40(06):935–44.

45. Strauss GP, Morra LF, Sullivan SK, Gold JM. The role of low cognitive effort and negative symptoms in neuropsychological impairment in schizophrenia. Neuropsychology. 2015; 29(2):282–91. doi: 10.1037/neu0000113 PMID: 25000322

46. Waltz JA, Schweitzer JB, Gold JM, Kurup PK, Ross TJ, Jo Salmeron B, et al. Patients with Schizophre-nia have a Reduced Neural Response to Both Unpredictable and Predictable Primary Reinforcers. Neu-ropsychopharmacology. 2008; 34(6):1567–77. http://www.nature.com/npp/journal/v34/n6/suppinfo/npp2008214s1.html. doi: 10.1038/npp.2008.214 PMID: 19052540

47. Morra LF, Gold JM, Sullivan SK, Strauss GP. Predictors of neuropsychological effort test performance in schizophrenia. Schizophrenia research. 2015; 162(1):205–10.

48. Patel D, Laws K, Padhi A, Farrow J, Mukhopadhaya K, Krishnaiah R, et al. The neuropsychology of the schizo-obsessive subtype of schizophrenia: a new analysis. Psychological medicine. 2010; 40(06):921–33.

49. Tyson PJ, Laws KR, Roberts K, Mortimer AM. Stability of set-shifting and planning abilities in patients with schizophrenia. Psychiatry research. 2004; 129(3):229–39. doi: 10.1016/j.psychres.2004.09.007 PMID: 15661316

50. Pousa E, Duñó R, Brébion G, David AS, Ruiz AI, Obiols JE. Theory of mind deficits in chronic schizo-phrenia: Evidence for state dependence. Psychiatry Research. 2008; 158(1):1–10. http://dx.doi.org/10.1016/j.psychres.2006.05.018. PMID: 18166230

51. Keane BP, Silverstein SM, Wang Y, Papathomas TV. Reduced depth inversion illusions in schizophre-nia are state-specific and occur for multiple object types and viewing conditions. Journal of Abnormal Psychology. 2013; 122(2):506–12. doi: 10.1037/a0032110 PMID: 23713504

52. Bell MD, Mishara AL. Does negative symptom change relate to neurocognitive change in schizophre-nia? Implications for targeted treatments. Schizophrenia Research. 2006; 81(1):17–27. http://dx.doi.org/10.1016/j.schres.2005.09.016. PMID: 16297601

53. Harvey PD, Koren D, Reichenberg A, Bowie CR. Negative symptoms and cognitive deficits: what is the nature of their relationship? Schizophrenia bulletin. 2006; 32(2):250–8. doi: 10.1093/schbul/sbj011 PMID: 16221995

54. Ortiz-Gil J, Pomarol-Clotet E, Salvador R, Canales-Rodríguez EJ, Sarró S, Gomar JJ, et al. Neural cor-relates of cognitive impairment in schizophrenia. The British Journal of Psychiatry. 2011; 199(3):202–10. doi: 10.1192/bjp.bp.110.083600 PMID: 21727234

55. Berge D, Carmona S, Rovira M, Bulbena A, Salgado P, Vilarroya O. Gray matter volume deficits and correlation with insight and negative symptoms in first-psychotic-episode subjects. Acta Psychiatr Scand. 2011; 123(6):431–9. Epub 2010/11/09. doi: 10.1111/j.1600-0447.2010.01635.x PMID: 21054282

56. Sanfilipo M, Lafargue T, Rusinek H, Arena L, Loneragan C, Lautin A, et al. Volumetric measure of the frontal and temporal lobe regions in schizophrenia: relationship to negative symptoms. Arch Gen Psy-chiatry. 2000; 57(5):471–80. Epub 2000/05/12. PMID: 10807487

10.2 PAPER II

Cognitive Profile in Ultra High Risk for Psychosis and Schizophrenia: A Comparison Using Coordinated Norms

Liss Anda[1,2,3*], Kolbjørn K. Brønnick[4,5], Jan Olav Johannessen[1,5], Inge Joa[1,5], Rune A. Kroken[3,6,7], Erik Johnsen[3,6,7], Maria Rettenbacher[8], Farivar Fathian[9] and Else-Marie Løberg[3,6,10,11]

[1] TIPS Network for Clinical Psychosis Research, Stavanger University Hospital, Stavanger, Norway, [2] Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway, [3] Division of Psychiatry, Haukeland University Hospital, Bergen, Norway, [4] SESAM Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway, [5] Department of Public Health, Faculty of Health Sciences, University of Stavanger, Stavanger, Norway [6] Norwegian Centre for Mental Disorders Research, Haukeland University Hospital, Bergen, Norway, [7] Department of Clinical Medicine, University of Bergen, Bergen, Norway, [8] Medical University Innsbruck, Innsbruck, Austria, [9] Outpatient Department, NKS Olaviken Gerontopsychiatric Hospital, Bergen, Norway, [10] Department of Addiction Medicine, Haukeland University Hospital, Bergen, Norway, [11] Department of Clinical Psychology, University of Bergen, Bergen, Norway

Background: Cognitive impairment is not only a core aspect of schizophrenia but also commonly observed in help-seeking youth at ultra high risk for psychosis (UHR), with potential implications for prognosis and individualized treatment. However, there is no consensus on the cognitive profile in the UHR state, partly due to lack of valid comparisons of performance in established schizophrenia and UHR.

Objectives: To compare the cognitive functioning and profile of UHR subjects to a sample with schizophrenia, they were split into two groups based on duration of illness. Comparisons were made using coordinated norms based on healthy controls reflecting the younger UHR age spectrum.

Methods: Participants for UHR ($n = 51$) and schizophrenia groups ($n = 19$ and $n = 22$) were included from the Prevention of Psychosis and Bergen Psychosis 2 projects. All subjects completed a comprehensive neurocognitive test battery aiming to measure speed of processing, working memory, verbal learning, reasoning, and problem solving, as well as visual problem solving. Cognitive functioning was compared between groups based on coordinated norms using z-scores derived by regression modeling from an age-matched healthy control group ($n = 61$).

Results: UHR subjects showed significantly impaired speed of processing ($p < 0.001$) working memory ($p = 0.042$) and verbal learning, reasoning, and problem solving ($p = 0.007$) as compared to the control group. Visual problem-solving skills appeared unimpaired. UHR subjects significantly outperformed the schizophrenia group with duration of illness >3 years for speed of processing and working memory (both $p < 0.001$). There were no significant differences in performance between the UHR group and the group with duration of schizophrenia <3 years.

Conclusion: Cognitive performance is impaired in UHR subjects as compared to healthy controls and should thus be monitored when a person is deemed at high risk of psychotic

illness. Spatial skills, as measured by tests using physical objects, appear less affected than other domains. The pattern of impairment is similar to that of a group with recent onset schizophrenia but is less severe than in a group with duration of illness <3 years.

INTRODUCTION

Cognitive impairment is a core characteristic of schizophrenia (1). The majority of patients with schizophrenia fall below the cognitive performance level expected according to premorbid functioning or parental educational levels (2). Cognitive impairment likely precedes the appearance of overt psychotic symptoms, and some authors suggest that it is a neurobiological marker for psychosis risk (3). Impairment in episodic and working memory, speed of processing, verbal fluency, attention, and executive functions have robustly been demonstrated (4). Impairment in cognitive functioning is associated with a higher likelihood of relapse (5), poor functional outcome (6), and worse quality of life (7) and is thus an important prognostic indicator in clinical settings.

If cognitive decline starts in the prodromal phase of schizophrenia (3), it could be hypothesized that cognitive impairment also presents a challenge for help-seeking young people at ultra high risk for psychosis (UHR). Cognitive impairment in UHR could affect both social and academic functioning as well as the ability to profit from psychosocial therapy and interventions, which are often the first choice for this patient group (8). Managing or ameliorating cognitive dysfunction in psychotic disorders is therefore central to clinical recovery and to helping people function in the community. In addition, understanding how UHR cognitive changes compare to those seen in full-blown psychosis may further the understanding of etiology and course in psychotic disorders.

Cognitive Impairment in the Psychosis Continuum

The continuum model of psychosis sees the psychosis spectrum as ranging from mild attenuated experiences in many otherwise healthy individuals, to clinically significant and severe symptoms in a few who fulfill diagnostic criteria for psychotic disorders (9). The UHR state falls into the milder end of this continuum, while schizophrenia is considered to be the most severe form in terms of symptom load and duration (10). In accordance with this, cognitive impairment in UHR appears to be milder than in schizophrenia. Furthermore, impairment in first-episode psychosis has been found to be less severe than in chronic schizophrenia (11). Alongside studies showing slightly greater impairment in persons with a longer duration of untreated psychosis, this might suggest that abnormal neurodevelopmental processes happen prodromally and continue after the onset of psychosis (12).

A meta-analysis found 20% (confidence interval, 17–25%) of UHR patients to develop full-blown psychosis (13, 14). UHR

individuals often seek help because psychosis-related symptoms and signs cause functional decline and reduced quality of life. Although up to 65% of UHR subjects clinically recover from attenuated psychosis symptoms within 2 years (15), they often continue to report other mental health problems, which require targeted intervention (16). Early intervention services aimed at reducing the duration of untreated psychotic symptoms may thus improve outcome in those at risk for psychosis (17) regardless of conversion status by paving the way for tailored support.

Understanding the cognitive profile of UHR as compared to general population controls and patients with schizophrenia may improve service delivery and individualized treatment and prognosis prediction for this group, potentially preventing psychosis conversion in some cases. Cognitive changes seem to predict conversion to psychosis in UHR individuals, with longitudinal studies indicating worsening cognitive functioning as an early sign of eventual full-blown psychosis (18). Distractibility has also been shown to predict the UHR marker of voice hearing in adolescents (19), indicating an association between cognitive functioning and psychosis symptoms.

Cognitive screening may contribute meaningfully to efforts to individualize early intervention services aimed at supporting UHR youth. Cognitive remediation training may improve cognitive functioning (20) and has few, if any, negative side effects, making it appropriate for UHR groups (21). Although the effect on symptom load appears to be marginal (22), improved cognition might improve function (23). Handling cognitive challenges is therefore important both for UHR patients who develop full-blown psychosis and to the large subgroup whose attenuated symptoms do not worsen, but for whom impaired cognitive functioning may still remain a problem (24). However, we cannot successfully provide this without more detailed knowledge about the nature of the cognitive challenges of this group.

UHR Groups and Cognitive Changes in Psychosis

It has been suggested that cognitive performance in UHR groups lie somewhere in between that of healthy controls and established psychotic illness (25). However, there is no clear consensus on the trajectory of cognitive changes ahead of and during psychotic illness. Subjects who later transit to psychosis have been found to show greater deficits than those who do not, albeit with modest effect sizes (26–28). These differences are not merely due to general cognitive ability (27). While some have argued that cognition declines across the course of psychotic illness (29), others have found no evidence of cognitive decline in patients with UHR, noting

that cognitive performances improve at follow-up (28). Our own research group similarly found significant cognitive improvement across the acute phase of psychosis (30). A recent 24-month longitudinal study of young people with early onset schizophrenia also found this group to have a similar cognitive course to healthy controls, albeit functioning at an overall lower level (31). Improvement has also been seen in first episode schizophrenia, even with test batteries designed to withstand learning effects (32). The only study to date to retest UHR subjects after 10 years found no decline in cognition except in tests of immediate verbal learning and memory (33). This study also found cognitive change over the decade not to be related to baseline IQ, symptomatic change, or transition status.

There is a similar lack of consensus on changes in the UHR phase in relation to individual cognitive domains. In their 2014 meta-analysis, Bora et al. found the greatest impairment across UHR groups in symbol coding tests and more general measures of visuospatial working memory (28). A meta-analysis by Fusar-Poli, Deste (26), however, found significantly lower general intelligence in subjects deemed at high risk of psychosis, with verbal and visual memory most impaired. They found no group differences in overall speed of processing, although also they noted that the digit-symbol coding task was the single test showing the biggest discrepancy between high-risk subjects and healthy controls. The notable variability in previous findings may be partly due to measurement discrepancies across studies. In addition, a variety of test batteries have been used. The UHR group is also clinically and demographically diverse. Getting a representative sample may be affected, e.g., by restricted access to early intervention services or mental health care in the area of recruitment. Comparing data from UHR groups to those from groups with psychosis also remains difficult due to the young age of the UHR population, which means that coordinated norms do not exist for many commonly used tests of cognitive functioning.

We designed the present study aiming to overcome challenges associated with young subject age using norms based on regression analyses of a control group sample, in order to allow for comparison with younger subjects across tests while adjusting for age and sex, thus enabling a comparison of cognitive profiles in UHR and schizophrenia. We also included both UHR subjects and two comparison schizophrenia groups from similar catchment areas, with universal access to free health care and well-structured clinical practices for early intervention in psychosis, as we aimed to get a more representative view of UHR cognitive performance than would be allowed when recruiting in a more restricted public health care system.

Aims and Hypotheses

The aim of the current paper is to examine the nature of cognitive dysfunction in UHR at the time of help seeking. UHR sample performance will be compared to performance in two groups with schizophrenia: one with recent onset of illness and one with longer duration of schizophrenia. Comparisons will be based on norms derived from healthy controls reflecting the younger

age spectrum. These comparison groups will also allow us to use cognitive performance to illuminate the continuum model of psychotic illness.

We hypothesize the UHR group performance to fall below that of the healthy controls but above that of the schizophrenia groups. A secondary hypothesis is that the performance of recent onset schizophrenia participants will fall between the performance of the UHR group and the group with longer duration of illness. Given that measures of working memory and processing speed are found to be significantly impaired across studies, we hypothesize that impairment especially will be evident in demanding tasks loading on these cognitive functions, with our tests specifically designed to explore this.

METHODS

Study Design

UHR subjects were included from the Prevention of Psychosis Project (POP), an early intervention and treatment study encouraging at-risk individuals through information campaigns to seek relevant and early professional support. Rolling inclusion of POP participants took place from March 2012 to December 2019 in health-care regions Stavanger and Fonna in Norway, with subjects assessed by low-threshold detection teams. POP offered participants a multimodal treatment program, adding antipsychotic medication at imminent risk of conversion only. The project aimed to significantly reduce the proportion of high-risk subjects whom convert to psychosis in the catchment areas and has been described in detail elsewhere (34). Participants in the current substudy were recruited between 2012 and 2016.

Schizophrenia subjects were drawn from the Bergen Psychosis Project 2 (BP2). BP2 consists of a pharmaceutical-industry-independent international and multisite pragmatic, randomized-controlled trial (RCT) comparing three antipsychotics (amisulpride, aripiprazole, and olanzapine) for effects and side effects, with the aim of improving the specificity of antipsychotic treatment. An observational cohort of patients with psychosis not eligible for the RCT was included for comparison. All participants were followed up for 12 months. Participants in the current substudy were recruited between 2013 and 2016 from hospital sites in Bergen, Stavanger, and Trondheim in Norway, as well as from Innsbruck, Austria.

Participants

UHR Subjects (N = 52)

Inclusion criteria for participants drawn from the POP project were age 13–65 years and meeting diagnostic criteria for prodromal syndrome according to the Structured Interview For Prodromal Syndromes (SIPS) (35). The SIPS describes three different ways of fulfilling prodromal syndrome criteria. These are as follows: (1) brief intermittent psychotic syndrome (BIPS) as defined by experience of frank psychotic symptoms scoring at least 6 on the SOPS scale at least once per month but only in the last 3 months. brief intermittent psychotic syndrome is separated from current psychotic disorder by frequency and

136

duration/urgency. (2) Attenuated positive symptoms syndrome, meaning recent experience of attenuated positive symptoms scored to 3–5 on the scales P1–P5 of SOPS, starting or worsening in the past 12 months and occurring at least once per month. (3) Genetic risk and deterioration syndrome, defined by a combined first-degree family history of nonaffective psychotic disorder and a 30% or greater estimated drop in function as measured by Global Assessment of Functioning score over the past 12 months. In addition to meeting prodromal syndromes criteria, participants were also required to have IQ ≥ 70, ability to understand and speak Norwegian, and ability to understand and sign an informed consent or assent for minors' document. Exclusion criteria were any current or lifetime psychotic disorder, if symptoms were better accounted for by an axis I, axis II, or substance use disorder, with the exception of schizotypal personality disorder, lifetime use of antipsychotic medication exceeding 4 weeks, or any known neurological or endocrine disorders that may have caused the presented psychotic symptoms. They were also required to not be using nor having used any antipsychotic medication (regardless of dosage) for more than 4 weeks lifetime.

Subjects With Schizophrenia (N = 48)

Subjects were included from the BP2 project if they had completed the comprehensive neuropsychological assessment forming part of their 3-month follow-up. Inclusion criteria for the RCT part of the BP2 were age >18, active psychosis as determined by a score ≥4 on either of the Positive and Negative Symptoms Scale (PANSS) interview (36) items for delusions (P1), hallucinatory behavior (P3), grandiosity (P5), suspiciousness/persecution (P6), or unusual thought content (G9); no known neurological or endocrine disorders likely to have caused the presented psychotic symptoms and the ability to understand and speak the site native language (in Norway or Austria). Inclusion criteria for the observational cohort part of the BP2 were age >16 and previous or current psychosis. Diagnoses were determined by the Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID I) (37), with the following ICD-10 disorders eligible for participation in the BP2 study: schizophrenia (F20), schizotypal disorder (F21), delusional disorder (F22), acute psychotic disorders (F23), schizoaffective disorder (F25), other organic psychotic disorders (F28), and unspecified nonorganic psychosis (F29). The current sub-study only included BP2 participants fulfilling criteria for F20 schizophrenia to ensure a more homogenous comparison group in relation to cognitive performance.

Healthy Control Subjects (N = 61)

Healthy controls were recruited at the Stavanger site as part of both POP and BP2 projects. They were recruited among Stavanger University Hospital employees and their networks, high schools in the local area and posters in social security offices (NAV), aiming to gender and age match UHR participants and cover the age range of both UHR and psychosis participant groups. Participants with a known first-degree family history of psychiatric disorder or current or past drug dependence (other than nicotine products) were excluded from participating. All

healthy controls received a small payment to cover travel costs and time.

Symptom and Functional Level Measures

UHR group baseline symptom load was measured by the SIPS interview (35). BP2 participants completed a PANSS assessment at baseline. A Structured Clinical Interview for the DSM-IV Axis I Disorders interview was administered to both groups by trained clinicians in order to determine diagnoses, with detailed results displayed in **Table 1**. Functioning was measured for all participants by the Global Assessment of Functioning, split version (38). All UHR subjects were antipsychotic naive (as per inclusion criteria) at the time of testing. Antipsychotic drug use in the schizophrenia group with psychosis was converted to defined daily doses (DDD), with DDD defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults" (39). The control group completed PQ21 as well as a MINI assessment in order to exclude any subjects with subthreshold psychotic symptoms or other mental illness. However, no control group participant was excluded due to this.

UHR subjects also completed a Norwegian version of the Premorbid Adjustment Scale (PAS) (40), a structured interview aiming to retrospectively assess social and academic premorbid adjustment. PAS yields five subscales used in the present study: Sociability and Withdrawal, Peer Relationships, Academic Achievement, Adaptation to School and Ability to Form Interpersonal and Sexual Relationships, each assessed for childhood (11 and younger), early and late adolescence (12–15 and 16–18 years), and adulthood (19 and older). For the purposes of simplified reporting, a mean social adjustment score was calculated by averaging the scores of Sociability and Withdrawal and Peer Relationships for each stage.

Cognitive Measures

A comprehensive neurocognitive test battery was administered to POP project UHR participants at baseline and to BP2 participants and healthy controls at their 3-month follow-up. The battery was designed to assess verbal functioning, visuo-spatial functioning, and executive functions. Tests included in the present study were Trail Making A (TMA) and Trail Making B (TMB) (41), the California Verbal Learning test (42), Wechsler Adult Intelligence Scale III tests for number span, letter number sequencing, vocabulary, and block design (WMS) (43), WMS spatial span (44), as well as Delis–Kaplan Executive Function System (D-KEFS) Color Word Interference Test (CWIT), and FAS verbal fluency tests (45). Trained staff administered all neurocognitive testing.

Statistical Analysis

All analyses were performed using the Statistical Package for the Social Sciences 25.0.

Calculation of Coordinated Norms

Neuropsychological score variables were assessed for normality by way of creating histograms for inspection, both overall and

TABLE 1 | Demographic variables and baseline cognitive test scores by group.

	UHR (n = 51)	Schizophrenia duration <3 years (n = 19)	Schizophrenia duration <3 years (n = 22)	Controls (n = 61)
Mean age (SD)	17.0 (2.9)	27.0	33.2	23.9 (10.8)
Female %	61.2	21.1	59.1	55.7
Measures of function				
Baseline GAF[1] functioning (SD)	49.4 (13.3)	47.4	46.3	88.6 (4.82)
Baseline GAF[1] symptoms (SD)	45.7 (8.4)	47.6	47.7	87.0 (5.96)
PAS2 Childhood social functioning mean (SD)	1.47 (1.27)	N/A	N/A	N/A
PAS[2] Childhood scholastic performance mean (SD)	2.41 (1.34)	N/A	N/A	N/A
PAS[2] Childhood adaptation to school mean (SD)	1.18 (1.10)	N/A	N/A	N/A
PAS[2] Early adolescence social functioning mean (SD)	1.70 (1.38)	N/A	N/A	N/A
PAS[2] Early adolescence scholastic performance mean (SD)	2.55 (1.37)	N/A	N/A	N/A
PAS[2] Early adolescence adaptation to school mean (SD)	1.80 (1.36)	N/A	N/A	N/A
Symptoms and clinical assessments				
SCID[3] diagnoses				
Schizophrenia F20.x		19	22	
Bipolar disorder II F31.x	1			
Depressive disorder F32.x-33.x	12			
Dysthymia F34.x	1			
Anxiety disorders F41.x	7			
OCD F42.x	1			
PTSD F43.1	2			
Adjustment disorder F43.2	1			
Somatoform disorder F45.x	1			
Substance use disorders F10.x-19.x	2			
Psychiatric disorder NOS F99.x	1			
Psychotic disorder NOS F29.x	3			
No diagnosis	17			
Mean age of onset for psychosis (SD)	N/A	25.7 (5.9)	22.6 (11.5)	
Mean years duration of illness (SD)	N/A	1.3 (0.85)	10.6 (8.5)	
AD medication naïve at baseline %	100	36.8	22.7	
DDD mean (SD)	N/A	1.8(0.6)	1.4 (0.7)	
PANSS[4] positive mean (SD)	N/A	19.8 (3.7)	21.3 (4.0)	
PANSS[4] negative mean (SD)	N/A	21.1 (6.2)	18.0 (6.5)	
PANSS[4] general mean (SD)	N/A	39.1 (7.8)	38.9 (8.4)	
SIPS[5] positive mean (SD)	10.7 (3.3)	N/A	N/A	
SIPS[5] negative mean (SD)	11.5 (6.1)	N/A	N/A	
SIPS[5] general mean (SD)	8.9 (3.6)	N/A	N/A	
Cognitive composites z-score group means (SD)				
Speed of processing[6]	−0.78 (0.89)	−0.97 (1.41)	−1.80 (1.13)	
Working memory[7]	−0.51 (0.82)	−0.18 (1.08)	−1.72 (1.66)	
Verbal learning, reasoning and problem solving[8]	−0.50 (0.65)	−0.59 (0.78)	−0.37 (1.12)	
Visual problem solving[9]	−0.12 (1.18)	−0.43 (1.17)	−0.40 (1.19)	

[1]GAF, Global Assessment of Functioning, [2]PAS, Premorbid Adjustment Scale; [3]SCID, Structured Clinical Interview for DSM-IV; [4]PANSS, Positive and negative symptoms scale; [5]SIPS, Structured Interview for Prodromal Symptoms; [6]Trailmaking A, WAIS coding, CWIT color, and word reading; [7]Trailmaking B, WAIS number span and letter number sequencing, inhibition, and inhibition and switching conditions from D-KEFS CWIT; [8]D-KEFS FAS, WAIS vocabulary, and CVLT; [9]WAIS block design and WMS spatial span.

within groups. We standardized test raw scores by calculating z values relative to the baseline performance of our group of healthy controls. Calculation of z-scores was done to allow for comparisons across domains and tests and also because the young age of the UHR group in particular meant that valid test norms do not exist. This was done by running linear regression analyses for each variable, using age and gender as predictor variables. Based on the results from these we calculated expected scores adjusted for age and gender for each subject. Individual subject z-scores were then calculated by subtracting the expected score from the observed score in each variable and then dividing by the standard deviation of the control group. For tests where a higher raw score indicates worse performance

(TMA, TMB, and CWIT), z-scores were inverted before further analyses. All negative z-scores thus indicate performance below that of controls.

Calculation of Cognitive Profile

For the purposes of the current study, test results were selected and grouped into cognitive domains according to existing literature and neuropsychological conventions (46). The cognitive domains used for the purposes of this study were speed of processing (TMA, WAIS digit symbol coding, CWIT color and word reading conditions), working memory (TMB, WAIS number span and letter number sequencing, inhibition, and inhibition and switching conditions from D-KEFS CWIT), verbal learning, reasoning, and problem solving

138

(D-KEFS FAS, WAIS vocabulary, and CVLT), and spatial reasoning (WAIS block design and WMS spatial span). The calculated mean z-score for the tests comprising each domain formed the score for each of these four domains.

ANOVA Group Comparison

Cognitive subscale z-scores were compared between the groups using one-way ANOVAs. The four comparison groups were UHR participants and two F20 groups, the first comprising participants with duration of illness up to 3 years (SZ1) and the second group with duration extending 3 years (SZ2), as well as healthy controls. Levene's test was used to check equality of variances between groups. Where the F value indicated significant between-group differences, post-hoc pairwise t tests were performed in order to assess these. The Siddaq correction was applied to adjust for multiple comparisons.

Correlational Analysis

We calculated Pearson correlations between the cognitive subscales and symptom scores, i.e., SIPS and PANSS scores, respectively, for the UHR and F20 groups. We also calculated the correlation between cognitive performance and antipsychotics DDD as well as duration of illness for the F20 groups.

RESULTS

Demographic variables for all three groups are displayed in **Table 1**. Owing to the young mean age of the UHR and healthy control groups (as young as 13, with many still living at home and in full-time mandatory education), years of education, living status, and employment levels were not compared between groups.

Neuropsychological Profile and Between-Group Differences

A one-way ANOVA of z-scores based on age- and gender-controlled norms revealed significant differences in cognitive performance between groups, with both the schizophrenia and UHR groups scoring lower than healthy controls. Between-group differences were significant for speed of processing [$F(3) = 18.24, p < 0.001$], working memory [$F(3) = 13.71, p < 0.001$], and verbal learning, reasoning, and problem solving [$F(3) = 4.94, p = 0.003$], but not for visual problem solving [$F(3) = 1.16, p = 0.327$]. Group cognitive profiles are displayed for comparison in **Figure 1**. The UHR group had significantly lower scores than the control group for speed of processing ($p < 0.001$), working memory ($p = 0.042$), and verbal learning, reasoning, and problem solving ($p = 0.007$). They scored significantly better than the longer duration of illness schizophrenia group for speed of processing and working memory (both $p < 0.001$). There were no significant differences in performance between the UHR group and the recent onset schizophrenia group in any domain. For complete results of pairwise comparisons, please refer to **Table 2**.

Correlational Analysis

Working memory performance was correlated with SIPS positive symptoms for the UHR group, while PANSS negative score was significantly correlated with verbal learning for participants with schizophrenia. However, neither of these correlations remained significant upon applying a Bonferroni correction for multiple comparisons. There were no significant correlations between DDD and cognitive domain scores. Complete results from correlation analyses are displayed in **Table 3**.

DISCUSSION

UHR subjects performed significantly worse than the healthy control group on measures of speed of processing, cognitive flexibility, and verbal learning, reasoning, and problem solving. This is in line with our hypothesis and confirms cognitive impairment as an observable early sign of a potential psychotic disorder. The UHR group also outperformed the schizophrenia group with duration of illness longer than 3 years on speed of processing and working memory. There were notably no significant differences in performance between the UHR group and the recent onset F20 group. The cognitive performance profile of the UHR group fell in between that of the longer duration schizophrenia group and that of the healthy controls while matching that of the recent onset participants. Our results support previous meta-analytic and review findings (26, 47) of impaired cognitive performance in UHR groups, with authors arguing for this as a measurable potential vulnerability marker preceding severe positive symptoms (3). Interestingly, the UHR group performance in tests of spatial abilities (WAIS block design and WMS spatial span) was almost identical to that of the control group. Our findings are similar to those of another recent study which found no impairment in visual skills in a clinical high-risk

FIGURE 1 | Cognitive profiles in UHR and groups with recent onset and longer duration schizophrenia. UHR, ultra high risk group; SZ1, group with recent onset schizophrenia (< 3); SZ2, group with remote onset schizophrenia (> 3 years). Error bars show 95% CI.
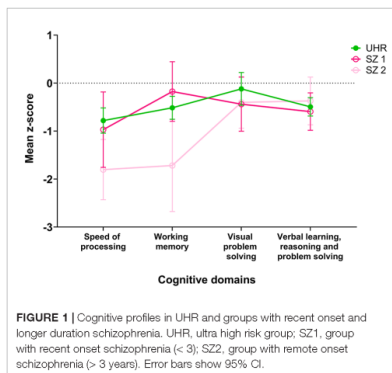
group, as opposed to in all other domains (48). Spatial abilities have previously been found to discriminate between UHR individuals who convert to psychosis and those who do not (49, 50). Others have found no such link (51, 52), although spatial abilities were found to be impaired. One study also found a link between spatial span and functional outcome (52), meaning that these skills could be important when working to limit functional loss in UHR individuals.

We suggest that the unimpaired spatial performance of the UHR sample in our study could, in part, be due to the inclusion of WAIS block design and WMS spatial span tests, both of which use physical test objects. Many studies have mainly used nontactile, screen-based tests, such as the delayed response task, rather than tests involving physical objects. Screen-based tests are likely to load more heavily on the working memory and visuospatial sketchpad aspect of spatial skills than do tests supported by physical objects. If so, this could indicate that the inclusion of physical objects may aid the cognitive functioning of this group. We have been unable to find any previous research directly comparing these two aspects of visuospatial functioning in UHR groups.

SZ1 group performance equaled that of the UHR participants. This was surprising, as we were expecting the UHR group to outperform SZ1. Significant differences were neither found in DDD of medication received nor in baseline antipsychotic naivete between the two F20 groups. The similarity to UHR performance in the SZ1 group might reflect the findings of other papers, which have found few significant performance differences between

UHR and first-episode psychosis groups while seeing greater impairments in more chronic schizophrenia (11). However, we hesitate to read too much into these results, as statistical power was low given the small subgroup size.

The significant difference in performance between the SZ1 and SZ2 groups might be explained in several different ways. Cognitive performance may decline over the course of illness with active psychosis being a neurotoxic state (4), although several authors have refuted this idea (12, 28). Another explanation may be that better cognitive performance equips people to better take advantage of and adhere to any treatment offered, thus aiding a quicker recovery. A final explanation which seems likely is that the recent onset SZ1 group is genetically diverse. It plausibly includes people likely to develop both chronic and less severe courses of illness, with better cognitive functioning as characteristic of those more likely to recover. Ultimately, only longitudinal studies, preferably also tracking genetic factors (53), may explain this pattern.

Our results lend support to previous findings that speed of processing, working memory, and verbal ability show particular impairment studies in both UHR and psychotic disorder groups (4). Tasks requiring speed and cognitive flexibility in manipulating information appear to present difficulties for both UHR and schizophrenia groups. Previous functional MRI studies have found changes in major associative fiber tracts/functional connectivity in UHR groups (54). DTI studies have found reductions in fractional anisotropy as well as increased diffusivity (55) in the UHR

TABLE 2 | Cognitive domains z-score comparisons between UHR, schizophrenia, and control groups.

Cognitive domain	F (sig)	p (UHR vs. SCZ1)	p (UHR vs. SCZ2)	p (UHR vs. CTR)	p (SCZ1 vs. SCZ2)	p (SCZ1 vs. CTR)	p (SCZ2 vs. CTR)
Speed of processing[1]	18.24 (<0.001)	0.981	<0.001**	<0.001**	0.080	0.002*	<0.001**
Working memory[2]	13.71 (<0.001)	0.770	<0.001**	0.042*	<0.001**	0.995	<0.001**
Verbal learning, reasoning, and problem solving[3]	4.944 (0.003)	0.998	0.998	0.007**	0.022	0.027*	0.303
Visual problem solving[4]	1.27 (0.327)	0.840	0.890	0.998	1.000	0.587	0.652

*p < 0.05, two-tailed. **p < 0.001, two-tailed UHR, ultra high-risk group; SCZ1, recent onset schizophrenia group; SCZ2, longer duration schizophrenia group; CTR, control group.
[1] Trailmaking A, WAIS coding, CWIT color, and word reading; [2] Trailmaking B, WAIS number span and letter number sequencing, inhibition, and inhibition and switching conditions from D-KEFS CWIT; [3] D-KEFS FAS, WAIS vocabulary and CVLT; [4] WAIS block design and WMS spatial span.

TABLE 3 | Correlations between cognitive domains and clinical variables.

	Speed of processing[3] Pearson correlation (p)	Working memory[4] Pearson correlation (p)	Visual problem solving[5] Pearson correlation (p)	Verbal learning, reasoning and problem solving[6] Pearson correlation (p)
UHR participants				
SIPS positive score[1]	−0.165 (0.278)	−0.305 (0.039)*	−0.134 (0.374)	−0.063 (0.682)
SIPS negative score[1]	0.141 (0.372)	0.137 (0.383)	0.083 (0.597)	−0.025 (0.875)
SIPS general score[1]	0.095 (0.544)	0.101 (0.514)	−0.048 (0.755)	0.175 (0.262)
F20 participants				
PANSS positive score[2]	0.101 (0.594)	−0.015 (0.938)	0.086 (0.597)	0.127 (0.434)
PANSS Negative score[2]	−0.043 (0.820)	0.117 (0.554)	−0.260 (0.105)	−0.374 (0.017)*
PANSS General score[2]	−0.086 (0.652)	−0.096 (0.626)	−0.275 (0.086)	−0.192 (0.234)
Antipsycotic_DDD	−0.071 (0.743)	−0.138 (0.540)	−0.123 (0.508)	−0.179 (0.336)

*p < 0.05, two-tailed. [1]SIPS, Structured Interview for Prodromal Symptoms; [2]PANSS, Positive and Negative Symptoms Scale; [3]Trailmaking A, WAIS coding, CWIT color, and word reading; [4]Trailmaking B, WAIS number span and letter number sequencing, inhibition, and inhibition and switching conditions from D-KEFS CWIT; [5]D-KEFS FAS, WAIS vocabulary and CVLT; [6]WAIS block design and WMS spatial span.

phase, indicating both demyelination and deterioration in the axonal membrane. Taken together, these studies suggest reduced connectivity in UHR. Our findings of impaired cognitive flexibility and speed can be consistent with reduced white matter connectivity, perhaps to a lesser extent than in schizophrenia given the higher speed of processing of UHR individuals. In line with this, reductions in white matter and abnormalities in white matter microstructure in prefrontal and temporal lobe areas have been found to be more pronounced in schizophrenia than in UHR groups.

Our findings highlight the importance of clinical attention to cognitive problems when aiming to alleviate distress in the UHR patient group. The cognitive impairment reported by our study suggest cognitive domains that should be targeted in the UHR groups in, e.g., academic settings. Working memory, attention, and speed of processing performance have been found to predict over half of the variance over time in school or work participation in clinically stable first-episode psychosis (56). A UHR treatment approach including focused interventions for cognitive deficits, such as psychoeducation, cognitive training, and physical exercise (57), may therefore be crucial in preventing further functional loss over time. The relationship between social and cognitive functioning would also be an interesting topic for future research.

Abnormal synaptic pruning in UHR groups (58) might explain their impaired speed of processing. Longitudinal research in healthy children has found a puberty-related dip in performance speed in tasks requiring working memory and decision making, linked by authors to normal synaptic proliferation at this stage (59). The same authors argue that healthy synaptic pruning after puberty ensures the more effective cognitive performance seen their young adult comparison sample. Any disturbance to this pruning process is likely to underpin cognitive impairment in UHR and schizophrenia when compared to healthy adults. Future research should investigate any associations between such pruning disturbances and not only cognitive impairment but also cognitive change and potential growth in UHR groups.

Despite the clinical diversity of the UHR group, the variance in performance is much greater in the schizophrenia group. One major reason for this is likely that they simply are a more diverse group. First of all, variance is to be expected in a group spanning all of adolescence in age. Second, the majority of our UHR sample will most likely not go on to develop full-blown psychosis. As with all cross-sectional UHR studies, our sample thus includes a number of false positives. Our results must therefore be interpreted with some caution when searching to elucidate the trajectory of cognitive changes in the UHR subgroup who go on to develop psychotic disorders. However, our findings are still able to inform clinical work with UHR groups, as our sample's diversity is representative of the variability inevitably seen in these patients.

Another possible contributor to the greater variability in the UHR group is that several different trajectories exist within the development of cognitive impairment between the stages of UHR to full-blown psychosis. It is also possible and likely that different aspects of cognition develop differently. As noted by Corigliano et al. (11), cross-sectional group data also mask potential differences between individual trajectories of cognitive functioning, where people may both improve or worsen, as well

as remaining stable. It is also possible that better cognitive performance at the UHR stage may ameliorate the course of illness by better absorbing any ensuing decrement in cognitive function as well as by improving the individual's ability to make use of any help and treatment offered. Worse performance in chronically ill groups might thus imply lower baseline functioning rather than an ongoing decline. Last, poor cognitive functioning in UHR may, to some degree, independently coexist with psychosis-like experiences. This idea is supported by the existence of some cognitive deficits in UHR individuals who do not develop psychotic disorder (60). Further longitudinal work is required to identify the path of each UHR person, to reveal any individual or group patterns of change. Our findings indicate that a decrement in cognitive functioning is in place and measurable before the appearance of clinically significant positive symptoms of psychosis. Cognitive impairment also appears to be more severe in participants with established illness. Although our cross-sectional design precludes us from concluding firmly, this may indicate that further cognitive changes take place during the transition from prodromal symptoms to full-blown psychosis. Previous work from our research group found cognitive improvement during the early treatment of a psychotic episode (30). However, the present study reinforces the fact that, despite this improvement, the decrement in functioning remains in schizophrenia even after the acute phase. Although not every UHR participant will develop psychotic disorder, our current findings indicate that cognition most likely continues to change between the UHR stage and established psychotic disorder, in line with a neurodevelopmental but not necessarily uniformly degenerative model of psychosis.

LIMITATIONS AND STRENGTHS

One limitation of this study is that it is cross-sectional, precluding anything but speculation about prediction of individual outcomes based on baseline findings. However, we hope that future longitudinal analyses of data from the POP project will allow us to investigate this. Another limitation is the amount of missing data, especially from the schizophrenia group. Naturally, more complete data would have been preferable, but is often difficult to achieve in this patient group for clinical and ethical reasons.

It is possible that some of the difference between the UHR and control group might be due to differences in education level. It is difficult to compare and control for this due to UHR subjects' young mean age. However, school dropout before the end of mandatory schooling at the age of 16 is extremely rare in Norway. Matching as to years of education would thus not yield much additional information and might even be misleading when including both under 18s and adults in the control group. The young age of participants also precluded us from adequately measuring and comparing social cognition between groups, which might have yielded interesting results.

Owing to the criteria for prodromal syndrome including both brief psychosis-like experiences and loss of function over time, setting an accurate age of onset is a challenge for this group. This is especially the case for the genetic risk and deterioration syndrome group where it can be difficult to determine an exact starting point for this loss of function. It was decided in our research group that we were unable to create a reliable "DUP-like" variable for this group, although the inclusion of such a variable would have been of interest.

One of the main strengths of our study is the presence of a control group. Given that UHR patients are quite young, validated norms do not exist for all cognitive tests. Use of an age-matched control group allowed us to create coordinated norms to compare UHR youth to a schizophrenia group from a similar geographical area.

We have also attempted to overcome the challenge in UHR research that lack of access to health-care services for disadvantaged groups restricts recruitment, making the sample less representative. Our current project ran as part of Norway's universal public health-care system, aiming to reach vulnerable youth across the catchment area. Despite the limitation on generalization caused by our relatively small sample size, we believe this strengthens our sample's representativeness.

A further strength of our study is its placement within the Norwegian public health-care system, allowing us to recruit a wide range of UHR youth from a variety of socioeconomic backgrounds, without impacting on their opportunity to get treatment at the same cost without enrolling in our study. We believe that this makes our sample more representative of the general Norwegian UHR population.

CONCLUSION

UHR subjects show impaired cognitive functioning in comparison with an age-matched healthy control group on speed of processing, working memory, and verbal learning, reasoning, and problem solving. Interestingly, spatial task performance appeared to be relatively unimpaired. UHR subjects performed better than a schizophrenia comparison group on speed of processing, but not in other measures. These findings highlight the importance of monitoring cognitive performance even in a prodromal phase of potential illness. Often less explored by clinicians than mood or attenuated psychotic symptoms, these symptoms may, in part, explain the high subjective distress reported by UHR groups, as cognitive impairment will impact both academic and social function.

DATA AVAILABILITY

Data are from the Prevention of Psychosis project and the Bergen Psychosis Project 2 study, whose authors may be contacted *via* the corresponding author email (lissgoril@gmail.com). Owing to ethical restrictions in this project, data must be stored on dedicated secure hospital servers, even when anonymized, and may only be shared with research partners involved in the project. However, if anyone wishes to access the data, this may be granted after an application process.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Regional Committee for Medical and Health Research Ethics West and South East, with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The POP study protocol was approved by the Regional Committee for Medical and Health Research Ethics: South-East Committee [REK Sør-Øst C (ref. 2009/949)] while the BP 2 project protocol was approved by the Regional Committee for Medical and Health Research Ethics: West Committee [REK Vest (ref. 2010/3387)]. The combination of data from the two projects was separately approved by the West Committee (REK Vest 2018/342-3).

AUTHOR CONTRIBUTIONS

FUNDING

ACKNOWLEDGMENTS

REFERENCES

1. Sheffield JM, Karcher NR, Barch DM. Cognitive deficits in psychotic disorders: a lifespan perspective. *Neuropsychol Rev* (2018) 28(4):509–33. doi: 10.1007/s11065-018-9388-2
2. Keefe RSE, Eesley CE, Poe MP. Defining a cognitive function decrement in schizophrenia. *Biol Psychiatry* (2005) 57(6):688–91. doi: 10.1016/j.biopsych.2005.01.003
3. Bora E, Lin A, Wood S, Yung A, McGorry P, Pantelis C. Cognitive deficits in youth with familial and clinical high risk to psychosis: a systematic review and meta-analysis. *Acta Psychiatr Scand* (2014) 130(1):1–15. doi: 10.1111/acps.12261
4. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts" 4. Clinical features and conceptualization. *Schizophr Res* (2009) 110(1–3):1–23. doi: 10.1016/j.schres.2009.03.005
5. Barder HE, Sundet K, Rund BR, Evensen J, Haahr U, ten Velden Hegelstad W, et al. Neurocognitive development in first episode psychosis 5 years follow-up: associations between illness severity and cognitive course. *Schizophr Res* (2013) 149 (1–3):63–9. doi: 10.1016/j.schres.2013.06.016

6. Lepage M, Bodnar M, Bowie CR. Neurocognition: clinical and functional outcomes in schizophrenia. *Can J Psychiatry* (2014) 59(1):5–12. doi: 10.1177/070674371405900103

7. Mortensen GL, De J, Holme M, Neve T, Torell PG, Eberhard J. Social aspects of the quality of life of persons suffering from schizophrenia. *Open J Psychiatry* (2016) 6:50–60. doi: 10.4236/ojpsych.2016.61005

8. The National Institute for Health and Care Excellence. (2016). Psychosis and schizophrenia in children and young people: recognition and management (National Clinical Guideline Number 155). Retrieved from https://www.nice.org.uk/guidance/cg155

9. Van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam LJPM. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. *Psychol Med* (2009) 39 (2):179–95. doi: 10.1017/S0033291708003814

10. Johns LC, Van Os J. The continuity of psychotic experiences in the general population. *Clin Psychol Rev* (2001) 21(8):1125–41. doi: 10.1016/S0272-7358(01)00103-9

11. Corigliano V, De Carolis A, Trovini G, Dehning J, Di Pietro S, Curto M, et al. Neurocognition in schizophrenia: from prodrome to multi-episode illness. *Psychiatry Res* (2014) 220(1):129–34. doi: 10.1016/j.psychres.2014.07.067

12. Rund BR. Does active psychosis cause neurobiological pathology? A critical review of the neurotoxicity hypothesis. *Psychol Med* (2014) 44(8):1577–90. doi: 10.1017/S0033291713002341

13. Fusar-Poli P, Cappucciati M, Borgwardt S, Woods SW, Addington J, Nelson B, et al. Heterogeneity of psychosis risk within individuals at clinical high risk: a meta-analytical stratification. *JAMA Psychiatry* (2016) 73 (2):113–20. doi: 10.1001/jamapsychiatry.2015.2324

14. Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch Gen Psychiatry.* (2012) 69(3):220–9. doi: 10.1001/archgenpsychiatry.2011.1472

15. Simon AE, Borgwardt S, Riecher-Rössler A, Velthorst E, de Haan L, Fusar-Poli P. Moving beyond transition outcomes: meta-analysis of remission rates in individuals at high clinical risk for psychosis. *Psychiatry Res* (2013) 209(3):266–72. doi: 10.1016/j.psychres.2013.03.004

16. The National Institute for Health and Care Excellence. (2014). Psychosis and schizophrenia in adults (NICE Clinical Guideline Number 178). Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK333029/.

17. Fusar-Poli P, Valmaggia L, Allen P, Galvan F, McGuire P, et al. Duration of untreated prodromal symptoms and 12-month functional outcome of individuals at risk of psychosis. *Br J Psychiatry* (2009) 194(2):181–2. doi: 10.1192/bjp.bp.107.047951

18. Lam M, Lee J, Rapisarda A, See YM, Yang Z, Lee SA, et al. Longitudinal cognitive changes in young individuals at ultra high risk for psychosis. *JAMA Psychiatry* (2018) 75(9):929–39. doi: 10.1001/jamapsychiatry.2018.1668

19. Løberg E-M, Gjestad R, Posserud M-B, Kompus K, Lundervold AJ. Psychosocial characteristics differentiate non-distressing and distressing voices in 10,346 adolescents. *Eur Child Adolesc Psychiatry* 2019:1–11. doi: 10.1007/s00787-019-01292-x

20. Loewy R, Fisher M, Schlosser DA, Biagianti B, Stuart B, Mathalon DH, et al. Intensive auditory cognitive training improves verbal memory in adolescents and young adults at clinical high risk for psychosis. *Schizophr Bull* (2019) 42 (suppl_1):S118–26. doi: 10.1093/schbul/sbw009

21. McGorry PD, Nelson B, Amminger GP, Bechdolf A, Francey SM, Berger G, et al. (2009). Intervention in individuals at ultra-high risk for psychosis: a review and future directions. J Clin Psychiatry, 70(9): 1206–12. doi: 10.4088/JCP.08r04491

22. Glenthøj LB, Hjorthøj C, Kristensen TD, Davidson CA, Nordentoft M. The effect of cognitive remediation in individuals at ultra-high risk for psychosis: a systematic review. *npj Schizophr* (2017) 3(1):20. doi: 10.1038/s41537-017-0021-9

23. Medalia A, Saperstein AM. Does cognitive remediation for schizophrenia improve functional outcomes? *Curr Opin Psychiatry* (2013) 26(2):151–7. doi: 10.1097/YCO.0b013e32835dcbd4

24. Proffitt T-M, Brewer WJ, Parrish EM, McGorry PD, Allott KA. Reasons for referral and findings of clinical neuropsychological assessment in youth with

mental illness: a clinical file audit. *Appl Neuropsychol Child* (2018) 7(2):164–74. doi: 10.1080/21622965.2017.1284663

25. Kim KR, Park JY, Song D–H, Koo HK, An SK. Neurocognitive performance in subjects at ultra high risk for schizophrenia: a comparison with first-episode schizophrenia. *Compr Psychiatry* (2011) 52(1):33–40. doi: 10.1016/j.comppsych.2010.04.010

26. Fusar-Poli P, Deste G, Smieskova R, Barlati S, Yung AR, Howes O, et al. Cognitive functioning in prodromal psychosis: a meta-analysis. *Arch Gen Psychiatry* (2012) 69(6):562–71. doi: 10.1001/archgenpsychiatry.2011.1592

27. Seidman LJ, Shapiro DI, Stone WS, Woodberry KA, Ronzio A, Cornblatt BA et. al. Association of neurocognition with transition to psychosis: baseline functioning in the second phase of the north american prodrome longitudinal study. *JAMA Psychiatry* (2016) 73(12):1239–48. doi: 10.1001/jamapsychiatry.2016.2479

28. Bora E, Murray R. 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* (2014) 40(4):744–55. doi: 10.1093/schbul/sbt085

29. Kahn RS, Keefe RSE. Schizophrenia is a cognitive illness: time for a change in focus. *JAMA Psychiatry* (2013) 70(10):1107–12. doi: 10.1001/jamapsychiatry.2013.155

30. Anda L, Brønnick KS, Johnsen E, Kroken RA, Jørgensen H, Løberg E-M. The course of neurocognitive changes in acute psychosis: relation to symptomatic improvement. *PloS One* (2016) 11(12):e0167390. doi: 10.1371/journal.pone.0167390

31. Teigset CM, Mohn C, Brunborg C, Juuhl-Langseth M, Holmén A, Rund BR. Do clinical characteristics predict the cognitive course in early-onset schizophrenia-spectrum disorders? *J Child Psychol Psychiatry* (2018) 59(9):1012–23. doi: 10.1111/jcpp.12896

32. Fu S, Czajkowski N, Torgalsbøen A-K. (2018). Cognitive improvement in first episode schizophrenia and healthy controls: a 6-year multi-assessment follow-up study. Psychiatry Res, 267: 319–26. doi: 10.1016/j.psychres.2018.06.016

33. Allott K, Wood SJ, Yuen HP, Yung AR, Nelson B, Brewer WJ, et al. (2018). Longitudinal cognitive performance in individuals at ultra high risk for psychosis: a 10-year follow-up. *Schizophr Bull*, sby143. doi: 10.1093/schbul/sby143

34. Joa I, Gisselgård J, Brønnick K, McGlashan T, Johannessen JO. Primary prevention of psychosis through interventions in the symptomatic prodromal phase, a pragmatic Norwegian Ultra High Risk study. *BMC Psychiatry* (2015) 15(1):89. doi: 10.1186/s12888-015-0470-5

35. Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Ventura J, McFarlane W, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull* (2003) 29(4):703–15. doi: 10.1093/oxfordjournals.schbul.a007040

36. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* (1987) 13(2):261–76. doi: 10.1093/schbul/13.2.261

37. Gibbon M, Spitzer RL, Williams JB, Benjamin LS, First MB. (1997). Structured clinical interview for DSM-IV axis II personality disorders (SCID-II) [Measurement instrument].

38. Jones SH, Thornicroft G, Coffey M, Dunn GJTBJOP. A brief mental health outcome scale: reliability and validity of the Global Assessment of Functioning (GAF). *Br J Psychiatry* (1995) 166 (5):654–9. doi: 10.1192/bjp.166.5.654

39. World Health Organisation. (2018) Collaborating Centre for Drug Statistics Methodology: definition and general considerations. Retrieved from https://www.whocc.no/ddd/definition_and_general_considera/

40. Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. *Schizophr Bull* (1982) 8(3):470–84. doi: 10.1093/schbul/8.3.470

41. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills* (1958) 8(3):271–6. doi: 10.2466/pms.1958.8.3.271

42. Delis D, Kramer J, Kaplan E, Ober B. (2012). California Verbal Learning Test II [Measurement instrument].

43. Wechsler D. *Wechsler adult intelligence scale-III*. San Antonio, TX: The Psychological Corporation (1997). doi: 10.1037/t49755-000

44. Wechsler D. *Wechsler memory scale (WMS-III)*. San Antonio, TX: Psychological Corporation (1997).

45. Delis D, Kramer JH, Kaplan E, Holdnack J. Reliability and validity of the Delis–Kaplan executive function system: an update. *J Int Neuropsychol Soc* (2004) 10(2):301–3. doi: 10.1017/S1355617704102191

46. Fett A-KJ, Viechtbauer W, Penn DL, van Os J, Krabbendam L. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neurosci Biobehav Rev* (2011) 35(3):573–88. doi: 10.1016/j.neubiorev.2010.07.001

47. Giuliano AJ, Li H, Mesholam-Gately RI, Sorenson SM, Woodberry KA, Seidman LJ. Neurocognition in the Psychosis Risk Syndrome: a quantitative and qualitative review. *Curr Pharmaceut Design* (2012) 18(4):399–415. doi: 10.2174/138161212799316019

48. Carrión RE, Walder DJ, Auther AM, McLaughlin D, Zyla HO, Adelsheim S, et al. From the psychosis prodrome to the first-episode of psychosis: no evidence of a cognitive decline. *J Psychiatr Res* (2018) 96:231–8. doi: 10.1016/j.jpsychires.2017.10.014

49. Wood SJ, Pantelis C, Proffitt T, Phillips L, Stuart G, Buchanan J-A, et al. Spatial working memory ability is a marker of risk-for-psychosis. *Psychol Med* (2003) 33(07):1239–47. doi: 10.1017/S0033291703008067

50. Brewer WJ, Wood SJ, Phillips LJ, Francey SM, Pantelis C, Yung AR, et al. Generalized and specific cognitive performance in clinical high-risk cohorts: a review highlighting potential vulnerability markers for psychosis. *Schizophr Bull* (2006) 32(3):538–55. doi: 10.1093/schbul/sbj077

51. Pukrop R, Ruhrmann S, Schultze-Lutter F, Bechdolf A, Brockhaus-Dumke A, Klosterkötter J. Neurocognitive indicators for a conversion to psychosis: comparison of patients in a potentially initial prodromal state who did or did not convert to a psychosis. *Schizophr Res* (2007) 92(1):116–25. doi: 10.1016/j.schres.2007.01.020

52. Goghari VM, Brett C, Tabraham P, Johns L, Valmaggia L, Broome M, et al. Spatial working memory ability in individuals at ultra high risk for psychosis. *J Psychiatr Res* (2014) 50:100–5. doi: 10.1016/j.jpsychires.2013.12.010

53. van Os J, Kenis G, Rutten BP. The environment and schizophrenia. *Nature* (2010) 468(7321):203–12. doi: 10.1038/nature09563

54. Samartzis L, Dima D, Fusar-Poli P, Kyriakopoulos M. White matter alterations in early stages of schizophrenia: a systematic review of diffusion tensor imaging studies. *J Neuroimaging* (2014) 24(2):101–10. doi: 10.1111/j.1552-6569.2012.00779.x

55. Carletti F, Woolley JB, Bhattacharyya S, Perez-Iglesias R, Fusar Poli P, Valmaggia L, et al. Alterations in white matter evident before the onset of psychosis. *Schizophr Bull* (2012) 38(6):1170–9. doi: 10.1093/schbul/sbs053

56. Nuechterlein KH, Subotnik KL, Green MF, Ventura J, Asarnow RF, Gitlin MJ, et al. Neurocognitive predictors of work outcome in recent-onset schizophrenia. *Schizophr Bull* (2011) 37(Suppl 2):S33–40. doi: 10.1093/schbul/sbr084

57. Firth J, Stubbs B, Rosenbaum S, Vancampfort D, Malchow B, Schuch F, et al. Aerobic exercise improves cognitive functioning in people with schizophrenia: a systematic review and meta-analysis. *Schizophr Bull* (2017) 43(3):546–56. doi: 101093/schbul/sbw115

58. Cannon TD, Chung Y, He G, Sun D, Jacobson A, van Erp TGM, et al. Progressive reduction in cortical thickness as psychosis develops: a multisite longitudinal neuroimaging study of youth at elevated clinical risk. *Biol Psychiatry* (2015) 77(2):147–57. doi: 10.1093/schbul/sbw115

59. McGivern RF, Andersen J, Byrd D, Mutter KL, Reilly J. Cognitive efficiency on a match to sample task decreases at the onset of puberty in children. *Brain Cognition* (2002) 50(1):73–89. doi: 10.1016/S0278-2626(02)00012-X

60. Simon AE, Grädel M, Cattapan-Ludewig K, Gruber K, Ballinari P, Roth B, et al. Cognitive functioning in at-risk mental states for psychosis and 2-year clinical outcome. *Schizophr Res* (2012) 142(1):108–15 doi: 10.1016/j.schres.2012.09.004

Doctoral Theses at The Faculty of Psychology, University of Bergen

1980	Allen, Hugh M., Dr. philos.	Parent-offspring interactions in willow grouse (Lagopus L. Lagopus).
1981	Myhrer, Trond, Dr. philos.	Behavioral Studies after selective disruption of hippocampal inputs in albino rats.
1982	Svebak, Sven, Dr. philos.	The significance of motivation for task-induced tonic physiological changes.
1983	Myhre, Grete, Dr. philos.	The Biopsychology of behavior in captive Willow ptarmigan.
	Eide, Rolf, Dr. philos.	PSYCHOSOCIAL FACTORS AND INDICES OF HEALTH RISKS. The relationship of psychosocial conditions to subjective complaints, arterial blood pressure, serum cholesterol, serum triglycerides and urinary catecholamines in middle aged populations in Western Norway.
	Værnes, Ragnar J., Dr. philos.	Neuropsychological effects of diving.
1984	Kolstad, Arnulf, Dr. philos.	Til diskusjonen om sammenhengen mellom sosiale forhold og psykiske strukturer. En epidemiologisk undersøkelse blant barn og unge.
	Løberg, Tor, Dr. philos.	Neuropsychological assessment in alcohol dependence.
1985	Hellesnes, Tore, Dr. philos.	Læring og problemløsning. En studie av den perseptuelle analysens betydning for verbal læring.
	Håland, Wenche, Dr. philos.	Psykoterapi: relasjon, utviklingsprosess og effekt.
1986	Hagtvet, Knut A., Dr. philos.	The construct of test anxiety: Conceptual and methodological issues.
	Jellestad, Finn K., Dr. philos.	Effects of neuron specific amygdala lesions on fear-motivated behavior in rats.
1987	Aarø, Leif E., Dr. philos.	Health behaviour and sosioeconomic Status. A survey among the adult population in Norway.
	Underlid, Kjell, Dr. philos.	Arbeidsløyse i psykososialt perspektiv.
	Laberg, Jon C., Dr. philos.	Expectancy and classical conditioning in alcoholics' craving.
	Vollmer, Fred, Dr. philos.	Essays on explanation in psychology.
	Ellertsen, Bjørn, Dr. philos.	Migraine and tension headache: Psychophysiology, personality and therapy.

1988	Kaufmann, Astrid, Dr. philos.	Antisosial atferd hos ungdom. En studie av psykologiske determinanter.
	Mykletun, Reidar J., Dr. philos.	Teacher stress: personality, work-load and health.
	Havik, Odd E., Dr. philos.	After the myocardial infarction: A medical and psychological study with special emphasis on perceived illness.
1989	Bråten, Stein, Dr. philos.	Menneskedyaden. En teoretisk tese om sinnets dialogiske natur med informasjons- og utviklingspsykologiske implikasjoner sammenholdt med utvalgte spedbarnsstudier.
	Wold, Bente, Dr. psychol.	Lifestyles and physical activity. A theoretical and empirical analysis of socialization among children and adolescents.
1990	Flaten, Magne A., Dr. psychol.	The role of habituation and learning in reflex modification.
1991	Alsaker, Françoise D., Dr. philos.	Global negative self-evaluations in early adolescence.
	Kraft, Pål, Dr. philos.	AIDS prevention in Norway. Empirical studies on diffusion of knowledge, public opinion, and sexual behaviour.
	Endresen, Inger M., Dr. philos.	Psychoimmuniological stress markers in working life.
	Faleide, Asbjørn O., Dr. philos.	Asthma and allergy in childhood. Psychosocial and psychotherapeutic problems.
1992	Dalen, Knut, Dr. philos.	Hemispheric asymmetry and the Dual-Task Paradigm: An experimental approach.
	Bø, Inge B., Dr. philos.	Ungdoms sosiale økologi. En undersøkelse av 14-16 åringers sosiale nettverk.
	Nivison, Mary E., Dr. philos.	The relationship between noise as an experimental and environmental stressor, physiological changes and psychological factors.
	Torgersen, Anne M., Dr. philos.	Genetic and environmental influence on temperamental behaviour. A longitudinal study of twins from infancy to adolescence.
1993	Larsen, Svein, Dr. philos.	Cultural background and problem drinking.
	Nordhus, Inger Hilde, Dr. philos.	Family caregiving. A community psychological study with special emphasis on clinical interventions.
	Thuen, Frode, Dr. psychol.	Accident-related behaviour among children and young adolescents: Prediction and prevention.
	Solheim, Ragnar, Dr. philos.	Spesifikke lærevansker. Diskrepanskriteriet anvendt i seleksjonsmetodikk.

	Johnsen, Bjørn Helge, Dr. psychol.	Brain assymetry and facial emotional expressions: Conditioning experiments.
1994	Tønnessen, Finn E., Dr. philos.	The etiology of Dyslexia.
	Kvale, Gerd, Dr. psychol.	Psychological factors in anticipatory nausea and vomiting in cancer chemotherapy.
	Asbjørnsen, Arve E., Dr. psychol.	Structural and dynamic factors in dichotic listening: An interactional model.
	Bru, Edvin, Dr. philos.	The role of psychological factors in neck, shoulder and low back pain among female hospitale staff.
	Braathen, Eli T., Dr. psychol.	Prediction of exellence and discontinuation in different types of sport: The significance of motivation and EMG.
	Johannessen, Birte F., Dr. philos.	Det flytende kjønnet. Om lederskap, politikk og identitet.
1995	Sam, David L., Dr. psychol.	Acculturation of young immigrants in Norway: A psychological and socio-cultural adaptation.
	Bjaalid, Inger-Kristin, Dr. philos.	Component processes in word recognition.
	Martinsen, Øyvind, Dr. philos.	Cognitive style and insight.
	Nordby, Helge, Dr. philos.	Processing of auditory deviant events: Mismatch negativity of event-related brain potentials.
	Raaheim, Arild, Dr. philos.	Health perception and health behaviour, theoretical considerations, empirical studies, and practical implications.
	Seltzer, Wencke J., Dr. philos.	Studies of Psychocultural Approach to Families in Therapy.
	Brun, Wibecke, Dr. philos.	Subjective conceptions of uncertainty and risk.
	Aas, Henrik N., Dr. psychol.	Alcohol expectancies and socialization: Adolescents learning to drink.
	Bjørkly, Stål, Dr. psychol.	Diagnosis and prediction of intra-institutional aggressive behaviour in psychotic patients
1996	Anderssen, Norman, Dr. psychol.	Physical activity of young people in a health perspective: Stability, change and social influences.
	Sandal, Gro Mjeldheim, Dr. psychol.	Coping in extreme environments: The role of personality.
	Strumse, Einar, Dr. philos.	The psychology of aesthetics: explaining visual preferences for agrarian landscapes in Western Norway.
	Hestad, Knut, Dr. philos.	Neuropsychological deficits in HIV-1 infection.

	Lugoe, L.Wycliffe, Dr. philos.	Prediction of Tanzanian students' HIV risk and preventive behaviours
	Sandvik, B. Gunnhild, Dr. philos.	Fra distriktsjordmor til institusjonsjordmor. Fremveksten av en profesjon og en profesjonsutdanning
	Lie, Gro Therese, Dr. psychol.	The disease that dares not speak its name: Studies on factors of importance for coping with HIV/AIDS in Northern Tanzania
	Øygard, Lisbet, Dr. philos.	Health behaviors among young adults. A psychological and sociological approach
	Stormark, Kjell Morten, Dr. psychol.	Emotional modulation of selective attention: Experimental and clinical evidence.
	Einarsen, Ståle, Dr. psychol.	Bullying and harassment at work: epidemiological and psychosocial aspects.
1997	Knivsberg, Ann-Mari, Dr. philos.	Behavioural abnormalities and childhood psychopathology: Urinary peptide patterns as a potential tool in diagnosis and remediation.
	Eide, Arne H., Dr. philos.	Adolescent drug use in Zimbabwe. Cultural orientation in a global-local perspective and use of psychoactive substances among secondary school students.
	Sørensen, Marit, Dr. philos.	The psychology of initiating and maintaining exercise and diet behaviour.
	Skjæveland, Oddvar, Dr. psychol.	Relationships between spatial-physical neighborhood attributes and social relations among neighbors.
	Zewdie, Teka, Dr. philos.	Mother-child relational patterns in Ethiopia. Issues of developmental theories and intervention programs.
	Wilhelmsen, Britt Unni, Dr. philos.	Development and evaluation of two educational programmes designed to prevent alcohol use among adolescents.
	Manger, Terje, Dr. philos.	Gender differences in mathematical achievement among Norwegian elementary school students.
1998 V	Lindstrøm, Torill Christine, Dr. philos.	«Good Grief»: Adapting to Bereavement.
	Skogstad, Anders, Dr. philos.	Effects of leadership behaviour on job satisfaction, health and efficiency.
	Haldorsen, Ellen M. Håland, Dr. psychol.	Return to work in low back pain patients.
	Besemer, Susan P., Dr. philos.	Creative Product Analysis: The Search for a Valid Model for Understanding Creativity in Products.

H	Winje, Dagfinn, Dr. psychol.	Psychological adjustment after severe trauma. A longitudinal study of adults' and children's posttraumatic reactions and coping after the bus accident in Måbødalen, Norway 1988.
	Vosburg, Suzanne K., Dr. philos.	The effects of mood on creative problem solving.
	Eriksen, Hege R., Dr. philos.	Stress and coping: Does it really matter for subjective health complaints?
	Jakobsen, Reidar, Dr. psychol.	Empiriske studier av kunnskap og holdninger om hiv/aids og den normative seksuelle utvikling i ungdomsårene.
1999 V	Mikkelsen, Aslaug, Dr. philos.	Effects of learning opportunities and learning climate on occupational health.
	Samdal, Oddrun, Dr. philos.	The school environment as a risk or resource for students' health-related behaviours and subjective well-being.
	Friestad, Christine, Dr. philos.	Social psychological approaches to smoking.
	Ekeland, Tor-Johan, Dr. philos.	Meining som medisin. Ein analyse av placebofenomenet og implikasjoner for terapi og terapeutiske teoriar.
H	Saban, Sara, Dr. psychol.	Brain Asymmetry and Attention: Classical Conditioning Experiments.
	Carlsten, Carl Thomas, Dr. philos.	God lesing – God læring. En aksjonsrettet studie av undervisning i fagtekstlesing.
	Dundas, Ingrid, Dr. psychol.	Functional and dysfunctional closeness. Family interaction and children's adjustment.
	Engen, Liv, Dr. philos.	Kartlegging av leseferdighet på småskoletrinnet og vurdering av faktorer som kan være av betydning for optimal leseutvikling.
2000 V	Hovland, Ole Johan, Dr. philos.	Transforming a self-preserving "alarm" reaction into a self-defeating emotional response: Toward an integrative approach to anxiety as a human phenomenon.
	Lillejord, Sølvi, Dr. philos.	Handlingsrasjonalitet og spesialundervisning. En analyse av aktørperspektiver.
	Sandell, Ove, Dr. philos.	Den varme kunnskapen.
	Oftedal, Marit Petersen, Dr. philos.	Diagnostisering av ordavkodingsvansker: En prosessanalytisk tilnærmingsmåte.
H	Sandbak, Tone, Dr. psychol.	Alcohol consumption and preference in the rat: The significance of individual differences and relationships to stress pathology
	Eid, Jarle, Dr. psychol.	Early predictors of PTSD symptom reporting; The significance of contextual and individual factors.

2001 **V**	Skinstad, Anne Helene, Dr. philos.	Substance dependence and borderline personality disorders.
	Binder, Per-Einar, Dr. psychol.	Individet og den meningsbærende andre. En teoretisk undersøkelse av de mellommenneskelige forutsetningene for psykisk liv og utvikling med utgangspunkt i Donald Winnicotts teori.
	Roald, Ingvild K., Dr. philos.	Building of concepts. A study of Physics concepts of Norwegian deaf students.
H	Fekadu, Zelalem W., Dr. philos.	Predicting contraceptive use and intention among a sample of adolescent girls. An application of the theory of planned behaviour in Ethiopian context.
	Melesse, Fantu, Dr. philos.	The more intelligent and sensitive child (MISC) mediational intervention in an Ethiopian context: An evaluation study.
	Råheim, Målfrid, Dr. philos.	Kvinners kroppserfaring og livssammenheng. En fenomenologisk – hermeneutisk studie av friske kvinner og kvinner med kroniske muskelsmerter.
	Engelsen, Birthe Kari, Dr. psychol.	Measurement of the eating problem construct.
	Lau, Bjørn, Dr. philos.	Weight and eating concerns in adolescence.
2002 **V**	Ihlebæk, Camilla, Dr. philos.	Epidemiological studies of subjective health complaints.
	Rosén, Gunnar O. R., Dr. philos.	The phantom limb experience. Models for understanding and treatment of pain with hypnosis.
	Høines, Marit Johnsen, Dr. philos.	Fleksible språkrom. Matematikklæring som tekstutvikling.
	Anthun, Roald Andor, Dr. philos.	School psychology service quality. Consumer appraisal, quality dimensions, and collaborative improvement potential
	Pallesen, Ståle, Dr. psychol.	Insomnia in the elderly. Epidemiology, psychological characteristics and treatment.
	Midthassel, Unni Vere, Dr. philos.	Teacher involvement in school development activity. A study of teachers in Norwegian compulsory schools
	Kallestad, Jan Helge, Dr. philos.	Teachers, schools and implementation of the Olweus Bullying Prevention Program.
H	Ofte, Sonja Helgesen, Dr. psychol.	Right-left discrimination in adults and children.
	Netland, Marit, Dr. psychol.	Exposure to political violence. The need to estimate our estimations.

	Diseth, Åge, Dr. psychol.	Approaches to learning: Validity and prediction of academic performance.
	Bjuland, Raymond, Dr. philos.	Problem solving in geometry. Reasoning processes of student teachers working in small groups: A dialogical approach.
2003 **V**	Arefjord, Kjersti, Dr. psychol.	After the myocardial infarction – the wives' view. Short- and long-term adjustment in wives of myocardial infarction patients.
	Ingjaldsson, Jón Þorvaldur, Dr. psychol.	Unconscious Processes and Vagal Activity in Alcohol Dependency.
	Holden, Børge, Dr. philos.	Følger av atferdsanalytiske forklaringer for atferdsanalysens tilnærming til utforming av behandling.
	Holsen, Ingrid, Dr. philos.	Depressed mood from adolescence to 'emerging adulthood'. Course and longitudinal influences of body image and parent-adolescent relationship.
	Hammar, Åsa Karin, Dr. psychol.	Major depression and cognitive dysfunction- An experimental study of the cognitive effort hypothesis.
	Sprugevica, Ieva, Dr. philos.	The impact of enabling skills on early reading acquisition.
	Gabrielsen, Egil, Dr. philos.	LESE FOR LIVET. Lesekompetansen i den norske voksenbefolkningen sett i lys av visjonen om en enhetsskole.
H	Hansen, Anita Lill, Dr. psychol.	The influence of heart rate variability in the regulation of attentional and memory processes.
	Dyregrov, Kari, Dr. philos.	The loss of child by suicide, SIDS, and accidents: Consequences, needs and provisions of help.
2004 **V**	Torsheim, Torbjørn, Dr. psychol.	Student role strain and subjective health complaints: Individual, contextual, and longitudinal perspectives.
	Haugland, Bente Storm Mowatt Dr. psychol.	Parental alcohol abuse. Family functioning and child adjustment.
	Milde, Anne Marita, Dr. psychol.	Ulcerative colitis and the role of stress. Animal studies of psychobiological factors in relationship to experimentally induced colitis.
	Stornes, Tor, Dr. philos.	Socio-moral behaviour in sport. An investigation of perceptions of sportspersonship in handball related to important factors of socio-moral influence.
	Mæhle, Magne, Dr. philos.	Re-inventing the child in family therapy: An investigation of the relevance and applicability of theory and research in child development for family therapy involving children.
	Kobbeltvedt, Therese, Dr. psychol.	Risk and feelings: A field approach.
2004 **H**	Thomsen, Tormod, Dr. psychol.	Localization of attention in the brain.

	Løberg, Else-Marie, Dr. psychol.	Functional laterality and attention modulation in schizophrenia: Effects of clinical variables.
	Kyrkjebø, Jane Mikkelsen, Dr. philos.	Learning to improve: Integrating continuous quality improvement learning into nursing education.
	Laumann, Karin, Dr. psychol.	Restorative and stress-reducing effects of natural environments: Experiencal, behavioural and cardiovascular indices.
	Holgersen, Helge, PhD	Mellom oss - Essay i relasjonell psykoanalyse.
2005 V	Hetland, Hilde, Dr. psychol.	Leading to the extraordinary? Antecedents and outcomes of transformational leadership.
	Iversen, Anette Christine, Dr. philos.	Social differences in health behaviour: the motivational role of perceived control and coping.
2005 H	Mathisen, Gro Ellen, PhD	Climates for creativity and innovation: Definitions, measurement, predictors and consequences.
	Sævi, Tone, Dr. philos.	Seeing disability pedagogically – The lived experience of disability in the pedagogical encounter.
	Wiium, Nora, PhD	Intrapersonal factors, family and school norms: combined and interactive influence on adolescent smoking behaviour.
	Kanagaratnam, Pushpa, PhD	Subjective and objective correlates of Posttraumatic Stress in immigrants/refugees exposed to political violence.
	Larsen, Torill M. B. , PhD	Evaluating principals` and teachers` implementation of Second Step. A case study of four Norwegian primary schools.
	Bancila, Delia, PhD	Psychosocial stress and distress among Romanian adolescents and adults.
2006 V	Hillestad, Torgeir Martin, Dr. philos.	Normalitet og avvik. Forutsetninger for et objektivt psykopatologisk avviksbegrep. En psykologisk, sosial, erkjennelsesteoretisk og teorihistorisk framstilling.
	Nordanger, Dag Øystein, Dr. psychol.	Psychosocial discourses and responses to political violence in post-war Tigray, Ethiopia.
	Rimol, Lars Morten, PhD	Behavioral and fMRI studies of auditory laterality and speech sound processing.
	Krumsvik, Rune Johan, Dr. philos.	ICT in the school. ICT-initiated school development in lower secondary school.
	Norman, Elisabeth, Dr. psychol.	Gut feelings and unconscious thought: An exploration of fringe consiousness in implicit cognition.

	Israel, K Pravin, Dr. psychol.	Parent involvement in the mental health care of children and adolescents. Emperical studies from clinical care setting.
	Glasø, Lars, PhD	Affects and emotional regulation in leader-subordinate relationships.
	Knutsen, Ketil, Dr. philos.	HISTORIER UNGDOM LEVER – En studie av hvordan ungdommer bruker historie for å gjøre livet meningsfullt.
	Matthiesen, Stig Berge, PhD	Bullying at work. Antecedents and outcomes.
2006 H	Gramstad, Arne, PhD	Neuropsychological assessment of cognitive and emotional functioning in patients with epilepsy.
	Bendixen, Mons, PhD	Antisocial behaviour in early adolescence: Methodological and substantive issues.
	Mrumbi, Khalifa Maulid, PhD	Parental illness and loss to HIV/AIDS as experienced by AIDS orphans aged between 12-17 years from Temeke District, Dar es Salaam, Tanzania: A study of the children's psychosocial health and coping responses.
	Hetland, Jørn, Dr. psychol.	The nature of subjective health complaints in adolescence: Dimensionality, stability, and psychosocial predictors
	Kakoko, Deodatus Conatus Vitalis, PhD	Voluntary HIV counselling and testing service uptake among primary school teachers in Mwanza, Tanzania: assessment of socio-demographic, psychosocial and socio-cognitive aspects
	Mykletun, Arnstein, Dr. psychol.	Mortality and work-related disability as long-term consequences of anxiety and depression: Historical cohort designs based on the HUNT-2 study
	Sivertsen, Børge, PhD	Insomnia in older adults. Consequences, assessment and treatment.
2007 V	Singhammer, John, Dr. philos.	Social conditions from before birth to early adulthood – the influence on health and health behaviour
	Janvin, Carmen Ani Cristea, PhD	Cognitive impairment in patients with Parkinson's disease: profiles and implications for prognosis
	Braarud, Hanne Cecilie, Dr.psychol.	Infant regulation of distress: A longitudinal study of transactions between mothers and infants
	Tveito, Torill Helene, PhD	Sick Leave and Subjective Health Complaints
	Magnussen, Liv Heide, PhD	Returning disability pensioners with back pain to work
	Thuen, Elin Marie, Dr.philos.	Learning environment, students' coping styles and emotional and behavioural problems. A study of Norwegian secondary school students.

	Solberg, Ole Asbjørn, PhD	Peacekeeping warriors – A longitudinal study of Norwegian peacekeepers in Kosovo
2007 H	Søreide, Gunn Elisabeth, Dr.philos.	Narrative construction of teacher identity
	Svensen, Erling, PhD	WORK & HEALTH. Cognitive Activation Theory of Stress applied in an organisational setting.
	Øverland, Simon Nygaard, PhD	Mental health and impairment in disability benefits. Studies applying linkages between health surveys and administrative registries.
	Eichele, Tom, PhD	Electrophysiological and Hemodynamic Correlates of Expectancy in Target Processing
	Børhaug, Kjetil, Dr.philos.	Oppseding til demokrati. Ein studie av politisk oppseding i norsk skule.
	Eikeland, Thorleif, Dr.philos.	Om å vokse opp på barnehjem og på sykehus. En undersøkelse av barnehjemsbarns opplevelser på barnehjem sammenholdt med sanatoriebarns beskrivelse av langvarige sykehusopphold – og et forsøk på forklaring.
	Wadel, Carl Cato, Dr.philos.	Medarbeidersamhandling og medarbeiderledelse i en lagbasert organisasjon
	Vinje, Hege Forbech, PhD	Thriving despite adversity: Job engagement and self-care among community nurses
	Noort, Maurits van den, PhD	Working memory capacity and foreign language acquisition
2008 V	Breivik, Kyrre, Dr.psychol.	The Adjustment of Children and Adolescents in Different Post-Divorce Family Structures. A Norwegian Study of Risks and Mechanisms.
	Johnsen, Grethe E., PhD	Memory impairment in patients with posttraumatic stress disorder
	Sætrevik, Bjørn, PhD	Cognitive Control in Auditory Processing
	Carvalhosa, Susana Fonseca, PhD	Prevention of bullying in schools: an ecological model
2008 H	Brønnick, Kolbjørn Selvåg	Attentional dysfunction in dementia associated with Parkinson's disease.
	Posserud, Maj-Britt Rocio	Epidemiology of autism spectrum disorders
	Haug, Ellen	Multilevel correlates of physical activity in the school setting
	Skjerve, Arvid	Assessing mild dementia – a study of brief cognitive tests.

	Kjønniksen, Lise	The association between adolescent experiences in physical activity and leisure time physical activity in adulthood: a ten year longitudinal study
	Gundersen, Hilde	The effects of alcohol and expectancy on brain function
	Omvik, Siri	Insomnia – a night and day problem
2009 V	Molde, Helge	Pathological gambling: prevalence, mechanisms and treatment outcome.
	Foss, Else	Den omsorgsfulle væremåte. En studie av voksnes væremåte i forhold til barn i barnehagen.
	Westrheim, Kariane	Education in a Political Context: A study of Konwledge Processes and Learning Sites in the PKK.
	Wehling, Eike	Cognitive and olfactory changes in aging
	Wangberg, Silje C.	Internet based interventions to support health behaviours: The role of self-efficacy.
	Nielsen, Morten B.	Methodological issues in research on workplace bullying. Operationalisations, measurements and samples.
	Sandu, Anca Larisa	MRI measures of brain volume and cortical complexity in clinical groups and during development.
	Guribye, Eugene	Refugees and mental health interventions
	Sørensen, Lin	Emotional problems in inattentive children – effects on cognitive control functions.
	Tjomsland, Hege E.	Health promotion with teachers. Evaluation of the Norwegian Network of Health Promoting Schools: Quantitative and qualitative analyses of predisposing, reinforcing and enabling conditions related to teacher participation and program sustainability.
	Helleve, Ingrid	Productive interactions in ICT supported communities of learners
2009 H	Skorpen, Aina Øye, Christine	Dagliglivet i en psykiatrisk institusjon: En analyse av miljøterapeutiske praksiser
	Andreassen, Cecilie Schou	WORKAHOLISM – Antecedents and Outcomes
	Stang, Ingun	Being in the same boat: An empowerment intervention in breast cancer self-help groups
	Sequeira, Sarah Dorothee Dos Santos	The effects of background noise on asymmetrical speech perception
	Kleiven, Jo, dr.philos.	The Lillehammer scales: Measuring common motives for vacation and leisure behavior
	Jónsdóttir, Guðrún	Dubito ergo sum? Ni jenter møter naturfaglig kunnskap.

	Hove, Oddbjørn	Mental health disorders in adults with intellectual disabilities - Methods of assessment and prevalence of mental health disorders and problem behaviour
	Wageningen, Heidi Karin van	The role of glutamate on brain function
	Bjørkvik, Jofrid	God nok? Selvaktelse og interpersonlig fungering hos pasienter innen psykisk helsevern: Forholdet til diagnoser, symptomer og behandlingsutbytte
	Andersson, Martin	A study of attention control in children and elderly using a forced-attention dichotic listening paradigm
	Almås, Aslaug Grov	Teachers in the Digital Network Society: Visions and Realities. A study of teachers' experiences with the use of ICT in teaching and learning.
	Ulvik, Marit	Lærerutdanning som danning? Tre stemmer i diskusjonen
2010 V	Skår, Randi	Læringsprosesser i sykepleieres profesjonsutøvelse. En studie av sykepleieres læringserfaringer.
	Roald, Knut	Kvalitetsvurdering som organisasjonslæring mellom skole og skoleeigar
	Lunde, Linn-Heidi	Chronic pain in older adults. Consequences, assessment and treatment.
	Danielsen, Anne Grete	Perceived psychosocial support, students' self-reported academic initiative and perceived life satisfaction
	Hysing, Mari	Mental health in children with chronic illness
	Olsen, Olav Kjellevold	Are good leaders moral leaders? The relationship between effective military operational leadership and morals
	Riese, Hanne	Friendship and learning. Entrepreneurship education through mini-enterprises.
	Holthe, Asle	Evaluating the implementation of the Norwegian guidelines for healthy school meals: A case study involving three secondary schools
H	Hauge, Lars Johan	Environmental antecedents of workplace bullying: A multi-design approach
	Bjørkelo, Brita	Whistleblowing at work: Antecedents and consequences
	Reme, Silje Endresen	Common Complaints – Common Cure? Psychiatric comorbidity and predictors of treatment outcome in low back pain and irritable bowel syndrome
	Helland, Wenche Andersen	Communication difficulties in children identified with psychiatric problems

	Beneventi, Harald	Neuronal correlates of working memory in dyslexia
	Thygesen, Elin	Subjective health and coping in care-dependent old persons living at home
	Aanes, Mette Marthinussen	Poor social relationships as a threat to belongingness needs. Interpersonal stress and subjective health complaints: Mediating and moderating factors.
	Anker, Morten Gustav	Client directed outcome informed couple therapy
	Bull, Torill	Combining employment and child care: The subjective well-being of single women in Scandinavia and in Southern Europe
	Viig, Nina Grieg	Tilrettelegging for læreres deltakelse i helsefremmende arbeid. En kvalitativ og kvantitativ analyse av sammenhengen mellom organisatoriske forhold og læreres deltakelse i utvikling og implementering av Europeisk Nettverk av Helsefremmende Skoler i Norge
	Wolff, Katharina	To know or not to know? Attitudes towards receiving genetic information among patients and the general public.
	Ogden, Terje, dr.philos.	Familiebasert behandling av alvorlige atferdsproblemer blant barn og ungdom. Evaluering og implementering av evidensbaserte behandlingsprogrammer i Norge.
	Solberg, Mona Elin	Self-reported bullying and victimisation at school: Prevalence, overlap and psychosocial adjustment.
2011 V	Bye, Hege Høivik	Self-presentation in job interviews. Individual and cultural differences in applicant self-presentation during job interviews and hiring managers' evaluation
	Notelaers, Guy	Workplace bullying. A risk control perspective.
	Moltu, Christian	Being a therapist in difficult therapeutic impasses. A hermeneutic phenomenological analysis of skilled psychotherapists' experiences, needs, and strategies in difficult therapies ending well.
	Myrseth, Helga	Pathological Gambling - Treatment and Personality Factors
	Schanche, Elisabeth	From self-criticism to self-compassion. An empirical investigation of hypothesized change prosesses in the Affect Phobia Treatment Model of short-term dynamic psychotherapy for patients with Cluster C personality disorders.
	Våpenstad, Eystein Victor, dr.philos.	Det tempererte nærvær. En teoretisk undersøkelse av psykoterapautens subjektivitet i psykoanalyse og psykoanalytisk psykoterapi.

	Haukebø, Kristin	Cognitive, behavioral and neural correlates of dental and intra-oral injection phobia. Results from one treatment and one fMRI study of randomized, controlled design.
	Harris, Anette	Adaptation and health in extreme and isolated environments. From 78°N to 75°S.
	Bjørknes, Ragnhild	Parent Management Training-Oregon Model: intervention effects on maternal practice and child behavior in ethnic minority families
	Mamen, Asgeir	Aspects of using physical training in patients with substance dependence and additional mental distress
	Espevik, Roar	Expert teams: Do shared mental models of team members make a difference
	Haara, Frode Olav	Unveiling teachers' reasons for choosing practical activities in mathematics teaching
2011 H	Hauge, Hans Abraham	How can employee empowerment be made conducive to both employee health and organisation performance? An empirical investigation of a tailor-made approach to organisation learning in a municipal public service organisation.
	Melkevik, Ole Rogstad	Screen-based sedentary behaviours: pastimes for the poor, inactive and overweight? A cross-national survey of children and adolescents in 39 countries.
	Vøllestad, Jon	Mindfulness-based treatment for anxiety disorders. A quantitative review of the evidence, results from a randomized controlled trial, and a qualitative exploration of patient experiences.
	Tolo, Astrid	Hvordan blir lærerkompetanse konstruert? En kvalitativ studie av PPU-studenters kunnskapsutvikling.
	Saus, Evelyn-Rose	Training effectiveness: Situation awareness training in simulators
	Nordgreen, Tine	Internet-based self-help for social anxiety disorder and panic disorder. Factors associated with effect and use of self-help.
	Munkvold, Linda Helen	Oppositional Defiant Disorder: Informant discrepancies, gender differences, co-occuring mental health problems and neurocognitive function.
	Christiansen, Øivin	Når barn plasseres utenfor hjemmet: beslutninger, forløp og relasjoner. Under barnevernets (ved)tak.
	Brunborg, Geir Scott	Conditionability and Reinforcement Sensitivity in Gambling Behaviour
	Hystad, Sigurd William	Measuring Psychological Resiliency: Validation of an Adapted Norwegian Hardiness Scale

2012 V	Roness, Dag	Hvorfor bli lærer? Motivasjon for utdanning og utøving.
	Fjermestad, Krister Westlye	The therapeutic alliance in cognitive behavioural therapy for youth anxiety disorders
	Jenssen, Eirik Sørnes	Tilpasset opplæring i norsk skole: politikeres, skoleledseres og læreres handlingsvalg
	Saksvik-Lehouillier, Ingvild	Shift work tolerance and adaptation to shift work among offshore workers and nurses
	Johansen, Venke Frederike	Når det intime blir offentlig. Om kvinners åpenhet om brystkreft og om markedsføring av brystkreftsaken.
	Herheim, Rune	Pupils collaborating in pairs at a computer in mathematics learning: investigating verbal communication patterns and qualities
	Vie, Tina Løkke	Cognitive appraisal, emotions and subjective health complaints among victims of workplace bullying: A stress-theoretical approach
	Jones, Lise Øen	Effects of reading skills, spelling skills and accompanying efficacy beliefs on participation in education. A study in Norwegian prisons.
2012 H	Danielsen, Yngvild Sørebø	Childhood obesity – characteristics and treatment. Psychological perspectives.
	Horverak, Jøri Gytre	Sense or sensibility in hiring processes. Interviewee and interviewer characteristics as antecedents of immigrant applicants' employment probabilities. An experimental approach.
	Jøsendal, Ola	Development and evaluation of BE smokeFREE, a school-based smoking prevention program
	Osnes, Berge	Temporal and Posterior Frontal Involvement in Auditory Speech Perception
	Drageset, Sigrunn	Psychological distress, coping and social support in the diagnostic and preoperative phase of breast cancer
	Aasland, Merethe Schanke	Destructive leadership: Conceptualization, measurement, prevalence and outcomes
	Bakibinga, Pauline	The experience of job engagement and self-care among Ugandan nurses and midwives
	Skogen, Jens Christoffer	Foetal and early origins of old age health. Linkage between birth records and the old age cohort of the Hordaland Health Study (HUSK)
	Leversen, Ingrid	Adolescents' leisure activity participation and their life satisfaction: The role of demographic characteristics and psychological processes

	Hanss, Daniel	Explaining sustainable consumption: Findings from cross-sectional and intervention approaches
	Rød, Per Arne	Barn i klem mellom foreldrekonflikter og samfunnsmessig beskyttelse
2013 V	Mentzoni, Rune Aune	Structural Characteristics in Gambling
	Knudsen, Ann Kristin	Long-term sickness absence and disability pension award as consequences of common mental disorders. Epidemiological studies using a population-based health survey and official ill health benefit registries.
	Strand, Mari	Emotional information processing in recurrent MDD
	Veseth, Marius	Recovery in bipolar disorder. A reflexive-collaborative exploration of the lived experiences of healing and growth when battling a severe mental illness
	Mæland, Silje	Sick leave for patients with severe subjective health complaints. Challenges in general practice.
	Mjaaland, Thera	At the frontiers of change? Women and girls' pursuit of education in north-western Tigray, Ethiopia
	Odéen, Magnus	Coping at work. The role of knowledge and coping expectancies in health and sick leave.
	Hynninen, Kia Minna Johanna	Anxiety, depression and sleep disturbance in chronic obstructive pulmonary disease (COPD). Associations, prevalence and effect of psychological treatment.
	Flo, Elisabeth	Sleep and health in shift working nurses
	Aasen, Elin Margrethe	From paternalism to patient participation? The older patients undergoing hemodialysis, their next of kin and the nurses: a discursive perspective on perception of patient participation in dialysis units
	Ekornås, Belinda	Emotional and Behavioural Problems in Children: Self-perception, peer relationships, and motor abilities
	Corbin, J. Hope	North-South Partnerships for Health: Key Factors for Partnership Success from the Perspective of the KIWAKKUKI
	Birkeland, Marianne Skogbrott	Development of global self-esteem: The transition from adolescence to adulthood
2013 H	Gianella-Malca, Camila	Challenges in Implementing the Colombian Constitutional Court's Health-Care System Ruling of 2008
	Hovland, Anders	Panic disorder – Treatment outcomes and psychophysiological concomitants
	Mortensen, Øystein	The transition to parenthood – Couple relationships put to the test

	Årdal, Guro	Major Depressive Disorder – a Ten Year Follow-up Study. Inhibition, Information Processing and Health Related Quality of Life
	Johansen, Rino Bandlitz	The impact of military identity on performance in the Norwegian armed forces
	Bøe, Tormod	Socioeconomic Status and Mental Health in Children and Adolescents
2014 V	Nordmo, Ivar	Gjennom nåløyet – studenters læringserfaringer i psykologutdanningen
	Dovran, Anders	Childhood Trauma and Mental Health Problems in Adult Life
	Hegelstad, Wenche ten Velden	Early Detection and Intervention in Psychosis: A Long-Term Perspective
	Urheim, Ragnar	Forståelse av pasientaggresjon og forklaringer på nedgang i voldsrate ved Regional sikkerhetsavdeling, Sandviken sykehus
	Kinn, Liv Grethe	Round-Trips to Work. Qualitative studies of how persons with severe mental illness experience work integration.
	Rød, Anne Marie Kinn	Consequences of social defeat stress for behaviour and sleep. Short-term and long-term assessments in rats.
	Nygård, Merethe	Schizophrenia – Cognitive Function, Brain Abnormalities, and Cannabis Use
	Tjora, Tore	Smoking from adolescence through adulthood: the role of family, friends, depression and socioeconomic status. Predictors of smoking from age 13 to 30 in the "The Norwegian Longitudinal Health Behaviour Study" (NLHB)
	Vangsnes, Vigdis	The Dramaturgy and Didactics of Computer Gaming. A Study of a Medium in the Educational Context of Kindergartens.
	Nordahl, Kristin Berg	Early Father-Child Interaction in a Father-Friendly Context: Gender Differences, Child Outcomes, and Protective Factors related to Fathers' Parenting Behaviors with One-year-olds
2014 H	Sandvik, Asle Makoto	Psychopathy – the heterogenety of the construct
	Skotheim, Siv	Maternal emotional distress and early mother-infant interaction: Psychological, social and nutritional contributions
	Halleland, Helene Barone	Executive Functioning in adult Attention Deficit Hyperactivity Disorder (ADHD). From basic mechanisms to functional outcome.
	Halvorsen, Kirsti Vindal	Partnerskap i lærerutdanning, sett fra et økologisk perspektiv

	Solbue, Vibeke	Dialogen som visker ut kategorier. En studie av hvilke erfaringer innvandrerungdommer og norskfødte med innvandrerforeldre har med videregående skole. Hva forteller ungdommenes erfaringer om videregående skoles håndtering av etniske ulikheter?
	Kvalevaag, Anne Lise	Fathers' mental health and child development. The predictive value of fathers' psychological distress during pregnancy for the social, emotional and behavioural development of their children
	Sandal, Ann Karin	Ungdom og utdanningsval. Om elevar sine opplevingar av val og overgangsprosessar.
	Haug, Thomas	Predictors and moderators of treatment outcome from high- and low-intensity cognitive behavioral therapy for anxiety disorders. Association between patient and process factors, and the outcome from guided self-help, stepped care, and face-to-face cognitive behavioral therapy.
	Sjølie, Hege	Experiences of Members of a Crisis Resolution Home Treatment Team. Personal history, professional role and emotional support in a CRHT team.
	Falkenberg, Liv Eggset	Neuronal underpinnings of healthy and dysfunctional cognitive control
	Mrdalj, Jelena	The early life condition. Importance for sleep, circadian rhythmicity, behaviour and response to later life challenges
	Hesjedal, Elisabeth	Tverrprofesjonelt samarbeid mellom skule og barnevern: Kva kan støtte utsette barn og unge?
2015 V	Hauken, May Aasebø	«*The cancer treatment was only half the work!*» A Mixed-Method Study of Rehabilitation among Young Adult Cancer Survivors
	Ryland, Hilde Katrin	Social functioning and mental health in children: the influence of chronic illness and intellectual function
	Rønsen, Anne Kristin	Vurdering som profesjonskompetanse. Refleksjonsbasert utvikling av læreres kompetanse i formativ vurdering
	Hoff, Helge Andreas	Thinking about Symptoms of Psychopathy in Norway: Content Validation of the Comprehensive Assessment of Psychopathic Personality (CAPP) Model in a Norwegian Setting
	Schmid, Marit Therese	Executive Functioning in recurrent- and first episode Major Depressive Disorder. Longitudinal studies
	Sand, Liv	Body Image Distortion and Eating Disturbances in Children and Adolescents
	Matanda, Dennis Juma	Child physical growth and care practices in Kenya: Evidence from Demographic and Health Surveys

	Amugsi, Dickson Abanimi	Child care practices, resources for care, and nutritional outcomes in Ghana: Findings from Demographic and Health Surveys
	Jakobsen, Hilde	The good beating: Social norms supporting men's partner violence in Tanzania
	Sagoe, Dominic	Nonmedical anabolic-androgenic steroid use: Prevalence, attitudes, and social perception
	Eide, Helene Marie Kjærgård	Narrating the relationship between leadership and learning outcomes. A study of public narratives in the Norwegian educational sector.
2015 H	Wubs, Annegreet Gera	Intimate partner violence among adolescents in South Africa and Tanzania
	Hjelmervik, Helene Susanne	Sex and sex-hormonal effects on brain organization of fronto-parietal networks
	Dahl, Berit Misund	The meaning of professional identity in public health nursing
	Røykenes, Kari	Testangst hos sykepleierstudenter: «Alternativ behandling»
	Bless, Josef Johann	The smartphone as a research tool in psychology. Assessment of language lateralization and training of auditory attention.
	Løvvik, Camilla Margrethe Sigvaldsen	Common mental disorders and work participation – the role of return-to-work expectations
	Lehmann, Stine	Mental Disorders in Foster Children: A Study of Prevalence, Comorbidity, and Risk Factors
	Knapstad, Marit	Psychological factors in long-term sickness absence: the role of shame and social support. Epidemiological studies based on the Health Assets Project.
2016 V	Kvestad, Ingrid	Biological risks and neurodevelopment in young North Indian children
	Sælør, Knut Tore	Hinderløyper, halmstrå og hengende snører. En kvalitativ studie av håp innenfor psykisk helse- og rusfeltet.
	Mellingen, Sonja	Alkoholbruk, partilfredshet og samlivsstatus. Før, inn i, og etter svangerskapet – korrelater eller konsekvenser?
	Thun, Eirunn	Shift work: negative consequences and protective factors
	Hilt, Line Torbjørnsen	The borderlands of educational inclusion. Analyses of inclusion and exclusion processes for minority language students
	Havnen, Audun	Treatment of obsessive-compulsive disorder and the importance of assessing clinical effectiveness

	Slåtten, Hilde	Gay-related name-calling among young adolescents. Exploring the importance of the context.
	Ree, Eline	Staying at work. The role of expectancies and beliefs in health and workplace interventions.
	Morken, Frøydis	Reading and writing processing in dyslexia
2016 H	Løvoll, Helga Synnevåg	Inside the outdoor experience. On the distinction between pleasant and interesting feelings and their implication in the motivational process.
	Hjeltnes, Aslak	Facing social fears: An investigation of mindfulness-based stress reduction for young adults with social anxiety disorder
	Øyeflaten, Irene Larsen	Long-term sick leave and work rehabilitation. Prognostic factors for return to work.
	Henriksen, Roger Ekeberg	Social relationships, stress and infection risk in mother and child
	Johnsen, Iren	«Only a friend» - The bereavement process of young adults who have lost a friend to a traumatic death. A mixed methods study.
	Helle, Siri	Cannabis use in non-affective psychoses: Relationship to age at onset, cognitive functioning and social cognition
	Glambek, Mats	Workplace bullying and expulsion in working life. A representative study addressing prospective associations and explanatory conditions.
	Oanes, Camilla Jensen	Tilbakemelding i terapi. På hvilke måter opplever terapeuter at tilbakemeldingsprosedyrer kan virke inn på terapeutiske praksiser?
	Reknes, Iselin	Exposure to workplace bullying among nurses: Health outcomes and individual coping
	Chimhutu, Victor	Results-Based Financing (RBF) in the health sector of a low-income country. From agenda setting to implementation: The case of Tanzania
	Ness, Ingunn Johanne	The Room of Opportunity. Understanding how knowledge and ideas are constructed in multidisciplinary groups working with developing innovative ideas.
	Hollekim, Ragnhild	Contemporary discourses on children and parenting in Norway. An empirical study based on two cases.
	Doran, Rouven	Eco-friendly travelling: The relevance of perceived norms and social comparison
2017 V	Katisi, Masego	The power of context in health partnerships: Exploring synergy and antagony between external and internal ideologies in implementing Safe Male Circumcision (SMC) for HIV prevention in Botswana

	Jamaludin, Nor Lelawati Binti	The "why" and "how" of International Students' Ambassadorship Roles in International Education
	Berthelsen, Mona	Effects of shift work and psychological and social work factors on mental distress. Studies of onshore/offshore workers and nurses in Norway.
	Krane, Vibeke	Lærer-elev-relasjoner, elevers psykiske helse og frafall i videregående skole – en eksplorerende studie om samarbeid og den store betydningen av de små ting
	Søvik, Margaret Ljosnes	Evaluating the implementation of the Empowering Coaching™ program in Norway
	Tonheim, Milfrid	A troublesome transition: Social reintegration of girl soldiers returning 'home'
	Senneseth, Mette	Improving social network support for partners facing spousal cancer while caring for minors. A randomized controlled trial.
	Urke, Helga Bjørnøy	Child health and child care of very young children in Bolivia, Colombia and Peru.
	Bakhturidze, George	Public Participation in Tobacco Control Policy-making in Georgia
	Fismen, Anne-Siri	Adolescent eating habits. Trends and socio-economic status.
2017 H	Hagatun, Susanne	Internet-based cognitive-behavioural therapy for insomnia. A randomised controlled trial in Norway.
	Eichele, Heike	Electrophysiological Correlates of Performance Monitoring in Children with Tourette Syndrome. A developmental perspective.
	Risan, Ulf Patrick	Accommodating trauma in police interviews. An exploration of rapport in investigative interviews of traumatized victims.
	Sandhåland, Hilde	Safety on board offshore vessels: A study of shipboard factors and situation awareness
	Blågestad, Tone Fidje	Less pain – better sleep and mood? Interrelatedness of pain, sleep and mood in total hip arthroplasty patients
	Kronstad, Morten	Frå skulebenk til deadlines. Korleis nettjournalistar og journaliststudentar lærer, og korleis dei utviklar journalistfagleg kunnskap
	Vedaa, Øystein	Shift work: The importance of sufficient time for rest between shifts.

	Steine, Iris Mulders	Predictors of symptoms outcomes among adult survivors of sexual abuse: The role of abuse characteristics, cumulative childhood maltreatment, genetic variants, and perceived social support.
	Høgheim, Sigve	Making math interesting: An experimental study of interventions to encourage interest in mathematics
2018 V	Brevik, Erlend Joramo	Adult Attention Deficit Hyperactivity Disorder. Beyond the Core Symptoms of the Diagnostic and Statistical Manual of Mental Disorders.
	Erevik, Eilin Kristine	User-generated alcohol-related content on social media: Determinants and relation to offline alcohol use
	Hagen, Egon	Cognitive and psychological functioning in patients with substance use disorder; from initial assessment to one-year recovery
	Adólfsdóttir, Steinunn	Subcomponents of executive functions: Effects of age and brain maturations
	Brattabø, Ingfrid Vaksdal	Detection of child maltreatment, the role of dental health personnel – A national cross-sectional study among public dental health personnel in Norway
	Fylkesnes, Marte Knag	Frykt, forhandlinger og deltakelse. Ungdommer og foreldre med etnisk minoritetsbakgrunn i møte med den norske barnevernstjenesten.
	Stiegler, Jan Reidar	Processing emotions in emotion-focused therapy. Exploring the impact of the two-chair dialogue intervention.
	Egelandsdal, Kjetil	Clickers and Formative Feedback at University Lectures. Exploring students and teachers' reception and use of feedback from clicker interventions.
	Torjussen, Lars Petter Storm	Foreningen av visdom og veltalenhet – utkast til en universitetsdidaktikk gjennom en kritikk og videreføring av Skjervheims pedagogiske filosofi på bakgrunn av Arendt og Foucault. *Eller hvorfor menneskelivet er mer som å spille fløyte enn å bygge et hus.*
	Selvik, Sabreen	A childhood at refuges. Children with multiple relocations at refuges for abused women.
2018 H	Leino, Tony Mathias	Structural game characteristics, game features, financial outcomes and gambling behaviour
	Raknes, Solfrid	Anxious Adolescents: Prevalence, Correlates, and Preventive Cogntive Behavioural Interventions

	Morken, Katharina Teresa Enehaug	Mentalization-based treatment of female patients with severe personality disorder and substance use disorder
	Braatveit, Kirsten Johanne	Intellectual disability among in-patients with substance use disorders
	Barua, Padmaja	Unequal Interdependencies: Exploring Power and Agency in Domestic Work Relations in Contemporary India
	Darkwah, Ernest	Caring for "parentless" children. An exploration of work-related experiences of caregivers in children's homes in Ghana.
	Valdersnes, Kjersti Bergheim	Safety Climate perceptions in High Reliability Organizations – the role of Psychological Capital
2019 V	Kongsgården, Petter	Vurderingspraksiser i teknologirike læringsmiljøer. En undersøkelse av læreres vurderingspraksiser i teknologirike læringsmiljøer og implikasjoner på elevenes medvirkning i egen læringsprosess.
	Vikene, Kjetil	Complexity in Rhythm and Parkinson's disease: Cognitive and Neuronal Correlates
	Heradstveit, Ove	Alcohol- and drug use among adolescents. School-related problems, childhood mental health problems, and psychiatric diagnoses.
	Riise, Eili Nygard	Concentrated exposure and response prevention for obsessive-compulsive disorder in adolescents: the Bergen 4-day treatment
	Vik, Alexandra	Imaging the Aging Brain: From Morphometry to Functional Connectivity
	Krossbakken, Elfrid	Personal and Contextual Factors Influencing Gaming Behaviour. Risk Factors and Prevention of Video Game Addiction.
	Solholm, Roar	Foreldrenes status og rolle i familie- og nærmiljøbaserte intervensjoner for barn med atferdsvansker
	Baldomir, Andrea Margarita	Children at Risk and Mothering Networks in Buenos Aires, Argentina: Analyses of Socialization and Law-Abiding Practices in Public Early Childhood Intervention.
	Samuelsson, Martin Per	Education for Deliberative Democracy. Theoretical assumptions and classroom practices.
	Visted, Endre	Emotion regulation difficulties. The role in onset, maintenance and recurrence of major depressive disorder.
2019 H	Nordmo, Morten	Sleep and naval performance. The impact of personality and leadership.

	Sveinsdottir, Vigdis	Supported Employment and preventing Early Disability (SEED)
	Dwyer, Gerard Eric	New approaches to the use of magnetic resonance spectroscopy for investigating the pathophysiology of auditory-verbal hallucinations
	Synnevåg, Ellen Strøm	Planning for Public Health. Balancing top-down and bottom-up approaches in Norwegian municipalities.
	Kvinge, Øystein Røsseland	Presentation in teacher education. A study of student teachers' transformation and representation of subject content using semiotic technology.
	Thorsen, Anders Lillevik	The emotional brain in obsessive-compulsive disorder
	Eldal, Kari	Sikkerheitsnettet som tek imot om eg fell – men som også kan fange meg. Korleis erfarer menneske med psykiske lidingar ei innlegging i psykisk helsevern? Eit samarbeidsbasert forskingsprosjekt mellom forskarar og brukarar.
	Svendsen, Julie Lillebostad	Self-compassion - Relationship with mindfulness, emotional stress symptoms and psychophysiological flexibility
2020 V	Albæk, Ane Ugland	Walking children through a minefield. Qualitative studies of professionals' experiences addressing abuse in child interviews.
	Ludvigsen, Kristine	Creating Spaces for Formative Feedback in Lectures. Understanding how use of educational technology can support formative assessment in lectures in higher education.
	Hansen, Hege	Tidlig intervensjon og recoveryprosesser ved førsteepisode psykose. En kvalitativ utforsking av ulike perspektiver.
	Nilsen, Sondre Aasen	After the Divorce: Academic Achievement, Mental Health, and Health Complaints in Adolescence. Heterogeneous associations by parental education, family structure, and siblings.
	Hovland, Runar Tengel	Kliniske tilbakemeldingssystemer i psykisk helsevern – implementering og praktisering
	Sæverot, Ane Malene	Bilde og pedagogikk. En empirisk undersøkelse av ungdoms fortellinger om bilder.
	Carlsen, Siv-Elin Leirvåg	Opioid maintenance treatment and social aspects of quality of life for first-time enrolled patients. A quantitative study.
	Haugen, Lill Susann Ynnesdal	Meeting places in Norwegian community mental health care: A participatory and community psychological inquiry

2020 H Markova, Valeria How do immigrants in Norway interpret, view, and prefer to cope with symptoms of depression? A mixed method study

Errata for
Cognitive change in Psychosis

Liss G Anda

Thesis for the degree philosophiae doctor (PhD)

at the University of Bergen

_____08.10.20__

(date and sign. of candidate)

Helen Green 08.10.20

(date and sign. of faculty)

Errata

Page 9-10:
Deleted the following abbreviations from abbreviation lists:
AAs: Atypical ("second-generation) antipsychotic drugs
FEP: First episode psychosis
FGA: First-generation antipsychotic drugs
GAF: Global Assessment of Functioning Scale – Split version
GAF-S: Global Assessment of Functioning Scale – Symptom subscale
GAF-F: Global Assessment of Functioning Scale – Functioning subscale
IGSIN: International Graduate School in Integrated Neuroscience
ITT: Intention to treat
NOS: Psychotic disorder not otherwise specified
SID: Substance induced psychosis
SSD: Schizophrenia spectrum disorders
TMA: Trail Making Test A
TMB: Trail Making Test B

Inserted the following abbreviations into list:
CBT: Cognitive-behavioural therapy
DSM-5: Diagnostic and Statistical Manual for Mental Disorders, 5th edition
D2: Dopamine 2 receptor
fMRI: Functional magnetic resonance imaging
PP: Per protocol
SIPS: Structured Interview for Prodromal Symptoms

Inserted "4th edition" to the description of DSM-IV

Page 11

Inserted "the tests of the Repeatable Battery for the Assessment of Neuropsychological Status"
Inserted brackets around "RBANS" abbreviation
Deleted "neurocognitive test battery"
Inserted "the Positive and Negative Syndrome Scale" and brackets around "PANSS"

Page 12
Inserted "deemed at ultra high risk for psychotic disorder"
Inserted brackets around "UHR"

Page 20
Inserted Diagnostic and Statistical Manual of Mental Disorders, 4th edition and brackets around "DSM-IV"
Diagnostic and Statistical Manual of Mental Disorders, 5th edition.
Inserted brackets around "DSM-5"
Inserted dopamine 2 and brackets around "D2"

Page 21
Inserted "dopamine" ahead of D1 receptor abbreviation

Corrected reference (Siris, 2000) formatting

Page 22
Inserted "International Statistical Classification of Diseases, 11th edition" and brackets around "ICD-11"

Page 23
Replaced "(SSD)" with "schizophrenia spectrum disorders" throughout page

Page 24
Expanded "UHR" to "a group of youth at ultra high risk for psychotic illness" and added brackets to "UHR"

Page 25
Replaced "SID" with "substance induced psychosis"
Replaced "SSD" with "schizophrenia spectrum disorders"
Replaced "SAD" with "schizoaffective disorder" throughout page

Page 27
Deleted "(DALYs)"

Pages 29, 31, 39, 42, 49, 71, 79, 89
Replaced "FEP" with "first episode psychosis" throughout pages

Page 32
Replaced "CT" with "computed tomography"

Page 33
Replaced "MRI" with "magnetic resonance imaging" throughout page
Replaced "DTI" with "diffusion tensor imaging" throughout page
Inserted "functional magnetic resonance imaging" and added brackets around "fMRI"
Replaced "WM" with "white matter"

Page 34
Replaced "PET" with "positron emission tomography"
Corrected reference formatting (Read, van Os, Morrison, & Ross, 2005)

Page 35
Deleted "(FGA)"

Page 36
Deleted "(AA)"

Page 36, 47, 97
Replaced "FGA" with "First-generation antipsychotic drugs" throughout pages

Page 37
Inserted brackets around "CBT" and added "cognitive-behavioural therapy"
Inserted "schizophrenia spectrum disorders"

Page 38
Deleted "(TMS)"
Replaced "VR" with "virtual reality"

Page 41
Replaced "WWII" with "World War II"

Page 44
Replaced "DLPFC" with dorsolateral prefrontal cortex"
Replaced "IFG" with "inferior frontal gyrus"

Page 45
Replaced "PFC" with "prefrontal cortex"
Repaired reference formatting "(Samartzis et al., 2014)"

Pages 46, 47, 48, 50, 76, 77, 82, 97
Replaced "(AA)" with atypical antipsychotics throughout pages

Page 47
Replaced "5hT2" with "5-hydroxytryptamine"
Replaced M3 with "muscarinic acetylcholine"
Replaced "H1" with "Histamine 1"
Corrected formatting of reference "(Chew et al., 2006)"

Page 52:
Inserted "including the BestIntro antipsychotic drug trial" to clarify
Deleted "(RCMRE)"

Page 53:
Inserted "Positive and Negative Syndrome Scale" and added brackets around "PANSS"
throughout page
Replaced "AP"s with "antipsychotic drugs" throughout page
Page 54
Replaced "SOPS scale" with "Scale of Prodromal Symptoms"

Page 55
Replaced "K-SADS" with "Kiddie Schedule for Affective Disorders and Schizophrenia"
Inserted "Structured Clinical Interview for the DSM-IV" and added brackets around "SCID".
Deleted "I" from "SCID-I"

Page 58
Replaced "SCI-PANSS" with "Structured Clinical Interview: Positive and Negative
Syndrome Scale"
Deleted "(CDUS/CAUS)"
Deleted "(GAF-F)"

Page 59
Inserted Delis Kaplan Executive Function System and added brackets to "D-KEFS"
Deleted "verbal fluency tests"
Deleted "DVT"

Replaced "CALCAP" with "California Computerized Assessment Package"

Page 60
Replaced Arabic numerals 1 and 2 with Roman numerals I and II

Page 61
Replaced "Fig 3" with "Note" in caption

Page 62
Inserted "defined daily doses" and added brackets to "DDD"
Deleted (RGs)
Deleted (BASG)
Replaced "ICH GCP (ICH)" with "International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Guideline for Good Clinical Practice"
Pages 63 and 64
Replaced "(WNRHA)" with "Western Norway Regional Health Authority"

Page 65
Inserted missing part of figure

Page 67
Deleted "Figure 2" and replaced with "Note:"

Page 68
Replaced "AP" with "antipsychotic" into heading

Page 69
Corrected figure number in caption

Page 71
Replaced "non-FEP " with "sample not consisting exclusively of first-episode psychosis participants"

Page 72
Replaced "AAs" with "Atypical antipsychotics" in heading

Page 74, 78, 79
Replaced "SZ" with "schizophrenia" throughout pages

Pages 74, 75, 78 and 79
Capitalized "Paper"
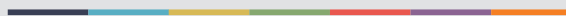
Page 77
Inserted "those of"

Page 92
Replaced "avg." with "average"
Page 93
Deleted "-I" twice from "SCID-I"

uib.no