C- reactive protein in schizophrenia-spectrum disorders; relationship to cognitive functions and medications

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Scientific environment

The presented work in this thesis was performed at the University of Bergen, Department of Clinical Medicine, Section of Psychiatry, and the Haukeland University Hospital, Division of Psychiatry in period 2014-2019. I have been since 1st May 2013 employed in the NKS Olaviken Gerontopsychiatric Hospital, which has financed my research.

Professor Erik Johnsen has been my main supervisor, and is affiliated with the University of Bergen, Department of Clinical Medicine, Section of Psychiatry, Haukeland University Hospital, Division of Psychiatry, Norwegian Centre for Mental Disorders Research (NORMENT), and has been project leader of BestIntro.

Co-supervisor Professor Else-Marie Løberg has been affiliated with the University of Bergen, Department of Biological and Medical Psychology and the Department of Clinical Psychology, and the Department of Addiction Medicine, Division of Psychiatry at the Haukeland University Hospital, and NORMENT. Co-supervisor Associate professor Rune A. Kroken has been affiliated with the University of Bergen, Department of Clinical Medicine, Section of Psychiatry, Haukeland University Hospital, Division of Psychiatry, and NORMENT.

This thesis is based on collaborative work with some other centres: NORMENT, K.G. Jebsen Centre for Psychosis Research, Stavanger University Hospital, St.Olav University Hospital, Trondheim in Norway, and the Medizinische Universität Innsbruck in Austria.

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Abstract

Background Schizophrenia spectrum disorders are severe mental illnesses characterized by psychotic symptoms, cognitive dysfunction and functional decline. Cognitive impairments have been recognized as core features of schizophrenia, with great impact on functional outcome. Emerging evidence indicates involvement of immune system and inflammation in the pathophysiology of schizophrenia, and elevation of the inflammatory marker C-reactive protein (CRP) has been observed with association to pathogenesis and symptomatology including cognitive dysfunctions.

Aims To investigate the association between CRP level and cognitive performance in both acute phase of psychosis (paper 1) and during a 6 month follow-up (paper 2), and study the differences between antipsychotics with regards to effect on CRP levels during a one year follow-up of schizophrenia spectrum disorders patients in acute phase psychosis (paper 3).

Methods Participants from the Bergen psychosis project study were assessed with measurement of the CRP level and cognitive assessments at baseline and first follow-up visit at discharge/latest after 6 weeks (paper 1), in addition to cognitive assessments after 3 months and 6 months (paper 2). Patients from BestIntro study were assessed with measurement of CRP level at baseline, and after 1, 3, 6, 12, 26, 39 and 52 weeks (paper 3).

Main results Inverse relationship between baseline CRP level and overall cognitive performance, delayed memory and attention were found. During the 6 month follow-up global cognitive performance improved, and was associated with the initial CRP level reduction (paper1 and 2). Amisulpride, aripiprazole and olanzapine showed different effects on CRP levels, with a statistically significant increase in CRP levels during the first 1-3 weeks which lasted for 52 weeks for all groups. The aripiprazole group showed decrease in CRP level during the first week of treatment, and the change in CRP differed depending on whether or not the patient was antipsychotic-

naïve (paper 3).

Conclusions Findings support an inflammatory component to the cognitive impairment in schizophrenia spectrum disorders, which is partly state dependent. The CRP level changes in the acute phase of psychosis may predict cognitive function in later phases. Amisulpride, aripiprazole and olanzapine showed different effects on the immune system in acute phase psychosis, which might be both phase related and dependent on whether or not there was prior use of antipsychotics. All three antipsychotics showed, however, an overall pro-inflammatory effect for the whole follow-up.

List of publications

This thesis is based on the following papers:

Paper I
Erik Johnsen[1], Farivar Fathian[1], Rune A. Kroken, Vidar M. Steen, Hugo A. Jørgensen, Rolf Gjestad, Else-Marie Løberg: **The serum level of C-reactive protein (CRP) is associated with cognitive performance in acute phase psychosis,** BMC psychiatry. 2016:16-60.
Johnsen and Fathian contributed equally and share the first authorship of this paper.

Paper II
Farivar Fathian, Else-Marie Løberg, Rolf Gjestad, Vidar M. Steen, Rune A. Kroken, Hugo A. Jørgensen, Erik Johnsen: **Associations between C-reactive protein levels and cognition during the first 6 months after acute psychosis,** Acta Neuropsychiatrica. 2018:1-10.

Paper III (Manuscript to be submitted)
Farivar Fathian, Rolf Gjestad, Rune A. Kroken Else-Marie Løberg , Vidar M. Steen, Solveig Klæbo Reitan, W. Wolfgang Fleichhacker, Maria Rettenbacher, Tor K Larsen, Inge Joa, Lena Antonsen Stabell, Eirik Kjelby, Igne Sinkevicute, Renata Alisauskiene, Erik Johnsen.: **Associations between C-reactive protein levels and antipsychotic treatment during 12 months follow-up period after acute psychosis.**

Abbreviations

5-HT	5-hydroxytryptamine (=serotonin)
ANOVA	analysis of variance
APA	American Psychiatric Association
BestIntro	Bergen-Stavanger-Innsbruck-Trondheim study
BP	Bergen psychosis project
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CDSS	Calgary Depression Scale for Schizophrenia
CGI-S	Clinical Global Impression – Severity scale
CNS	central nervous system
CSF	cerebrospinal fluid
DDD	defined daily dose
DSM	Diagnostic and Statistical Manual for Mental Disorders
DTI	diffusion tensor imaging
EPS	extra-pyramidal symptoms
FEP	first-episode psychosis
FGA	first generation antipsychotic
GABA	gamma-amino-butyric acid
GAF-S	Global Assessment of Functioning Scale – Symptom subscale
GAF-F	Global Assessment of Functioning Scale – Functioning subscale
GCP	Good Clinical Practice
HLA	human leucocyte antigens
HPA axis	hypothalamus-pituitary-adrenal axis
ICD	International Statistical Classification of Diseases

ICH-GCP	International Conference on Harmonisation - Good Clinical Practice
IL	interlukin
INF	interferon
ITT	Intention-to-treat analysis
KYNA	kynurenic acid
MADRS	Montgomery-Åsberg Depression Rating Scale
MNAR	missing not at random
MR/MRI	magnetic resonance /imaging
NMDA/R	N-methyl-D-aspartate/ receptor
NSAIDs	nonsteroidal anti-inflammatory drugs
OR	odds ratio
PANSS	the Positive and Negative Syndrome Scale for Schizophrenia
RBANS	the Repeatable Battery for the Assessment of Neuropsychological Status
RCT	randomized controlled trial
R/Ra	receptor/receptor antagonist
RMSEA	the Root Mean Square Error of Approximation
RR	relative risk
SCID-1	Structured Clinical Interview for DSM-IV Axis I disorders
SD	standard deviation
SGA	second generation antipsychotic
SPSS	Statistical Package for the Social Sciences
TGF	transforming growth factor
TNF	tumor necrosis factor
WHO	World Health Organization

Contents

1. Introduction

1.1 History of schizophrenia

Schizophrenia spectrum disorders are severe and often chronic mental illnesses characterized by a heterogenic set of positive, negative, cognitive, mood, motor symptoms and functional decline with a lifetime prevalence close to 1% (1). The schizophrenia spectrum and other psychotic disorders according to The Diagnostic and Statistical Manual of Mental Disorders of American Psychiatric Association, Fifth edition (DSM- 5) introduces a conceptual psychosis continuum, where the differentiation between various forms of psychotic disorders is based on the level, number, and duration of psychotic signs and symptoms (2). Schizophrenia has been widely studied as a specific disease entity for the past century, but its precise nature, causes and pathogenesis remains unknown (3).

In this thesis, the terminology of schizophrenia-spectrum disorders will therefore, be used as the common/modern definition for psychotic disorders including schizophrenia as the most studied disease entity in this spectrum.

The history of schizophrenia as a disease entity dates back to the 19th century. Griesinger (4) described in 1891 conditions reflecting today's chronic schizophrenia as a secondary development in a primary mood disorder and assumed a unitary psychosis disease entity. Hecker (5) described hebephrenia in 1871, a syndrome consisting of early onset of psychosis, affect and behavioural features, formal thought disorder, and a deteriorating course (5), followed by Kahlbaum's clinical method developed in 1874, where psychiatric entities were based on the entire course of the illness consisting of prodromal phase, acute and outcome (6). In 1919 Kraepelin (7) recognized similarities between patients with catatonia, hebephrenia, and paranoid dementia regarding adolescent or early adult onset, deterioration tendency and an outcome of mental dullness or dementia, a group he called dementia praecox (1, 7, 8).

Bleuler (9) defined in 1919 a set of fundamental symptoms that he considered unique to schizophrenia. He considered delusions and hallucinations as accessory symptoms of schizophrenia, whereas the disintegration of different psychic functions, with fundamental symptoms of loosening of association, blunt or incongruous affect, ambivalence, and autism to be present in all patients, known as Bleuler's 4, and now considered as negative symptoms (1, 9, 10).

In 1946 Jaspers (11) proposed that impairment of empathic communication was the basic defect in schizophrenia (1, 11), followed by Schneider's (12) high-valued 11 first-rank symptoms in 1959, formerly considered as pathognomonic. These symptoms were audible thoughts, voices heard arguing, voices heard commenting on ones actions, the experiences of influences playing on the body (somatic passivity experiences), thought withdrawal and other interferences with thoughts, diffusion of thoughts, delusional perception, and all feelings, impulses (drives) and volitional acts that are experienced by the patient as the work, or influence of others, which are now considered as the positive symptoms of schizophrenia (12, 13).

The further conceptualization, current definition, and diagnosis of schizophrenia are presented in next chapter.

1.2 Clinical features and diagnosis

Schizophrenia is essentially characterized by a set of signs and symptoms, including distortions of thinking and perception, cognitive impairments, motor symptoms, avolition and apathy, communication difficulties and limited affective expression. These abnormalities are classified in positive, negative, cognitive, disorganization, mood and motor symptom dimensions, which are expressed differentially among patients and through the illness course (1, 14, 15).

1.2.1 Symptomatology

Positive symptoms

Positive symptoms are related to impaired reality testing and include delusions, hallucinations, and other reality distortions. Delusions of control, thought insertion, withdrawal and broadcasting, all from the Schneiderian first-rank symptoms have been traditionally linked to schizophrenia, but persecutory delusions and delusion of reference are most frequent (16). Hallucinations in all five sensory modalities can occur, however, auditory hallucinations are the most common. The reality distortion with positive symptoms marks the formal clinical onset of the illness. By using the Positive and Negative Syndrome Scale (PANSS) (17), (see below), a threshold for psychosis can be operationalized according to the scores for particular items (1, 18, 19).

Negative symptoms

Negative symptoms are characterized by blunting or loss of a variety of affective functions, including dysfunctions in affective experiences and expression, abulia (loss of motivation), alogia (poverty of speech), anhedonia (inability to experience pleasure), avolition (lack of initiative), apathy (lack of interest), and reduced social drive (20, 21).

Disorganization of thinking and behavior

Disorganized thinking (formal thought disorders) is typically inferred from the individual's speech. Patients may switch from one topic to another (derailment or loose associations), or answer to questions as obliquely related or completely unrelated (tangentiality). Rarely, speech may be so severely disorganized that is nearly incomprehensible (incoherence or ''word salad''). Symptoms of disorganization have been identified as risk factors for a worse course of illness, and poor outcome (22, 23).

Mood and other symptoms

Patients with schizophrenia frequently manifest mood symptoms, and may show increased emotional reactivity together with positive symptoms, called the emotional paradox (24). Significant depressive symptoms are seen in a majority of schizophrenia patients, can occur in any phase of the illness, and increase through an acute psychosis phase (25-27).

Patients with schizophrenia may manifest other symptoms or clinical features such as psychomotor symptoms, (28, 29), the full-blown catatonic syndrome with stupor or excitement states, echolalia, echopraxia, automatic obedience, waxy flexibility, and extreme negativism (30), anxiety (31) and neurological deficits (32-35). Cognitive symptoms are discussed in greater detail due to the relevance for this thesis.

Cognitive symptoms

Kraepelin (7) described the disorder by using the term ‘’dementia praecox’’ that means literally cognitive decline with onset in youth. Positive symptoms have been considered as the most prominent features of the schizophrenia spectrum disorders for almost a century, but cognitive dysfunctions are recognized as core features of schizophrenia during the last decade (36-39). Cognitive symptoms have greater impact on functional outcome than the psychotic symptoms (40-46), and are present early in the disease course. While psychotic symptoms usually appear approximately in the age of 18-25 years old, cognitive deficits are observed much earlier in patients who develop schizophrenia (47). Children and adolescents who later develop schizophrenia show deficits in general cognitive abilities in terms of IQ and academic achievement (48-50), and specific premorbid impairments in a number of cognitive domains (51-53). It has been suggested that premorbid cognitive deficits support the neurodevelopmental model of schizophrenia, with mild abnormalities in cognitive development as the earliest signs of the illness (50, 54). Furthermore, cognitive dysfunction in schizophrenia is considered as signalling aberrant neurodevelopment during the first two decades of life (48, 49, 55). The presence of cognitive deficits years prior to the onset of psychotic symptoms suggests that cognitive dysfunction is

at the core of schizophrenia, with abnormal neurodevelopment manifesting through performative lag as early as preschool age (56).
Moreover, robust impairments across multiple domains of cognitive functioning are highly prevalent, and observed in more than 80% of patients with schizophrenia-spectrum disorders and can be detected in the premorbid phase of illness (39, 57). The cognitive impairments in schizophrenia are observed across all phases of illness and is predominantly generalized (58, 59), but also with additional impairments in specific domains of episodic memory, processing speed, verbal fluency, attention, executive functions and working memory. Literature reporting specific domain impairment show, however, mixed results (60) (61-68).
Many studies have indicated that the cognitive impairments seem to stabilize after the first episode of psychosis (69, 70), although there have also been some findings suggesting cognitive improvements (71-75).

A review of 163 publications of longitudinal studies of patients with schizophrenia (60) showed that cognitive impairment in first-episode schizophrenia patients is similar to the impairment seen in chronic stages. Moreover, a meta-analysis of 23 studies of medication-naïve first-episode patients revealed medium to large effect sizes in all cognitive domains compared to healthy controls, with the largest impairment in verbal memory, processing speed, and working memory (76). These findings support the presence of significant cognitive impairment in the early stages of psychosis independent of antipsychotic medication use.

1.2.2 Onset and course

Schizophrenia is characterized by a sequential course consisting of premorbid- phase, prodromal phase, the first-episode psychosis (FEP), repeated episodes of psychosis, inter-episode remission, stable phase/plateau and recovery. More rarely, schizophrenia can have an acute debut (1).

Premorbid phase

Significant numbers of investigations including birth-cohort observations have identified premorbid abnormal intellectual, social, affective, behavioral and academic functioning, in addition to delayed motor coordination development and abnormal motor functioning, and neurocognitive deficits (77).

Prodromal phase

The time preceding the first onset of psychosis has been described as the prodrome, and is characterized by subthreshold psychotic symptoms, in addition to a range of other clinical signs including cognitive deficits, negative symptoms, mood symptoms, and decline in function (47, 78). The duration of the prodromal phase varies from months to years, with a mean of approximately 5 years (79, 80). Psychotic experiences, ranging from mild attenuated experiences in healthy individuals to clinically full-blown psychosis in a few, have been suggested as continuum model of psychosis, with the ultrahigh risk for psychosis (UHR) close to the mild end (81, 82). One sixth to one-half of individuals, (depending on the population studied and criteria utilized) who seek treatment and meet the criteria for UHR develop schizophrenia (83-85).

Onset, the initial psychotic episode and course of the illness

For practical purposes, the development of frank psychotic symptoms defines the formal onset of the first episode of schizophrenia, consistent with Criterion A in the DSM-5 itemizing hallucinations, delusions, disorganized speech/ behavior, and negative symptoms. To meet this criterion, individuals should have two of these five symptoms for one month (or less if appropriately treated). International Statistical Classification of Diseases and Related Health Problems (ICD)- 10 uses a similar definition of schizophrenia.

The onset of schizophrenia generally occurs at the age of 15-45 years, however, it can rarely debut before puberty or after the age of 50 years (86, 87). The first episode is typically initiated with an increase in mood and negative symptoms, considered as the prepsychotic phase, and followed by increasing positive symptoms until reaching a

peak, recognized as psychotic phase (88-90). The course of schizophrenia after the FEP varies across patients, characterized by exacerbations and remissions, with different degree of psychotic symptoms through the course of the illness. About 20% have only one episode.

1.2.3. Comorbidities

Patients with schizophrenia show increased rates of a range of comorbid medical and psychiatric diseases (91, 92). The prevalence of depressive disorder in schizophrenia has been reported to be around 40%, (27), and it is linked to poorer outcomes in schizophrenia (93). Other frequent comorbidities are anxiety and related disorders in schizophrenia (94).

Furthermore, the prevalence of substance use (e.g., alcohol, cannabis, and cocaine) in patients with schizophrenia is as high as about 5 times of general population (95-97). Individuals with schizophrenia and substance abuse show higher rates of relapse, rehospitalization, violence, poor social functioning, medication non-adherence, worse clinical outcomes, and higher suicide risk (97, 98).

Medical comorbidity

Schizophrenia is associated with a substantially decreased life expectancy of 15–25 years compared to the general population, with somatic diseases being a major cause for all these years of lost life (99). Smoking, low physical activity, obesity, hypertension, dyslipidemia, and elevated serum glucose levels are more common in individuals with schizophrenia than the general population (100-107). Atypical antipsychotics in addition to unhealthy life styles leading to dyslipidemia, hyperglycemia, and overweight, contribute to somatic comorbidities, including the metabolic syndrome and cardiovascular disease (108). However, a 4-years follow-up study of all individuals in Sweden with schizophrenia diagnoses found the highest overall mortality among patients with no antipsychotic exposure, compared with age- and gender-matched controls. The authors suggested that other factors than

antipsychotic use in adequate dosage might be involved in both excess overall and cardiovascular mortality in schizophrenia (109). Furthermore, increased risk for metabolic syndrome in drug-naïve patients and in first-degree relatives of schizophrenia patients (110), increased cardiovascular disease risk in young drug-naïve patients with higher cholesterol levels, increased insulin resistance (111), and shared genetic risk for cardiovascular risk factors and psychotic disorders, indicate shared pathophysiology independent of atypical antipsychotics among some of the patients (112). Individuals with schizophrenia have in addition increased risk for developing autoimmune diseases, infections, chronic obstructive pulmonary disease (COPD) and cancers (99). Smoking and poor health care and unhealthy life style might increase the risk of infections, COPD, some types of cancer, however, genetic link between schizophrenia and autoimmune diseases, cardiovascular disorders and type 2 diabetes have been suggested (113). The autoimmune comorbidity will be discussed more detailed in the pathophysiology section.

1.2.4 Diagnosis and related aspects

Since the pathophysiology of schizophrenia spectrum disorders has not been fully clarified yet, the diagnosis is according to ICD-10 and Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 still based on symptom-related clinical criteria comprising certain psychopathologic features and the disease course (114, 115). The two major international diagnostic classification systems are developed by the World Health Organization (WHO) and the American Psychiatric Association (APA), respectively. WHO was entrusted with ICD in 1948 and published the 6th version, ICD-6. The ICD has been revised and published in a series of editions to reflect advances in health and medical science over time. It is the diagnostic classification standard for all clinical and research purposes.

DSM is the other authoritative manual that defines and classifies mental disorders in order to improve diagnoses, treatment, and research.

The diagnoses broadly described as schizophrenia spectrum disorders according to ICD-10 diagnoses of F20-29 is considered as the non-affective pshychoses, separated from affective disorders (used in the inclusion process of the thesis projects), which are defined in the DSM-5 as schizophrenia (F20), schizophreniform disorder (F20.8), schizotypal disorder (F21), delusional disorder (F22), brief psychotic disorder (F23), and schizoaffective disorder (F25). The diagnostic category "Schizophrenia and other psychotic disorders" in the DSM-4 is changed to "Schizophrenia Spectrum and Other Psychotic Disorders" in the DSM-5 (116).

1.3 Epidemiology

A systematic review of the epidemiology of schizophrenia found median incidence (the number of new cases per given population per year) estimates of 15.2 per 100 000, median lifetime prevalence (proportion of surviving individuals with a schizophrenia during a specified period) of 4.0 per 1000 and lifetime morbid risk (likelihood of developing schizophrenia during lifetime) 7.2 per 1000. Rates vary depending on the diagnostic definition of schizophrenia used (117). The evidence indicates that the incidence of schizophrenia is related to sex with a median male: female rate ratio of 1.4 (117, 118). Various risk factors for the development of schizophrenia have been identified. A meta-analysis of 38 studies compared different schizophrenia risk factors, suggesting 3 levels of risk (119). The highest risk factors are having a first-degree relative with schizophrenia (RR 6.99–9.31), or being the offspring of an immigrant from selected countries (RR 4.5). Intermediate risk factors include infection with Toxoplasma gondii (OR 2.73), being an immigrant from and to selected countries (RR 2.7), being born (RR 2.24) in or raised in (RR 2.75) an urban area, cannabis use OR 2.10–2.93), having minor physical anomalies (OR 2.23), or having a father 55 or older (OR 2.21). Low-risk factors include a history of traumatic brain injury (OR 1.65), sex abuse in childhood (OR 1.46), obstetrical complications (OR 1.29–1.38, having a father 45 or older (OR 1.38–1.66), specific genetic

polymorphisms (OR 1.09–1.24), birth seasonality (OR 1.07–1.95), maternal exposure to influenza (RR 1.05) (119).

Stress mediated pathways have been suggested to be involved in some of the above-mentioned risk factors, such as migrant status, by social defeat/ethnic minority (117, 120, 121), and urbanity by overcrowded stress in addition to environmental pollutants (122). Epidemiological studies of seasons of birth show an excess of winter births in individuals with schizophrenia in Northern hemisphere (123, 124), and with lower grade of excess in the Southern Hemisphere (123, 125, 126). Infections, temperature, length of photoperiod, nutritional factors and toxic factors have been suggested as potential mechanisms involved in seasonal variations of birth in schizophrenia (123, 126, 127). As mentioned in a previous section a systematic review including 37 studies showed a median standardized mortality ratio, all- cause of 2.6 for patients with schizophrenia which indicates a two- three fold increased risk of mortality compared to general population (McGrath, Saha et al. 2008). Suicide contributes to the increased mortality associated with schizophrenia (128). Besides, patients with schizophrenia have increased mortality risks due to comorbid somatic conditions (129).

Maternal and childhood infections, childhood trauma, autoimmunity, together with the genetical aspects of the pathophysiology will be further discussed in details following the presentation of immunity and inflammation.

1.4 Pathophysiology

The pathophysiology of schizophrenia consists of both structural and functional aberrations. Schizophrenia is, however, characterized by a spectrum of neurobiological abnormalities which have been linked to putative etiological factors (130). This section will focus mainly on cross-talk between signalling and inflammatory aspects.

1.4.1 Neurotransmitter signaling

Neurotransmitter systems in the brain, particularly dopamine have been the mainstream research focus regarding pathogenesis of schizophrenia (131).

Dopamine

The initiating source of the dopamine hypothesis of schizophrenia was based on studies on amphetamine and other substances with evidence of increase of extracellular concentrations of dopamine inducing psychotic symptoms similar to schizophrenia (132-134). Clinical studies showed furthermore, that the effectiveness of antipsychotic drugs was related to their affinity for dopamine receptors, suggesting abnormalities in dopamine receptor density leading to schizophrenia (135, 136). Evidence from positron emission tomography (PET) studies have shown reduced cerebral blood flow in the frontal cortex, suggesting regional brain dysfunction in schizophrenia. However, the term hypofrontality, originated from the low cerebrospinal fluid (CSF) dopamine metabolite levels, reflecting cortical dopamine metabolism, and was assumed to indicate reduced frontal dopamine levels (137). Schizophrenia was thus suggested to be characterized by frontal hypodopaminergia resulting in striatal hyperdopaminergia (137). Similarities between the behaviour of animals and humans with frontal lobe lesions and the negative symptoms of schizophrenia, suggest that the negative symptoms could be related to frontal hypodopaminergia. Positive symptoms are suggested to result from striatal hyperdopaminergia, since higher dopamine metabolite levels are found to be related to greater positive symptom load and response to antipsychotic drugs (138). Dopamine deficiency within dorsolateral prefrontal cortex leads to cognitive dysfunction. Both preclinical and clinical studies have shown relationships between prefrontal dopamine function and working memory, suggesting that insufficient D1 receptor signaling in this area is involved in cognitive impairment (139). Furthermore, a meta-analysis of PET and single photon emission computed tomography (SPECT) imaging studies of dopaminergic function showed that presynaptic dopaminergic function (dopamine synthesis capacity, dopamine release

and synaptic dopamine levels), dopamine transporter and dopamine receptor availability were altered in schizophrenia, but there was no difference in dopamine transporter availability (140).

In the latest version of the dopamine hypothesis dopamine signalling is considered as the final common pathway to psychosis in schizophrenia, in which multiple factors interact resulting in dopamine dysregulation at the presynaptic dopaminergic control level (137). However, limitations of the dopamine hypothesis have been revealed during the last 20 years, and alternative models have been developed, including also a role for glutamate transmission and other systems (141).

Glutamate

Glutamate is the most abundant excitatory neurotransmiter in the brain. Glutamatergic neurotransmission is conducted through metabotropic and ionotropic

Glutamate receptors, each subdivided in 3 groups. The ionotropic N-methyl-D-aspartate receptors (NMDAR) have particular relevance for psychosis, and will be in focus in this section. Glutamatergic pathways are linked to the cerebral cortex, limbic system, and the thalamus regions. There are increasing evidence of glutamate involvement in schizophrenia (142). Glutamatergic models were originally based on the observation of schizophrenia-like psychotic symptoms and neurocognitive deficits induced by the psychotomimetic agents such as phencyclidine (PCP) and ketamine by blocking neurotransmission at NMDAR (143, 144). NMDAR are located throughout the brain. Furthermore, NMDAR are located in brain circuits, which regulate dopamine release, indicating that dopaminergic deficits in schizophrenia might also be secondary to glutamatergic dysfunction (145). It has been suggested that dopamine has a modulatory effect on glutamate performance, and dopamine changes might thus affect NMDA activity (146). Furthermore, some of the products of brain inflammation, such as kynurenic acid (KYNA) and quinolenic acid bind to NMDAR, however with opposite effects.

Other neurotransmitters

Other neurotransmitters such as serotonin (147), acetylcholine (148, 149), and Gamma-Aminobutyric Acid (GABA) (150-152) have also been suggested to be involved in the pathogenesis of schizophrenia, but further discussions are beyond the scope of this thesis.

The above-mentioned multi-neurotransmitter models illustrate the neurochemical imbalances in various neurotransmitter systems involved in the pathophysiology of schizophrenia. Both etiological, epidemiological, and treatment challenges point to additional involved mechanisms. Antipsychotic drugs have mainly focused on dopaminergic antagonism at the D2 receptors, counteracting the hyperdopaminergia in nigrostriatal and mesolimbic systems. Current clinically available drugs effectively target the positive symptoms of psychosis such as hallucinations and delusions in the majority of first-episode patients, but show smaller effect sizes for negative symptoms and cognitive dysfunctions (153), indicating involvement of other pathophysiological mechanisms in addition to hyperdopaminergia. Interestingly, considerable cross-talk between neurotransmitter systems and inflammatory constituents exist in schizophrenia as will be further elaborated in the next section.

1.4.2 Immunity and Inflammation

The idea that inflammation might lead to psychosis started as early as the history of the schizophrenia syndrome, where Kraepelin (7) suggested that dementia praecox was caused by autointoxication from a focal somatic infection (154). Clinical observations of psychotic-, mood symptoms, and cognitive impairment often during or after an infectious condition together with discovery of Treponema pallidum in 1905 as the aetiology of syphilis and associated psychosis, might have been the basic start of the inflammation theory (155). A potential role of inflammation in the pathogenesis of psychosis was introduced in 1918, by the observation of 200 reported cases of post-influenza psychosis, in which one-third had similar clinical manifestations as dementia praecox (156, 157).

In this section, immunity and inflammatory processes relevant to schizophrenia will be discussed. First, a general overview of the innate and adaptive immune systems will be presented. Next, cytokines involved in the immune response will be presented, leading to the final section elaborating on CRP, which is the main focus of this thesis. The human immune system has two different parts; the innate system (inborn), the oldest part and the first barrier with unspecific response to pathogens, and the adaptive system (acquired) which responds to specific antigens with long-lasting recognition (158, 159). The cells of the innate system are dendritic cells, macrophages, granulocytes, mast cells, and natural killer cells, and the humoral responses of the innate system consist of the complement system, cytokines, interferons and extracellular enzymes. The cells of the adaptive system are the B- and T lymphocytes, and the antibodies are the humoral part of the adaptive system. As a response of the innate system to microorganisms, physical stress, aseptic tissue injury or ischemia, an inflammatory process develops (158). Toll-like receptors (TLRs) located at the macrophages have an essential role in inducing phagocytosis and production of albumin, fibrinogen, serum amyloid A protein and CRP, all as acute phase proteins (160). An acute response may in addition lead to cytokine production, which stimulates B- and T lymphocytes to create antigen specific responses. In an adaptive response, contact with a specific antigen (protein or polysaccharide part of pathogen) stimulates naïve T cells to proliferate and differentiate into decision-making effector cells.
Moreover, the evidence suggests cellular activation of microglia particularly in the hippocampus and whole-brain gray matter in individuals with schizophrenia (161, 162). Disturbances of other immune cells are also identified in patients with schizophrenia, but are considered beyond the scope of this thesis.

1.4.2.1 Cytokines

Cytokines are low-molecular weight proteins produced and secreted by different immune cells and other cells in response to environmental triggers, and play an essential role in early host defense against microorganisms. The innate immunity is

mediated by cytokines by inducing protective local inflammation and systemic acute phase responses. Cytokines are also involved in initiating, amplifying, mediating, and regulating adaptive immunity, and can cause tissue damage under excessive responses or autoimmunity (163-166). Furthermore, cytokines show effects on the recruitment and activation of lymphocytes, in addition to the control of immune cell differentiation and homeostasis. Some cytokines induce cell apoptosis and inhibition of protein synthesis by direct effector mechanisms. They bind to specific receptors on the membrane of target cells, trigger signal transduction pathways and subsequently alter gene expression in the target cells. Cytokines are grouped according to their main production sites and functions in the peripheral immune system. Cytokines Interlukin (IL)-1ß, IL-6, IL-2, IL-12, Interferon (IFN)-γ, and tumor necrosis factor (TNF)-α are often classified as pro-inflammatory cytokines due to their roles in the early defense against infection and the initiation and/or progression of inflammatory processes. IL-10, IL-4 and transforming growth factor (TGF)-ß are considered as anti-inflammatory cytokines, and limit both production and activity of many pro-inflammatory cytokines (167, 168). However, this dual categorization is questioned, since some of the cytokines pose both properties depending on the context (169). Cytokines and their receptors are expressed by glial and neuronal cell types in the adult central nervous system (CNS) (170). The fact that many cytokines and their receptors are constitutively expressed during fetal brain development in humans, might suggest their roles in the regulation of brain development (171). Therefore abnormal levels of cytokines during early brain development theoretically might influence neurodevelopmental processes with susceptibility for different complex brain disorders like schizophrenia (172).

Several reviews and meta-analysis studies have revealed alterations in cytokine levels in patients with schizophrenia (173, 174). Increased levels of the IL-1Ra, sIL-2R, IL-6 (175), increase in IL-1 β, IL-6 and TGF-β during acute exacerbations and FEP (176), increased levels of IL-1b, sIL-2R, IL-6, and TNF-a in drug-naive FEP (177), and elevation of IL-6, TNF-α, IL-1Ra, and sIL-2R in acute episodes (178) are some of the findings.

Furthermore, negative associations between pro-inflammatory cytokine levels, such as IL-2, IFN-γ, and TNF-α and prefrontal cortical thickness in individuals at risk of psychosis who develop a psychotic disorder (179) support the potential role of cytokines in the pathophysiology of psychotic disorders.

IL-1, IL-6 and TNF-α are considered to have major roles in the immune dysregulation pathway of schizophrenia, interact with CRP, and are reviewed in detail in the following.

IL-1 with its role in the differentiation and function of lymphoid cells is a central mediator of innate immunity and inflammation. It is mainly produced by activated macrophages, activated by for instance IFN- γ and bacterial products. The IL-1 family includes predominantly pro-inflammatory cytokines IL-1α, IL-β, IL-18, IL-33, IL-36α, IL36-β, IL36-γ, IL-1Ra, IL-36Ra, IL-38 and one anti-inflammatory cytokine IL-37. All cells of the innate immune system are affected by IL-1 family members. Binding of IL-1 initiates and strengthens the acute phase response by inducing fever, which in turn increases migration of leucocytes, by stimulating the acute phase proteins such as CRP, by activation of the hypothalamus-pituitary-adrenal (HPA) axis with cortisol regulating, and by inducing adhesion molecules with increase in leucocyte recruitment (158, 180).

IL-6 is produced by immune cells, adipocytes, skeletal muscle cells and endothelial cells, and the IL- 6 receptor (IL-6R) is located on macrophages, lymphocytes, neutrophils and hepatocytes. IL-6R exists in a soluble form (s); sIL-6R with circulating IL-6/sIL-6R complex. SIL-6R is formed by proteolytic shedding mostly from the surface of neutrophils and monocytes (181). The shedding process is stimulated by several factors including CRP (through this mechanism amplifies the IL-6 signaling), and IL-8 (182-184). In acute inflammation, IL-6 stimulates the expansion and activation of T cells and differentiation of B cells, and modulates the synthesis of acute phase reactants such as CRP, fibrinogen and albumin (185-188). Furthermore, other manifestations of acute inflammation, such as fever, activation of the HPA axis, anorexia, and lethargy are induced by IL-6 (185).

TNF-α is another pro-inflammatory cytokine with important functions in innate and adaptive immunity, cell proliferation and apoptotic processes. It is produced in macrophages, monocytes, T cells, adipocytes, fibroblasts and smooth muscle cells, with binding to TNF-RI and TNF-RII. These receptors are located on all human body cells except erythrocytes (189).TNF- α together with IL-6 and IL-1ß stimulate the CRP production (190, 191). Moreover, chronic inflammation is a common risk pathway for cardiovascular diseases and type 2 diabetes frequently observed in schizophrenia (190).

Taken together, evidence on alterations in cytokines level- and expression with normalization after treatment, and correlations between elevations in some of these cytokines and brain structure suggest that at least some of the cytokines may contribute to the pathophysiology in schizophrenia.

1.4.2.2 CRP

CRP is a protein synthesized in the liver, and was originally discovered in 1930 (192), due to the identification of a substance in the serum of patients with acute inflammation reacting with antibody against the carbohydrate (C) of the pneumococcus capsule. Hepatocytes are responsible for the synthesis of blood CRP (Gabay and Kushner, 1999), however, in obese individuals CRP is probably also produced by adipocytes leading to an increase in CRP (193, 194). CRP has a role in the innate immune system, and activates the complement cascade by binding to the surface of microbes or elements released from damaged cells (195). CRP as an acute-phase reactant with its well-established range interval has been considered as a reliable marker of inflammation for many decades (196).

There are several causes of increased CRP levels including acute and chronic states of infectious or non-infectious conditions, such as tissue and cell damage due to trauma. CRP is mainly induced by the IL-6 action on the gene responsible for transcription of CRP during the acute phase of an inflammatory or infectious process (197-199). However, IL-1, glucocorticoids and complement activation products, act in parallel with IL-6 and enhance its effect (199).

In daily clinical practice, a blood specimen is taken from a peripheral vein, and fasting is not required before the blood draw. The used high-sensitivity (hs)-CRP is usually reported in mg/L, allows a lower detection limit of 0.1mg/L (196, 200).

Certain medications, such as non-steroidal anti-inflammatory drugs (NSAIDs) will decrease CRP levels, however some studies show no association between for instance low dose aspirin use and CRP levels (201-203). The decreased CRP levels occur with both NSAIDs and statins by reduction in inflammatory response. Magnesium supplementation can also decrease CRP levels among individuals with CRP >3mg /L (204).

The level of CRP in healthy persons are generally considered to be < 3mg/L. CRP levels in the 3-10 mg/L range suggest low-grade inflammation, while CRP levels >10mg/L may suggest an inflammatory condition (205), and might be associated with infection in about 80% of cases (206). Moreover, elevations in CRP levels are associated with different factors including age, body mass index and smoking (207-210). Several studies have, however, reported marginal variations in the level of CRP related to age, gender and ethnicity (211-214). Minor CRP elevations are shown in individuals with low socio- economic status which might be attributed to the higher prevalence of infections and diseases (215), and poor dietary supply of nutrients in this group (208). CRP is also considered as a risk marker for cardiovascular events, with a threshold of CRP ≥ 2 to indicate increased cardiovascular risk (216) in the general population, and for mortality related to vascular and non-vascular diseases, several cancers and lung disease (217).

CRP and mental disorders

The association between the level of CRP and different mental disorders has been investigated for decades (218-226). The association between CRP and schizophrenia has been studied both with regards to its putative role in the pathogenesis and in relation to the symptomatology (227). In schizophrenia, elevated serum levels of CRP

have been found in some studies (228, 229), and the results from 2 meta-analysis are presented here.

A meta-analyses including 85 000 participants from 26 studies of CRP levels in individuals with schizophrenia showed moderately increased CRP levels regardless of the use of antipsychotics. The extent of the increase in CRP levels was associated with the severity of positive symptoms, and BMI (230). Another meta-analysis showed moderately increased level of CRP in individuals with schizophrenia, irrespective of study region, sample size of included studies, patient mean age, age of onset and BMI (227). Moreover, associations between elevated serum levels of CRP and more severe psychopathology (228, 231), treatment resistance (232), negative symptoms (233, 234), positive symptoms (234), depressive symptoms (235) and cognition (236, 237) have been found.
Moreover, a large genome-wide association (GWAS) study (238) and also a 2-Sample Mendelian Randomization Study (239) showed a preventive effect of genetically elevated levels of CRP on schizophrenia risk. The authors from the latter study speculated that the blockade of IL-6 signalling, and lower levels of CRP might increase susceptibility to early life infection, with possible increased risk of schizophrenia.

1.4.2.3 Neuroinflammatory signalling

There is evidence for various CRP related alterations in the CNS, such as associations between elevated CRP levels- and cerebral microstructural disintegration (240), blood-brain barrier permeability (241), white matter pathology (242), and reduced cortical thickness in frontal, insula, and temporal brain regions (237). Moreover, cytokines alterations have been suggested to be involved in neuroinflammatory processes, examples are the findings of a role for IL-6 and TNF-α in activating the hypothalamic–pituitary–adrenocortical axis (243, 244). Brain imaging studies have been conducted to demonstrate neuroinflammatory signaling, including PET, Magnetic resonance imaging (MRI) spectroscopy, diffusion tensor imaging (DTI).

Associations between DTI measures and the levels of IL-6 and CRP suggest the contribution of IL-6 and CRP to impaired anisotropy of water diffusion in immune related neural pathways (245). To what extent findings of a pro-inflammatory state in peripheral blood reflect brain inflammation needs to be clarified. The interactions between inflammatory markers and neurotransmitters might, however, shed light on the neuroinflammatory pathways. There is evidence on interactions between interleukins and neurotransmitter systems in schizophrenia (Figure 1), revealing an important role of at least two interleukins. IL-1β induces rat mesencephalic progenitor cells to be converted into a dopaminergic phenotype, and IL-6 decreases the survival of serotonergic neurons in the fetal brain (246, 247).

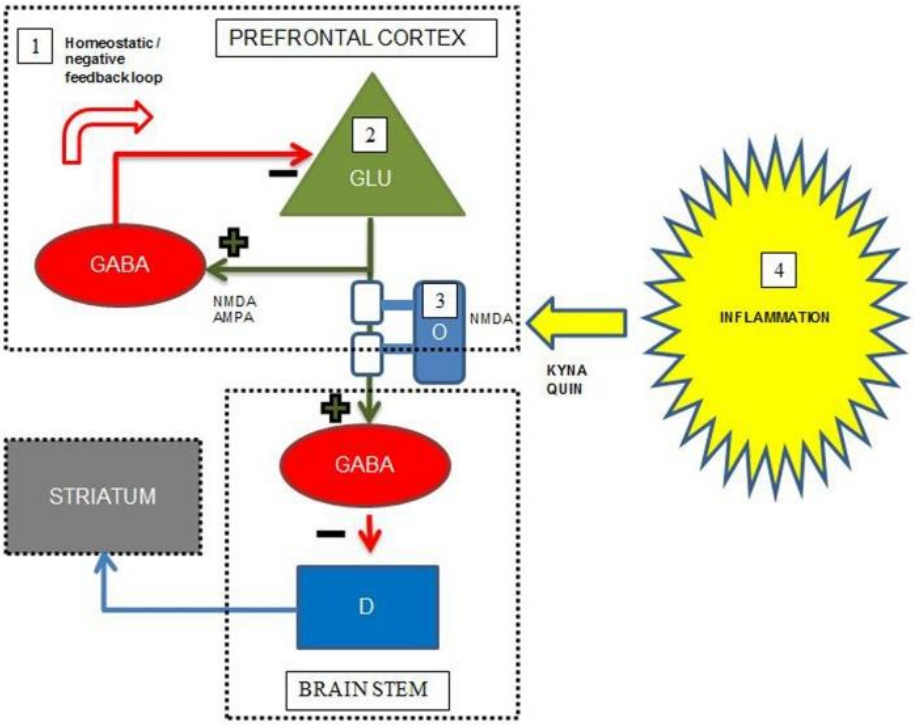

Figure 1.Simplified putative interplay between selected neurotransmitters, oligodendrocytes, and inflammation in the pathology of cognitive dysfunctions in schizophrenia.

GLU = excitatory pyramidal glutamatergic neuron, GABA = inhibitory GABAergic interneuron, D = dopaminergic neuron, O = oligodendrocyte with white myelin sheets enclosing the pyramidal cell axon, KYNA = kynurenic acid, QUIN = quinolinic acid. Adapted from (153) with permission.

Evidence from viral-like infection models in animal studies have shown increase in the number of mesencephalic dopaminergic neurons in the fetus brains (248), and association between chronic administration of IF-α and reduction in striatal dopamine release (249). These findings point to various effects of inflammation on dopaminergic neurotransmission in schizophrenia. Moreover, glutamate is involved in cytokine directed tryptophan-kynurenine metabolism, mediated via NMDAR (250-252). KYNA as the only known naturally occurring NMDAR antagonist in the human CNS is one of the intermediate neuroactive products in the kynurenine pathway (253). It is suggested that the immune response might inhibit indoleamine 2,3-dioxygenase (IDO), resulting in increased production of KYNA, with consequent antagonism at NMDAR and a lack of glutamate neurotransmission (254, 255).

1.4.2.4 Genetical aspects of immunity and inflammation in schizophrenia

GWAS have revealed a multitude of genetic risk variants with low effect (256), which indicates that environmental factors interacting with the genetic background contribute to the pathophysiology of schizophrenia (257). Findings from GWAS estimated that in schizophrenia about 8.300 single nucleotide polymorphisms (SNP)s contribute to a common risk of 32% (258). Furthermore, one of the largest schizophrenia GWAS conducted by the Schizophrenia Working group of the Psychiatric Genomics Consortium, including a total of 36,989 schizophrenia cases and 113,075 controls, has identified 128 independent genome-wide significant associations spanning 108 loci. The fact that associations were enriched among genes expressed in tissues that play important roles in immunity, independent of gene expression in brain, supports the hypothesized link between the immune system and schizophrenia (113). Significant association with several markers spanning the major

histocompatibility complex (MHC) region on chromosome 6 is consistent with an immune component to schizophrenia risk (131).

Moreover, findings from Danish national registers showed that a history of any autoimmune disease was associated with a 45% increase in risk for schizophrenia, that might indicate direct involvement of human leucocyte antigens (HLA) or physical closeness between loci for the autoimmune disorders and schizophrenia in HLA regions (259), which might support the correlation between immune responses and disease risk (260).

1.4.2.5 Environmental risk factors

Schizophrenia as a complex disorder is caused by both genetic and environmental factors and their interactions. Twin studies show a heritability of about 60– 80% in schizophrenia (261), which is higher than non-twin, with estimates ranging from 64% to 47.3% (262, 263). Different environmental factors in addition to a strong genetic contribution (264) seems to increase the risk of schizophrenia and other psychoses (265). Some of the following environmental factors are mentioned in the section of epidemiology, and are further discussed here due to their inflammatory aspects. Environmental factors are proposed to explain up to 60% of the risk (Benros et al., 2011). Factors involve prenatal or postnatal phases critical for CNS development, via a primary cerebral insult or pathological process long before the clinical manifestation of the illness (266-273). Perinatal factors including maternal infections, hypoxia, stress and malnutrition are, however, relevant for a small proportion of schizophrenia cases (114, 274-277).

Maternal infections

Several epidemiological studies have demonstrated an increased risk for schizophrenia in offspring of mothers exposed to influenza (278-280), although a meta-analysis found the validity of the serological studies related to the pandemic in1957 to be limited, due to high risk of misclassification of timing of exposure (281).

Infections with other viruses such as rubella, measles, varicella-zoster, polio, cytomegalovirus, and herpes simplex virus type 2, in addition to parasites such as Toxoplasma gondii, and genital/reproductive infections are associated with an increased risk of schizophrenia (119, 282-289). Furthermore a systematic review of prenatal maternal infection indicates that such infections with any of a number of pathogens are associated with the risk of schizophrenia –related psychosis in adult offspring (290).

Interestingly, associations between increased maternal serum levels of inflammatory markers such as CRP (291), pro-inflammatory cytokines IL-8 and TNF-α with increased risk of schizophrenia have been shown (292, 293). Moreover, elevated maternal anti-inflammatory cytokines; IL-4, IL-5 and IL-13 in pregnancy were associated with decreased risk of schizophrenia (294). It has been suggested that the induction of pro-inflammatory cytokines by the maternal immune system might have implications on altering early brain development, which can increase the risk of schizophrenia and related disorders (172, 295, 296). Furthermore, there is evidence for the association between obstetric complications and early-onset schizophrenia, which might indicate the involvement of neurodevelopmental impairment (275, 297, 298). Hypoxia is suggested as a possible mechanism between some of perinatal abnormalities and schizophrenia (299). Fetal hypoxia might lead to neuronal death, white matter damage with impaired myelination and reduced growth of dendrites (300). Hypoxia suppresses glutamate transport in astrocytes and therefore promotes extracellular accumulation of glutamate (301). Excess of glutamate might damage oligodendroglia and myelin with effects on oligodendrocyte differentiation, resulting in synaptic imbalance between axons and oligodendroglia, and dysfunction of the glial network of oligodendrocytes and astrocytes (302, 303). Furthermore, activation of microglia by hypoxic periods might mediate cell damage through nitric oxide synthase production, which links neonatal hypoxia to inflammatory processes (304).

To summarize, evidence indicate that in susceptible individuals, genetic and environmental factors might interact with abnormal cytokine signaling, myelin

damage and glial changes leading to abnormal in utero and early postnatal neurodevelopment. Thus, inflammation might act as a potential common mediator of other known prenatal and perinatal risk factors for schizophrenia (305).

Childhood infections

Childhood CNS infection have been associated with increased risks of subclinical psychotic symptoms in adolescence and schizophrenia later in adult life (292, 306-311). Furthermore, in a follow-up study of male participants with two or more hospitalizations for infections before the age of three, an 80% higher risk of schizophrenia were observed (312).

In a meta-analysis, a longitudinal association between higher serum CRP levels in adolescence and subsequent schizophrenia, as well as earlier age of onset have been shown (313). The immune response phenomenon of kindling, have been suggested as a possible mechanism, in which, an initial immune response to a stimulus, for instance stress or infection, strengthens the response and/or lowers the threshold for a response to future exposure to the same stimulus (314). This hypothesis supports the increased vulnerability or schizophrenia by stimulation of an inflammatory response both in the mothers in the second trimester or in the offspring, during the CNS developing phase. In the CNS, stress may cause activation and proliferation of microglia, which in turn may mediate the cytokine effects (315). Pro-inflammatory cytokine release has been described as common mechanism of infectious processes (316, 317).

Childhood trauma

Several studies have identified higher frequency of childhood maltreatment in patients with severe mental disorders including schizophrenia (318-320). Findings from a study of childhood trauma which compared patients with schizophrenia spectrum disorders and substance abuse showed that 64.9 % of patients from both groups were exposed to childhood trauma (321). Elevated emotional reactivity to stress,

alterations in the HPA axis, or augmentation of the effect of childhood trauma due to have been proposed as involved mechanisms (322-324). With regards to inflammation, findings from FEP studies show that only cases exposed to childhood trauma demonstrated higher levels of CRP (318) and TNF-α- (325) compared with a healthy control group. In a study of individuals with psychosis spectrum disorder with a diagnosis of schizophrenia or bipolar disorder, elevated CRP levels and higher BMI levels were found in both groups, and the level was also associated with the number of abuse types, emotional, physical or sexual abuse (319). The authors suggested that trauma-related immune activation and CRP elevation in patients with schizophrenia and bipolar disorders could be mediated by higher BMI, but the direction of this relationship needs to be clarified.

In a recent study of patients with schizophrenia/schizoaffective or psychotic bipolar disorders pro-inflammatory cytokines IL-6, TNF- α and CRP were higher only in the schizophrenia group compared with healthy controls, and CRP levels were positively associated with sexual abuse only in the schizophrenia group (320). Associations between increased pro-inflammatory cytokines and CRP levels, and childhood trauma in schizophrenia, might thus suggest the role of early trauma exposure on activation of immune system.

Autoimmunity

Associations between autoimmune disorders and schizophrenia has been shown repeatedly, and recent studies suggest an autoimmune model for schizophrenia (326). Findings from birth registry studies have shown positive association between a range of autoimmune related disorders such as multiple sclerosis, systemic lupus erythematosus, autoimmune thyrotoxicosis, autoimmune hepatitis, psoriasis and diagnosis of schizophrenia or psychosis (259, 327-330). However, an inverse correlation in prevalence between rheumatoid arthritis and schizophrenia has been documented (328, 331-333). In a Danish cohort study a significant relationship between autoimmune disease, the number of severe infections, and the risk of schizophrenia were found, that might suggest a common pathogenic mechanism

(334). Moreover, a history of an infection, and exposure to anti-infective agents such as antibiotics, as well as having a family member with schizophrenia elevated significantly the risk for developing an autoimmune disease (327, 335). Interestingly, it is suggested that a contemporary inflammatory process associated with autoimmune disease and/or infection might affect the brain through increased permeability of the blood-brain barrier mediated by autoantibodies and cytokines (336). Autoimmune encephalitis with psychotic symptoms is considered as a disease entity of organic psychosis with autoantibodies against synaptic and neuronal cell surface antigens such as NMDAR (115, 337, 338).

To summarize, the causes of schizophrenia are not fully clarified yet, but evidence from several studies suggest that the disorder might be a product of gene and environmental factors interacting during critical neurodevelopmental time points (113, 339-342). The very elegant summarizing message (326) should be adapted as whole; Studies in schizophrenia reveal an intricate association of environmentally-driven immune activation in concert with a disrupted genetic template.

1.5 Treatment of schizophrenia

Management of patients with schizophrenia consist of various therapeutic approaches including pharmacological treatments, psychologic interventions, especially cognitive behaviour therapy (343, 344), family interventions (344-346), work/employment supports (347), social- and life skills training (344, 348), and cognitive enhancement programs (349, 350). Exercise interventions are shown to improve both the psychiatric and comorbid somatic conditions (351). Moreover, a review of studies on music therapy showed that music therapy used as add-on to standard treatment might improve negative and general symptoms, as well as quality of life in patients with schizophrenia (352). In a meta-analysis a better treatment effect was shown in the patients who received adjunct music therapy regarding negative symptoms, mood symptoms, and positive symptoms (353). Finally, the treatment of comorbid somatic condition is an essential part of the management of patients with schizophrenia (354).

Furthermore, over the past two decades there has been increasing interest in psychological and pharmacological interventions to prevent or delay the transition of the prodromal state to florid psychosis, with mixed results (355-360). Such interventions can in addition, treat current co-morbidities such as depressive or anxiety symptoms, and might improve outcome in individuals at risk for psychosis. With already engaged treatment, in case of transition to psychosis, the duration of untreated psychosis can be minimized, and might improve outcome (356, 357).

1.5.1 Antipsychotic drugs

The discovery of chlorpromazine in the 1950s (361-363) and development of clozapine in 1958 (364) are considered as two major milestones in the pharmacological treatment of schizophrenia (365). The first antipsychotic drugs developed in the 1950s and 1960s were characterized by dopamine D2 receptor antagonisms of varying potency among the different agents, and are nowadays generally classified as first generation antipsychotics (FGA) or typical antipsychotic drugs. FGAs such as haloperidol and perphenazine are all targeting the striatal hyperdopaminergia, and the main mechanisms of action are related to their D2 receptor antagonism (136). The side effect profiles of the FGAs include extrapyramidal symptoms (EPS), and the emergence of EPS was for a long time considered necessary for their antipsychotic efficacy. This dogma was challenged by a group of German researchers, who subsequently demonstrated the efficacy of clozapine, an agent that had the “atypical” characteristic of being a very efficacious antipsychotic drug despite very low propensity for inducing EPS (364). Despite the association of striatal dopamine blockade with the risk of EPS, it is important to note that this is not the critical site of action for therapeutic effect, which occurs most prominently in the mesolimbic brain system (366). During the past five decades several FGA and later second generation antipsychotics (SGA)s have been developed, which all block D2 striatal receptors (367). The SGAs are pharmacologically characterized by relatively weaker affinity for the D2 receptor compared to the FGAs, and a strong affinity for the serotonergic 5 hydroxytryptamine 2A (HT2A) receptor

(368, 369). An exception to this general rule concerns amisulpride, which despite having an "atypical" profile clinically, only targets the dopaminergic system with high-affinity and highly selective D2/D3 receptor antagonism (370). It is suggested that its selective affinity for dopamine receptors in the limbic structures, but not in the striatum, leads to a low risk of extrapyramidal side effects (371). Furthermore, it has been suggested that in low doses it preferentially blocks presynaptic dopamine autoreceptors, which facilitates dopaminergic transmission with effects on negative symptoms (372).

Aripiprazole is distinguished from other antipsychotics by its partial agonist activity at D2, D3, 5-HT1A, and 5-HT2C receptor targets (373-375). *In vitro*, aripiprazole is a neutral antagonist or very weak partial agonist at 5-HT2A and 5-HT7, and is an inverse agonist at 5-HT2B receptors (374). As a D2 receptor partial agonist with moderate intrinsic activity, aripiprazole might functionally antagonize transmission at postsynaptic D2 receptors in neural systems with high dopaminergic tone, as in the striatal dopamine system of schizophrenic patients, which may account for its effects on positive symptoms. Oppositely, it may activate postsynaptic D2 receptors in neural systems with low dopaminergic tone, as in the mesocortical system, which may account for its putative effects on negative and cognitive symptoms in patients with schizophrenia. Besides partial agonist activity at D2 receptors, aripiprazole's agonist activity at 5-HT1A receptors, from partial to full agonist depending on the cellular system, may also contribute to its efficacy and reduced side effects, relative to FGAs. Aripiprazole activates 5-HT1A receptors, reducing serotonin release and subsequently increasing dopamine release in the cortex, which might improve negative and cognitive symptoms of schizophrenia (376). Relative to other SGAs, such as clozapine and olanzapine, aripiprazole has a lower weight gain-inducing propensity (377), as SGAs are potent 5-HT2C and H1 antagonists or inverse agonists contributing to their tendency to induce weight gain (377). Aripiprazole is conversely a partial agonist at the 5-HT2C receptor, similar to lorcaserin, an effective weight reducing agent with selective 5-HT2C agonism (377). Aripiprazole with its different dopamine receptor-binding profile is sometimes referred to as a third-generation

antipsychotic, and its stabilizing function leads to symptoms improvement and lower potential for EPS, sedation, and hyperprolactinemia compared to other antipsychotics (378).

There are, however, some limitations to the dopamine hypothesis in schizophrenia. Current antipsychotics are mainly effective against positive symptoms, while they are less effective against negative symptoms and cognitive dysfunctions (153, 379). The fact that clozapine shows a unique therapeutic efficacy in many of non-responder patients despite low affinity for/occupancy at D2 receptors, questions the D2 receptor's role as a global phenomenon in all patients with psychosis (137, 380). Furthermore, current treatments in psychosis, including psychosocial interventions and antipsychotic medications, have few if any beneficial effects on cognitive performance (153, 381-386). There are, however, findings of significant improvements in cognition in early-psychosis patients, using atypical or typical antipsychotics (384, 387), together with meta-analysis findings of no global differences in cognition for typical versus atypical anti-psychotics (385).

1.5.2 Pro-cognitive effects of antipsychotic drugs

Effect of antipsychotics on cognition has been widely studied (71-74). In a randomized double-blind treatment trial including 817 schizophrenia patients, who received one of the following antipsychotics olanzapine, perphenazine, quetiapine, risperidone, and ziprasidone a small but significant improvement in cognitive ability in all cognitive domains, and with all of the antipsychotics were found after two months (388). A follow-up study of first-episode schizophrenia spectrum disorders with follow-up intervals of 1-year and 3-years showed improvement of the cognitive performance in all domains (70). Another longitudinal study demonstrated improvement of general cognitive function, working memory, and verbal learning after 12 weeks, but these changes were mediated by improvements in both positive and negative symptoms (389).

To summarize, current antipsychotic treatment options in patients with schizophrenia have small beneficial effects on cognitive performance (153, 381-385).

1.5.3 Anti-inflammatory effects of antipsychotic drugs

The immune modulatory effects of antipsychotics have been studied, also with regards to the impact on levels of inflammatory markers, however, with mixed results.

General effects on inflammation

There have been several studies including patients with schizophrenia in order to clarify the effects of SGAs on the levels of inflammatory markers such as CRP and cytokines (230, 390-394).

With regards to effects of antipsychotics on cytokines, the results are mixed. Meta-analyses and other studies of the antipsychotics have revealed both anti- and pro-inflammatory effects by alterations in the levels of IL-1β, IFN-γ, IL-6, TGF- β, IL-1b, TNF-α, IFN- γ, IL-12, IL-23, IL-1RA, sTNF-R1, IL-10, IL-4, and IL-2 (176, 391, 395-398).

Effects on CRP

There are several studies with a focus on CRP levels in patients with schizophrenia, and the results are mixed. A meta-analysis of 26 studies including 85 000 participants showed moderately increased CRP levels in schizophrenia regardless of the use of antipsychotics, and with not significant changes between the first episode of psychosis and progression of the illness (230). Findings from a study of the effects of the antipsychotics olanzapine, risperidone, ziprazidone, quetiapine and perphenazine on CRP levels showed that olanzapine and quetiapine had the highest median levels for CRP after 3 months treatment (393). The 18-month repeated measures CRP analysis confirmed significantly higher values for olanzapine in those with low baseline CRP (393). In a recent study aripiprazole was the only antipsychotic drug associated with decreased CRP levels compared to the other antipsychotics;

quetiapine, olanzapine, amisulpride, clozapine, loxapine, risperidone zuclopenthixol, paliperidone, and cyamemazine (399). Findings from a study of patients with schizophrenia consisting of 67 antipsychotic medicated and 28 psychotropic medication-free schizophrenia patients showed a significantly higher level of CRP and IL-6 among the antipsychotic medicated patients(400). In a 4- weeks follow-up study of 17 chronic schizophrenia patients, previously medicated with typical or atypical oral antipsychotics (haloperidol, perazine, zuclopenthixol, perphenazine, ziprazidone, risperidone, quetiapine, olanzapine, and amisulpride) switching to aripiprazole showed a significant reduction in CRP level (391). Taken together the results from studies regarding the effects of antipsychotics on the levels of inflammatory markers including CRP and cytokines are mixed, and there is in addition a gap between results and possibilities for individualized treatments with anti-inflammatory capabilities in patients with detected low-grade inflammatory status.

2. Aims of the study

The overall aim of this thesis was to investigate the CRP levels and changes isolated and in relation to cognition in a current episode of psychosis in clinically relevant sample. The investigations were conducted in a pragmatic design.

Specific aims

1. To investigate the relationship between CRP level and cognition in the acute phase of psychosis (paper 1).
2. To study the correlation between initial changes in CRP levels and later changes in cognition during the first 6 months after acute psychosis (Paper 2).
3. To investigate the effect of antipsychotic drug treatment on CRP levels in acute phase of psychosis and throughout the 1-year follow-up (paper 3).

3. Methods

3.1 Setting

3.1.1 Recruiting centers

Bergen psychosis Project (BP)

Haukeland University hospital, Bergen, 226 patients

BestIntro

Haukeland University Hospital, Bergen 102 patients
Stavanger University Hospital, Stavanger 13 patients
Medizinische Universität Innsbruck, Innsbruck 24 patients
St. Olav's University Hospital, Trondheim 5 patients

3.2 Study population

Patients with an acute psychotic episode and indication for oral antipsychotic treatment were included in the studies.

3.2.1 Inclusion and exclusion criteria

BP

The inclusion criteria were as following:

- Age ≥ 18 years.
- Admitted to the psychiatric emergency ward for symptoms of psychosis, determined by a score of ≥ 4 on one or more of the PANSS (17) items of

delusions (P1), hallucinations (P3), grandiosity (P5), suspiciousness/ persecution (P6) or unusual thought content (G9).

- Being able to cooperate on clinical and laboratory assessments.
- Being candidate for oral antipsychotic drug therapy with one of the four first-line atypical antipsychotics available in Norway.

The current first-line atypical antipsychotics of the trial were risperidone, olanzapine, quetiapine, and ziprasidone. Patients were included consecutively due to psychosis based on the presence of psychotic symptoms independent of the diagnostic group. The diagnostic evaluations were conducted by the treating clinicians. The participants had to meet ICD-10 (401) diagnostic criteria for schizophrenia, schizoaffective disorder, acute and transient psychotic disorder, delusional disorder, drug-induced psychosis, bipolar disorder except manic psychosis, and major depressive disorder with psychotic symptoms. The initiation of antipsychotic treatment before the determination of diagnosis was conducted in order to keep the naturalistic design similar to common clinical practice.

The exclusion criteria were being unable to use oral antipsychotics, candidates for electroconvulsive therapy, experiencing a manic psychosis state, being unable to cooperate reliably during investigations, not understanding Norwegian language, organic brain disorder, such as dementia, and using clozapine.

BestIntro

The inclusion criteria were as following:

- Age ≥ 18 years.
- Symptoms of psychosis compatible with a diagnosis within the schizophrenia spectrum according to (F20-F29) of the ICD-10 (401) and DSM-4 (402).
- A score of ≥ 4 on one or more of defining PANSS items P1, P3, P5, P6 or G9.
- Being candidate for oral antipsychotic drug treatment determined by their treating physician or psychiatrist.

All patients were informed about the project by oral and written information, and written informed consent was necessary before inclusion. The diagnoses were determined by the study personnel consisting of specialists in psychology, residents and psychiatrists under supervision of senior consultant psychiatrists using the Structured Clinical Interview for the DSM-IV, (SCID-I) (402).
The exclusion criteria included diagnosis other than the schizophrenia spectrum, not understanding Norwegian language, organic psychosis; antibody- verified limbic encephalitis, hypersensitivity to the active substances, pregnancy, lactation, and contraindications for the respective study drugs.

3.2.2 Withdrawal criteria

The criteria for study withdrawal were serious somatic events with indication for specific follow-up different from the protocol of the trials, pregnancy, and inevitable indication for concomitant use of more than one antipsychotic drug. Meanwhile, change of antipsychotic medication due to inadequate efficacy, side effects or interactions was not considered as an exclusion criterion.

3.3 Study design

BP

The BP was a 2-year, prospective and pragmatic antipsychotic drug trial (403), and patients were consecutively recruited during March 2004- February 2009. The participants were admitted at psychiatric emergency ward of the Haukeland University Hospital in Bergen, Norway, which had a catchment area of about 400,000. Assessments were performed at baseline, discharge or latest after 6 weeks, after 3, 6, 12 and 24 months. The assessments were conducted by raters blinded to the treatment. The patients were consecutively randomized to a sequence for treatment with 1 of 4 atypical antipsychotics consisting of olanzapine, quetiapine, risperidone or ziprasidone. The patient was offered the first drug in a random sequence. The

randomization was open to the patient and treating psychiatrist/ physician, who both could discard the number 1 atypical antipsychotic on the list, due to medical contraindications or previous adverse experiences with the drug. The next drug on the list could then be chosen, and the same principle was followed throughout the sequence. In each sequence, the atypical antipsychotic listed as number 1 defined the Randomization group, and the chosen atypical antipsychotic, regardless of randomization group, defined the First choice group. If a patient already used an antipsychotic medication at admission, no wash-out was performed before starting the study medication. In the case of randomization to the already used drug, the agent would be continued, with possibility for dose adjustment. The treatment regimen was open for the patient and physician. The minimum interval accepted for the first follow-up was one week, and discharge from the hospital before one week was the main reason for drop-out between baseline and discharge.

BestIntro

The BestIntro was a 1-year, randomized, head-to-head comparison study of amisulpride, aripiprazole and olanzapine. The participants were assessed at baseline, after 1week, 3 weeks, 6 weeks, 3 months, 6 months, 9 months and 12 months. Patients were consecutively recruited between October 2011- December 2017 through a multi-centre cooperation between the Division of Psychiatry at Haukeland University Hospital, Stavanger University Hospital, and St. Olav University Hospital in Norway and the Medizinische Universität Innsbruck in Austria. The randomization and process were practically identical to the above –mentioned procedure for BP, however with some differences regarding assessments, which will be discussed under data and variables.

3.4 Treatment

The study medications were prescribed as tablets, and the patient's psychiatrist or treating physician had the responsibility for the initiation, dosage and any subsequent

changes or termination of the study medication. The dosage of the antipsychotic drug or other medication was within the dosage range set by the Summary of Product Characteristics. The dosage ranges for BestIntro were 50-1200 mg/ day for amisulpride, aripiprazole 5-30 mg/ day for aripiprazole and 2.5-20 mg/ day for olanzapine. In order to resemble usual clinical practice, concomitant medications were permitted with the exception of additional antipsychotic drugs which were not allowed, in line with current treatment guidelines (404). The exception was cross-titration during antipsychotic drug switches.

3.5 Data and variables

BP

The assessment included background information, medical history, laboratory blood tests including CRP, urinalysis for illicit drugs and ECG at admission, while measurement of blood pressure, BMI, and psychometric assessments were conducted at all visits. Blood samples were collected from the fasting patients at 08-10 a.m. for analyses of CRP levels. There was a change in the laboratory's CRP analysis methods in January 2005, and hence only data obtained after this change is reported in the present work. The method used is the Tina-quant C-reactive Protein (Latex) from Roche Modular P®, which measures CRP levels >1.00 mg/L.

The psychometric assessment instruments were internationally certified, and assessed symptomatology of psychosis with PANSS, depression with Calgary depression rating scale (CDSS) (405), illicit drug use with Clinical drug and alcohol use scales (CDUS/CAUS) (406), general clinical impression with Clinical global impression (CGI) (407) and functioning with Global assessment of functioning-split version, Functions scale (GAF-F) (402). Cognitive functions were assessed with the Repeatable battery for the assessment of neuropsychological status (RBANS) (408, 409), Trail making test (410), Controlled Oral Word Association Test COWAT (411);

Rey Osterrieth Complex Figure Test (ROCF) (412); California Computerized Assessment Package-Continuous Performance Test (CalCAP CPT) (413); The California Verbal Learning Test (CVLT) (414); Wechsler Adult Intelligence Scale-III-Revised (WAIS-III-R) (415) and Wechsler Memory Scale-Revised (WMS)-R (416). Cognitive functions were assessed according to the Table1.

Table 1. Neuropsychological assessment by cognitive subdomain and time.

	T1 (Baseline)	T2 (4 weeks*)	T3 (3 months)	T4 (6 months)
Verbal abilities	RBANS A language	RBANS B language	WAIS-III Similarities WAIS-III Vocabulary COWAT Letters/animals	COWAT Letters/animals
Visuospatial abilities	RBANS A visuospatial/ constructional	RBANS B visuospatial/ constructional	WAIS-III Digit Symbol-coding WAIS-III Block design ROCF Copy	ROCF Copy
Attention	RBANS A attention	RBANS B attention	WAIS-III Digit Span Digit Vigilance Test (time) CalCAP CPT (Choice Reaction Time/Sequential Reaction Time) Trail Making test B Stroop colour/word conflict (time)	WAIS-III Digit Span CalCAP CPT (Choice Reaction Time/Sequential Reaction Time) Stroop colour/word conflict (time)
Learning	RBANS A immediate memory	RBANS B immediate memory	CVLT-II (Immediate Recall) WMS-R Logical Memory WAIS-III Digit Span	WMS-R Logical Memory WAIS-III Digit Span
Memory	RBANS A delayed memory	RBANS B delayed memory	CVLT-II (Delayed Recall) ROCF Delayed recall	ROCF Delayed recall

Notes:

*****Mean follow-up time at T2 was 4.1 weeks after baseline. RBANS (Repeatable Battery for the Assessment of Neuropsychological Status); WAIS-III (Wechsler Adult Intelligence Scale); COWAT (Controlled Oral Word Association Test); ROCF (Rey Osterrieth Complex Figure Test); CalCAP CPT (California Computerized Assessment Package-Continuous Performance Test); WMS-R (Wechsler Memory Scale-Revised).

BestIntro

The assessment procedures resembled BP, except for the neurocognitive assessment blood tests, and additional structural and functional MRI. Blood tests were conducted at all visits and included CRP, in addition to urinalysis for illicit drugs. Blood samples were collected from the fasting patients 08-10 a.m. The CRP level was measured by the Tina-quant C-reactive protein (Latex) method from Roche Modular P®, which measures CRP levels > 1 mg/L. The neurocognitive assessments of the BestIntro are not discussed in this thesis, since paper 3 from this study investigated the CRP levels, and not cognitive function.

3.6 Statistics

SPSS software version 20.0 and 24.0 were used for baseline analyses, group comparisons and predictions (417). Descriptive analyses were mean, standard deviation (SD), and frequency. Comparisons were analysed with correlations and multiple regressions for continuous data, analysis of variance (ANOVA) and Independent samples T-tests for differences in continuous variables on group factors, while cross tabulations with χ^2 tests were used for categorical data. Linear regression analyses were also used for adjusting for potential confounders. The level of statistical significance was set at $\alpha = 0.05$, two-sided.

Mplus version 7 and 8 were used to estimate level and change in all three studies (418, 419). Standard Mplus models use all available data under the “missing at random” assumption (420, 421), which minimize the effect of missing data and improves the generalizability (422, 423).

The robust maximum likelihood was used to give unbiased standard errors if outcome variables were found to be non-normal (424). If analyzing more than two measurement points (paper 2 and 3), linear change was first tested and evaluated with standard fit measures (425, 426). Satisfactory fit is indicated by statistically non-significant chi-square, normed fit index (NFI) and Tucker-Lewis index (TLI) < .95, and root mean square error of approximation (RMSEA) < .05 (close fit), < .08 (fair fit) or < .10 (Mediocre fit), including RMSEA confidence intervals and probability of close fit in the population (427, 428). In addition, the residual results and plots of the observed and estimated level and change were used to evaluate the standard linear change assumption. If model did not fit data very well, latent piecewise models or contrast score models (latent variable difference model) were tested, describing limited intervals or differences between the measurement points. If models were found to be too simple (paper 1), or too complex regarding shape of change and the number of estimated parameters, residuals or other parameters had to be fixed to zero in order to identify the model (429, 430). In paper 3, lag one residual relations were estimated in order to account for stability in variance not accounted for the model (431).

After fitting the level and change, predictors were added to the model. Control variables were accounted for in order to reduce biases. Variables not accounting for any relations were removed and model re-estimated based on a backward hierarchical procedure (432), a procedure that improves the probability to reveal suppressor relationships. In paper 3, two contrast variables were used to analyze medication differences of aripiprazole and olanzapine in relation to the reference drug amisulpride. Model constraints were used to compare the two regression weights also to compare the difference between aripiprazole and olanzapine. Both randomized and actual used medications were analyzed in separate models. Interaction terms were added to study medication differences dependent on relevant covariate variables.

3.7 Approvals and ethical considerations

The BP and the Best Intro were approved by the Regional Committee for Medical Research Ethics West-Norway and the Norwegian Social Science Data Services. The projects were financed by the Research Council of Norway, the Western Norway Regional Health Authority and Division of Psychiatry, Haukeland University Hospital, and were independent of financial or marketing support from the pharmaceutical industry.

Regarding the BP, the approval was granted to a two phase design. The first phase (quality assurance phase) was from admission to discharge/latest after 6 weeks, and was approved by the ethics committee to include the eligible patients prior to informed consent, assuring all acute psychotic patients guideline-concordant treatment. The second phase (research phase) was from discharge/latest after 6 weeks, based on informed consent, and included follow-up visits 3, 6, 12, and 24 months after admission. The procedures of this phase were beyond usual clinical standard, such as collections of data for use in psychiatric basic research within genetics and brain functional imaging.

The BestIntro was in addition approved by the Norwegian Medicines Agency, the Etikkommission der Medizinische Universität Innsbruck, and the Austrian Federal Office for Safety in Health Care (BASG). The Best Intro was conducted in accordance with Good Clinical Practice (GCP) standards (433), and the Norwegian Health Research Act (434). Clinical monitoring in accordance with International Conference on Harmonisation - GCP (ICH-GCP) was conducted by the Department of Research and Development, Haukeland University Hospital in Norway, and by the Clinical Trial Centre at the Medical University Innsbruck in Austria. Informed consent was needed prior the RCT inclusion and randomization.

4. Results

4.1 Paper I

A total of 124 consecutive patients in acute phase of psychosis admitted to the psychiatric emergency unit were included in this study, a sub-study of the BP (67.7% male, and mean age 33.5 years). At admission 51.6% of patients were antipsychotic-naïv, with a mean CRP level of 3.6 (SD 5.2), and mean overall cognitive function t-score of 37.8 (SD 7.7). This study reported data for all groups collectively, as cross-sectional baseline comparisons of treatment groups revealed no differences between the medication groups. The main findings were an inverse relationship at baseline between serum levels of CRP and overall cognitive performance, as well as for the subdomains delayed memory and attention. The association between overall cognitive function and CRP levels was particularly strong for the subgroup with schizophrenia. A total of 62 patients were retested for cognitive function at follow-up after 28.3 days (SD 11.1), and there was no association between CRP levels and cognitive function at the end of the acute phase. Furthermore, the baseline CRP level predicted the overall cognitive change during the follow-up interval. There were no statistically significant associations between the CRP level and the scores of PANSS total, PANSS positive, negative, and general psychopathology subscales, the CDSS, the GAF-F, and the CGI.

4.2 Paper II

A total of 208 (68.8 % male and mean age 33.5 years) consecutive BP patients in acute phase of psychosis who had data in one or more of the outcome variables of CRP and/or cognition were included in this study. This study reported data for all treatment groups collectively, and did not compare treatment groups. Measurements of CRP and cognitive performance were conducted at baseline (T1) and after 28.3 days on average (T2). Cognition was also assessed after 3 months (T3) and 6 months (T4). At baseline the mean CRP level was 4.0 (SD 8.3), the mean overall cognitive

function t-score was 38.3 (7.7), and 44.2 % were antipsychotic- naïve. The main finding of the present study was that the global cognitive performance continued to improve from the initial phase of acute psychosis (T1-T2) to the later phase (T2-T4), and this improvement was predicted by the reduction of the CRP level as observed during the initial phase (T1-T2) of the treatment. Patients with most reduction in CRP showed the most improvement in global cognitive performance, compared to those with a smaller reduction or an increase in CRP. The different cognitive subdomains showed different time-dependent profiles of improvement, with memory and attention improving significantly also in the later phases. An inverse association between change in CRP level and verbal abilities (T2–T4 interval), and attention (T2–T3 interval) were found, in addition to similar associations for some of the other cognitive subdomains. For patients with CRP < 10 mg/L (N = 191), the association between changes in global cognitive performance (T2-T4), verbal abilities (T2-T4), and attention (T2-T3), and CRP level changes remained unchanged. After adjustment for the covariates metabolic syndrome, smoking, being medication naïve, illicit drug use, and the educational level, the association between baseline CRP level and global cognitive performance for the whole follow-up remained essentially unchanged. In sensitivity analysis of the sub-sample of patients diagnosed within the schizophrenia spectrum change in CRP did not predict change in global cognition score, but predicted change in attention for the T1-T2 and T3-T4 intervals respectively.

4.3 Paper III

A total of 128 (64% male, and mean age 31.9 years) consecutive in- and out-patients with symptoms of acute phase psychosis were included in this study. The patients were recruited through the BestIntro study, of which 39% were antipsychotic-naïve. The sample represented patients with symptoms of acute psychosis compatible with schizophrenia spectrum disorders. There was a statistically significant increase in CRP levels during the first 1-3 weeks of the study for the whole group, and the increased levels lasted for 52 weeks. The three antipsychotics showed different effects on CRP levels, with aripiprazole reducing it for the first week of treatment.

Antipsychotic-naïve patients had lower levels of CRP, but had an increase upon medication similar to the previously medicated patients.

Analyses of interaction effects revealed an initial increase followed by decrease of CRP levels in drug-naïve aripiprazole treated patients, with the opposite pattern for previously medicated patients. Besides, lower baseline level in CRP was associated with being medication naïve, having lower BMI levels and the absence of CVD. The present study also found that a higher baseline BMI was associated with stronger reduction in CRP in the 1-3 weeks interval.

5. Discussion

5.1 Discussion of main results

In this section the results from paper 1 and paper 2 will be discussed first, since the papers were thematically united on the association between CRP level and cognitive function. The results from paper 3 with regard to the effect of antipsychotics on CRP will be thereafter be discussed.

5.1.1 Association between CRP level and cognitive function

The main findings of paper 1 were the inverse relationship between baseline CRP level and overall cognitive performance, delayed memory, and attention, respectively. The findings are in line with one of the first studies on this topic, where elevated CRP level was associated with cognitive impairment in individuals with schizophrenia (236), followed by other studies on this topic (435-437). However, paper 1 adds new evidence also with regards to the longitudinal perspective, and antipsychotic-naïve patient group. In one of studies, elevated CRP levels were correlated with poorer cognitive functioning of general intellectual ability, abstract reasoning, memory, working memory, semantic memory, learning abilities, attention, mental flexibility, and processing speed (435). A recent study found significant working memory differences between elevated (CRP $\geq$ 3) and normal CRP levels in chronically ill patients, which sustained after adjusting for BMI (237). Moreover, the same study showed for the first time that CRP level significantly and inversely, predicted the cortical thickness in most (8/9) of the brain regions, specially involving frontal lobe which might be especially sensitive to inflammation (237). An inverse relationship between CRP levels and cortical thickness in prefrontal regions, and reduced memory performance in patients with schizophrenia support the evidence for involvement of inflammatory processes in the cognitive impairments in psychosis (438-441).

In our sub-analyses of only patients with CRP levels < 15 mg/ L (to exclude acute inflammation), strengthening of the inverse association between CRP levels and overall cognitive performance was observed, while the association remained significant between CRP levels and the cognitive subdomains except immediate memory. Secondary analysis including only the schizophrenia sub-group showed that the inverse association between CRP levels and overall cognitive performance was markedly increased, which might indicate that in the schizophrenia sub-group the acute phase inflammatory response underpins the cognitive dysfunction.

There was in addition a significant increase in cognitive performance between baseline and follow-up after 4/latest 6 weeks, with a stronger increase in overall cognition in patients with higher baseline CRP levels. This effect might be at least partly due to the illness phase, with regard to cases of first-episode psychosis/ hyper-acute state and reflecting the higher baseline CRP level. The patients were included before providing the informed consent, which might have contributed indirectly to assessment in an earlier phase of psychosis.

We, however, did not find statistically significant correlations between CRP level and other measures of psychopathology including psychosis symptoms, depression, or functioning. This is in line with the above-mentioned study (237) and another cross-sectional study (236), where no association between CRP and PANSS symptom severity was found. A potential explanation might be the fact that cognitive symptoms often manifest prior to psychotic symptoms. However, there are also findings on greater severity of negative and general symptoms in patients with schizophrenia associated with elevated CRP levels (228).

Moving to paper 2, the main findings were that the global cognitive performance continued to improve beyond the initial phase (T1-T2) of acute psychosis to the later phase T2-T4, however, being most pronounced during the T1-T2 (T1: baseline, T2: after 4 weeks/latest 6 weeks, T3: 3 months and T4: 6 months). Similar associations were found for several of the cognitive subdomains, such as improvement in verbal abilities, learning and attention during the T1–T2 interval, and in memory and

attention during the T2–T4 interval, respectively. The course of cognitive performance in patients with acute psychosis has been studied over decades. Several studies have suggested stability or decline in cognitive functioning (442-445). However, there is increasing evidence for improvement in cognitive function. A follow-up study of FEP schizophrenia spectrum disorders with intervals of 1-year and 3-years showed that, the cognitive performance of the patients improved in all domains similar to controls, except for verbal and visual memory, which showed greater improvement in controls (70). Another longitudinal study demonstrated improvement of general cognitive function, working memory, and verbal learning after 12 weeks, but these changes were mediated by improvements in both positive and negative symptoms (389). A recent longitudinal study of FEP patients showed improvement in verbal- learning and fluency after one year (446). Similarly, cognitive improvement in almost all domains was found in schizophrenic adolescents, after six months of treatment with antipsychotics (447). Improvement in working memory after 12 weeks of antipsychotic treatment in FEP antipsychotic-naïve patients is among recent findings (448).

Regarding our observations of interval related improvements of cognitive performance, they might be influenced by the phase where treatment was initiated. In first episode patients, significant improvement in cognition has been reported in FEP patients from as early as 3 months after treatment (389), after 3-years (449) and up to 5-years follow-up of FEP or recent-onset schizophrenia (450). Cognitive function in the chronic stage of the illness is described as static, with no significant improvements (451). These finding together with our results might support the idea that by adequate treatment in the early stages of psychosis, the greater improvements in cognition will be achieved.

We found furthermore, that a reduction in the CRP level in the T1-T2 interval was associated with an increase in global cognitive performance and verbal abilities in the T2–T4 interval, respectively, and in attention for the T2–T3 interval. Sub-analysis of patients with CRP < 10 mg/L, showed sustained above-mentioned results. Secondary analysis of the sub-sample of schizophrenia spectrum disorders showed that change in

CRP level did not predict T2-T4 change in the global cognitive performance, but predicted improvement in attention for the T1-T2 and T3-T4 intervals. Our findings are in contrast to another longitudinal study, where CRP levels did not predict changes in cognitive performance (452), which, however, included chronic phase patients with average illness duration of 22.5 years, reflecting a lower potential for improvements in inflammatory correlated cognitive dysfunction. Another study showed that elevated CRP levels (3-10 mg/L) at baseline predicted significant worsening of PANSS- positive and general psychopathology, but not cognitive symptoms, which is different from our study results. Their participants were, however, not in acute phase psychosis (453). Our findings indicates that our sample represent early phase of acute psychosis, and suggests that reduction of CRP level during the initial phase of acute psychosis, have impact on improvement in cognitive functioning in later phases.

Finally, after adjustment for the covariates metabolic syndrome, smoking, being medication-naïve, illicit drug use, and the educational level, the association between baseline CRP level and global cognitive performance for the whole follow-up remained essentially unchanged. Overall, with some differences after adjustment for confounders, and sub-group analysis, baseline CRP level and changes were associated with different pattern of improvement in cognitive functioning in our 6 months follow-up study of the patients with patients admitted for acute psychosis. There was, thus of essential interest to investigate whether different atypical antipsychotics can show any anti-inflammatory effects via changes in CRP level.

5.1.2 Effect of antipsychotics on CRP level

The main findings in BestIntro study regarding CRP levels, were the statistically significant differences between the study antipsychotics, and modification of the relationship between antipsychotic drug and CRP by previous exposure to antipsychotic drugs. We showed also an increase of CRP levels in the 1-3 weeks interval for the whole group.

In the group of aripiprazole as First choice drug there was a statistically significant reduction of the CRP level compared to olanzapine and amisulpride during the first week of treatment. Our findings are in line with results from the study of 405 stable patients with schizophrenia, which found that aripiprazole was the only antipsychotic drug associated with decreased CRP levels compared to the other antipsychotics; quetiapine, olanzapine, amisulpride, clozapine, loxapine, risperidone zuclopenthixol, paliperidone, and cyamemazine (399). Their CRP cut-off was dichotomized as detectable/undetectable, and the authors mentioned the recommended cut-off of CRP <3 mg/L, but they used this approach to manage the statistical challenge of CRP distribution, which might lead to loose possibility of 0 mg/L <normal CRP level < 3 mg/. The results identified however, the reduction of CRP levels, which is the main aim of this topic. Another longitudinal study of aripiprazole 4 weeks follow-up in patients with chronic schizophrenia showed reduction in CRP levels (391).

Our other finding of the CRP lowering effect of aripiprazole in patients with prior use of antipsychotics might reflect a potential anti-inflammatory effect of aripiprazole on the pro- inflammatory state associated with earlier medications or a more advanced phase of the disorder. Antipsychotics might lead to metabolic changes including weight gain, increased lipid levels and increased CRP levels. Findings from The Clinical Antipsychotic Trials of Intervention Effectiveness Study (CATIE) showed an increase in CRP levels after 3 months treatment with antipsychotics (including perphenazine, olanzapine, quetiapine, ziprasidone, and risperidone, and 45% used antipsychotics at baseline), and the highest median levels for CRP were found for quetiapine and olanzapine groups (454). A recent 12 months follow-up study of FEP showed significant increase of CRP levels, weight gain, and increase in waist circumference, whereas 89% of patients used antipsychotics at baseline including olanzapine, risperidone, quetiapine and others (aripiprazole, sertindole, ziprazsidone) (455). In another study of patients with schizophrenia who used olanzapine, quetiapine, clozapine or risperidone significantly higher levels of CRP and IL-6 were shown compared to non-medicated group (400).

In our study the aripiprazole group showed furthermore, an increase in CRP levels for the last follow-up period 39-52 weeks among those previously antipsychotic medicated, whereas the antipsychotic- naive patients had a significant reduction in CRP levels for this period.

Taken together, we identified a pattern of initial increase followed by decrease of CRP levels in drug-naïve aripiprazole treated patients, with the opposite pattern for previously medicated patients. This might indicate an initial pro-inflammatory activation followed by a subsequent anti-inflammatory effect in the drug-naïve group. The interpretation of this pattern can only be speculative, but could include factors such as delayed anti-inflammatory effect of aripiprazole or contrasting effects of the drug in different phases of the psychosis. A recent study of schizophrenia out-patients with at least 1 year antipsychotic treatment showed substantially elevation of CRP levels in acute psychosis in 60% of the patients compared to 43% of chronically ill patient. The latter group showed significantly lower CRP levels than the acute psychosis group, suggesting the decreasing effect of antipsychotic treatment, and inflammatory response in acute psychosis phase. They found furthermore, a significant decrease in CRP levels at repeat admission compared to initial admission, but CRP at both admissions was significantly elevated compared to the clinical cut-off of <3 mg/L. The authors commented that after adjustment for BMI, with remained elevated neutrophil/lymphocyte ratio (NLR), the elevated inflammation would not be fully explained by BMI in acute phase psychosis (237). Furthermore, antipsychotics overall, seem to increase levels of CRP in the long term. As CRP may be associated with the increased risk of CVD seen in patient groups using these medications this is an important finding that needs further exploration as a potential target to reduce morbidity and mortality in this patient group

The mechanisms by which antipsychotic medications affect the inflammatory pathways remain unknown. Several studies have shown alterations in the levels of cytokines in both pro- and anti-inflammatory directions following antipsychotic drug use in FEP patients and individuals with schizophrenia with acute phase psychosis (176, 394, 395, 398). In our study aripiprazole seemed to differ from both amisulpride

and olanzapine, regarding the changes in CRP levels, and findings with regard to the potential anti-inflammatory effect of aripiprazole are presented here.

In the above-mentioned study of 4 weeks treatment with aripiprazole (391) reduction of several pro-inflammatory cytokines (IL-6, TNF-α, IL-1ß, IFN-γ, IL-12, IL-23) and 2 anti-inflammatory cytokines (IL-4, TGF-ß1) respectively, together with markedly increase in anti-inflammatory cytokine IL-10 were found, supporting the immune-modulatory effect of aripiprazole.

Reduction of IL-6 and TNF-α independent of metabolic effects have been also shown in an ex vivo study by stimulation of human blood mononuclear cells with olanzapine or aripiprazole, suggesting the reduced secretion of inflammatory cytokines in human immune cells by olanzapine and aripiprazole (456). In an rodent study of microglial cells, aripiprazole inhibited release of TNF-α from IF-γ-activated microglial cells modulated by intracellular calcium signalling (457). In an ex vivo study of macrophage-like cells, aripiprazole inhibited strongly and dose-dependently production of the inflammatory mediators nitric oxide and prostaglandin E_2, by suppressing intracellular inflammatory pathways in macrophage like cells (458). Overall, existing evidence suggest that aripiprazole affects different cellular pathways, in addition to effects on gene expression different from other antipsychotics (459). An *in vivo* study showed that *acute* administration of aripiprazole did not have effects on dopamine release in the medial prefrontal cortex or the striatum, but it could strongly increase levels of dopamine extracellular metabolites and inhibit levels of extracellular serotonin metabolites in both regions. Meanwhile, *chronic* administration of aripiprazole showed 'stabilization' of dopaminergic effects, with a reduction in dopamine concentrations and weaker effects on both dopamine and serotonin extracellular metabolites (460). The different effects of aripiprazole depending on the administration duration might partly explain the time/phase effect pattern identified in our study, however without a direct link to the inflammatory pathways.

Moving beyond the level of the specific study medications, in line with existing evidence lower baseline levels of CRP were associated with being antipsychotic-naïve, having lower BMI levels and low levels of CVD risk factors (230, 461-463). In a recent study of 106 patients with schizophrenia, BMI was positively correlated with CRP levels, independent of age, sex, race, education or cotinine (a metabolite of nicotine) levels (464). Furthermore, CRP was negatively correlated with HDL in the total sample, in the overweight/obese patients, and not in the normal-weight patients. The authors interpretation was that overweight/obesity was associated with increased inflammation and dyslipidemia in patients with schizophrenia (464), in line with our finding of which, a higher baseline BMI was associated with stronger reduction in CRP in the 1-3 weeks interval. Taken together, the stronger CRP reduction in these putatively more inflammatory challenged groups points toward an immune-modulatory effect of antipsychotics. An indirect effect of aripiprazole via its lower propensity to induce metabolic changes than olanzapine and the other new generation antipsychotics might also have contributed to the CRP reduction.

To summarize, we found a statistically significant different CRP altering profile in the patient group who received aripiprazole, with initial significant CRP reduction in patients who used antipsychotics prior to inclusion compared to antipsychotic-naïve patients after one week of treatment. An opposite pattern was observed during the last 3 months of treatment.

Our findings are in line with some other studies so far, as they confirm differences between antipsychotics regarding effects on the immune system, yet the role of the influence of possible mediating effects of metabolic changes induced by different antipsychotics needs to be elucidated in further studies,

5.1.3 Clinical implications

To summarize, there is evidence for low-grade inflammation in around 40% of patients with schizophrenia (465-467), with identified elevated levels of CRP at least in a proportion of individuals with schizophrenia (227, 228, 231, 468, 469). However,

a recent meta-analysis of immune parameters and their variability in patients with psychosis showed elevated levels of IL-6, IFN-γ, and IL-17 (robust to sensitivity analysis) in antipsychotic-naïve FEP patients. IL-6 showed reduced variability in patients, suggesting this cytokine to be a core component of the pathophysiology of psychosis. The unimodal distribution of raw data in 94% of psychotic patients and 100% of controls suggests that alterations in the immune system are rather a general feature of psychosis than an immune subtype of psychosis (470).
Overall, we have shown the essential role of inflammatory pathways in schizophrenia by investigating the impact of CRP level and changes in both acute phase psychosis and in later phases with regard to symptomatology, especially cognitive impairment. Finally, we showed and discussed the different effect pattern of study antipsychotic drugs on CRP levels.

The measurement of CRP is reliable, widely used in clinical practice, and therefore, might have potential to be used in both screening, and follow-up of patients with immunologically activated component. The fact that elevated CRP levels are correlated with decreased cortical thickness in several brain regions, cognitive dysfunction, more severe symptomatology, poor prognosis support the role of CRP in schizophrenia spectrum disorders. Furthermore, elevated CRP is associated with cardiovascular risk for CRP > 2 mg/L (471), and increased all- cause mortality (472). There is, therefore convincing that the lower CRP level, the better outcome. The easily and consistently measurement of CRP in conjunction with diagnosis could be used to identify patients in inflammatory activated state, which might provide a guidance regarding the proper choice of antipsychotic drug with/ without adjunctive anti-inflammatory agents.

5.2 Methodological considerations

5.2.1 Research design

The BP and BestIntro studies had similar clinical inclusion criteria for acute phase psychosis by a threshold of ≥ 4 on essential positive symptom items of the PANSS in line with other antipsychotic trial designs (473). However, the BP by including both depressive episode with psychotic symptoms, and drug-induced psychosis patients were diagnostically more heterogeneous than BestIntro, and considered to be as naturalistic as possible. Subsequent statistical sub-analysis in paper 1 and 2 were, thus, conducted to manage the heterogeneity. The paper 1 included all patients who had both baseline CRP measurement, and cognitive assessment, respectively. The paper 2 included all patients with data on one or more of the outcome variables (N = 208), which provided analysis of a larger sample size. The BP study had a long follow-up interval of 2 years, which was a challenging aspect of the study design. However, with regard to the longitudinal perspective of paper 2, a follow-up interval of 6 months was chosen, in order to investigate the potential inflammatory related improvement of cognitive function.

5.2.2 Assessment

The baseline data for paper 1 were based on the baseline CRP levels, and cognitive assessments using RBANS, while the first follow-up after 4 weeks/latest after 6 weeks were consisting only cognitive assessments. The lacking of the CRP level at follow-up was, however, handled by the appropriate statistical model. Reliability testing was performed for the PANSS ratings in both BP and BestIntro. The diversity of cognitive assessments in BP was another challenging aspect of paper 2. The RBANS (short battery) was used at baseline because of the active psychotic conditions that did not allow for a more comprehensive battery, and because the RBANS can be repeated. We used a more comprehensive cognitive battery after 3 months (T3) to increase the clinical validity. In a preliminary analysis, a satisfactory

relationship between the RBANS and equivalent domains from the more comprehensive neuropsychological battery 3 months later emerged, even despite symptom-level differences at the two time points (474). A more detailed explanation for the complexity of cognitive assessments is provided in the manuscript of paper 2. With regard to the assessments in BestIntro relevant for paper 3, the same assessment approaches were conducted in all follow-up visits.

5.2.3 Statistical considerations

The used statistical models, such as latent growth model (LGC), were selected in the project planning phase. In addition to analysing level and change, both at group mean and individual level, this model uses all available data. As for instance in paper 2, data from patients with even only one observed value were used. Given the expected and challenging missing data, it is essential that this model manage this challenge by using all available data. Thus, LGC improves the generalizability of the results. The ordinary listwise deletion methods, like ANOVA repeated measures, result in lack of important information and restrict the generalizability to the population of patients being able to participate at all visits. Furthermore, LGC makes it possible to analyse data from different number of visits with different follow-up intervals. However, these and most other methods do not rule out the possible "missing not at random" (MNAR) assumption, since we did not have the possibility to investigate the reasons or conditions among the dropping out participants. Sensitivity analyses could have been used to test the stability of parameter estimates under MNAR. However, such models have strict statistical assumptions, and such modelling was decided not to be included in the presented studies, which is important, as evaluating the quality of the studies is related to both precision of estimates and statistical power. Some models used, particularly the full model in paper 3, are complex with a large number of estimated parameters. Simulation could have been done in order to ensure statistical power in all parameters. However, no earlier studies with same model analysed in equal sample of patients have been found. Therefore, no ad hoc simulation could be

analysed. Regarding precision, the results should be replicated in samples larger in size.

5.3 Strengths and limitations

Strengths

The randomized naturalistic design is the main strength of both drug trial studies, with consecutive inclusion of patients with acute psychosis. Furthermore, the longitudinal perspective of studies was an essential strength, since most of the inflammatory-based studies are cross-sectional. Regional Committee for Medical Research Ethics allowed eligible patients to be included before informed consent were provided, and thus, the patients who were included in the first phase of the BP study might reflect the very initiate phase of acute phase psychosis. The relatively high percentage of antipsychotic naïve patients (51.6% in paper 1, 44.2% paper 2, and 39% paper 3) was an advantage with regard to the investigation of inflammatory processes involved in the pathogenesis of schizophrenia. Both studies were pharmaceutical industry independent.

Limitations

There are some limitations to the BP and BestIntro studies. The BP participants as mentioned earlier, were diagnostically heterogeneous, which makes the inference to certain diagnostic subgroups questionable. However, sensitivity analyses were used to provide results also at subgroup level. Diagnoses were obtained by the treating psychiatrist or psychologist, that might have reduced inter- therapist diagnosis reliability. In the BestIntro, this limitation effect was taken to account, and structured clinical interviews and diagnostic evaluations and conclusions were conducted by study psychiatrists or specialists in psychology. Both studies had substantial attrition, particularly in BP study (62 of 124 patients were assessed at the first follow-up regarding paper 1). Furthermore, the only available measurements of inflammatory

markers were the serum CRP levels, and white blood cell count (WBC) with cell type differentiation was unfortunately not conducted.

We used cut-off of CRP ≤ 15 mg/l in paper 1, different from paper 2 and paper 3, which had cut-off of CRP ≤ 10 mg/l. Our choice of cut-off in paper 1 was based on the few existing publications focusing on CRP, and it was our first inflammatory related investigation. However, with increased evidence for the potential role of CRP in schizophrenia, we adjusted the CRP cut-off for paper 2 in line with other existing publications. The studies did not have a healthy control group, and thus, all participants were medicated by study medications, which might have influenced the raters conclusions.

6.Concluding remarks

The presented findings support following conclusions:

BP

- CRP level in acute phase of psychosis is inversely associated with overall cognitive performance, as well as for the cognitive subdomains delayed memory and attention. The association between overall cognitive function and CRP levels was particularly strong for the subgroup with schizophrenia.
- The global cognitive performance improved predominantly in the initial phase of acute psychosis, and continued to improve in the later phase at least up to 6 months.
- The improvement in global cognitive impairment was predicted by the reduction of the CRP level in the initial phase. The different cognitive subdomains showed different time-dependent profiles of improvement, with memory and attention improving significantly also in the later phases.

BestIntro

- There were differences between three atypical antipsychotics amisulpride, aripiprazole, and olanzapine regarding change of the CRP levels, both in acute and later phases of psychosis in schizophrenia spectrum disorders. The aripiprazole group showed a reduction of the CRP level compared to either olanzapine or amisulpride group, during the first week of treatment.
- There was different pattern of change in CRP levels depending on the history of previous antipsychotic use. The aripiprazole group showed an initial increase followed by decrease of CRP levels in drug-naïve patients, with an opposite pattern for previously medicated patients.

7. Future perspectives

Findings from the present study necessitate further investigations on the association between CRP levels and symptomatology including cognitive dysfunction in patients with schizophrenia spectrum disorders (BestIntro data). Furthermore, the effects of atypical antipsychotic drugs on potential link between CRP changes and symptomatology should be clarified.

Other inflammatory markers such as cytokines as well as complement system related research in conjunction with genetical and brain imaging approaches, will provide essential evidence in this field, in order to achieve further understanding of the involvement of the inflammatory pathways in pathogenesis and treatment opportunities for patients suffering from long lasting burden of this disease group.

The prospective endpoint might be the identification of the individuals with low-grade inflammatory status, representing candidates for certain antipsychotics with favourable immune-modulatory profile and/or adjunctive anti-inflammatory agents.

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The serum level of C-reactive protein (CRP) is associated with cognitive performance in acute phase psychosis

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Abstract

Background: Inflammatory processes have been implicated in the etiology of schizophrenia and related psychoses, in which cognitive deficits represent core symptoms. The aim of the present study was to investigate possible associations between the level of the inflammation marker C-reactive protein (CRP) and cognitive performance in patients through the acute phase of psychosis.

Methods: A total of 124 patients were assessed at admittance to hospital and 62 patients were retested at discharge or after 6 weeks at the latest, with measurements of the CRP levels and alternative forms of the Repeatable Battery for the Assessment of Neuropsychological Status.

Results: There was an inverse relationship between overall cognitive performance and CRP level at admittance. The association increased in sub-analyses including only patients with schizophrenia. In cognitive subdomain analyses statistically significant inverse associations were found between the CRP level and Delayed memory and Attention, respectively. No associations were found between CRP level and other measures of psychopathology including psychosis symptoms, depression, or functioning. At follow-up the association between CRP level and cognition was no longer present. There was a significant increase in cognitive performance between baseline and follow-up. There was a stronger increase in overall cognition scores in patients with higher baseline CRP levels.

Conclusions: The findings indicate that signs of inflammation may serve as a state-dependent marker of cognitive dysfunctions in acute psychosis.

Trial registration: ClinicalTrials.gov ID; NCT00932529, registration date: 02.07.2009

Keywords: Schizophrenia, Cognition, Inflammation, CRP

Background

Schizophrenia and related psychoses are severe mental disorders characterized by positive and negative psychotic symptoms, cognitive dysfunction and functional decline, with a lifetime prevalence close to 1 % [1]. Positive symptoms were until recently considered the most prominent features of the disorders as reflected also in the major diagnostic manuals, but cognitive dysfunctions have for the last decade been recognized as core features of schizophrenia [2–5], and with greater impact on functional outcome than the psychotic symptoms [6–10]. The etiology of schizophrenia remains to be clarified, but genetic as well as environmental factors convey risk [11]. Involvement of inflammation and the immune system in the pathophysiology of schizophrenia has received particular attention in recent years, fueled also by the genome wide association study (GWAS) findings of associations between markers in the immune system including the major histocompatibility complex and schizophrenia risk [12–15]. Furthermore, preclinical-, postmortem-, brain imaging-, and pharmacological studies, as well as clinical evidence from drug naïve first

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episode patients, strongly suggest a role for the immune system in schizophrenia development (see for example [16–18] for updated reviews). Emerging evidence indicates that immuno-inflammatory processes may be particularly relevant to the cognitive dysfunctions of schizophrenia [19–21].

The C-reactive protein (CRP), an acute-phase reactant synthesized in the liver, has for many decades been considered a reliable marker of inflammation [22]. With regards to cognition, a negative correlation has been found between CRP levels and cognitive impairment in the elderly, although not consistently [23, 24]. Scattered reports also exist of inverse associations between CRP levels and cognitive function in severe depression [25], and in bipolar disorder [26]. In schizophrenia, a recent meta-analysis by Fernandes et al. [27] consistently found elevated serum levels of CRP in both first episode and chronic phase patients, irrespective of medication status. Furthermore, an association between CRP levels and positive symptoms but not negative symptoms of psychosis was found. To the best of our knowledge, investigations of associations between the CRP level and cognitive dysfunction in schizophrenia are however scarce, although an association between CRP levels and cognitive functioning in patients with predominantly chronic schizophrenia has been reported in one cross-sectional study [28]. Studies involving patient samples representative of the acute and early phases of psychosis are missing, as are studies with longitudinal measurements. We have previously demonstrated a statistically significant time effect for overall cognitive improvement in acutely admitted psychosis patients during 24 months of follow-up [29], but have not so far examined changes in the acute phase.

The main aim of our study was accordingly to investigate the association between the CRP level and cognitive performance in a clinically representative sample of patients with psychosis acutely admitted to hospital, with repeated measurements in the acute phase.

Methods

The materials and methods used have been described in greater detail elsewhere [30]. The study is part of a pragmatic, randomized trial comparing second generation antipsychotics (SGAs) in the treatment of psychosis. The present paper reports data obtained at baseline in patients who underwent cognitive assessments at admittance and at discharge or after maximally 6 weeks if not already discharged (termed as follow-up). This time period corresponds to the acute phase of treatment. Patients were consecutively recruited from March 2004 until February 2009 from the Haukeland University Hospital with a catchment population of about 400,000. The study was approved by the Regional Committee for Medical Research Ethics, and by the Norwegian Social Science Data Services. The study was publicly funded and did not receive any financial or other support from the pharmaceutical industry. The Regional Committee for Medical Research Ethics allowed eligible patients to be included before informed consent was provided, thus entailing a clinically relevant representation in the study. The patients were asked at follow-up for written informed consent. All adult patients were eligible for the study if they were acutely admitted to the emergency ward for symptoms of active psychosis as determined by a score of ≥4 on one or more on the items Delusions, Hallucinatory behavior, Grandiosity, Suspiciousness/persecution, or Unusual thought content in the Positive and Negative Syndrome Scale (PANSS) [31] and were candidates for oral antipsychotic drug therapy. Accordingly the patient inclusion encompassed the consecutive recruitment of a clinically representative sample of psychosis patients acutely admitted to hospital. All eligible patients met the ICD-10 diagnostic criteria (http://apps.who.int/classifications/icd10/browse/2010/en) for schizophrenia, schizoaffective disorder, acute and transient psychotic disorder, delusional disorder, drug-induced psychosis, bipolar disorder except manic psychosis, or major depressive disorder with psychotic features. The diagnoses were determined by the hospital's psychiatrists or specialists in clinical psychology. Patients were excluded from the study if they were unable to use oral antipsychotics, were suffering from manic psychosis or for other behavioural or mental reasons related to the state of illness were unable to cooperate with assessments, did not understand spoken Norwegian, were candidates for electroconvulsive therapy, or were medicated with clozapine on admittance. Patients with drug-induced psychoses were included only when the condition did not resolve within a few days and when antipsychotic drug therapy was indicated.

Clinical assessments

Before inclusion, eligible patients underwent the PANSS structured clinical interview. Intra-class correlation coefficients (ICC) were calculated based on inter-rater assessments and showed high inter-rater reliability (0.92). Furthermore, the Calgary Depression Scale for Schizophrenia (CDSS) [32], and the Clinical Drug and Alcohol Use Scales (CDUS/CAUS) [33] were used, and the patients were rated according to the Clinical Global Impression—Severity of Illness scale (CGI-S) [34], and the Global Assessment of Functioning—Split Version, Functions scale (GAF-F) [35]. A blood sample was collected from the patients between 08 and 10 a.m. for analyses of CRP levels. There was a change in the laboratory's CRP analysis methods in January 2005, and hence only data obtained after this change is reported in

the present work. The method used is the Tina-quant C-reactive Protein (Latex) from Roche Modular P®, which measures CRP levels >1 mg/L. Antipsychotic drug doses were converted to defined daily doses (DDDs), in accordance with the World Health Organization Collaborating Center for Drug Statistics Methodology (http://www.whocc.no/atc_ddd_index/). The basic definition of the DDD unit is the assumed average maintenance dose per day for a drug used for its main indication in adults.

Cognitive assessment

Cognitive assessments were conducted at baseline and at follow-up. A brief neuropsychological screening instrument with alternative forms; the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), was used to minimize potential practice effects [36–38], since longitudinal studies on cognitive functioning usually do not address the issue of practice effects sufficiently [39, 40]. Practice effects can be particularly evident when there are short time intervals between repeated neuropsychological testing, and the effect seems to be strongest from baseline to the second testing [41, 42]. The RBANS has previously shown good reliability and validity in psychosis [43]. It takes only about 30 min to complete, making it practical and feasible to use in the acute phases of psychosis. The five cognitive domains were: Language; Visuospatial/ constructional; Immediate memory; Delayed memory; and Attention. Raw scores from the neuropsychological variables were converted to t-scores by means of the norms from the manual [44]. The final summary score based on the mean t-scores across the five cognitive domains defined the overall cognitive function t-score.

Statistical procedures

Categorical and continuous data at baseline were analyzed using exact χ^2 – tests and one-way ANOVAs in the SPSS software, version 20.0 (IBM SPSS Statistics, 2011). To investigate the association between cognitive performance and CRP levels bivariate analyses of correlation were conducted. This was followed by linear regression analyses to adjust for potential confounders between cognition and CRP. These confounders included years of education, as a proxy for socioeconomic status which may have an impact on both CRP levels and cognitive performance [45]; medication status (i.e. being antipsychotic drug naïve or previously exposed to antipsychotic drugs) prior to inclusion, as antipsychotics may influence both CRP levels and cognition [46, 47]; tobacco smoking, which has been associated with both elevation of CRP levels [48, 49] and enhancement of cognition [50, 51]; drug abuse, as a relationship between drug abuse and CRP has been established [52, 53]; and finally, cardiovascular risk, as CRP has been identified as a risk factor for cardiovascular disease (CVD) [54, 55] and CVD has been associated with cognitive impairment [56, 57]. A CVD risk score was calculated based on the International Diabetes Federation metabolic syndrome definition cut-off values (http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf), by which each factor (obesity, raised triglycerides, reduced HDL cholesterol, raised blood pressure, and raised fasting plasma glucose) was dichotomized as absent (0) or present (1), giving rise to a maximal sum score of 5 for the individual factors.

Latent Growth Curve (LGC) models of level and change in CRP and cognition were analyzed with the Mplus program, version 7.20 [58]. Such models describe both mean levels and individual variations in level and change. In addition, the relation between level and change is estimated. Because of only two measurement points, baseline and follow-up, the residuals had to be pre-specified in order to identify the model [59]. Mplus allows unequal individual time-spaced observations to be analyzed [60], and time was specified as weeks. The default estimator for LGC modelling is maximum likelihood with robust standard errors (MLR), which is robust for non-normal data [60, 61]. Standard Mplus models use all available data under the "missing at random" assumption and minimize the effect of missing data [62, 63]. First, unconditional separate LGC models were analyzed, then a model integrating level and change in both CRP and cognition was used in order to study the relation between baseline levels in one variable as a predictor of changes in the opposite variable, after accounting for the control covariates. Variables not accounting for any relations were removed and model re-estimated based on a backward hierarchical procedure [64].

The level of statistical significance was set at $\alpha = 0.05$, two-sided.

Results

A total of 124 patients were included with serum CRP level measurements and cognitive assessments at baseline. The demographic and clinical characteristics are shown in Table 1. One patient used concomitant anti-inflammatory medication (prednisolone). None of the included patients were diagnosed with inflammatory- or immunological disorders or infections during the study.

Baseline

The mean CRP level with standard deviation (SD) at admission was 3.6 (5.2) mg/L and the mean overall cognitive function t-score was 37.8 (7.7).

The cognitive subdomain t-scores were 40.5 (7.8); 45.8 (12.7); 35.7 (10.2); 37.6 (12.1); and 29.5 (8.9) for Language; Visuospatial/ constructional abilities, Immediate

Table 1 Baseline demographics and clinical characteristics ($N = 124$)

Characteristics		
Gender	N	% of sample
Male	84	67.7
Female	40	32.3
Antipsychotic drug naïve	64	51.6
Alcohol use last 6 months		
None	17	13.7
Misuse	15	12.1
Illicit drug use last 6 months		
None	82	66.1
Use/ Misuse	25	20.2
Current tobacco smoking	64	51.6
Diagnosis[a]		
Schz and related	67	57.8
Acute	8	6.9
Drug-induced	21	18.1
Affective	11	9.5
Rest	9	7.8
	Mean	SD/ range
Age	33.5	12.4/18–65
Body Mass Index	23.5	4.6/ 15.8–40.3
Years of Education	12.5	2.7/ 8–22
PANSS Total	73.4	11.9/ 45–98
PANSS Positive	20.1	4.1/ 12–30
PANSS Negative	19.0	6.9/ 7–38
PANSS General	34.3	6.4/ 20–56
CDSS	6.2	5.0/ 0–23
GAF-F	30.5	4.9/ 18–45
CGI	5.2	0.6/ 4–6
RBANS t-score	37.8	7.7/ 20.2–58.8

N number of patients, *SD* standard deviation; Antipsychotic drug naive = No life-time exposure to antipsychotic drugs before index admission; Misuse = Misuse or Dependence according to the Clinical Drug and Alcohol Use Scales (CDUS/CAUS), patients with no illicit drug use could be included in the category alcohol use last 6 months; Schz and related = Schizophrenia and related disorders: Schizophrenia, schizo-affective disorder, acute polymorphic psychotic disorder with symptoms of schizophrenia, acute schizophrenia-like psychotic disorder, delusional disorder; Acute = Acute psychosis other than those categorized under Schz and related; Affective = Affective psychosis; Rest = Miscellaneous psychotic disorders. All diagnoses are according to ICD-10; *PANSS* the Positive and Negative Syndrome Scale, *CDSS* the Calgary Depression Scale for Schizophrenia, *GAF-F* the Global Assessment of Functioning, split version, Functions scale, *CGI* the Clinical Global Impression, severity of illness scale, *RBANS* the Repeatable Battery for the Assessment of Neuropsychological Status

[a]Patients with missing diagnoses are not included in the list

memory; Delayed memory; and Attention, respectively (Fig. 1).

In the primary analyses, the Pearson correlation test revealed a statistically significant inverse relationship between overall cognitive performance and CRP level at baseline (Pearson correlation $r = -0.247$, R2 = 0.061, $p = 0.006$) (Fig. 2). In a linear regression model with overall cognitive performance as the dependent variable and CRP, years of education, antipsychotic drug status before inclusion, tobacco smoking status, drug abuse, and CVD risk score as independent variables, the association remained statistically significant between cognitive performance and CRP ($B = -0.290$; Beta = −0.198; $p = 0.031$). No interaction effects were found between CRP and any of the other independent variables that significantly improved the model. In the secondary analyses there were statistically significant inverse associations between CRP level and Delayed memory ($B = -0.484$; Beta = −0.213; $p = 0.02$) and Attention ($B = -0.404$; Beta = −0.239; $p = 0.012$), whereas no association was found between CRP and Language, Visuospatial/constructional abilities, or Immediate memory, respectively. In a sensitivity analysis that included also the PANSS positive symptoms scale score, the results remained unchanged.

In Pearson correlation tests of the relationships between CRP and the PANSS total score, the scores of the PANSS positive, negative, and general psychopathology subscales, the CDSS, the GAF-F, and the CGI, respectively, no statistically significant correlations were found ($r < 0.100$ for all).

Based on visual inspection of the CRP levels versus overall cognitive performance scatterplot, the bulk of data were in the lower end of the CRP levels (Fig. 2). Accordingly sub-analyses were conducted that included only patients with CRP levels <15 mg/ L ($N = 119$). The inverse association between CRP levels and overall cognitive performance was strengthened ($B = -0.741$; Beta = −0.300, $p = 0.001$). In the cognitive subdomains statistically significant associations with CRP levels were found for all domains except Immediate memory. When only the schizophrenia subgroup ($N = 36$) was included, the inverse association between CRP levels and overall cognitive performance was markedly increased (($B = -1.031$; Beta = -0.529; $p = 0.006$).

In sensitivity analyses that included only the subgroup of drug naïve patients ($N = 64$), the inverse relationship between CRP level and overall cognitive performance remained essentially unchanged compared to in the primary analyses with the full sample, although the correlation was no longer statistically significant ($B = -0.568$; Beta = −0.194; $p = 0.187$).

In sensitivity analyses excluding the patient using prednisolone the results were unchanged.

Follow-up

A total of 62 patients were retested using the RBANS B at follow-up. The mean interval between baseline and follow-up was 28.3 (11.1) days. The mean PANSS total and CGI-S scores were 53.9 (13.9) and 3.6 (1.0),

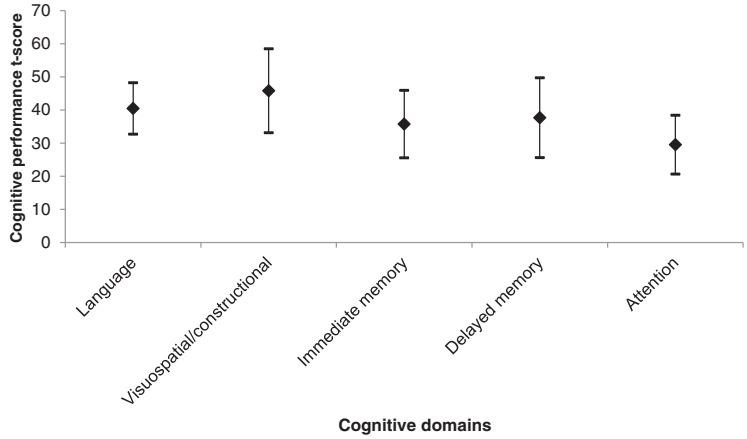

Fig. 1 Cognitive performance by functional domain. Notes: ♦ = mean t-score with bars representing plus/minus 1 standard deviation from the mean

respectively, corresponding to being mildly ill. There were no statistically significant differences between those tested only at baseline and those with follow-up tests for any of the clinical or demographic characteristics at baseline presented in Table 1. Medication details are displayed in Table 2.

The distribution of CRP levels and overall cognitive performance is displayed in Fig. 3. The mean CRP level and overall cognitive performance were 4.6 (10.6) mg/L and 41.3 (7.1), respectively. The association between CRP level and overall cognitive performance was not statistically significant at follow-up ($B = -0.045$; Beta = −0.066; $p = 0.627$). In sensitivity analyses that included also duration of treatment between baseline and follow-up, as well as the mean defined daily dose of antipsychotics for the latter 7 days before follow-up, the results remained unchanged. In sensitivity analyses excluding the single patient using prednisolone, the results were also unchanged.

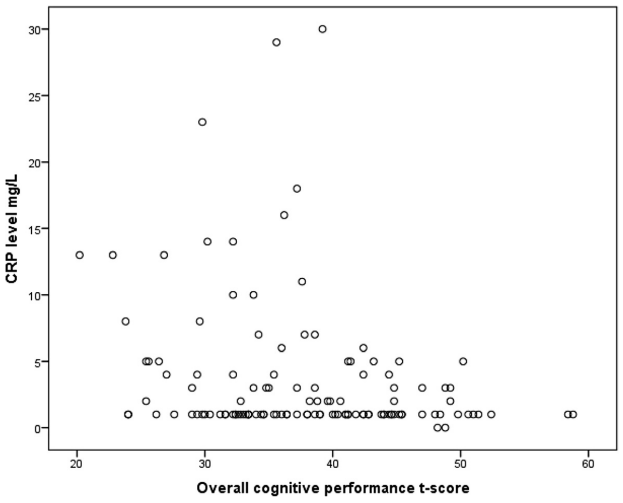

Fig. 2 Association between CRP level and overall cognitive performance at baseline. Notes: Scatter plot of overall cognitive performance versus CRP level ($N = 124$). Pearson correlation $r = -0.247$, r2 = 0.061, $p = 0.006$. In sensitivity analyses excluding outliers with CRP >15 ($N = 119$): Pearson correlation $r = -0.346$, r2 = 0.120, $p = 0.000$

Table 2 Antipsychotic drug use at discharge/ 6 weeks

	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole
	N = 14	*N* = 21	*N* = 14	*N* = 10	*N* = 1
	Mean (SD/ range)	Mean (SD/ range)	Mean (SD/ range)	Mean (SD/ range)	Mean (SD/ range)
Mean dose (mg/ d)	3.3 (1.2/2.0–6.0)	16.6 (4.7/10.0–25.0)	480.4 (218.9/175.0–800.0)	82.0 (38.2/20.0–160.0)	5.0 (-)
Serum level (nm/ L)[a]	58.5 (33.3/ 27.0–147.0)	115.5 (70.3/47.0–302.0)	546.8 (585.3/ 62.0–1817.0)	88.6 (89.3/ 13.0–323.0)	141 (-)

N number of patients, *SD* standard deviation, *mg/d* milligrams per day, *nm/L* nanomoles per litre. There was missing medication data on 1 patient and 1 patient had discontinued the antipsychotic medication

[a]Reference ranges: Risperidone 30–120; Olanzapine 30–200; Quetiapine 100–800; Ziprasidone 30–200; Aripiprazole 200–1300

The results from the LGC models are presented in Table 3 with mean and individual variation in baseline level and change, and the relation between baseline level and change. There was no statistically significant mean increase in CRP, but considerable and statistically significant individual variation in the change (Table 3). The relation between baseline level and change was not statistically significant.

Regarding cognition, there was a statistically significant mean increase over time, however; with some patients changing more than others indicated by statistically significant variance. For this variable it was found a negative relationship between baseline score and degree of change, which indicates stronger rate of change for patients with lower baseline scores. Figure 4 illustrates this with mean change over a four week period and changes for patients with lower (−1 SD) and higher (+1 SD) baseline scores.

The results from the final model consisting of two growth processes with level and change in CRP and overall cognition showed that baseline level in CRP could predict changes in overall cognition ($b = 0.04$, $p = 0.000$), after accounting for the covariate variables. Changes in overall cognition were not related to changes in CRP ($b = -0.02$, $p = 0.764$). The covariate variables showed smokers to have less increase over time than non-smokers ($b = -0.18$, $p = 0.001$) and that baseline CRP level was moderated by the CVD risk baseline level (interaction term: $b = -0.06$, $p = 0.041$). The main effect of CVD risk was not found to be statistically significant ($b = 0.34$, $p = 0.072$). This finding indicates a stronger increase in overall cognition scores in patients with higher baseline CRP levels, however, with stronger increases in patients with lower degree of CVD risk scores, and in non-smokers.

Discussion

The main finding of the present study was an inverse relationship at baseline between serum levels of CRP and overall cognitive performance, as well as for the

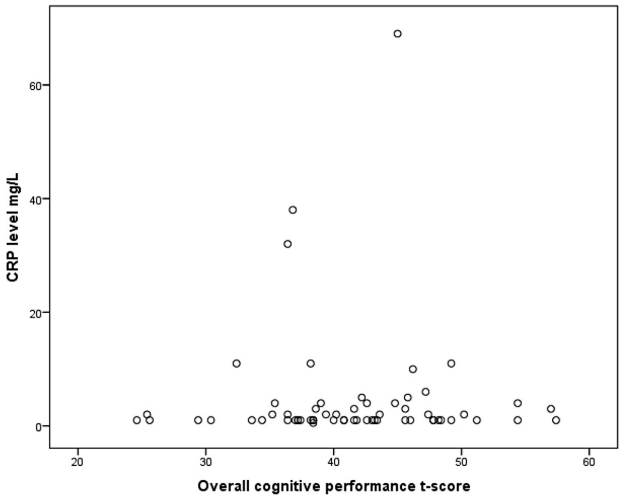

Fig. 3 Association between CRP level and overall cognitive performance at follow-up. Notes: Scatter plot of overall cognitive performance versus CRP level ($N = 62$). Pearson correlation $r = 0.007$, r2 = 0.000, $p = 0.958$. In sensitivity analyses excluding outliers with CRP >15 ($N = 60$): Pearson correlation $r = 0.005$, r2 = 0.000, $p = 0.972$

Table 3 Level and change results for CRP level and overall cognition based on latent growth curve models

	Baseline (I)		Change (S)		Relation $_{I,S}$	
	Mean	Variance	Mean	Variance	Cov	r
CRP level	2.76***	9.70	0.98	26.52	−1.33	−.08
Overall cognition	37.92***	60.83	0.95***	3.66	−5.53	−.37**

The model describes mean level and individual variations in baseline and change over time. The relation between intercept (I) and slope (S) describes the relation between baseline level and rate of change (covariances and correlations). *Cov* covariance, *r* correlation coefficient
** $P < .01$, *** $P < .001$

subdomains Delayed memory and Attention, in a clinically relevant sample tested in the acute phase of psychosis. The association was particularly strong for the subgroup with a diagnosis of schizophrenia. At follow-up, which in time correspond to the end of the acute phase, the association was no longer present. The finding was restricted to cognitive performance, as none of the other psychometric parameters tested were associated with the CRP level. The CRP level at baseline predicted the overall cognitive change.

Our results are consistent with those of Dickerson et al. [28], who reported an inverse relationship between CRP levels and cognitive performance but no association towards other measures of psychopathology. Our study adds new knowledge by including a consecutive sample of patients acutely admitted for psychosis, with measurements both at hospital admission and at discharge or after maximally 6 weeks, thus giving the possibility to analyze the data also with regard to longitudinal changes. We argue that this period of time reflects the phase of treatment with the most severe symptoms, supported by the decrease of the CGI-S scores from markedly ill at baseline to mildly affected at follow-up. Interestingly, the negative association between CRP levels and overall cognitive performance was present only at baseline. Since the sample at follow-up was smaller than at baseline, the lack of statistically significant difference at follow-up could be due to insufficient statistical power. However, the correlation was reduced substantially at follow-up, approaching zero, which makes the lack of association unlikely to be a sample size problem. Another possibility might be that the attrition was not at random, giving rise to selection bias at follow-up compared to the sample at baseline. This seems unlikely, however, as attrition was not related to any baseline characteristics. Finally, cognitive dysfunction might theoretically be associated with positive symptoms of psychosis, and the positive symptoms could accordingly confound the association between CRP and cognitive performance, which could also explain why the association between CRP and cognitive performance disappeared in remission. A sensitivity analysis was therefore undertaken to adjust for the potential contribution from positive symptoms, but the results remained unchanged, which is also in line with the finding of a meta-analysis on the subject [65]. Taken

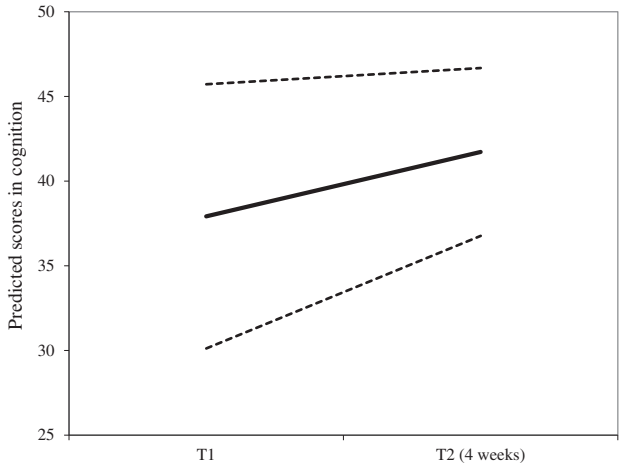

Fig. 4 Model estimated cognitive change during follow-up. Notes: The figure shows mean change and change based on ± 1 SD baseline level. Patients with lower cognitive scores had a higher rate of change. SD = standard deviation

together, the inverse association between CRP and cognition may accordingly be interpreted as at least partly state dependent.

In our study, there was no association between CRP or any of the clinical variables, which is not entirely in line with the findings in the meta-analysis by Fernandes et al. [27], who found an association between CRP and positive but not negative symptoms. The meta-analysis was based on about 2,000 schizophrenia subjects and healthy controls, and the apparent lack of an association in our much smaller sample may be related to insufficient statistical power. Our results are, however, in correspondence with the Dickerson et al. [28] study finding no association between CRP and any psychiatric symptoms.

The mean overall cognitive t-score increased significantly between baseline and follow-up, and although the mean CRP levels were almost identical at the assessment points, the distribution changed substantially towards the cognitive t-scores. Furthermore, the baseline CRP level was found to predict change of cognitive performance. Hypotheses regarding the biological substrate mediating the inflammation-related effects on cognition can only be speculative. There is however phase-specific fluctuations reported for both myelin integrity and glutamate levels in schizophrenia [66–70]. Considerable cross-talk has been suggested between immuno-inflammatory processes, myelin, and glutamate in schizophrenia, as recently reviewed by Kroken et al. [21]. CRP is known to activate complement, and the complement system have demonstrated different and somewhat paradoxical effects in the central nervous system (CNS) [71–73]. Some of these effects could be relevant to neurodegeneration and inflammation in several brain disorders including Alzheimer's disease [72]. Inflammatory processes may also decrease the blood–brain-barrier integrity, leaving the CNS more vulnerable to complement protein infiltration from the periphery [74].

The present study also supplements the findings of Dickerson et al. [28], as more than half the sample was antipsychotic drug naïve, which could be used as a proxy for early stage psychosis. The sub-analyses in the drug-naïve patients revealed similar findings to those of the total sample, with almost identical B and Beta values. The non-significant p-value is probably related to insufficient statistical power in the small sample of drug naïve patients. This interpretation is further supported by the fact that entering medication status into the regression did not change the association between CRP and cognition, which might indicate that the association between CRP levels and cognition was not a result of longstanding psychosis or medication (adverse) effects.

The cognitive deficits in schizophrenia are generally considered to be stable over time [75, 76]. At odds with this, we have previously reported an overall cognitive performance improvement across time that was considered clinically significant, and with some differential cognitive effectiveness among different second generation antipsychotics when data from the whole follow-up period was analyzed [29]. In the present study, all but one patient used antipsychotics at follow-up. It cannot be ruled out that the significant cognitive improvement observed also in the acute phase is antipsychotic drug-related, but due to the lack of a placebo group no firm conclusions can be drawn. It should be noted that anti-inflammatory effects of antipsychotic drugs have been reported in several studies [77, 78], providing a putative link to any cognitive enhancement mediated by the drugs in the present study.

We found significant inverse associations between CRP levels and Delayed memory, and Attention subdomains, respectively, whereas no significant associations were present for the other subdomains. Aas et al. [79] found overall cognitive impairment present already in first episode psychosis patients with the largest effect sizes for verbal memory, executive function, and general IQ. Correspondingly, a global impairment was found across all the subdomains in our sample, the Attention subdomain had the lowest t-score, followed closely by the Immediate memory and Delayed memory subdomains. Seeking reasons for the associations with CRP levels being present only in some of the subdomains is outside the scope of this study. It is nevertheless an interesting observation that the inverse association is present in the subdomains showing the most pronounced impairments which might indicate a greater vulnerability to inflammation-related processes compared to other subdomains of cognition.

Some limitations to the study should be mentioned. Minor elevations in the CRP levels are associated with numerous conditions and although we adjusted for several potential confounders we may have missed other unknown or hidden confounders between CRP levels and cognitive performance. However, most of the conditions associated with minimal CRP elevations do not have an apparent relationship towards cognitive function, making them less likely to confound the results presented here. As already discussed, the attrition rate was substantial, and selection bias cannot be ruled out, although attrition was not related to any baseline characteristics. We used only CRP as a measure of inflammation, and clearly a broader display of inflammatory markers would have added further strength to the study. Finally, although the association found for the primary outcome was highly statistically significant, the explained variance was only modest.

Conclusions

Despite the limitations mentioned, the data support an inflammatory component to the cognitive impairment in

schizophrenia and related psychoses, which may be at least partly state dependent. Several anti-inflammatory agents have shown promising results as add-ons to antipsychotic drug treatment in schizophrenia [80, 81]. Future studies should prospectively and repeatedly examine longitudinal changes in CRP and other markers of inflammation, and their association with cognitive performance. If our results are replicated, anti-inflammatory drugs may be especially beneficial in the acute phase of psychosis for cognitive enhancement.

Competing interest

EML has received honoria in relation to the development of the Norwegian version of the RBANS by Pearson Assessment.
EJ, FF, RAK, VMS, HAJ, and RG report no conflicts of interest related to the present work.

Authors' contributions

All authors made substantive intellectual contributions to the study. EJ was the co-designer of the study, collected data, undertook the statistical analyses, and wrote the first draft of the manuscript; FF contributed in analyses and interpretations of the data, and co-drafted the first manuscript; RAK collected data, contributed in analyses and interpretations of the data, and helped draft the manuscript; VMS was the co-designer of the study, contributed in the interpretations of the data, and helped draft the manuscript; HAJ designed the study, assisted in data collection, contributed in analyses and interpretations of the data, and contributed to the drafting of the manuscript; RG contributed in the statistical analyses and interpretations of the data, and contributed to the drafting of the manuscript; EML collected data, contributed in analyses and interpretations of the data, and helped draft the manuscript. All authors have read and given final approval of the latest version of the manuscript.

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Associations between C-reactive protein levels and cognition during the first 6 months after acute psychosis

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Original Article

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Abstract

Objective: Inverse relationships between the C-reactive protein (CRP) levels and cognitive performance in acute psychosis have been demonstrated. We aimed to investigate how the serum level and initial change of CRP in acutely admitted patients with psychosis was correlated with cognitive performance during a 6-months follow-up period. *Methods:* The study is part of a pragmatic, randomised trial comparing four different second-generation antipsychotic drugs, and consists of 208 acute phase patients recruited at admittance for psychosis. This study reports data for all groups collectively, and does not compare treatment groups. Measurements of CRP and cognitive performance were conducted at baseline (T1) and after 4 weeks on average after inclusion (T2). Cognition was also assessed after 3 months (T3) and 6 months (T4) of follow-up. *Results:* Global cognition improved during the follow-up period of 6 months, especially in the T1–T2 interval. The different cognitive subdomains showed different time-dependent profiles of improvement, with memory and attention improving significantly also in the later phases. Reduction of the CRP level during the initial follow-up interval (T1–T2) was associated with increased overall cognitive performance in the T2–T4 interval, but not in the T1–T2 interval. For the cognitive subdomains, we found an inverse association between change in CRP level and verbal abilities (T2–T4 interval), and attention (T2–T3 interval). *Conclusion:* These findings indicate that initial changes in the serum level of CRP in the acute phase of psychosis may predict cognitive function in later phases of the disease.

Trial registration

ClinicalTrials.gov ID; URL: http://www.clinicaltrials.gov/:NCT00932529

Significant outcomes

- Global cognition and several cognitive subdomains continued to improve beyond the initial phase of acute psychosis treatment and into the later phase of follow-up.
- Reduction of the C-reactive protein (CRP) level in the initial acute phase was associated with delayed improvement of global cognition. Inverse associations between CRP levels and cognitive subdomains were found for learning, verbal abilities, and attention.

Limitations

- There was considerable attrition in the study during follow-up.
- CRP was the only inflammatory marker measured in the study.

Introduction

Cognitive dysfunctions are core features of schizophrenia that detrimentally affect functional outcome (1–3). The neurobiological disturbances involved in cognitive dysfunctions are, however, largely unknown. Abnormal myelination, white matter changes, and

immunological processes, including low-grade inflammatory responses, have been suggested as possible mechanisms (4). Many studies have indicated that the cognitive impairments seem to stabilise after the first episode of psychosis (5,6), although there have also been some findings suggesting cognitive improvements (7–10). The inconsistent literature might at least in part be explained by differences in the patient samples, the duration of follow-up, and the cognitive test batteries. Taken together, recent findings indicate that cognitive dysfunction is not always irreversible and can be dynamic, especially in the acute phases (11,12). Importantly, current treatment options in psychosis, including psychosocial interventions and antipsychotic medications, have few if any beneficial effects on cognitive performance (4,13–17). Thus, this central area of dysfunction in psychosis is in need of a better understanding and novel treatment approaches.

Inflammation has been the focus of recent studies addressing the pathophysiology of psychotic disorders. Immune abnormalities in the blood, cerebrospinal fluid, and central nervous system, including immune cell numbers, inflammatory markers, and antibody titers, have been demonstrated in schizophrenia (18–23). There is increasing evidence for underlying inflammatory mechanisms relevant to cognitive functioning (4,24–26). Indeed, neuroinflammation with white matter pathology has been demonstrated in the early stages of psychosis (27), and it has been suggested that these changes can lead to both structural and functional dysconnectivity and cognitive dysfunction (21). Low-grade elevation of the CRP, a well characterised and standardised marker of inflammation (28), has been found in some studies in schizophrenia (29–35). An inverse association between the serum levels of CRP and cognitive function has been reported (18,36,37). However, these studies are predominantly cross-sectional and include patients in the chronic phase. This might restrict the generalisability of the results, and longitudinal studies with repeated cognitive assessments are scarce.

We have recently shown an inverse association between the serum level of CRP and cognitive performance in the acute phase of psychosis (11). What remains unresolved, however, is whether the levels and change of CRP in the initial phase of acute psychosis influence cognition in later phases. The main aim of this study was therefore to investigate how the CRP level in the first acute phase of psychosis correlates with cognitive function during a 6 months follow-up.

Material and methods

The study is part of a pragmatic, randomised trial comparing four different second-generation antipsychotics in the treatment of psychosis (Fig. 1). Importantly this study reports data for all treatment groups collectively, and does not compare treatment groups. We have previously published cross-sectional comparisons of treatment groups, and no differences were found (11). The main objective of the present study was to investigate overall associations between longitudinal changes in CRP and cognition in the whole group. The clinical sample and methods have been described in detail elsewhere (38).

Clinical sample

The sample consists of 208 consecutive, acute phase patients recruited at admittance for psychosis, who underwent CRP measurements and cognitive assessment. The project was designed and approved by the Ethics committee with two phases: The first was the quality assurance phase from admission to discharge or 6 weeks at the latest, and was approved by the Ethics Committee without the requirement of informed consent as this phase included only elements of best clinical practice. At admission all psychotic patients admitted to the hospital for symptoms of acute psychosis were consecutively included, if they were to use the hospital's standard antipsychotic medication regimen, and could cooperate with clinical assessments of condition. This phase should assure that psychosis patients were offered best-quality guideline-concordant treatment for psychosis. The second phase (research phase) was based on informed consent provided at discharge or after 6 weeks at the latest. This included invitation to visits and tests at 3, 6, 12, and 24 months after admission. In this part of the project there were procedures beyond usual clinical standard, such as collections of data for use in psychiatric basic research within genetics and brain functioning.

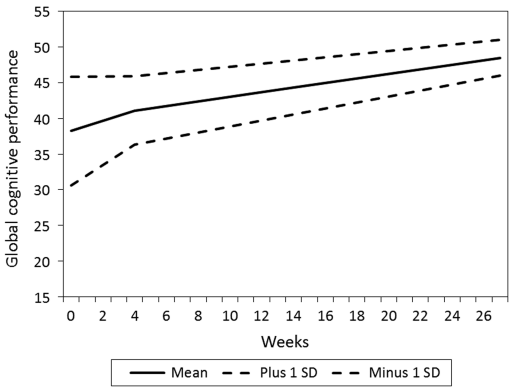

Figure 1. Estimated mean level and change in global cognitive score over time, with standard deviations to display individual variation ($N = 181$).

The recruitment period was from March 2004 until February 2009 at Haukeland University Hospital, Bergen, Norway, with a catchment population of about 400 000. The study was approved by the Regional Committee for Medical Research Ethics, and by the Norwegian Social Science Data Services. The study was publicly funded and did not receive any financial or other support from the pharmaceutical industry.

All adult patients were eligible for participation if they were acutely admitted to the emergency ward for symptoms of active psychosis, as determined by a score of ≥4 on one or more on the items Delusions, Hallucinatory behaviour, Grandiosity, Suspiciousness/persecution, or Unusual thought content in the Positive and Negative Syndrome Scale (PANSS) (39) and were candidates for oral antipsychotic drug therapy. All eligible patients met the International Statistical Classification of Diseases and Related Health Problems (ICD)-10 diagnostic criteria (http://apps.who.int/classifications/icd10/browse/2010/en) for schizophrenia, schizoaffective disorder, acute and transient psychotic disorder, delusional disorder, drug-induced psychosis, major depressive disorder with psychotic features, bipolar disorder except manic psychosis. Manic psychosis was excluded based on *a priori* expectation that these patients would not be able to cooperate with the assessments in the acute phase.

Table 1. Neuropsychological assessment by cognitive subdomain and time

Cognitive subdomain	T1 (baseline)	T2 (4 weeks*)	T3 (3 months)	T4 (6 months)
Verbal abilities	RBANS A language	RBANS B language	WAIS-III similarities WAIS-III vocabulary COWAT letters/animals	COWAT letters/animals
Visuospatial abilities	RBANS A visuospatial/ constructional	RBANS B visuospatial/ constructional	WAIS-III digit symbol-coding WAIS-III block design ROCF copy	ROCF copy
Attention	RBANS A attention	RBANS B attention	WAIS-III digit span Digit vigilance test (time)CalCAP CPT (choice reaction time/sequential reaction time) Trail making test B Stroop colour/word conflict (time)	WAIS-III digit span CalCAP CPT (choice reaction time/ sequential reaction time) Stroop colour/word conflict (time)
Learning	RBANS A immediate memory	RBANS B immediate memory	CVLT-II (immediate recall) WMS-R logical memory WAIS-III digit span	WMS-R logical memory WAIS-III digit span
Memory	RBANS A delayed memory	RBANS B delayed memory	CVLT-II (delayed recall) ROCF delayed recall	ROCF delayed recall

CalCAP CPT, California Computerized Assessment Package-Continuous Performance Test; COWAT, Controlled Oral Word Association Test; CVLT, California Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; ROCF, Rey Osterrieth Complex Figure Test; WAIS-III, Wechsler Adult Intelligence Scale; WMS-R, Wechsler Memory Scale-Revised.
*Mean follow-up time at T2 was 4.1 weeks after baseline.

Patients were excluded from the study if they were unable to use oral antipsychotics, were suffering from manic psychosis or, for other behavioural or mental reasons related to the state of illness, were unable to cooperate with assessments, did not understand spoken Norwegian, were candidates for electro-convulsive therapy, or were medicated with clozapine on admittance. Patients with drug-induced psychoses were included only when the condition did not resolve within a few days and when antipsychotic drug therapy was indicated.

The patients were assessed at baseline (T1: $N = 208$ with data on CRP level and/or cognition), at the first follow-up (on average after 4 weeks; T2: $N = 103$), at the second follow-up after 3 months (T3: $N = 43$), and at the third follow-up after 6 months (T4: $N = 35$). This period corresponds to the treatment of the acute phase during which the largest reduction of psychotic symptoms is seen, and treatment response is expected in the majority of patients (40).

Clinical and biochemical assessments

Eligible patients underwent the PANSS structured clinical interview at baseline, before inclusion. All tests were performed by personnel independent of the clinical departments, who were trained and with inter-rater reliability training. Intra-class correlation coefficients were calculated based on inter-rater assessments and showed high inter-rater reliability (0.92). Furthermore, the Calgary Depression Scale for Schizophrenia (41), and the Clinical Drug and Alcohol Use Scales (42) were used, and the patients were rated according to the Clinical Global Impression-Severity of Illness Scale (43), and the Global Assessment of Functioning-Split Version, Functions Scale (44). Illicit drug use data was based only on information from the participant.

For analysis of CRP, a blood sample was collected from the patients in the fasting state between 08:00 and 10:00 h in the morning at baseline (T1) and after 4 weeks follow-up (T2). The laboratory changed the routine CRP analysis method in January 2005, and hence only data obtained after this revision is used in the present work. The CRP level was measured by the Tina-quant C-reactive Protein (Latex) method from Roche Modular P® (Mannheim, Germany), which measures CRP levels >1 mg/l.

Cognitive assessment

Cognitive assessments were conducted at baseline (T1) and follow-up (T2, T3, and T4). A brief neuropsychological screening instrument with alternative forms; the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), was used to minimise potential practice effects (45–47), since longitudinal studies on cognitive functioning usually do not sufficiently address the issue of practice effects (48,49). The RBANS has previously shown to have good reliability and validity in psychosis (47). To increase clinical validity, a more comprehensive cognitive battery, but with the same cognitive subdomains, was administered at T3 (Table 1). In a preliminary analysis, a satisfactory relationship between the RBANS/short battery and equivalent domains from the long battery/more comprehensive neuropsychological battery 3 months later emerged, even despite of symptom-level differences at the two time points (50). The five cognitive domains were the same as for the RBANS: Language; Visuospatial/constructional; Immediate memory; Delayed memory; and Attention. We have used the already set domains from the RBANS, which does not include executive functioning. We do argue, however, that both Trails B and Stroop do depend as much on attentional resources, as executive functioning making it correct to group them together with the Attention domain. If we had an executive domain we would have grouped in this domain also. The policy of grouping test with several domains when they do capture several cognitive processes is what we consider the most transparent way of taking the complexity into account. The grouping of WAIS III digit span with both Attention and Learning was done for the same reason. In addition, in the before mentioned preliminary analysis, this method of grouping

the tests was the one that obtained a satisfactory relationship with the RBANS (50). Raw scores for the neuropsychological variables were converted to *t*-scores using the best available norms from corresponding manuals (when available) or published papers. The final summary score based on the mean *t*-scores across the five cognitive domains defined the overall cognitive function *t*-score. Neuropsychological assessment by cognitive domain and time are shown in Table 1.

Statistical analyses

Descriptive statistics (mean, standard deviation, frequency) and independent sample-*t*-test were analysed with SPSS version 24.0. The program Mplus 8 (51) was used to analyse the level and change in variables with latent growth curve and time contrast models (52). The standard linear change assumption was tested based on the goodness of fit measures, residual results, and plots of the observed and estimated change model were used to decide the change pattern. If this assumption was not met, piecewise growth was explored. If the model indicated one piece based on two measurements only, this part is a difference score model (53). Some residuals had to be set as constant to fit such a model. The models were evaluated based on their goodness of fit measures, as follows: threshold values in comparative fit index and Tucker–Lewis index beyond 0.95; root mean error of approximation (RMSEA) < 0.05 as close fit, RMSEA <0.08 as fair fit, and RMSEA <0.10 as a mediocre fit (52). Model fit measures were presented for unconditional level and change models, but not for prediction models, as these models solely are predictions with statistical significant and non-significant relations and not structural models. The estimator was set to maximum likelihood with robust standard errors (MLR) to account for non-normality in data (54). The full information maximisation likelihood (FIML) method uses all available data under the assumption that missing data are random ('Missing at Random') (51,54). Thus, the level and change results are estimated and not observed values based on all observations. After analysing the variables separately, level and change in CRP were related to levels and changes in neurocognitive scales. A sensitivity analysis was performed for CRP levels <10 mg/l.

Finally, we controlled for confounders, known to have impact on both CRP level and cognition, as metabolic syndrome, smoking, being antipsychotic medication-naive, illicit drug use, and educational level (11).

Results

The study included 208 patients with data in one or more of the outcome variables. At baseline, there were CRP measurement for 158 patients and cognitive assessments for 169 patients and a total of 123 patients had both measurements. In total, 181 patients had observations on cognitive performance and 169 on CRP at any time point. The demographic and clinical characteristics are shown in Table 2. The patients that were tested only at baseline were not statistically different from those with follow-up data for the clinical or demographic characteristics at baseline, with the exception of a higher PANSS negative subscale score in patients with baseline test only compared to those with two or more visits [independent samples *t*-test: $p = 0.034$; mean difference 2.2 points; 95% confidence interval (CI): 0.2–4.2], and fewer years of education (independent samples *t*-test: $p = 0.027$; mean difference, 0.8 years; 95% CI: 0.10–0.6).

Table 2. Baseline demographics and clinical characteristics ($N = 208$)

Characteristics	*N*	%	
Male	143	68.8	
Antipsychotic drug naive	92	44.2	
Alcohol abuse last 6 months	22	10.6	
Illicit drug use last 6 months	139	66.8	
Current tobacco smoking	103	49.5	
Diagnosis*			
Schiz and related	106	53.2	
Drug-induced	28	14.1	
Affective	23	11.6	
Acute psychosis	17	8.5	
Other	25	12.5	
	Mean	SD	Range
Age	33.5	13.1	17–73
Body mass index	23.7	4.8	15.8–42.6
Years of education	12.5	2.8	8.0–22.0
PANSS total	74.1	13.2	44–111
PANSS positive	19.9	4.4	11–32
PANSS negative	19.6	7.4	7–39
PANSS general	34.6	6.7	20–56
CDSS	6.6	5.2	0–23
GAF-F	30.7	6.0	2–62
CGI	5.2	0.6	4–6
RBANS	38.3	7.7	20.2–58.8
CRP	4.0	8.3	0–89

N, number of patients; Antipsychotic drug naive, no life-time exposure to antipsychotic drugs before index admission; Abuse, abuse or dependence according to the Clinical Drug and Alcohol Use Scales (CDUS/CAUS), patients with no illicit drug use could be included in the category alcohol use last 6 months; Schz and related, schizophrenia and related disorders: Schizophrenia, schizoaffective disorder, acute polymorphic psychotic disorder with symptoms of schizophrenia, acute schizophrenia-like psychotic disorder, delusional disorder; Acute psychosis, acute psychosis other than those categorised under Schz and related; Affective, bipolar and unipolar depression; Other, miscellaneous psychotic disorders.

CDSS, the Calgary Depression Scale for Schizophrenia; CGI, the Clinical Global Impression, severity of illness scale; CRP, C-reactive protein (mg/l); GAF-F, the Global Assessment of Functioning, split version, Functions scale; PANSS, the Positive and Negative Syndrome Scale; RBANS, the Repeatable Battery for the Assessment of Neuropsychological Status.

All diagnoses are according to ICD-10;

*Patients with missing diagnoses are not included in the list. According to the naturalistic design, patients were included on the basis of the presence of active psychosis as determined by the PANSS, and not based on diagnosis.

Levels and changes in cognitive performance

The mean and individual levels and changes in cognitive subdomains are presented in Table 3. The mean level of global cognitive performance increased over time in a non-linear manner, being most pronounced in the T1–T2 interval (Fig. 1). The figure also shows more individual change variation in the T1–T2 interval than in the later intervals. Statistically significant improvements over time were also found for verbal abilities,

Table 3. Levels and changes in global cognition and cognitive subdomains over time

	T1 Level (I)			Change T1–T2 (S1)				Change T2–T4 or change T2–T3 (S2)*				Change T3–T4 (S3)*			
Scale	Mean	SD	*p*	Mean	*p*	SD	*p*	Mean	*p*	SD	*p*	Mean	*p*	SD	*p*
Global performance	38.3	7.6	0.000	2.9	0.000	4.9	0.000	1.4	0.000	1.1	0.003				
Verbal abilities	40.1	8.4	0.000	6.0	0.000	6.8	0.000	0.2	0.643	2.0	0.002				
Visuospatial abilities*	47.3	12.1	0.000	1.4	0.148	10.1	0.000	−0.7	0.295	5.1	0.000	2.1	0.000	3.2	.004
Learning	35.8	8.1	0.000	2.9	0.000	1.7	0.078	−0.3	0.315	1.9	0.000				
Memory*	38.1	12.1	0.000	1.2	0.326	11.3	0.000	2.8	.000	4.8	.000	3.0	.000	2.3	.000
Attention*	29.7	9.0	0.000	3.5	0.000	7.4	0.000	4.2	.000	4.0	.000	0.4	.167	2.1	.000

The time unit for change is months. T1, baseline; T2, 4 weeks; T3, 3 months; T4, 6 months.
S1: change from T1–T2; S2: change from T2–T4 if supported by data; and S3: change T3–T4. Change in the T3–T4 interval was estimated if a linear change from T2–T4 was not supported. In these models, S2 consists of the change between T2–T3.
Group mean and individual differences (standard deviation, SD) for both level and change are reported.
Statistical *p*-values are presented for individual differences at baseline level (T1 Level), and mean change and individual differences in change (standard deviation).
*Three change factors had to be estimated: S1: T1–T2; S2: T2–T3; and S3: T3–T4.

learning and attention in the T1–T2 interval, and for memory and attention in the T2–T4 interval, respectively. Individual differences in change (standard deviation) were also present. Some patients improved their performance, whereas others showed decline. The goodness of fit measures showed close fit between model and data for global cognitive performance, verbal abilities and learning scales, while the other three scales were based on saturated models and thereby giving no fit measures (please see Supplementary Table 1).

The relationship between levels and changes in CRP and cognition

The mean change in CRP from T1 to T2 was not statistically significant (0.52 mg/l/ month, $p = 0.652$, baseline mean level: 3.99 mg/l, SD = 8.32). However, the individual variation in change was statistically significant (SD = 12.13, $p = 0.031$). In the total sample, a reduction in the CRP level from T1 to T2 was associated with an increase in global cognitive performance in the T2–T4 interval, whereas no such association was found between CRP and cognition during the T1–T2 interval (Table 4). Patients with most reduction in CRP also were the patients with most improvement in global cognitive performance, illustrated with a steeper increase in their performance, compared to those with a smaller reduction or an increase in CRP (Fig. 2).

For the cognitive subdomains, we observed a statistically significant association between reduction of the CRP level and increase in verbal abilities for the T2–T4 interval and in attention for the T2–T3 interval (Table 4).

For patients with CRP <10 mg/l ($N = 191$), the results remained unchanged regarding the association between changes in global cognitive performance (T2–T4), verbal abilities (T2–T4), and attention (T2–T3), and CRP level changes. However, we also found additional statistically significant associations in this subsample compared to the total sample (Table 4).

A separate model for the sub-sample of patients diagnosed within the schizophrenia spectrum showed that change in CRP level did not predict T2–T4 change in the global cognitive performance as was found in the total sample ($b = -0.01$, $p = 0.208$). Two new statistically significant associations were found between change in CRP level and attention in the T1–T2 interval ($b = 0.12$, $p = 0.045$) and in the T3–T4 interval ($b = 0.03$, $p = 0.026$).

Finally, the models were adjusted for the covariates metabolic syndrome, smoking, being medication naïve, illicit drug use, and the educational level. The association between baseline CRP level and global cognitive performance for the whole follow-up remained essentially unchanged. Baseline CRP level and visuospatial performance in the T3–T4 interval was no longer statistically significant ($p = 0.120$), whereas a statistically significant association was found between CRP baseline level and this subdomain in the T1–T2 interval ($b = 0.66$, $p = 0.018$). CRP level change and verbal abilities in the T2–T4 interval was no longer statistically significant associated ($p = 0.067$), while such an association was found in the T1–T2 interval ($b = -0.09$, $p = 0.039$). Additional statistically significant associations were found between CRP baseline level and attention in the T3–T4 interval ($b = 0.31$, $p < 0.001$), and CRP level change and attention in the T1–T2 interval ($b = 0.12$, $p = 0.045$), and in the T3–T4 ($b = 0.03$, $p = 0.026$), respectively.

A separate model for the sub-sample of patients diagnosed within the schizophrenia spectrum showed some differences. Change in CRP did not predict T2–T4 change in the global score as it did in the total sample ($b = -0.01$, $p = 0.208$), whereas change in CRP was found to be associated with change in attention for the T1–T2 ($b = 0.12$, $p = 0.045$) and T3–T4 ($b = 0.03$, $p = 0.026$) intervals, respectively.

In the schizophrenia group, the inclusion of covariates showed that higher CRP baseline level was related to lower baseline level in global cognitive performance ($b = -0.26$, $p = 0.036$). CRP baseline level was found to be associated with verbal abilities in the T1–T2 interval ($b = 0.64$, $p = 0.016$). In addition, CRP level change was found to be associated with verbal abilities in ($b = -0.09$, $p = 0.024$) and learning in the T1–T2 interval ($b = -0.04$, $p = 0.009$). The model with the attention outcome variable did not converge, even after increasing the number of iterations.

Discussion

The main finding of the present study was that the global cognitive performance continued to improve from the initial phase (baseline to 4 weeks) of acute psychosis to the later phase (4 weeks to 6 months), and was predicted by the reduction of the CRP level as observed during the initial phase (baseline to 4 weeks) of the

Table 4. Baseline level and changes over time in cognitive performance predicted by baseline and change in C-reactive protein (CRP) level

	Total sample						Subsample (CRP <10 mg/l)					
	CRP level T1			CRP change T1–T2			CRP level T1			CRP change T1–T2		
	b	β	*p*	*b*	β	*p*	*b*	B	*p*	*b*	β	*p*
Global performance												
T1	−0.35	−0.37	0.002	–	–	–	−0.70	−0.17	0.059	–	–	–
T1–T2	0.13	0.21	0.455	−0.01	−0.03	0.748	0.95	0.34	0.013	−0.02	−0.04	0.573
T2–T4	0.08	0.54	0.025	−0.02	−0.18	0.004	−0.07	−0.12	0.684	−0.02	−0.14	0.026
Verbal abilities												
T1	−0.35	−0.35	0.120	–	–	–	−0.75	−0.17	0.095	–	–	–
T1–T2	0.13	0.17	0.610	−0.06	−0.10	0.124	1.11	0.30	0.082	−0.07	−0.09	0.103
T2–T4	0.11	0.39	0.197	−0.04	−0.23	0.003	0.17	0.15	0.600	−0.03	−0.14	0.039
Visuospatial abilities												
T1	−0.28	−0.19	0.067	–	–	–	−0.49	−0.07	0.434	–	–	–
T1–T2	0.56	0.44	0.059	0.04	0.05	0.724	0.94	0.16	0.146	0.05	0.05	0.684
T2–T3	−0.31	−0.48	0.111	−0.05	−0.11	0.416	−0.96	−0.34	0.048	−0.06	−0.11	0.311
T3–T4	0.16	0.40	0.022	0.01	0.02	0.699	0.53	0.29	0.043	0.01	0.02	0.663
Learning												
T1	−0.32	−0.32	0.024	–	–	–	−0.47	−0.10	0.337	–	–	–
T1–T2	−0.01	−0.04	0.916	−0.02	−0.17	0.198	0.54	0.44	0.008	−0.02	−0.10	0.112
T2–T4	−0.09	−0.37	0.200	0.01	0.06	0.512	−0.58	−0.54	0.041	0.01	0.05	0.360
Memory												
T1	−0.63	−0.41	0.002	–	–	–	−1.30	−0.10	0.000	–	–	–
T1–T2	0.25	0.18	0.288	−0.06	−0.06	0.501	0.62	0.44	0.144	−0.06	−0.05	0.488
T2–T3	0.06	0.10	0.673	0.05	0.13	0.142	0.23	0.15	0.300	0.05	0.10	0.143
T3–T4	−0.15	−0.50	0.260	−0.02	−0.11	0.074	−0.22	−0.30	0.222	−0.02	−0.10	0.080
Attention												
T1	−0.42	−0.38	0.001	–	–	–	−1.06	−0.21	0.002	–	–	–
T1–T2	0.50	0.54	0.191	0.10	0.16	0.096	1.75	0.43	0.001	0.06	0.07	0.304
T2–T3	−0.12	−0.26	0.903	−0.08	−0.24	0.003	−0.43	−0.19	0.225	−0.06	−0.14	0.047
T3–T4	−0.06	−0.21	0.684	0.03	0.17	0.070	0.63	0.56	0.003	0.02	0.11	0.040

The table presents results for all patients (i.e. total sample) and patients with CRP <10 mg/l (i.e. subsample). The time unit for change is months.
Relations are given by unstandardised and standardised regression weights (*b* and β).

treatment. Similar associations were found for several of the cognitive subdomains. These findings might indicate a prolonged effect of inflammatory processes on cognition after an acute psychosis, stretching beyond the initial phase.

The stability of cognitive dysfunctions in patients with psychosis has been debated for decades. Most studies have suggested stability or decline in cognitive functioning (55–58). A study of first-episode schizophrenia spectrum disorders and controls with follow-up intervals of 1-year and 3-years showed that, although patients performed worse than controls at any given time, the cognitive performance of the patients improved in a similar way as the controls in all domains, except for verbal and visual memory, which showed greater improvement in controls (6). Another longitudinal study demonstrated improvement of general cognitive function, working memory, and verbal learning after 12 weeks, but these changes were mediated by improvements in both positive and negative symptoms (59).

There is substantial evidence that inflammatory processes are involved in the cognitive performance in psychosis (23,60,61). Oxidative stress and inflammation have been suggested to be associated with specific aspects of cognitive functioning in first-episode psychosis patients (62). Of particular interest, several studies have shown a link between CRP and cognitive function (25,29,37,63,64). CRP levels have been associated with cognitive impairment in patients with schizophrenia (25,36). In one study, abnormal CRP levels were correlated with poorer cognitive

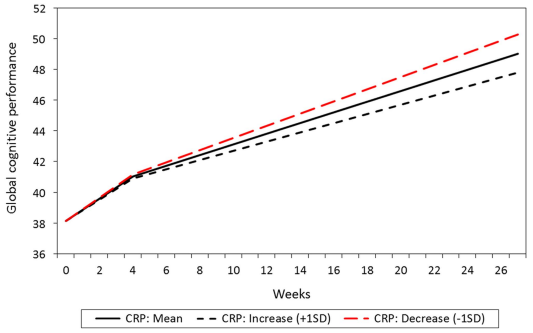

Figure 2. Relationship between estimated level and change in C-reactive protein (CRP) and global cognitive performance total score ($N = 208$).

functioning of general intellectual ability, abstract reasoning, memory, working memory, semantic memory, learning abilities, attention, mental flexibility, and processing speed (25). In another, longitudinal study, CRP levels did not predict changes in cognitive performance (65), but this study included chronic phase patients with an average illness duration of 22.5 years, who are likely to have a lesser potential for inflammation related cognitive improvements.

Taken together, the present study supports a link between inflammation and cognitive performance in schizophrenia. Our study shows that early low-grade inflammation can predict cognitive improvement in later phases. Some studies have suggested that low-grade inflammation as indicated by elevated CRP levels is related to cerebral microstructural disintegration, involving frontal lobe executive functions (66). It has been suggested that increased levels of CRP can increase blood–brain barrier permeability, which might lead to inflammatory-related cognitive impairment (67). As neuroinflammation has been demonstrated to be associated with white matter pathology (27), any psychosis-related inflammation could, in principle, have a negative impact on brain tissue components of relevance to cognition, and the reversibility of such effects would likely include more slow regenerative processes.

There are some limitations to this study. First, attrition was substantial, but generally not related to any of the baseline characteristics except a higher PANSS negative subscale score and lower educational level in those patients tested only at baseline. As negative symptoms have been found to correlate with cognitive dysfunctions (12), those with the most pronounced cognitive difficulties may have dropped out during follow-up.

It is, however, difficult to predict how any selective dropout might have biased our results. Furthermore we used statistical methods that reduce the effect of missing data (68), and give improved statistical power and generalisability to the results, as all information in the data set is taken into consideration, rather than using the listwise deletion method that gives a net sample based on intact data in all variables under the assumption of missingness to be completely at random. However, the FIML method does not rule out the possibility of missingness to be non-random. The study included several models for different outcome variables in the total sample and in the schizophrenia sub-sample. In addition, several covariate variables were included in sensitivity analyses. This strategy has implication for statistical power, which has consequences particularly for small effects. Studies with larger samples are needed to increase the validity of our findings.

Being exploratory, we did not adjust for multiple testing. The high number of tests could theoretically result in statistical type I error. However, we find it very unlikely that such a high number of statistically significant findings could be the result of chance.

According to the naturalistic design, patients were included on the basis of the presence of active psychosis as determined by the PANSS, and not based on diagnosis. Hence all patients were psychotic and in need of antipsychotic medication. The lack of specific diagnosis for nine patients probably reflects that some patients may have dropped out or been discharged before the treating clinician were able to make a proper diagnostic evaluation. This is clearly a limitation, but the direction of any influence on our results is difficult to predict.

Moreover, CRP was the only inflammatory marker that was measured, at baseline and the first follow-up (T2). Further measurements during the follow-up period would have allowed for analyses of associations between potential later changes in the CRP level and cognitive performance. We are also aware of the limitation that other factors potentially confounding the relationship between CRP and cognition might exist that we have not accounted for, although many relevant factors were included in the analyses. Finally, the cognitive test battery at the T3 follow-up was more comprehensive but assessed the same cognitive domains as the test battery at T1, T2, and T4. We have no reason to suspect that this difference could have influenced the results.

We have shown that initial changes in the serum level of CRP in the acute phase of psychosis may predict cognitive function in later phases of the disease. These findings create an opportunity for future RCT research efforts to develop more individualised treatments with add-on anti-inflammatory agents (69). Some efforts have already been made in this field of research, but the results are mixed. A double-blind, randomised, placebo-controlled, add-on study with Celecoxib, a cyclo-oxygenase-2 inhibitor showed significant effect on the total PANSS score and the cognition factor of PANSS scale in patients with schizophrenia (70). N-acetyl cysteine significantly improved working memory compared to placebo in patients with psychosis, however, these preliminary data require replication (71). A double-blind, randomised study with minocycline treatment was associated with improvement in negative symptoms and executive functioning in early phase schizophrenia (72), whereas another study with add-on minocycline treatment showed improvement in negative symptoms, but not in cognition (73). Aspirin given as add-on treatment in another study reduced the total and positive PANSS score, but did not affect cognitive function (74). Finally, omega-3 fatty acid (ethyl eicosapentaenoic acid) add-on treatment did not affect cognition, positive or negative symptoms (75). Possible explanations for the equivocal findings might at least in part be related to small, unselected samples both with and without signs of an increased inflammatory status, with predominantly chronic phase psychosis, and with anti-inflammatory agents under investigation typically of low anti-inflammatory potency (76). Therefore, a more targeted approach might be to investigate more potent anti-inflammatory agents, for example, corticosteroids, in selected samples with signs of low-grade inflammation as determined by, for example, elevated CRP levels.

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study. F.F. designed the study, contributed to the statistical analyses and interpretations of the data, and wrote the first draft of the manuscript. E.-M.L. collected data and contributed to interpretations of the data and drafting the manuscript. R.G. contributed to the statistical analyses and interpretations of the data and contributed to the drafting of the manuscript. R.A.K. collected data and contributed to interpretations of the data and drafting of the manuscript. V.M.S. was the co-designer of the project and contributed to the interpretations of the data and drafting of the manuscript. H.A.J. designed the project, assisted in data collection and contributed to interpretations of the data and drafting of the manuscript. E.J. was the co-designer of the project, collected data, contributed to the statistical analyses, and co-drafted the manuscript. All authors have read and given final approval of the latest version of the manuscript.

Statement of interest. E.-M.L. has received honoraria in relation to the development of the Norwegian version of the RBANS by Pearson Assessment. E.J., F.F., R.G., V.M.S., R.A.K. and H.A.J. report no conflicts of interest related to the present work.

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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