UiT The Arctic University of Norway

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Childhood Trauma in Schizophrenia Spectrum Disorders:

A comparison to substance abuse disorders, and relation to cognitive performance and antipsychotic treatment outcomes.

Nina Mørkved

A dissertation for the degree of Philosophiae Doctor - January 2022

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Scientific environment

This Ph.D. thesis has examined the relation of childhood trauma (CT) and schizophrenia spectrum disorders (SSDs) and was written between 2016 to 2021 while working as a clinical psychologist at the District Psychiatric Centre in Mosjøen, Helgeland Hospital, and as a Ph.D. student. The Ph.D. studies were based at the Department of Psychology, Faculty of Health Science, at the UiT The Arctic University of Norway. The research project was funded mainly by grants from Northern Norway Health (Helse Nord RHF), but also supported by Helgeland Hospital.

The current thesis was based on data from two research projects. SSDs patients in Paper I, II and III, were included from the Berge-Stavanger-Trondheim-Innsbruck (BeSt InTro) trial; a pragmatic, naturalistic and semi-randomized controlled trial comparing the effectiveness of three antipsychotic drugs in patients with SSDs. The BeSt InTro was conducted by the Bergen Psychosis Research group (BPRG) lead by professor Erik Johnsen, in collaboration with research sites in Stavanger and Trondheim, Norway, and Innsbruck, Austria. Patients with substance abuse disorders (SUDs) in Paper I was included from the Trauma and adult mental health research project, a cross-sectional study assessing traumatic experiences in high-risk clinical and non-clinical groups conducted by The Trauma Psychology Research group (TPRG) lead by associate professor emeritus Dagfinn Winje.

My main supervisor Else-Marie Løberg, professor and specialist in clinical psychology, was part of the BPRG (co-Principal investigator) and BeSt InTro study. She was affiliated with the Division of Psychiatry, Haukeland University Hospital, and the Department of Clinical Psychology at the University of Bergen. In addition, she was affiliated with the Department of Addiction Medicine, Haukeland University Hospital, and the Department of Biological and Medical Psychology, University of Bergen, during parts of the dissertation period. Co-supervisor Erik Johnsen, professor, and psychiatrist was affiliated with the Department of Clinical Medicine, University of Bergen, and NORMENT Centre of Excellence, Haukeland University Hospital and with the Division of Psychiatry, Haukeland University Hospital.

Co-supervisor Dagfinn Winje, associate professor emeritus and specialist in clinical psychology, was affiliated with the Department of Clinical Psychology at the University of Bergen. Lastly, co-supervisor Jens C. Thimm, associate professor and specialist in clinical psychology, was affiliated with the Department of Psychology at UiT The Arctic University of Norway and the Centre for Crisis Psychology at the University of Bergen, in Norway.

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Abbreviations

AAPs: Atypical antipsychotics

CBT: Cognitive-behavioural therapy

CDSS: Calgary depression scale for schizophrenia

CT: Childhood trauma

CTQ-SF: Childhood trauma questionnaire short-form

DDD: Defined daily doses

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

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

D_2: Dopamine 2 receptor

DUP: Duration of untreated psychosis

FEP: First episode psychosis

ICD: International Statistical Classification of Diseases

ITT: Intention to treat

MD: Missing data

PANSS: Positive and Negative Syndrome Scale for Schizophrenia

PP: Per protocol

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

SD: Standard deviation

SE: Standard error

SUDs: Substance abuse disorders

SSDs: Schizophrenia spectrum disorders

SPSS: Statistical Package for the Social Sciences

TPRG: Trauma psychology research group

UHR: Ultra High Risk for psychosis

Abstract

Childhood trauma (CT) is commonly reported in schizophrenia spectrum disorders (SSDs) and may influence the development and treatment of SSDs. The current dissertation set out to test the specificity of CT in SSDs by comparing the frequency and severity of CT and CT subtypes in SSDs to patients with substance use disorders (SUDs) (Paper I). Additionally, the relationship between cognitive functioning, a marker of vulnerability for psychosis, and CT was examined (Paper II). Finally, the general and differential effect of CT on three types of antipsychotics (amisulprid, aripiprazole or olanzapine based on randomization), were studied (Paper III). For all studies SSDs were defined as F20-F29 in the ICD-10. Paper I included patients with SUDs defined as F10-19 in the ICD-10. The Childhood Trauma Questionnaire Short-Form (CTQ-SF) was used to retrospectively measure overall exposure to CT and CT subtypes (physical, sexual, and emotional abuse, and physical and emotional neglect), grouped into none-low and moderate-severe levels of CT. A comprehensive neuropsychological test battery was used to capture cognitive functioning, and covered verbal abilities, visuospatial abilities, learning, memory, attention/working memory, executive abilities, and processing speed.

In Paper I, no group differences emerged for the frequency and severity of CT and CT subtypes between the patients with SSDs (n = 57) and patients with SUDs (n = 57). In both groups 64.9 % reported exposure to ≥ 1 moderate to severe CT subtype. In Paper II there were no general and differential effect of CT and CT subtypes on global cognitive performance and most of the cognitive domains for the SSDs patients (n = 78). The CT subtype physical neglect, however, significantly predicted impaired attention/working memory abilities in SSDs. In Paper III there were no differences for the general antipsychotic effectiveness at 52 weeks shown by psychosis symptom change for patients with SSDs with CT (n = 55) as compared to SSDs with no CT (n = 43). The CT group showed less decrease in symptoms from baseline to 26 and 39 weeks, and for olanzapine the CT group showed less decrease in overall psychosis symptoms form baseline to 12, 26, 39 and 52 weeks, and for general psychopathology symptoms at weeks 12, 26 and 52.

In can be concluded that CT is frequently reported in SSDs, although not unique for SSDs in comparison to SUDs. Further, the CT subtype physical neglect appears to be related to cognitive functioning. In addition, CT may be associated with a slower antipsychotic treatment response in SSDs. Trauma-informed treatment may be warranted patients with SSDs and patients with SUDs.

List of papers

Paper I: Mørkved, N., Winje, D., Dovran, A., Arefjord, K., Johnsen, E., Kroken, R.A., Anda-Ågotnes, L.G., Thimm, J.C., Sinkeviciute, I., Rettenbacher, M., & Løberg, E.M. (2018). Childhood trauma in schizophrenia spectrum disorders as compared to substance abuse disorders. *Psychiatry Research 261*, 481-487.

Paper II: Mørkved, N., Johnsen, E., Kroken, R.A., Gjestad, R., Winje, D., Thimm, J.C., Fathian, F., Rettenbacher, M., Anda, L.G., & Løberg, E.M. (2020). Does childhood trauma influence cognitive functioning in schizophrenia? The association of childhood trauma and cognition in schizophrenia spectrum disorders. *Schizophrenia Research: Cognition,* 21, 100179.

Paper III: Mørkved, N., Johnsen, E., Kroken, R.A., Winje, D., Larsen, T.K., Thimm, J.C., Rettenbacher, M.A., Bartz-Johannesen C.A., & Løberg, E.M. (under review) Impact of childhood trauma on general and differential antipsychotic effectiveness in schizophrenia spectrum disorders: A prospective, pragmatic, semi-randomized trial. *Schizophrenia Research*.

1 Introduction

1.1 Psychosis

Psychosis embodies a heterogeneous set of mental disturbances to perceptual experience, thought processes, emotions, and behavior, with characteristic symptom dimensions often divided into positive (e.g., hallucinations and delusions) and negative (e.g., avolition, apathy) symptoms (Lieberman & First, 2018). Although being an important clinical feature observed in schizophrenia spectrum disorders (SSDs), psychosis is not unique to schizophrenia (Howes & Kapur, 2009). Subclinical symptoms and some degree of psychotic experiences are quite common in the general population (Linscott & Van Os, 2013). Psychosis and psychosis imitating symptoms may arise during periods of extreme stress, following substance abuse or exposure to certain illegal substances, due to organic brain diseases or other medical conditions, or with no apparent trigger at all. Further, symptoms of psychosis or psychotic episodes feature in a variety of mental health disorders: SSDs including schizoaffective disorders and delusional disorders, bipolar disorders, severe depression, substance induced psychotic disorders, borderline personality disorders, and post-traumatic stress-disorder. Psychoses can be broadly divided into idiopathic psychoses, psychoses due to a medical condition (including neurodegenerative disorders) and toxic psychoses (medication, substance use) (Lieberman & First, 2018).

Psychosis is characterized by a fluctuating course, developing from a high-risk or premorbid state, possibly transitioning to an acute phase of psychosis, to the more prolonged remission and recovery phases. Psychosis patients are at risk for experiencing more than one episode of psychosis: Estimates of relapse rates in the early course of psychosis have varied from about 30 to 55 % within the first years after illness debut, with medication non-adherence, substance use and poor premorbid adjustment being associated with an increased risk of relapse (Alvarez-Jimenez et al., 2012; Winton-Brown et al., 2017). The past decades, more optimistic views of psychosis outcomes have evolved, with an increased focus on remission and recovery as well as the implementation of early intervention services (Lally et al., 2017; McGorry et al., 2010). To date, whether a given individual with psychosis will respond to the initiated treatment, is highly unpredictable. Despite vast research efforts, the etiology or pathways underlying the development of psychosis and psychotic disorders remain complex and multifactorial, with consequences for tailoring an optimal and individualized treatment regimen and course for individuals suffering from psychosis.

1.1.1 Symptom dimensions

Psychosis in SSDs consists of a heterogeneous presentation of positive, negative, affective, cognitive, disorganization, and psychomotor symptoms. The clinical picture is highly variable, as symptoms from one or more of the following dimensions may be present and fluctuate during the course of illness (Lieberman & First, 2018).

Clinical presentations of delusions and hallucinations are grouped as positive psychosis symptoms (Tandon et al., 2009), meaning symptoms that are added to normal behavior. Firm beliefs of being controlled, persecuted, or that of experiencing broadcasting or insertion of thoughts are characteristics associated with psychotic delusions. These are fixed and false beliefs, and difficult to sway. Hallucinations may occur in all sensory modalities (e.g., visual, smell, auditory, touch or taste). Auditory hallucinations, such as hearing voices, are most commonly reported in SSDs (Tandon et al., 2009). A recent meta-analysis reported associations between negative or maladaptive cognitive appraisals of voices and level of distress experienced by individuals with SSDs (Tsang et al., 2021). Visual, olfactory or tactile hallucinations in combination with rapid functional decline and abrupt symptom onset may be associated with substance induced psychosis or psychosis due to organic diseases (Lieberman & First, 2018). Impaired reality testing, understood as a collapse in the ability to distinguish internal experiences from external reality, marks the illness onset. A vague feeling of being persecuted develops into believing the danger is very real and life threatening. Being convinced of persecution or impending death is thus related to a severe deficit in the ability to question internal beliefs. Hallucinations and delusions are according to the aberrant salience hypothesis linked to abnormalities in mesostriatal dopamine functioning (Howes & Kapur, 2009; Kesby et al., 2018). Aberrant salience describes how positive symptoms may arise from a hyperdopamine-related dysfunction in the brain's reward system, leading random stimuli that would normally be unnoticed or dismissed as irrelevant, to be assigned significance (Roiser et al., 2013).

Negative symptoms describes the loss or absence of normal functions or abilities such as negative affective experiences or expressions, or a lack of interest, initiative and motivation (Tandon et al., 2009), and have mainly been described as a core component of schizophrenia (Correll & Schooler, 2020) but also in UHR and first episode samples (Rammou et al., 2019; Yung et al., 2019). Negative symptoms can be grouped into two factors: diminished expression of affect and alogia, and avolition such as anhedonia and asociality (Blanchard & Cohen, 2006). Some may experience a decreased ability to verbally expressing themselves. These symptoms are important contributors to the loss of social and vocational functioning, as

well as the long-term disability seen in the many patients with SSDs (Correll & Schooler, 2020). Negative symptoms are commonly reported as part of the initial clinical picture in the developing illness development but may occur in any phase of the disorder (Galderisi et al., 2018). Also, they are quite common: up to 60% of SSDs patients may experience negative symptoms that warrant clinical attention (Correll & Schooler, 2020). Negative symptoms may be primary symptoms of SSDs, or secondary to side-effects of antipsychotic medication, social or environmental deprivation or comorbid mood disorders such as depression. Also, while positive symptoms often respond favorably to treatment, negative symptoms in schizophrenia have been described as difficult to treat (Fusar-Poli et al., 2014). The neurobiological basis for negative symptoms is unclear, but has been linked to dopamine hypofunction in the mesocortical pathway (Howes & Kapur, 2009).

Moreover, disorganization is yet a symptom dimension associated with schizophrenia, and entails conceptual disorganization and bizarre behavior (Ventura et al., 2010). Additionally, symptoms associated with formal thought disorders are often understood as part of the disorganized symptoms. The severity of disrupted thought processes may range from mild cases of fragmentation in normal thought processes being expressed as circumstantiality and tangentiality, to more severe presentations of incoherence and 'word salads' (Tandon et al., 2009). The clinical picture of disorganization also includes neologisms (made-up words), echolalia (repetition of spoken words) and poverty of thought content as well as a loss of meaningful associations. Disorganization in SSDs have been identified as associated with a worse course of illness (Metsänen et al., 2006), as well as strongly related to decreased functioning (Rocca et al., 2018). Symptoms of disorganization are more strongly related to neurocognition and cognitive functioning in SSDs than to the positive symptom dimension (Minor & Lysaker, 2014; Ventura et al., 2010), although the neurobiological basis for disorganized symptoms is unclear. A study by Cancel et al. (2015) suggested that severe stress, such as childhood neglect, was associated with reduced grey matter volume in SSDs compared to healthy controls, which in turn was associated with symptoms of disorganization.

Mood-related affective symptoms include both an increased anxiety, emotionality and arousal experienced in association to positive symptoms, in addition to depressive symptoms. Mood symptoms may precede psychosis onset by several years, be persistent throughout the florid phase and when recovering from psychosis (Tandon et al., 2009). Comorbid anxiety disorders and symptoms have been reported as prevalent, as well as related to antipsychotic side-effects, increased clinical severity and poorer outcomes in SSDs (Braga et al., 2013).

High rates of depressive symptoms and suicidal behavior has been reported after first episodes of psychosis (Coentre et al., 2017). Rates of depression in SSDs varies considerably (20 – 60 %) depending on illness phase (ultra high-risk, prodromal, chronic) or state (acute, post-psychosis) (Upthegrove et al., 2017). Depressive symptoms in SSDs have been associated with, and challenging to differentiate from, negative psychosis symptoms (Upthegrove et al., 2017), as well as with decreased adherence to and side-effects of antipsychotic treatment, poor quality of life, worse long-term functioning and less likelihood of remission in first episode psychosis (FEP) (Conley et al., 2007; McGinty & Upthegrove, 2020; Sonmez et al., 2016).

Furthermore, schizophrenia has been described as a cognitive disorder (Kahn & Keefe, 2013). Cognitive symptoms seen in SSDs are clinically expressed as impairments in domains such as processing speed, executive functions, or verbal abilities. Being highly prevalent in SSDs, cognitive symptoms are thought to quite robustly distinguish SSDs patients from healthy controls (Tandon et al., 2009). The clinical importance of the cognitive aspects of SSDs are highlighted by an addition to the ICD-11, where cognitive symptoms will be specifically coded for (Valle, 2020). Cognitive impairments in SSDs which is the focus of Paper II, are described more thoroughly in Section 1.5.

1.2 Schizophrenia spectrum disorders (SSDs)

Schizophrenia, which lies at the severe end of the psychosis continuum, is characterized as a severe mental disorder associated with fundamental changes in thinking, perception, emotions, and reality distortions (hallucinations and delusions). The symptoms often first appear in the second or third decade of life (Lieberman & First, 2018). Historically, symptoms seen as part of the clinical picture in schizophrenia have been described for centuries, whereas the more modern understanding and descriptions dates to Kraeplin and ‘dementia praecox’ in the late 1800s (Tandon et al., 2009). Schizophrenia is a heterogenous clinical syndrome comprising several psychopathology domains, and the individual symptom manifestation varies greatly (Buchanan & Carpenter, 1994; Fusar-Poli et al., 2014). Schizophrenia is described as related to other affective as well as non-affective disorders (Murray et al., 2004).

Despite being a relatively low-frequent disorder, schizophrenia is a major burden for society. The median incidence rate (the number of new cases within the population per year) has been estimated to about 15.2 pr 100 000 individuals (McGrath et al., 2004), and the prevalence rates (the number of cases with the illness present in a population at a given time)

varies, but are estimated to about 0.5 % to 1.6 % worldwide (Saha et al., 2005; Simeone et al., 2015). Gender differences in prevalence rates have been debated, but a higher incidence has been reported in men compared to women with SSDs (Ochoa et al., 2012). Furthermore, schizophrenia ranks among the top 20 leading causes of disability globally – not solely due to the schizophrenia syndrome, but also related to the added cost of comorbid medical conditions associated with SSDs. The economic costs are vast: yearly costs in Norway were estimated to about 890m USD associated with SSDs (Evensen et al., 2015). In the US, the economic burden was found to range from 94m USD to 102 billion USD per year (Chong et al., 2016; Marcus & Olfson, 2008). According to Kennedy et al. (2014) the added costs related to treatment-resistant schizophrenia were about 3 to 11-fold higher than for the general schizophrenia population, highlighting the need for developing and optimizing effective treatments.

Several lines of research report high mortality rates for patients diagnosed with schizophrenia (Laursen et al., 2014), and that the mortality gap between SSDs and the general populations has worsened the past decades (Saha et al., 2007). A 12-fold risk of dying from suicide was reported for SSDs patients compared to the general population (Saha et al., 2007), and a reduced life expectancy of about 10 to 20 years has been reported, due to the risk of suicide in addition to increased risk of natural causes of death related to physical illnesses (Laursen et al., 2014). Additionally, SSDs are more prone to accidents in general (Laursen et al., 2014; World Health Organization, 2020b). Decreased life expectancy is further associated with preventable somatic disorders such as cardiovascular and metabolic diseases and infections, which are possibly diagnosed late and insufficiently treated in SSDs (Laursen et al., 2014; Saha et al., 2007). The mortality rate in SSDs is further assumed to be associated with side-effects from antipsychotic medication, and as well as to factors associated with an unhealthy lifestyle such as smoking, substance abuse, and poor diet (Laursen et al., 2012).

Research on social and environmental factors, in addition to neurobiological processes involved in the development of SSDs, has gained considerable attention the past decades. There is now increasing acceptance of a bio-psycho-social model for psychosis and schizophrenia. Various risk factors for SSDs have been suggested, which either alone or in combination may influence the likelihood of developing SSDs: immigration, infection with Toxoplasma gondii, growing up in urban areas, substance use such as cannabis, toxins, older paternal age, pregnancy or birth complications, if mother was exposed to the influenza virus during pregnancy, social isolation, and exposure to childhood trauma (CT) (Stilo & Murray, 2019; Torrey et al., 2012). CT, involving experiences of abuse and neglect, has been

increasingly acknowledged as a potential risk factor for SSDs the past decades. Lines of research have linked CT in SSDs to pathophysiological processes implicated in SSDs, such as HPA-axis aberrances, stress-sensitization, inflammation, genetic polymorphisms, and cognitive impairments (Misiak et al., 2017). CT, on which this thesis has an explicit focus, is covered thoroughly in Sections 1.6. Moreover, schizophrenia has been described as a highly heritable disorder (Ripke et al., 2020). Family and genetic risk factors involved in SSDs include a family history of psychosis (especially first-degree relative) and common and rare genetic variants have been implicated (Ripke et al., 2020). No directly causative genes for SSDs have been identified, thus there is possibly genetic polymorphisms, polygenetic inheritance and genetic heterogeneity underlying SSDs (Greenwood et al., 2007).

SSDs are classified according to criteria defined by the official diagnostic manuals: the International Statistical Classification of Diseases and Related Health Problems 10 (ICD-10) (World Health Organization, 1992), and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). SSDs according to the ICD-10 encompasses schizophrenia, non-affective psychoses and related disorders as described in section F20 – 29 (World Health Organization, 1992): F20 Schizophrenia, F21 Schizotypal disorder, F22 Persistent delusional disorder, F23 Acute and transient psychotic disorders, F24 Induced delusional disorder, F25 Schizoaffective disorder, F28 Other nonorganic psychotic disorder, and F29 Unspecified nonorganic psychosis. These diagnostic categories were developed to group the clinical presentations seen in patients with differing symptom constellations and courses of illness. In reality, the diagnostic boundaries are overlapping, and there is great heterogeneity in symptom constellations. The at-present dominating symptoms may fluctuate as part of the natural course of illness, or in response to psychosocial or pharmacological treatment (Howes & Kapur, 2009). The diagnosis of schizophrenia is differentiated from the other psychotic disorders by severity, longer duration, and number of symptoms. The symptom combinations are vast, leading to a great deal of clinical heterogeneity in SSDs. Of note, the substance-induced psychoses, organic psychoses, or affective psychoses are in the ICD-10 and DSM-5 described in separate sections than the SSDs.

Onset of symptoms are often, but not exclusively, seen in late adolescence or early adulthood. After illness debut, about 20% experience only one episode of psychosis, and many patients are at risk of developing a more prolonged and chronic course of illness (Alvarez-Jimenez et al., 2012). It is not uncommon to experience periods of remission followed by periodical symptom exacerbations or a new full blown acute psychotic episode.

In contrast to the historical view of SSDs as inevitably leading to chronic illness and disability, many will eventually obtain partial or full remission, with increased quality of life and differing degrees of participation and functioning in the society.

The diagnostic process of SSDs is based primarily on patient history, observation of behavior, subjective reports, and mental status examination (Lieberman & First, 2018), which could be challenged by co-existing substance use, as well as lack of insight, and will often require multiple points of encounter with the individual. Furthermore, having enough time for observation during a substance free period is of importance (≥ one month of symptom duration according to the ICD-10), as is the exclusion of organic brain disease or other medical conditions, and assessment of whether affective symptoms are prominent, primary, or possibly developed secondarily to the psychosis. Multiple outpatient encounters could be challenged by a lack of adherence or motivation to treatment, in addition to suspiciousness towards health care personnel. The assessment of psychotic symptoms can be aided by using validated and reliable clinical interviews or assessment tools, such as the Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS) (Opler et al., 1999), or the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID; Spitzer, Williams, Gibbon, & First, 1992), which was used in the present thesis.

Traditionally, the diagnoses related to SSDs have been viewed categorically. This is however debated and contrasted to that of being part of a continuum to other major psychiatric disorders (Angst, 2002; Moller, 2003). The present thesis adheres to the classification systems as described in the ICD-10 (World Health Organization, 1992) and DSM-5 (American Psychiatric Association, 2013).

1.2.1 A current and more optimistic view of SSDs

Contrary to the early descriptions of schizophrenia and psychotic disorders as treatment-resistant and as inevitable deteriorating brain disorders associated with long-term disability, more optimistic views and perspectives have evolved the past decades. The understanding of psychoses and schizophrenia have evolved from traditional categorical models to a continuum-based alternative perspective accounting for premorbid states, the prodromal phase, to full-blown psychotic episodes (DeRosse & Karlsgodt, 2015). The view of schizophrenia itself has also shifted from deterministic pessimism to hopes of recovery and remission, also in line with a more phase-oriented view of psychotic illnesses. Psychoses are now increasingly considered to be dynamic processes developing and fluctuating in phases over time, consistent with a dimensional view of mental disorders (Johannessen & Joa, 2021).

Adopting a dimensional perspective of SSDs acknowledges and capture the variation seen for psychosis symptoms (Heckers et al., 2013). The present thesis has chosen to focus on SSDs, and not solely on the diagnosis of schizophrenia, to grasp the symptomatic and diagnostic overlap associated with psychotic illnesses as categorized in the diagnostic systems.

Moreover, the optimism is also evident in the increased focus on early intervention services in FEP aimed to shorten the duration of untreated psychosis (DUP) in an effort to improve long-term prognosis and outcomes (McGorry et al., 2010). Early intervention and recognition may also contribute to reducing stigma associated with psychosis and SSDs. Early intervention services have been associated with better outcomes in terms of hospitalization, symptoms, functioning, and recovery (Correll et al., 2018). In blunt contrast to the early pessimistic view of outcomes from psychoses, there has been an explicit focus on remission and recovery, in line with what is considered important from service-users' perspectives. Possibilities for improvement and regaining social and occupational functioning have been increasingly recognized (Zipursky et al., 2013). This is reflected in research on recovery processes, which entails symptomatic improvements as well as improved functioning (e.g., social, occupational and educational domains), and a specified criteria for duration of more than one year (Lally et al., 2017), whereas remission describes reduction of key symptoms to mild levels for at least six months (Andreasen et al., 2005). Remission rates are estimated to about 60 % in FEP, whereas recovery rates were about 40 % in FEP, which was somewhat higher than what has been reported for more 'chronic' SSDs (Lally et al., 2017). Rates of remission and recovery in FEP and multi-episode psychotic disorders have traditionally varied depending on definition, criteria for duration, and sample (Lally et al., 2017). Further, FEP has been found to benefit from interventions aimed at occupational and academic functioning and recovery such as individual placement and support (IPS) (Hegelstad et al., 2019; Killackey et al., 2019). The paradigm shift from pure biology and physiology to the recognition of environmental factors and stress in the understanding of psychoses and SSDs have been important in expanding the perspectives on early intervention and prevention, illness detection, and psychological and psychosocial treatments of SSDs.

1.3 Etiology in SSDs

Despite vast efforts to understand and map the pathophysiology underlying SSDs, the precise mechanisms are not fully understood. To date, both structural and functional aberrations are thought to lie at the basis of SSDs. Other areas of interest are inflammation, infectious agents and microbiomes, and gene-environment interactions (Torrey & Yolken, 2019). Research on

illness etiology and development has traditionally focused on neurobiological substrates or candidate genes underlying SSDs (Cantor-Graae, 2007), although environmental influences or interactions are increasingly recognized (Thomas et al., 2019).

1.3.1 Structural abnormalities

Bleuler (1911/1950) and Kraepelin (1919/1971) who were the first to describe what is today known as SSDs, suggested that the etiology would be closely linked to brain abnormalities. Due to the methodology at the time, the identified abnormalities were small, leading to a more pessimistic view of the possibility of finding a structural basis for the disorder (Shenton et al., 2001). However, early findings from a seminal study using computer assisted tomography (CAT) in the 70s showed enlarged lateral ventricles in SSDs (Johnstone et al., 1976) - findings that were later elaborated upon and challenged by research using more advanced magnetic resonance imaging (MRI) (Shenton et al., 2001). The advent of MRI imaging led to increased knowledge on the neuropathology involved in SSDs. Indeed, SSDs have been found to be associated with alterations in brain structure and functions related to various brain systems, such as the prefrontal and medial temporal lobes (Karlsgodt et al., 2010). Ventricular enlargement has been tied to poor functional outcome in SSDs and FEP (Alkan et al., 2020; Mitelman et al., 2010), however, may not be specific to SSDs as it may occur in Alzheimer's disease (Shenton et al., 2001) and other mental health disorders such as bipolar disorder (Hauser et al., 2000). Further aberrations have been related to reduced brain volume, especially for grey matter, the frontal and temporal regions, and the limbic system (Haijma et al., 2013). Abnormalities have been identified in the medial and neocortical temporal lobe regions, including the amygdala, hippocampus and parahippocampal gyrus (Shenton et al., 2001). The structural abnormalities may be present already at illness onset in drug naïve SSDs patients (De Peri et al., 2021). However, although making progress in our understanding of the pathophysiological processes involved in SSDs, structural imaging techniques such as CT and MRI in relation to clinically relevant biomarkers needs more research and lacks specificity (Lieberman & First, 2018).

More recently developed techniques using diffusion tensor imaging (DTI) alone and in combination with functional MRI (fMRI) enables investigation of white matter fiber bundles (anatomical connectivity) and neuronal activation (functional connectivity) in the brain (Fitzsimmons et al., 2013). In addition to grey matter abnormalities mentioned above, aberrations in white matter have been found in SSDs (Karlsgodt et al., 2010). Findings in SSDs based on DTI and fMRI indicate connectivity abnormalities in frontal and temporal

regions. However, the specific relation between these abnormalities, their sequence and onset, and relation to specific outcomes, is unknown and warrants more investigation.

1.3.2 Neurotransmitters

Multiple neurotransmitters are likely to be involved in SSDs. One of the most researched and long-lasting theories on the development of SSDs, and especially positive symptoms, is the dopamine hypotheses (Howes & Kapur, 2009), partly based on the propensity of dopamine D2 antagonists to alleviate psychosis symptoms, and dopamine-boosting drugs to exacerbate psychosis (Hirvonen & Hietala, 2011). It has continued to evolve since the 1970s, and the first version of the dopamine hypothesis described 'hyperdopaminergica'. To combat the psychosis, the focus was on receptor-blocking, but there was no framework for differentiating dopamine abnormality to symptom dimensions in SSDs. The reconceptualization seen in version II proposed that the dopamine abnormalities were characterized by subcortical and striatal hyperdopaminergica linked to positive symptoms, and prefrontal hypodopaminergica associated with negative symptoms (Davis et al., 1991). No clear descriptions were presented of the etiological origins or specifics underlying the dopamine abnormalities (Howes & Kapur, 2009). Only between 1991 and 2009, there were more than 6700 published papers on dopamine and schizophrenia (Howes & Kapur, 2009), providing a picture of the vast research interest in dopamine. The dopamine hypothesis 'version III' suggests that multiple hits interact - such as a fronto-temporal dysfunction, genes, stress, and substance use, in order to result in the dopamine abnormalities and dysregulation which is now demonstrated to lie at the presynaptic dopaminergic level instead of at the dopamine D_2 receptors. The dopamine abnormalities are linked to aberrant salience involved in positive symptoms of psychosis (Howes & Kapur, 2009). Aberrant salience describes the process of over-attribution of meaning to seemingly irrelevant stimuli in the environment, involving both rewarding and aversive signaling which in turn may make an array of stimuli or events in the environment seem pregnant with significance (Howes & Nour, 2016).

However, although dopamine dysregulation has received the most attention, there may be other transmitters in play, such as the glutamate, GABAergic, opioid, cholinergic, or serotonergic systems (Eggers, 2012; Kapur & Remington, 1996; Laruelle, 2014; Lieberman & First, 2018; Stahl, 2018). For instance, no differences were found in terms of dopamine levels between treatment resistant SSDs and healthy controls (Demjaha et al., 2012). Aberrations related to the excitatory glutamate neurotransmitter system, especially the N-methyl-D-aspartate (NMDA) receptor, may have explanatory power as it has been linked to dopamine

release (Keshavan et al., 2011). Genes associated with SSDs have been found to be related to glutaminergic transmission (Carter, 2006; Ripke et al., 2020; Schizophrenia Working Group of the Psychiatric Genomics, 2014). Glutamate NMDA receptors was found to be associated with more amphetamine-induced dopamine release in healthy humans (Kegeles et al., 2000), indicating interactions with subcortical dopamine regulation (Hirvonen & Hietala, 2011). Other lines of inquiry found that the inhibitory GABA system could be abnormal in SSDs, possibly linked to neural synchrony and cognitive functioning in SSDs. However, therapeutic agents impacting on the glutaminergic or GABAergic systems in the treatment of SSDs remains to be established (Keshavan et al., 2011). Studies have indicated the possibility of decreased seretonin 5-HT2a binding in SSDs, but results have been mixed (Hirvonen & Hietala, 2011).

1.3.3 Immune system and inflammation

An inflammatory response involving mast or killer cells, cytokines, interferons, or T-lymphocytes, can develop in response to an antigen or microorganism in the body. The theory of the potential impact of inflammatory mechanisms in SSDs originated in 1918 (Menninger, 1994), and have since then become increasingly prominent. C-reactive protein, a marker of inflammation, was found to be increased in SSDs as compared to controls (Dickerson et al., 2013), and an increase in overall inflammation measure was found in SSDs as compared to FEP and controls (Dickerson et al., 2015). A cohort study in Denmark found autoimmune diseases to be associated with an increased risk of SSDs of about 30% (Benros et al., 2014). A review of 99 studies found increased levels of cytokine abnormalities to indicate an inflammatory process involved in schizophrenia (Rodrigues-Amorim et al., 2018). Immunological responses have been tied to genetic risk factors as well as environmental risk factors such as pollution, maternal exposure to infections during pregnancy, and early life stress (Comer et al., 2020). Relatedly, psychoneuroimmunology has been defined as ‘interactions between behavior, neural, and endocrine functions, and immune processes’ (Ader et al., 1995), and the bidirectional pathways between the brain and immune system are indeed prone to adverse environmental influences, such as stressful life experiences and emotional states (Ader, 2001). Associations have been found between inflammatory markers of a proinflammatory state in SSDs patients with CT experiences (Di Nicola et al., 2013). The immune system has been suggested as a link between the genetic and environmental influences, possibly through influencing on the regulation of neuronal development, synaptic plasticity and behavior (Comer et al., 2020). However, the specific mechanisms for these

interrelations remain poorly understood, and research are heterogenous in terms of the studied treatment groups, medication, and inflammatory markers. Many research groups are to date working intensively to identify clinically relevant biomarkers for SSDs, such as inflammatory profiles, as a possible characteristic of a subtype of schizophrenia patients, as well as disentangling the causal direction between inflammation and SSDs (Feigenson et al., 2014).

1.3.4 Genetics

High heritability estimates from family and twin studies of 80 – 85 % have suggested a strong genetic influence in the development of schizophrenia (Pearlson & Folley, 2008). Some claim that genetic factors play a determining role in predisposing towards SSDs (Gareeva & Khusnutdinova, 2018). Others have suggested that the heritability estimates are overestimations due to inherent flaws in the monozygotic and dizygotic twin study design assumptions regarding shared environment, minimal gene-environment interactions, increased birth complications, and sample selection (Torrey & Yolken, 2019). The specific genetic components and interactions underlying SSDs have proven to be complex and heterogenous (Henriksen et al., 2017). About 100 loci, implicated in the dopamine synthesis, calcium channel regulation, immunity, and glutamate receptors, have been identified as related to schizophrenia, but does however only explain a small proportion of the variance implicated in SSDs (Ripke et al., 2020). Also, considerable genetic overlap between SSDs and other mental health disorders have been reported (Carroll & Owen, 2009).

In sum, the etiology of SSDs remains to be completely understood despite a vast amount of research in areas ranging from biology to genetics to psychology. Other lines of inquiry pertain to the possible gene - environment interactions at play in SSDs (Van Os et al., 2008), suggesting that the combined effect is larger than the effect of genes or environmental factors alone. The ‘two hit hypothesis’ integrates these perspectives where early genetic and developmental vulnerability (first hit) contributes to making the individual vulnerable for illness development when faced with adverse environmental factor(s) later on (second hit) (Bayer et al., 1999; Keshavan et al., 2011). A prevailing perspective suggests interactions between predisposing genes and exposure to various environmental factors, such as childhood trauma or substance use. Varying levels of evidence for epigenetic modulation have been found for genes involved in neurotransmission and transmitters, such as catechol-O-methyltransferase (COMT) or brain-derived neurotropic factor (BDNF), neurodevelopment and immune functioning (Smigielski et al., 2020). Epigenetics describe the process of regulating gene expression levels, where genes switched on and off can contribute to

pathogenesis (Ferrari et al., 2018). DNA methylation, one of several mechanisms for gene expression regulation, is a dynamic process which is susceptible to environmental influences, proposed as an explanation for discordance observed in twin studies on SSDs (Roth et al., 2009). CT has been suggested as a potential candidate for influencing on the development of SSDs through epigenetic processes, however, drawing definitive conclusions about epigenetic modifications due to CT is not possible to date (Tomassi & Tosato, 2017).

1.3.5 Stress

Stress in the present thesis is understood as related to severe adverse events or severe psychosocial traumas. The stress-vulnerability model launched by Zubin in 1977 suggested that underlying genetic factors contributed to the individual vulnerability for the development of mental health disorders after exposure to environmental risk factors (van Os et al., 2010). The neural diathesis-stress model of psychosis was proposed by Walker and Diforio (1997) and updated in 2008 (Walker et al., 2008). Here it was suggested that the hypothalamic-pituitary-adrenal (HPA) stress cascade could lead to neural circuit dysfunction and ultimately altering the dopamine signaling involved in triggering and exacerbating psychotic symptoms (Pruessner et al., 2017; Stilo & Murray, 2019). Exposure to stress typically affects multiple systems, especially the sympatho-adrenal medullary system (SAM) and the HPA-axis. Neurotransmitters, enzymes, and hormones will be released when both systems are activated. The HPA-axis has however received the most attention (Pruessner et al., 2017). Clinically, stress has been thought to be of influence in SSDs patients. Through 'expressed emotions' (EE) within the family, stress could be a contributing factor in symptom exacerbation and decompensation after illness onset (Nuechterlein, Dawson, et al., 1992; Nuechterlein, Snyder, et al., 1992), and EE has therefore been targeted by various family-oriented interventions. Individuals identified as at high risk for developing SSDs showed a higher reactivity to stress as well as less protective factors compared to healthy controls and FEP (Pruessner et al., 2011). The lack of efficient coping strategies as well as cognitive impairments may contribute to decreasing the stress tolerance in some SSDs patients (Gispen-de Wied, 2000). Further, a vast body of research now indicates that adverse stressful life events such as CT could be related to SSDs (see Varese et al., 2012 for review).

Although stress has been implicated in etiological processes as well as in illness exacerbation, the specific pathogenetic mechanisms remain unresolved. HPA-axis activation has been tied to other known pathophysiological processes in SSDs, such as neuroinflammation, neurodevelopment and epigenetics, and possibly also influencing

dopamine regulation, although the research is limited and inconclusive (Pruessner et al., 2017). The development of SSDs has been associated with stress via HPA-axis dysfunction and subsequent release of corticosteroids such as cortisol (Gispen-de Wied, 2000). A prolonged elevated cortisol level in response to psychosocial stress was found to be associated with white matter (WM) deficits in SSDs as compared to healthy controls (Goldwaser et al., 2021). WM deficits was in turn linked to the connection of cortical and limbic structures, possibly mediating the HPA response to stress in SSDs (Dedovic et al., 2009; Goldwaser et al., 2021), in support of the diathesis-stress model. Patients with SSDs have shown an increase in morning baseline cortisol level (Walker et al., 2013), as well as abnormal levels of cortisol during the day (Mondelli et al., 2010). Other research reported on an abnormal (Aas, Dazzan, Mondelli, et al., 2011) and blunted cortisol awakening response (Day et al., 2014), possibly related to CT (Ciufolini et al., 2019). However, not all studies have replicated the findings regarding cortisol in SSDs (Pruessner et al., 2017). The role of stress has also been implicated in other psychiatric disorders, such as major depressive disorders and PTSD, and there has been a heterogeneity and poor correspondence in measures of cortisol hampering comparison across studies (Zorn et al., 2017). Other complexities in the literature obscuring the findings on cortisol and SSDs concerns the effects of study design (cross-sectional or longitudinal), concomitant psychotropic medications, gender differences, and sociodemographic factors (Pruessner et al., 2017).

1.3.6 Illicit substance use

Illicit substance use and addiction is highly prevalent and has been deemed a risk factor for SSDs (Hunt et al., 2018; McCreadie & Scottish Comorbidity Study, 2002). Substance abuse has been reported in about 30 – 50 % of patients with SSDs, and substances like alcohol, cannabis, cocaine, as well as nicotine use, is commonly reported (Menne & Chesworth, 2020). Especially cannabis, amphetamines, and methamphetamines, have been frequently described in SSDs, and possibly increases the risk for developing SSDs (Alisauskiene et al., 2021; Alisauskiene et al., 2019; Menne & Chesworth, 2020).

Studies on cannabis-use in SSDs have indicated that cannabis-users show an earlier onset of psychosis, possibly related using high-potency cannabis, and it has been suggested that the risk may increase in a dose-dependent manner (Di Forti et al., 2014; Helle et al., 2016; Henquet et al., 2005; Large et al., 2011). Cannabis seems to influence on the risk of SSDs through the effect of tetrahydrocannabinol on endogenous cannabinoid receptors distributed in brain areas linked to SSDs, possibly increasing dopamine levels (Løberg et al.,

2014). Other research has highlighted the potential role of amphetamine and methamphetamine use in the development of SSDs (Bramness et al., 2012).

Use and misuse of illicit substances in patients with SSDs have been associated with increased morbidity, mortality and worse overall outcomes related to more hospitalizations, non-compliance to treatment, proneness to violence, and increased rates of suicide (Green et al., 2007; Green & Khokhar, 2018; Hasan et al., 2020). There may be shared genetic vulnerability factors contributing to risk of substance use in SSDs (Khokhar et al., 2018), and there is a continued debate about which comes first - the substance use or the psychosis. Several hypotheses have launched to explain this complex relation. The primary addiction hypothesis describes shared vulnerability and susceptibility towards SSDs and drug abuse, and the two-hit hypothesis concerns increased risk for developing SSDs following exposure to drug abuse and other environmental risk factors. Furthermore, the self-medication hypothesis describes that development of drug abuse based on amelioration of symptoms associated with SSDs (Menne & Chesworth, 2020).

1.4 Treatment in SSDs

1.4.1 Antipsychotic treatment

To date and for the past 70 years, antipsychotics (APs) have been mainstay and considered the first-line treatment option for FEP, recurring episodes of psychosis and SSDs (National Institute for Health and Care Excellence, 2014; Norwegian Directorate of Health, 2013). Pharmacologically oriented treatments of psychosis with APs in SSDs aim to ameliorate acute symptoms of psychosis as well as maintaining the improvement throughout the recovery phase, and thus remain an important part of treatment for all phases of the psychosis (Kreyenbuhl et al., 2010; National Institute for Health and Care Excellence, 2014). Continuation of treatment with APs for a minimum of 1 – 2 years after the first presentation of psychosis is recommended to minimize the risk of relapse, and five years continued treatment is recommended in case of relapse (National Institute for Health and Care Excellence, 2014; Norwegian Directorate of Health, 2013).

APs are classified according to their pharmacological properties, and their effect and side-effect profiles are thought to be related to differences in receptor profiles between the different APs. There are various terms used to describe the different types of antipsychotics developed since the 1950s. First-generation antipsychotics (FGA) revolutionized the field of pharmacologic treatment of schizophrenia in the 1950s due to the serendipitous discovery and introduction of chlorpromazine (Haddad & Correll, 2018). Chlorpromazine, originally

developed for preoperative anxiety (Conley & Kelly, 2005), enabled an increased possibility of continuing treatment in the community instead of long-term hospital wards (Solmi et al., 2017). The FGAs are associated with variating sedative effects in addition to ameliorating positive symptoms.

Clozapine was approved and launched in 1989 and represented the first drug classified as a second-generation antipsychotic (SGA) (Conley & Kelly, 2005; Kane et al., 1988). Overall, APs will exert some degree of functional antagonism of dopamine D_2 receptors, and the effect of APs has been described as proportional to the effect on the dopamine receptors (Howes & Kapur, 2009). APs and the various SGAs commonly used to date, will differ in their affinity for other neurotransmitter systems besides the dopaminergic (such as the serotonergic or histaminergic). FGAs or typical antipsychotics (TAs) are characterized by a strong D_2 antagonism, whereas the SGAs or AAPs show a weaker antagonistic D_2 binding and stronger serotonin 5HT2A receptor action (Norwegian Directorate of Health, 2013; Solmi et al., 2017). SGAs often have less dopamine-related side-effects such as extrapyramidal symptoms (EPS), as well as a broader receptor profile as compared to the FGAs/TAs. AAPs are associated with side-effects such as disturbance in glucose and lipid metabolism and weight gain (Miyamoto et al., 2005). Clozapine, which produces few EPS, has shown therapeutic efficacy in treatment refractory psychosis (Warnez & Alessi-Severini, 2014). However, clozapine is associated with more severe side-effects such as seizures, myocarditis, and agranulocytosis, therefore indicated mainly in treatment refractory psychotic disorders. Moreover, there are differences within the classes of SGAs or AAPs in terms of effect, side effects and indications for off-label use.

Treatment with APs are prone to some challenges. Poor compliance or treatment adherence is quite common in SSDs, despite increasing the risk of relapse (Bowtell et al., 2018). As symptoms improve from the acute phase, the side-effects such as weight gain, could outweigh the initial benefits experienced in the acute phase of treatment. Also, there is not a clearly defined ideal of what constitutes the optimal antipsychotic treatment length for a given individual with SSDs. There is a need for large-scale research to sufficiently understand the risk and benefit balance associated with receiving long-term treatment with APs, and to identify clinically meaningful predictors for risk and benefits from long-term use between subgroups of service users (Bjornestad et al., 2017)

The picture is further complicated as a proportion of SSDs patients will require additional psychotropic medication such as antidepressants, sedatives, or mood stabilizers, although the effectiveness of concomitant medications during treatment with APs is uncertain

(Chakos et al., 2011; Stroup et al., 2019). Some studies have found a significant variability in the clinical response to antipsychotics, with about one third of patients not responding favorably to treatment (Demjaha et al., 2017; Dold & Leucht, 2014), whereas about 60 % in a sample of FEP showed symptom improvement (Kahn et al., 2008). A recent review reported that patients treated with APs showed greater symptom improvement and less heterogeneity in response to antipsychotic treatment as compared with placebo (McCutcheon et al., 2021).

Although being a cornerstone of the recommended treatment approaches for psychosis in SSDs, not all patients will achieve the desired effect of antipsychotic treatment. The absence of a clinically meaningful response, or even resistance to treatment, poses a critical challenge, as it has been tied to clinical deterioration, increased rates of hospitalization, a more chronic course of illness, the possible neurotoxic effect of relapses, as well as suicide, poor quality of life, and lower levels of functioning (Bozzatello et al., 2019). Carbon and Correll (2014) claimed that the search for predictors for clinical outcomes dates to the early days in the field of psychiatry, although the research literature on predictive factors for lack of a favorable response is sparse. Several potential modifiable and nonmodifiable predictors for reduced antipsychotic treatment effect have been proposed. Non-adherence to antipsychotics and the lack of an early treatment effect have been associated with a reduction in therapeutic response and remission (Carbon & Correll, 2014). On a group level, better response to treatment was predicted by female gender, no previous experience with antipsychotics, shorter DUP (Zhu et al., 2017), as well as a first episode of psychosis (Bozzatello et al., 2019). Longer DUP has been associated with poorer response to treatment in FEP (Cavalcante et al., 2020). Poor response to treatment can be separated into patient-related factors such as decreased premorbid functioning and lower educational levels, and illness-related factors such as negative symptoms, earlier age of onset, lack of early treatment response, as well as non-adherence to treatment (Bozzatello et al., 2019). Knowledge regarding neurobiological abnormalities possibly associated with treatment response are unclear and limited, however the activity of the dopamine system has been implicated (Howes & Kapur, 2009), in addition to reduced grey matter volume (Palaniyappan et al., 2013) and cortisol and inflammatory biomarkers (Mondelli et al., 2015).

The literature on the possibility of cumulative lifetime adversities and CT as possible predictors for antipsychotic treatment response in SSDs is scarce but gradually accumulating (Hassan & De Luca, 2015). CT has been associated with greater illness severity as well as poorer outcomes, although the findings are mixed (see Section 1.6.5). Identifying which SSDs individuals who will successfully respond to treatment might potentially reduce the amount of

medication we use and improve trajectories of the illness. Thus, delineating factors associated with improved or reduced AP treatment effectiveness is deemed important for a more tailored, personalized care for SSDs individuals.

1.4.2 Psychosocial and psychological interventions

Clinical guidelines include recommendations on psychosocial treatment options as an addition to or in lieu of medically oriented treatments (National Institute for Health and Care Excellence, 2014; Norwegian Directorate of Health, 2013). Psychosocial and psychological interventions may help with compliance to antipsychotics (Lindenmayer et al., 2009), and are considered an important part of an integrated biopsychosocial perspective in the treatment of psychosis (Norwegian Directorate of Health, 2013).

Cognitive-behavioral therapies (CBT) for psychotic disorders are specifically recommended and have shown treatment effects on psychosis symptoms and levels of functioning (Bighelli et al., 2021). CBT for psychosis include a collaborative assessment and improvement of old and new coping strategies and cognitive schemas, and evaluation and modification of beliefs related to delusions and hallucinations. However, the effect of CBT for psychosis has been found to be in the small range (Laws et al., 2018), also after controlling for factors such as publication bias, masking, and randomization (Jauhar et al., 2014). Whereas CBT is concerned with individual beliefs and disentangling the links between thoughts, feelings, actions, and symptoms, metacognitive therapies aim to increase the cognitive flexibility and modify metacognitive (‘thoughts about thoughts’) beliefs (Lysaker et al., 2018; Moritz et al., 2019). Moreover, cognitive remediation (CR) training has been deemed promising for targeting cognitive symptoms often inadequately improved by antipsychotics (Barlati et al., 2013). Core features of CR are cognitive exercise, the development of problem solving abilities, and the transfer of learnt abilities to real-life situations (Bowie et al., 2020). CR thus aims at developing cognitive strategies in cooperation with an active and trained therapist, and has been found effective on cognitive and functional outcomes (Vita et al., 2021).

Third-wave psychological therapies include mindfulness-based approaches for psychosis, which focus on being present here and now, acceptance, detachment, awareness, and compassion, aiding in regulating negative emotions and alleviating distress associated with psychosis (Khoury et al., 2013). Research has further suggested that trauma-focused interventions, such as eye movement desensitization and reprocessing (EMDR) and prolonged exposure therapy, may be effective in treating trauma symptoms in SSDs (van den Berg et al.,

2015). Although trauma-focused therapies for psychosis have shown promising effects on positive symptoms, more research is needed to support clinical recommendations for treatment of psychosis-related trauma symptoms (Brand et al., 2018).

Family interventions and psychoeducation have been found to reduce relapse rates in FEP (Bighelli et al., 2021; Camacho-Gomez & Castellvi, 2019), possibly through reduction of expressed emotion (McFarlane, 2016), and focus on developing coping skills and an increased understanding of what the patient is experiencing (Burbach, 2018). Multiple-family groups was found superior to single family groups (McFarlane, 2016). Family interventions have been found effective in improving outcomes in terms of symptoms and functioning and are furthermore related to the recovery perspective in SSDs (Bighelli et al., 2021; Morin & Franck, 2017).

Although the etiology and pathways leading to psychotic illnesses are still not fully understood, this has not hindered the development of new psychosocial and psychological approaches. Recovery-oriented approaches are aimed towards attaining a subjectively meaningful and valuable life and are related to improved social and occupational functioning. High rates of unemployment have been frequently reported in FEP and SSDs (Ajnakina et al., 2021; Kooyman et al., 2007). The IPS model is a form of supported employment approach developed to improve access to education and employment for individuals with severe mental illness (Modini et al., 2016). The IPS has shown good results for academic and occupational recovery and rehabilitation in FEP and SSDs, and is now regarded as the gold standard for vocational rehabilitation (Modini et al., 2016). Furthermore, physical exercise, arts and music therapy, and social contact, are other examples of more recently developed and recommended interventions (National Institute for Health and Care Excellence, 2014; Norwegian Directorate of Health, 2013). Arts and music therapy has shown positive effects on positive and negative psychosis symptoms in inpatients and outpatients (Geretsegger et al., 2017). Physical exercise has been recommended as some individuals with SSDs are prone to obesity and cardiometabolic diseases, partly owing to unhealthy lifestyle factors such as smoking, lack of physical activity, and unhealthy diets, as well as antipsychotic medication, and negative and cognitive psychosis symptoms (Dauwan et al., 2016). Physical exercise should be part of an integrated and individualized treatment plan for individuals with a psychotic illness.

Lastly, scientific and technical advances are being made, with the development of new non-medical treatment approaches. One such approach is non-invasive transcranial magnetic

stimulation (Aleman et al., 2018) and virtual reality based and digitally and smartphone delivered interventions show promising results (Rus-Calafell & Schneider, 2020).

1.5 Cognitive functioning in SSDs

Neuropsychology describes how a person's cognition and behaviour relates to the brain and nervous system. Cognition entails information processing and includes a variety of conscious mental abilities: from general intelligence, attention, memory, and processing speed to decision making and problem solving. Cognitive impairment often refers to underperformance when compared to population norms, or at the individual level as impairment following illness or damage to the brain. Cognitive performance in SSDs is usually assessed using neuropsychological tests. Studies on cognitive impairment in SSDs have varied in their approach and methodology, from employing established consensus test batteries to more purposely designed batteries related to the individual study (Keefe et al., 2003). The absence of a consensus in this area has been described as an impediment to standardized evaluation of new treatments aimed at improving cognition (Nuechterlein & Green, 2006).

SSDs are now described and recognized as disorders of cognition and cognitive impairments (Kahn & Keefe, 2013). From World War II and for the past 20 years, there has been an increased focus on the assessment and measurement of cognitive impairments, in addition to more specifically linking cognition to symptoms of schizophrenia (Green & Harvey, 2014). The recognition of cognitive impairments as core aspects of SSDs related to psychosocial and functional recovery, is underlined by the inclusion cognitive deficits as symptom specifiers in the ICD-11 and the DSM-5 (Kahn & Keefe, 2013; Valle, 2020).

Research has indicated that SSDs patients may show impairments in global cognitive functioning as well as specific cognitive domains such as executive functioning, attention, various aspects of memory, processing speed and motor abilities (Schaefer et al., 2013; Aas, Dazzan, et al., 2014). Cognitive deficits have been found present before psychosis illness onset, and to fluctuate during the course of illness, in addition to clinically present as highly heterogenous among SSDs patients (Anda et al., 2019; Tandon et al., 2009). Cognitive impairments in SSDs are related to poorer social and occupational functioning (Green, 2016). Men have tended to exhibit more cognitive deficits and unfavorable course compared to women with SSDs (Kocsis-Bogar et al., 2018; Mendrek & Mancini-Marie, 2016). Although studies have shown variation, SSDs patients have been found to perform about 1 – 2 SD below what is considered the population norm (Kahn & Keefe, 2013). Additionally, it has

been argued that some SSDs patients perform worse at the individual level than would be expected given their premorbid functioning and the level of their parents' education (Kremen et al., 2000).

The effect of antipsychotics on cognitive impairment in SSDs remains controversial (Keefe & Harvey, 2012). One of the advantages associated with the introduction of AAPs was related to effects on cognitive functioning in contrast to their 'first generation' counterparts (Harvey & Keefe, 2001). However, cognitive deficits in SSDs are to date often minimally affected by antipsychotic medication as compared to the effects on other symptom dimensions although AAPs do tend to be more beneficial compared to FGA/TAs (Harvey & Keefe, 2001). Results from the CATIE study on SSDs indicated that APs show similarities in effect on cognition across chemical classes (Keefe et al., 2007). A recent study by our research group found that SSDs showed cognitive improvements after 12 months following onset of a new course of AAP treatment, but the cognitive changes were unrelated to the type of drug received during the study period (Anda et al., 2021).

Reported levels of cognitive impairments in SSDs are unequivocal, and the factors underlying this heterogeneity is poorly understood, and the findings are inconclusive. Impairments in cognitive functioning in patients with SSDs have been proposed associated with general IQ abilities, neural correlates, psychosis symptom dimensions, educational and vocational status, gender, age of onset, and CT (Anda et al., 2016; Bergh et al., 2016; de Gracia Dominguez et al., 2009; Jirsaraie et al., 2018; Khandaker et al., 2011). Research on the associations between psychosis symptom dimensions and cognitive impairment in patients with SSDs have most consistently shown associations with negative and disorganized symptoms (Bergh et al., 2016; de Gracia Dominguez et al., 2009; O'Leary et al., 2000; Zanelli et al., 2010). Auditory hallucinations have been found related to impaired auditory attentional control (Løberg et al., 2015). A meta-analysis did not find associations between positive symptoms and cognitive impairments (de Gracia Dominguez et al., 2009). Negative symptoms were associated with deficits in executive functioning (Nieuwenstein et al., 2001), and reduced cognitive impairments in the acute phase of psychotic disorders were found to be largely explained by the improvement of negative symptoms (Anda et al., 2016). de Gracia Dominguez et al. (2009) found that heterogeneity of the psychopathology in SSDs showed differential relations to neurocognitive deficits, as well as moderate associations for negative and disorganized symptoms to verbal fluency, and reasoning and problem solving, respectively. No such relations were found for positive or depressive symptoms (de Gracia Dominguez et al., 2009). Negative and cognitive symptoms appear to respond more poorly to

medication as compared to positive psychosis symptoms (Foussias & Remington, 2008), and may be conceptualized as related but separate constructs.

Furthermore, cognitive functioning in SSDs has been associated with genetic factors and general IQ. Low adulthood IQ was found to be a risk factor for schizophrenia (Khandaker et al., 2011), and cognitive impairments have been found in unaffected first-degree relatives of SSDs patients (Snitz et al., 2006). Heritability estimates of IQ varies from 40 to 80 % (Deary et al., 2006; Nisbett et al., 2012), and high IQ has been proposed as a protective factor for SSDs (Khandaker et al., 2011). Cognitive impairment in SSDs implies that there may be brain damage or dysfunction, although research is lacking (Ortiz-Gil et al., 2011). Although the specific neural correlates underlying cognitive impairments in SSDs are not entirely understood, there is research indicating that global and specific cognitive deficits may be associated with reduced grey matter volumes in the dorsal lateral prefrontal cortex and hippocampus, as well as reduced white matter volumes in SSDs and healthy persons (Jirsaraie et al., 2018). Ortiz-Gil et al. (2011) however found no differences in terms of brain volume or lateral ventricular volume when comparing a sample of SSDs to healthy controls. They suggest that cognitive impairment in SSDs rather show correlates in altered brain functioning as compared to brain structures.

Suggested psychosocial and environmental influences on cognitive functioning in SSDs span from education to socioeconomic status (SES), CT, and substance abuse. Research on illicit substance use in relation to cognitive abilities in SSDs has been inconsistent. Although substance use has been associated with deficits in cognitive function in healthy individuals, findings especially regarding polysubstance use on the cognitive performance in SSDs are not conclusive (Donoghue & Doody, 2012). For instance, cannabis in relation to cognitive abilities in SSDs has been associated with both impairments (D'Souza et al., 2005), and better cognitive performance in psychotic disorders (Løberg & Hugdahl, 2009). Relatedly, Weibell et al. (2019) reported a positive effect on cognition for FEP patients who stopped using illegal substances during the first two years of treatment. Moreover, Bergh et al. (2016) found in a 10-year follow-up study of SSDs patients that the observed variation in general cognitive functioning could be explained by educational and vocational status, in addition to premorbid academic functioning, which could reflect the level of cognitive abilities at the time of measurement. Furthermore, CT has been proposed as potentially related to the heterogeneity in cognitive impairments observed in patients with SSDs. This is further elaborated upon in Section 1.6.4.

1.6 Childhood trauma (CT)

The past decades, adverse childhood events have been increasingly acknowledged to impact negatively on adulthood mental health. Consequences of child maltreatment comprise lifelong impairments in somatic and mental health, leading to negative occupational outcomes affecting negatively on economic and social development across the world (World Health Organization, 2020a). Prevalence of CT in the general population varies greatly, depending on measurement, country, study design and definitions, and ranges from 16 – 60 % in general population samples (Copeland et al., 2018; Hussey et al., 2006; Kessler et al., 2010; Koenen et al., 2010; May-Chahal & Cawson, 2005; Moody et al., 2018). The occurrence of CT is quite common, and types of CT are often interrelated. Numerous studies have brought support for the notion that CT might contribute to adverse consequences for health and behavior across the lifespan (Jaffee, 2017; Kessler et al., 2010). CT has been associated with or implicated in a wide range of mental health issues, including specific disorders such as SSDs, PTSD, or depressive disorders. Teicher and Samson (2013) reported that CT increased the risk for mental health disorders in addition to negatively influencing the illness severity. If CT was eradicated, analyses have indicated a reduction of mental health disorders of about 30 % (Kessler et al., 2010), whereas the number of people with psychotic disorders would be reduced with 33 % (holding other risk factors constant and assuming causality) (Varese et al., 2012). According to Kessler et al. (2010) interpersonal trauma in early life has the most severe consequences. Possibly, CT exerts negative influences on child development in behavioral, emotional, social, physical, and cognitive areas (Carr et al., 2013).

Childhood adversities and maltreatments are captured and described by a variety of terms in the extant literature: CT, early life stress (ELS), childhood adversities, adverse childhood experiences (ACE), and childhood maltreatment. Childhood maltreatment was defined by the WHO as “all forms of physical and emotional ill-treatment, sexual abuse, neglect, and exploitation that results in actual or potential harm to the child’s health, development or dignity” (World Health Organization, 2020a). The concept of ELS comprise childhood and adolescent traumatic experiences, such as parental loss or divorce, having caregivers with psychiatric disturbances, childhood illnesses, family violence, absence of basic care, abandonment, deprivation of food and shelter, and lack of encouragement and support (Carr et al., 2013). Moreover, ACEs include three types of childhood abuse (emotional, physical, and contact sexual abuse) as well as five different exposures to household dysfunction (exposure to alcohol or other substance abuse, mental illness, violent treatment of mother or stepmother, criminal behavior in the household, parental separation, or

divorce). The understanding of CT, on which the current thesis was based, comprises of sexual, emotional, and physical abuse, and physical and emotional neglect (Bernstein et al., 2003). Physical abuse describes any experiences of physical assault that imposes a risk of or actual injury to the child, sexual abuse covers experiences of sexual contact or conduct involving a child, and emotional abuse describes any assault on the child's wellbeing or sense of worth. Physical neglect comprises the failure to provide for the child's basic physical needs, and emotional neglect describes the failure of caregivers to provide basic emotional and psychological needs (Bernstein et al., 2003). A challenge highlighted by Kessler et al. (2010) concerns measurement of CT, as most studies have either focused on a single type of exposure, such as sexual abuse, or a composite measure of CT.

Inconsistencies in assessment tools used by different research projects have hindered valid and reliable comparisons between studies, and one of the challenges identified in the CT research concerns the variety of assessment tools developed to measure CT retrospectively. CT questionnaires and interviews aim to investigate the occurrence, severity, subtypes, timing, and relation to perpetrator. They are usually not diagnostic tools per se (Popovic et al., 2019). The CT questionnaires covers different aspects related to childhood abuse or neglect: physical, sexual, or emotional abuse; physical and emotional neglect; household dysfunction, including witnessing violence towards caregivers or siblings; peer victimization and bullying. One of the most widely used retrospective self-report measurements in the general population (Viola et al., 2016) and in SSDs (Jiang et al., 2018; Teicher & Parigger, 2015), which is also the basis for the CT data in the present thesis, is the self-report questionnaire Childhood Trauma Questionnaire Short-Form (CTQ-SF) (Bernstein et al., 2003). The CTQ-SF is described in detail in Section 3.3.1. Several reviews have been conducted to evaluate CT assessment instruments (e.g., Burgermeister, 2007; Saini et al., 2019; Satapathy et al., 2017). Space limitations preclude a comprehensive review of all available CT assessment tools and is beyond the scope of this thesis, however a short summary follows. The Child Experience of Care and Abuse Questionnaire (CECA-Q) is frequently used, and was developed by Bifulco et al. (2005). The CECA-Q is a self-report questionnaire used to assess the lack of parental care and parental physical and sexual abuse from any adult occurring before 17 years of age. The Traumatic Life Events Questionnaire examines potentially traumatic events more broadly, and inquiries about the frequency and severity of reported natural disasters, warfare, unexpected death of close relations and sexual abuse (Kubany et al., 2000). The Adverse Childhood Experiences is a questionnaire evaluating seven categories of adverse childhood experiences: emotional, physical, or sexual abuse, violence against mother, substance use or

suicidal ideation or mental disorders in close relatives, or imprisonment in the family (Felitti et al., 1998). The Personal Safety Questionnaire mainly focuses on physical or sexual abuse (Straus & Douglas, 2004) whereas the Child Sexual Assaults Scale developed by Koss et al. (1987) mainly targets occurrences of sexual abuse. The Maltreatment and Abuse Chronology of Exposure (MACE) is a self-report scale aimed at assessing ten types of maltreatment (such as neglect, abuse, interparental violence, peer victimization) in addition to assessing the developmental time course of exposure to maltreatment (Teicher & Parigger, 2015). Although retrospective self-report CT instruments are widely used there are several interviews targeted towards CT assessment. The Early Trauma Inventory (ETI) is a 56-item clinician administered interview for assessing childhood abuse and general trauma, such as parental loss or natural disasters (Bremner et al., 2000). The Childhood Experience of Care and Abuse is a semi-structured interview developed to assess experiences of childhood neglect and abuse (Bifulco et al., 1994), and the Child Abuse and Neglect Interview Schedule-Revised is aimed at measuring exposure to maltreatment, violence, and parenting practices (Ammerman et al., 1993). There is to date no consensus on how to best measure and capture experiences of CT retrospectively. A systematic review identified 52 different instruments aimed at assessing CT, whereas only eight of those showed moderate to strong methodological qualities according to the Consensus-based Standards for the selection of health Measurement InstrumeNts (COSMIN) (Saini et al., 2019). The variation between the instruments in terms of methodology and psychometric properties is vast, and superiority of an instrument over the others has not been established. However, the CTQ-SF is highlighted as one of the instruments most thoroughly examined in terms of indices of reliability and validity (Saini et al., 2019).

1.6.1 CT and mental health disorders

CT has been related to a range of childhood and adulthood mental disorders as well as the overall severity (Carr et al., 2013; Jaffee, 2017; Kessler et al., 2010; Read et al., 2005). Predictors of risk for exposure to childhood maltreatment encompass lower socioeconomic status (SES), younger maternal age, antisocial behavior in the family, and if the perpetrator him or herself was exposed to maltreatment (see Jaffee, 2017 for a review). CT has been associated with a range of adulthood mental health disorders, from anxiety disorders and PTSD, major depressive disorder and mood disorders, sexual dysfunction, personality disorders, psychosis and SSDs, eating disorders, dissociative disorders and suicidality, substance abuse, multiple personality disorder, phobias, irritable bowel syndrome, rheumatoid

arthritis, and autoimmune disorders (Carr et al., 2013; Copeland et al., 2018; Mulvihill, 2005; Read et al., 2005). The lifetime exposure to multiple traumas may predict symptom severity in relation to posttraumatic stress, dissociation, anxiety, depression, anger, and somatic complaints (Briere et al., 2008; Cloitre et al., 2009). Early life stress and childhood maltreatment have been found to be involved in predisposing, triggering, maintaining, and aggravating mental health disorders during adulthood (Carr et al., 2013).

The seminal ACE study by Felitti et al. (1998) studied the impact of ACEs on health behavior and outcomes by measuring childhood abuse and household dysfunction. Almost 50 % of the 9500 respondents reported at least one ACE, and 25 % of the responders reported two or more ACEs (Felitti et al., 1998). A dose-response association was found: as the ACE score increased, the mean number of comorbid outcomes also increased. Reporting ≥ 4 ACEs were associated with a 4 – 12-fold increased risk for substance abuse, depression and suicide attempts as compared to those reporting only one ACE. Exposure to multiple traumas especially early in life, may be associated with more complex clinical presentations. Symptom complexity was related to cumulative CT in a sample of university students (Briere et al., 2008). A prospective population-based study further indicated that cumulative CT was associated with more adulthood psychiatric disorders, to poorer functional outcomes related to health, increased risk for engaging in risk behavior, as well as lower levels of educational, financial, and social functioning (Copeland et al., 2018). The association persisted after controlling for childhood psychiatric disorders, adverse family-related circumstances, and exposure to trauma in adulthood. This study did however not include psychotic disorders and SSDs, also known to be associated with CT.

1.6.2 CT in SSDs

The role of CT in SSDs was controversial at first, possibly due to fear of blaming the mother as in the 1970s, in addition to methodological weaknesses (small, selected, heterogenous samples) in the earliest research studies (Hammersley et al., 2008; Lidz, 1977). Read (1997) was among the first to summarize existing research on CT in SSDs, and the field made significant developments throughout the 1990s and 2000s (Friedman et al., 2002; Ross et al., 1994). Read et al. (2005) stated that the accumulated evidence pointed towards the possible etiological influence and causality of CT in the development of psychosis. However, according to Morgan and Fisher (2007) and Bendall et al. (2008), the argument of causality was flawed as it was based on studies with inherent methodological issues: misleading estimates of physical and sexual abuse; small, highly selected, and heterogenous samples;

broad variation in CT definitions and crude measures of abuse, as well as mixed results from the available studies. As a stark contrast, the evidence of CT in psychosis was described as 'controversial and contestable' (Morgan & Fisher, 2007 pp. 8). Studies tended to be uncontrolled comparisons, correlational, and did rarely control for potential demographic confounders (Morgan & Fisher, 2007; Read et al., 2005). The past decades, the methodology and scientific rigor has improved, and an increasing body of research points towards associations between CT and SSDs (Bonoldi et al., 2013; Fisher et al., 2012; Larkin & Read, 2008; Misiak et al., 2017; Stanton et al., 2020; Varese et al., 2012). The British National Survey of Psychiatric Morbidity from 2004, which included 8580 adults, reported that individuals suffering from psychosis were 15 times more likely to have been sexually abused (Bebbington et al., 2004). Experiences of physical, sexual, and emotional abuse before 16 years of age were associated with a 2.5 to 9.3 increased likelihood of psychotic symptoms or severe clinical psychosis in a prospective general population study including 4085 individuals (Janssen et al., 2004). An increasing number of traumatic events have been associated with more psychotic symptoms, supported by a study on bullying and psychotic experiences (Lataster et al., 2006). Our research group found that SSDs patients reported more frequent and severe CT as compared to a matched clinical sample: almost 70% in the SSDs group reported ≥ 1 CT compared to 38% in the non-psychotic comparison group (Mørkved et al., 2017).

CT has been suggested as a risk factor for psychosis and SSDs (Kelleher et al., 2013; Stanton et al., 2020; van Nierop, Lataster, et al., 2014; Varese et al., 2012). A seminal meta-analysis reported a 3-fold likelihood of reporting CT exposure in patients with psychosis and SSDs (Varese et al., 2012). As compared to healthy controls, patients with SSDs reported more childhood maltreatment and psychotic symptoms, although the strength of the relationship did not differ between the groups (DeRosse et al., 2014). Trauelsen et al. (2015) reported that almost 90 % of FEP patients reported one or more CT compared to 37% of the non-clinical controls. As the risk of psychosis increased 2.5-fold for each additional adversity, the authors suggested CT as a large, shared effect for the risk of psychosis (Trauelsen et al., 2015). Support has been found for a dose-response relationship for CT in relation to the severity of SSDs (Heins et al., 2011; Kelleher et al., 2013; Larkin & Read, 2008; van Nierop, Lataster, et al., 2014). Childhood adversities were more frequently reported in psychosis patients than controls, and a higher trauma load was found related to an increase in psychosis symptoms (Schalinski et al., 2019).

Longitudinal and prospective studies have also indicated a relation between CT and psychotic symptoms and disorders (Arseneault et al., 2011; McKay et al., 2021; Rossler et al., 2014; Schreier et al., 2009). CT was strongly predictive of psychotic experiences in a prospective study of adolescents, and a dose-response relationship was found for the severity of bullying and subsequent risk for psychosis (Kelleher et al., 2013). Additionally, their results were interpreted as indicative of temporality between CT and the onset of psychotic experiences: the cessation of bullying was related to cessation of the psychotic experiences (Kelleher et al., 2013). A prospective community study over 30 years reported that childhood adversity was related to subsequent subclinical psychosis symptoms, however not for 'schizophrenia nuclear symptoms' (Rossler et al., 2014).

CT has been related to clinical and functional aspects associated with SSDs, such as worse functioning in social, academic, and vocational areas in FEP and those with established SSDs (Cotter et al., 2015; Stain et al., 2014). CT has been tied to an earlier age of illness onset (İngeç & Evren Kılıçaslan, 2020), as well as a longer DUP, which was associated with CT in hospitalized FEP patients (Broussard et al., 2013). Interpersonal trauma occurring before 18 years of age was significantly associated with longer DUP in FEP (Haahr et al., 2018). The relation between CT and SSDs may differ between the genders, although research has yielded mixed results. CT was associated with increased risk for psychosis in females but not males with low social support. The CT subtype emotional abuse was more frequently reported in females, whereas physical or emotional neglect were reported at higher rates in males (Pruessner et al., 2019). Additionally, CT was related to worse long-term functioning in male participants only (Pruessner et al., 2019).

Moreover, the extant literature on CT in SSDs is not conclusive when compared to CT in other disorders. A systematic meta-analysis of 25 case-control, cohort, and cross-sectional studies indicated a medium to large effect of childhood adversity in SSDs (Matheson et al., 2013). A higher incidence of CT in SSDs was found when compared to non-psychiatric controls and anxiety disorders, however, no difference was found when comparing CT in SSDs to affective psychoses, depressive disorders, and personality disorders. More CT was found for dissociative disorders and PTSD compared to schizophrenia (Matheson et al., 2013). The authors highlighted that the relationship between CT and SSDs lacks specificity.

In sum, although research has pointed to a relation between CT and SSDs, the vast body of literature is not conclusive. Advances have been made from the earliest research in terms of using validated measures of CT, and although up for debate, retrospective CT reports from patients with SSDs have shown reasonable reliability and validity (Fisher, Craig,

Fearon, Morgan, Dazzan, Lappin, Hutchinson, Doody, Jones, McGuffin, et al., 2011). Further, the sample sizes have increased, and are often less heterogenous, in addition to focusing on FEP and high-risk groups and not exclusively on the most severely ill, capturing different phases of psychotic illnesses. Further, potential demographic and clinical confounding sources have to a greater extent been controlled for. While some argues for a potential causal relationship between CT and SSDs, others are still critical due to the methodological challenges that still prevail: a considerable number of cross-sectional designs employing retrospective CT measures, lack of proper control or comparison groups, and unclear definitions of CT making study comparisons difficult. Thus, the precise nature of the relation between CT and SSDs still is not fully resolved.

1.6.3 Proposed mechanisms for CT and the relation to SSDs

Although an increasing body of research supports the relation between CT and SSDs, potential mechanisms underlying this relationship is however unresolved. There are several lines of inquiry aimed to unravel how CT may increase the risk of developing SSDs, spanning from psychology to biology. Suggested psychological mechanisms have focused on cognitive schemas, affective pathways, experience of social defeat, disrupted attachment styles, and dissociative mechanisms (Misiak et al., 2017). Biologically based mechanisms include HPA-axis dysfunction, inflammatory and metabolic dysregulation, as well as epigenetics and gene – environment interactions (Misiak et al., 2017). Relatedly, Popovic et al. (2019) suggest three main pathophysiological pathways for how CT may impact the development of SSDs: the neurobiological pathway, the genetic pathway and the epigenetic pathway. Findings from biological and psychological research on CT in SSDs were also integrated and synthesized in the traumagenic neurodevelopmental model launched by Read et al. (2001) and revisited in 2014 (Read et al., 2014).

Psychological mechanisms

Attachment style describes the cognitive and emotional development founded in the early relationship to primary caregivers, and reflect internal representations of self in relation to others, as well as strategies for dealing with distress (Bartholomew & Horowitz, 1991). Attachment has been tied to psychotic experiences in clinical and non-clinical samples (Korver-Nieberg et al., 2014). Insecure attachment style has gained attention as a potential mediator for CT in the development of SSDs (Chatziioannidis et al., 2019; Sitko et al., 2014), and has been linked to symptoms of paranoia in psychosis (Lavin et al., 2020). Insecure anxious and avoidant attachment were found to mediate the association between childhood

neglect and psychotic experiences in a nationwide epidemiological investigation (Sitko et al., 2014), and insecure attachment mediated the relation between CT in SSDs as compared to healthy controls (Chatziioannidis et al., 2019). Moreover, cognitive-oriented models have suggested that pre-existing negative believes about the self in combination with a threatening appraisal towards other people contribute to a feeling of paranoia which lies at the basis for delusions in psychosis (Fowler et al., 2006). Negative core beliefs and dissociation were suggested to mediate the association between trauma and subsequent psychosis symptoms in a non-clinical sample (Fowler et al., 2006) and a clinical sample of SSDs (Kilcommons & Morrison, 2005).

The concept of dissociation captures the disruption of the normally fully integrated functions of consciousness, such as memory, identity, and perceptive abilities (American Psychiatric Association, 2000; Sun et al., 2018), and could be associated with psychosis experiences such as impaired reality testing (Kilcommons & Morrison, 2005). Indeed, dissociation was found related to positive psychosis symptoms such as hallucinations, delusions and paranoia, as well as disorganization in SSDs (Longden et al., 2020). Dissociation may be an initial response to CT influencing the development of adulthood psychopathology (Read et al., 2001), and furthermore, indirectly influencing or mediating the association between CT and SSDs (Pearce et al., 2017; Sun et al., 2018). Sun et al. (2018) found dissociation to mediate the relation between CT and delusions in a sample of FEP. Relatedly, dissociation was found to mediate the link between CT and psychotic experiences, in addition to attachment style as a mediator for paranoia in patients with psychosis (Pearce et al., 2017). Also, more severe CT was associated with the severity of dissociative symptoms when comparing FEP patients to 'chronic' SSDs patients and community controls (Braehler et al., 2013).

According to the social defeat theory (Selten & Cantor-Graae, 2005), CT may contribute to the risk of psychosis through exposure to a subordinate social position (Selten et al., 2013). Social defeat describes the exclusion from a majority group, and was proposed as a common factor for CT and migration in predicting an increased risk for psychosis (Selten et al., 2013). The role of social defeat in the association between CT and psychosis was investigated by van Nierop, van Os, et al. (2014), who found social defeat to mediate CT and later psychosis in psychotic disorders and the general population. Relatedly, research has focused on the relevance of an affective pathway to psychotic disorders (Misiak et al., 2017; van Nierop et al., 2015). Emotional reactivity to stress was suggested as an indicator of an environmental liability to psychosis (Myin-Germeys & van Os, 2007), and CT was related to

an admixture of various affective symptom domains across diagnostic boundaries and possibly linked specifically to reality distortion (van Nierop et al., 2015). Indeed, affective symptoms were found associated with reality distortion in a general population sample (Kramer et al., 2014).

Biological mechanisms

CT may be understood as a severe form of prolonged and chronic stress. The diathesis-stress model of psychosis posits that patients with psychosis have a vulnerability to stress which during stressful circumstances increases the risk for psychosis (Mondelli et al., 2010). An enhanced stress-reactivity has been suggested as a cardinal feature of SSDs, and possibly also related to CT experiences (Read et al., 2005). Walker and Diforio (1997) identified a unique neural response for the HPA-axis activation related to a dopamine overactivation in patients with SSDs. Exposure to psychosocial stressors was suggested to exacerbate symptoms seen in SSDs (Walker et al., 2008). The authors suggested that the adrenal cortex secretes glucocorticoids such as cortisol after being stimulated or activated by adrenocorticotrophic hormones produced by the pituitary gland. The hippocampus has a high density of cortisol receptors and is involved in modulation of the HPA-axis activation through a negative feedback process. During prolonged and severe exposure to stress and cortisol release, the HPA-axis may be permanently altered, influencing the negative feedback system that slows down the HPA activation (Walker & Diforio, 1997). CT could possibly have a neurodevelopmental adverse effect and affect the catecholamine and dopamine systems through interaction with the HPA-axis involved in stress regulation (Bonoldi et al., 2013; Heim et al., 2000). Lardinois et al. (2011) found increased levels of emotional and psychotic reactivity to stress in a sample of psychosis patients reporting exposure to CT. Bebbington (2009) stated that stress appears to trigger psychotic symptoms, and that patients suffering from psychotic disorders have a greater vulnerability to stress than the general population. Stress-sensitivity in relation to CT in SSDs was also described in the traumagenic neurodevelopmental model (Read et al., 2014).

Other lines of inquiry have focused on neuronal substrates underlying CT in SSDs. Emotional neglect in SSDs was found to be negatively associated with total grey matter volume, especially in the dorsolateral prefrontal cortex (Cancel et al., 2015), and CT was associated with decreased volume in areas associated with the amygdala and hippocampus in FEP patients (Aas, Navari, et al., 2012). CT is thus hypothesized to exert prolonged and deleterious effects on the developing brain, contributing to triggering the onset of psychosis.

Studies have focused particularly on hippocampal and amygdala brain regions, which have been implicated in the HPA-axis (Misiak et al., 2017).

Neither the brain nor the immune system is fully formed at birth and may be prone to adverse effects of CT. Research has examined whether CT may interact with the immune system and inflammatory mechanisms in the development of SSDs (Danese & Lewis, 2017). Experiences of childhood maltreatment and markers for inflammation were investigated in the prospective Dunedin Multidisciplinary Health and Development Study (Poulton et al., 2015). Cumulative CT exposure was found to be associated with inflammation markers 20 years later, after controlling for confounders such as SES, IQ, adulthood stressors, unhealthy behaviors, and acute infections at the time of inflammation assessments. Elevated levels of systemic inflammation are quite consistently reported in studies on psychotic disorders. CT was found to moderate systemic inflammation and grey matter changes in people with psychosis (Quide et al., 2021). Furthermore, CT exposed FEP patients showed increased C-reactive protein levels compared to non-exposed FEP patients (Di Nicola et al., 2013). However, findings concerning specific inflammatory markers have been mixed (Quide et al., 2019).

Moreover, the BDNF is a protein involved in neuronal growth, neuroplasticity, and neurotransmitter release in the brain. Deficiency of the BDNF and the BDNF Val66Met polymorphism have been tied to CT as well as being implicated in aspects of SSDs (Alemany et al., 2011; Bi et al., 2018; Misiak et al., 2017; Sahu et al., 2016; Aas et al., 2013). Decreased levels of BDNF have been described as a potential biomarker for SSDs (Sahu et al., 2016). Aas et al. (2013) found a relation between the BDNF Val66Met polymorphism, CT, and brain abnormalities in psychoses (SSDs and bipolar disorders). Lower BDNF plasma levels were associated with CT in a sample of FEP as compared to healthy controls (Theleritis et al., 2014). The BDNF Val66Met polymorphism has been associated with CT and a subsequent risk for symptoms related to SSDs (Bi et al., 2018). BDNF met carriers who reported high CT exposure showed more brain abnormalities and worse cognitive performance (Aas et al., 2013), and SSDs patients who were BDNF met carriers showed volume loss in hippocampal areas of the brain (Aas, Haukvik, et al., 2014)

Gene – environment interactions

Gene – environment interactions are proposed as important considerations in the hypothesized causality for CT in SSDs (van Winkel et al., 2013). It has been suggested that a genetic predisposition could account for early adversity as well as psychotic symptoms. Individual

vulnerability may increase the risk of victimization via features associated with psychosis, such as cognitive impairment (van Winkel et al., 2013). However, there are challenges in defining the genetic risk underlying psychosis, which render studies of this alternative explanation a challenge for science (van Winkel et al., 2013). There are other possibilities of gene – environment interactions and epigenetic processes involved in the relationship between CT and SSDs suggested as potential mechanisms explaining why some and not everyone exposed to CT are prone to develop psychotic symptoms or SSDs later in life (Alemany et al., 2011; Misiak et al., 2015; Tomassi & Tosato, 2017). Aas, Djurovic, et al. (2012) found a significant interaction between serotonin transporter gene 5-HTTLPR variants, linked to an altered stress-response, and CT, on cognitive dysfunction in patients with psychotic disorders. The catechol-O-methyltransferase (COMT) genotype and the FK506 binding protein 5 (FKBP5) gene have received some attention (Alemany et al., 2016). The FKBP5 gene has been implicated in regulation of glucocorticoid receptors related to the HPA-system response to stress. The effect of CT in relation to cognitive performance was moderated by the FKBP5 in a study of SSDs and healthy controls (Green et al., 2015). The COMT Val158Met polymorphism has been implicated in cognitive performance, metabolism of catecholamines, and prefrontal dopamine levels. Met carriers showed worse cognitive outcomes associated with CT in a study of SSDs patients (Green et al., 2014). The results were consistent with previous research on how genetic factors might have a moderating effect on CT, and further that childhood adversities through an interaction with the COMT genotype might result in an increased dopamine activity (Green et al., 2014). Although CT has been related to altered brain structure and functioning across disorders (Teicher & Samson, 2013; Teicher et al., 2016), the role of CT in psychopathological brain changes in psychotic disorders remains unclear and warrants further investigation (Quide et al., 2021).

1.6.4 CT in relation to cognitive performance in SSDs

In separate lines of inquiry, both CT and cognitive impairments have been implicated in SSDs (Bora et al., 2009; Varese et al., 2012). CT could be a contributing factor for the decreased cognitive performance seen in patients with SSDs, but studies have been inconclusive and the precise nature of the relation remains unclear (Dauvermann & Donohoe, 2019). Research has indicated that CT could be associated with worse cognitive functioning in SSDs (Quide et al., 2017; Shannon et al., 2011; Aas, Dazzan, Fisher, et al., 2011). The results are however equivocal (van Os et al., 2017). CT was even found related to better cognitive abilities in SSDs reporting CT (Ruby et al., 2017). Shannon et al. (2011) reported that patients with

'chronic' SSDs and CT experiences performed worse on working memory and verbal memory tasks compared to the no CT SSDs group, after controlling for IQ and depressive symptoms. Aas, Dazzan, Fisher, et al. (2011) found in their study of FEP compared to healthy controls that CT was associated with reduced scores on attention, concentration, processing speed, language, and verbal intelligence, particularly for male patients with affective psychosis. CT was furthermore significantly associated with variation in cognition in SSDs and healthy participants, a relation that was not explained by acute stress reactivity (Rokita et al., 2021). On the other hand, van Os et al. (2017) investigated CT in relation to cognitive alterations in SSDs compared to siblings and a healthy control group in a longitudinal study. CT was associated with reduced IQ points in healthy controls, however this reduction was smaller in patients' siblings, as well as non-significant in SSDs. Relatedly, a meta-analysis has indicated that the association between CT and overall cognition was stronger in healthy controls as compared to patients with a psychotic disorder (Vargas et al., 2019).

The heterogeneity in the findings regarding CT and cognitive functioning in SSDs could possibly be explained by CT subtypes (physical, emotional, sexual abuse, or physical and emotional neglect) or the co-occurrence of CT (Schalinski et al., 2018; Schalinski et al., 2016). Research by Schalinski et al. (2018) indicated that abuse and neglect occurring at the age of 3 could be related to impairment in specific cognitive domains, such as attention, working memory abilities, and learning. Research has also indicated relations between subtypes of CT and overall cognitive abilities as well as specific cognitive abilities such as attention and language (Li et al., 2017). Reduced cognitive test scores were reported for SSDs patients compared to healthy controls, and a relation between the co-occurrence of CT subtypes and decreased global cognition and delayed memory found for both SSDs and healthy controls (Kasznia et al., 2021). The co-occurrence of CT as well as younger age of CT exposure were associated with decreased cognitive scores in the domain of attention in patients with SSDs (Kasznia et al., 2021). However, they did not control for psychosis symptoms, previously found to influence cognitive performance in SSDs (de Gracia Dominguez et al., 2009). Other lines of research have indicated the presence of gender differences: male SSDs patients tend to report more cognitive deficits, whereas women have been found to report more CT, although the results have yielded mixed findings (Kocsis-Bogar et al., 2018).

Suggested mechanisms for the relation between CT and cognitive performance in SSDs are linked to a pre-existing genetic vulnerability in SSDs related to abnormal stress-response adding to or interacting with the effects of CT and cognitive impairments (Aas,

Dazzan, et al., 2014). Exposure to CT during sensitive periods of brain development could be associated with aberrant development or interaction with different brain structures such as the PFC and hippocampus, which may relate to the subsequent development of specific symptoms and aspects of cognitive impairment in SSDs in line with a neurodevelopmental framework (Schalinski et al., 2019; Schalinski et al., 2018; Schalinski et al., 2016; Teicher et al., 2016).

In sum, the literature is not conclusive about whether early adversity such as CT is related to global or specific cognitive domains in SSDs, and potential clinical and demographic confounders into this relation have received little attention (Vargas et al., 2019). Research is needed to clarify the potential contribution of CT and CT subtypes to cognitive performance in SSDs while considering clinically meaningful confounders also known to influence cognitive abilities, such as educational levels, medication, and psychosis symptom load.

1.6.5 CT in relation to antipsychotic treatment effectiveness in SSDs

There is vast heterogeneity in the clinical course of SSDs. Research on environmental factors, such as CT, and implications for the variability in antipsychotic treatment effectiveness in SSDs is scarce and highly understudied (Thomas et al., 2019). Across diagnostic categories, CT has been tied to less favourable outcomes in relation to pharmacotherapies. Less effect of antidepressants was predicted by CT in patients with major depressive disorder (MDD) (Nikkheslat et al., 2020). Poorer outcomes after 8 weeks were associated with CT in patients with MDD receiving antidepressants (escitalopram, sertraline, or venlafaxine) in a randomized clinical trial, as well as a possible differential effect of CT occurring between 4 – 7 years and treatment with sertraline (Williams et al., 2016).

Moreover, CT has been associated with characteristics relevant for the treatment response in SSDs: an earlier onset age, increased symptom severity, more comorbidities, lower social and academic functioning, as well as a poorer clinical course (Thomas et al., 2019). Exposure to CT was in a meta-analysis related to the persistence of psychotic symptoms and a possible relation of CT to long-term outcomes in psychotic disorders was suggested (Trotta et al., 2015). CT has further been related to alterations of the HPA-axis and stress-regulation, associated with lower levels of glucocorticoids in SSDs patients with CT experiences (Ciufolini et al., 2019; Thomas et al., 2019). Decreased glucocorticoids was in turn tied to non-response to antipsychotic treatment in SSDs (Mondelli et al., 2015).

Moreover, CT in SSDs has been related to higher levels of inflammatory markers, which is further related to non-response to antipsychotic treatment (Dennison et al., 2012).

However, CT in relation to antipsychotic treatment effectiveness in SSDs remains unresolved and research findings are mixed. Trotta et al. (2016) found no robust associations between CT and lack of remission or the course of psychosis over the 1-year follow-up period in FEP patients. CT was unrelated to psychiatric symptoms but associated with less improvement in psychosocial functioning over 18 months in a small sample of patients with severe mental illness (n = 31) (Davidson et al., 2009). Information on type or dosage of medication was however not available. Mondelli et al. (2015) investigated cortisol and inflammatory biomarkers, and included recent and early life stress, as predictors for AP treatment response in FEP patients. The patient group was divided into treatment responders and non-responders after 12 weeks of clinician-led treatment with AP. There were no significant differences in terms of recent or early life stressors between the responders and non-responders (Mondelli et al., 2015). The FEP patients reported higher levels of recent stress and CT compared to healthy controls. The authors hypothesize that high levels of stress in psychosis are associated with a more general activation of the stress response system in psychosis as measured by cortisol awakening response and inflammatory markers, and not directly with the AP treatment response per se (Mondelli et al., 2015). Moreover, CT was related to symptom severity but did not predict differences in symptomatic change between the CT and no CT groups in a longitudinal study over three years (van Dam et al., 2015). Lifetime adversities were examined in relation to AP treatment resistance in patients with SSDs (Hassan & De Luca, 2015). About 42 % of the sample was classified as being treatment resistant and reported exposure to 4.5 traumatic events compared to 2.5 in the non-resistant group. The treatment-resistant group was characterized by alcohol/drug abuse, suicide attempts, family history of psychosis, earlier age of illness onset, longer illness duration and longer DUP as compared to non-resistant patients. After adjusting for these variables, only recent stressful events and childhood sexual abuse remained significant predictors for AP treatment resistance (Hassan & De Luca, 2015). FEP AP responders and non-responders were compared in terms of differences in CT and psychosis symptoms at baseline (Misiak & Frydecka, 2016). CT, and especially emotional abuse, was more frequently reported by non-responders after 12 weeks of AP treatment. In a sample of FEP (affective and non-affective) compared to healthy controls, CT was associated with severity of symptoms at baseline and follow-up, as well as slower improvement rates in terms of functioning after 12 months (Aas et al., 2016). However, the study did not include information on type of antipsychotic

medication. In a five-year follow-up of the sample in Trotta et al. (2016), aspects of CT were associated with less likelihood of remission and less medication adherence (Ajnakina et al., 2018). No information on type of antipsychotic medication were included, such as types of oral tablets or injectables. A slower treatment response was found for patients with 'high CT' exposure compared to 'low CT' exposure that was treated with a long-acting injectable (flupenthixol decanoate) over 24 months (Kilian et al., 2020). The 'high CT' group received higher doses of medication, interpreted as decreased response to treatment. The observed between-group differences in symptom severity did however not differ significantly at follow-up after 24 months of treatment. A study by Pruessner et al. (2021) found that FEP (affective and non-affective) patients reporting high CT exposure as compared to low CT exposure, showed higher psychosis symptom severity and were less likely to receive remission after 24 months of treatment. The effect of CT on remission was however non-significant after adjusting for antipsychotic medication (Pruessner et al., 2021). The study did not include information on what type of AP, nor investigate potential differences between different types of medications.

As outlined in Section 1.4.1 on antipsychotic treatment in SSDs, although all AAPs are functional D2 antagonists, the various types of AAPs such as olanzapine, aripiprazole, and amisulpride, are heterogenous in terms of receptor bindings, and exert their effect by targeting different neurotransmitter systems to different degrees. Research have indicated that SSDs patients differ in response to different antipsychotics (Johnsen et al., 2020), although between-drug differences have been described as small (Johnsen & Jorgensen, 2008). Predicting who will profit from or achieve symptomatic improvement following antipsychotic treatment is challenging (Solmi et al., 2017). Theoretically it is possible that there may be a differential effect of CT on antipsychotic effectiveness for different AAPs, and that increased knowledge on CT in relation to AP effectiveness may aid in clinical decision-making processes in SSDs.

In sum, most studies on CT in SSDs the past decades have focused on establishing associations of CT in SSDs, and not specifically on CT and implications for treatment (Trotta et al., 2016). Especially studies aimed at clarifying the relation of CT to specific antipsychotics are scarce. Naturalistic and pragmatic trials mimicking clinical practice may have advantages in providing knowledge transferable to routine clinical settings. Increased knowledge on whether and how environmental factors, such as CT, may impact on treatment effectiveness in SSDs is deemed important for a more personalized and tailored treatment of care as well as identifying individuals at risk of poorer outcomes.

1.6.6 CT in relation to substance abuse disorders (SUDs)

The WHO conceptualizes substance abuse disorders (SUDs) as the harmful or hazardous use of psychoactive substances, including alcohol or illicit drug use, which places a significant burden on individuals, their families, and the society. SUD is a potentially severe disorder which was acknowledged as a mental health disorder in the 1980s. Impairment across a vast range of areas in the patient's life, as well as an increased risk of premature death are potential consequences for SUDs patients (Strada et al., 2017). SUDs, including alcohol and drug addiction, pose enormous costs on society: medical costs due to the addiction and comorbid medical disorders, loss of productivity, as well as costs related to the criminal justice system (Kreek et al., 2005).

Heritability estimates related to vulnerability for addiction range from 30 to 60 % (Kreek et al., 2005). Genetic and environmental factors may however interact on the transitions from use to abuse. The WHO classifies mental and behavioral disorders due to psychoactive substances into ten different classes: alcohol, opioids, cannabis, sedatives, cocaine, stimulants (i.e., caffeine), hallucinogens, tobacco, volatile solvents, and the use of multiple psychoactive substances (World Health Organization, 2007). SUDs are rated top of the list among leading causes of disability across the world and is commonly reported among patients with mental disorders, as they frequently co-occur (European Monitoring Centre for Drugs and Drug Addiction, 2013; Santucci, 2012). It is however not clear what comes first: the mental disorders or the SUDs. For instance, determining the correct diagnosis when separating substance induced psychosis and a primary psychotic disorder is challenging, but crucial for providing the optimal treatment and care (Weibell et al., 2013).

Risk factors assumed to be involved in the development of SUDs range from pre-existing mental health disorders, early exposure to stress, access to drugs, genetic vulnerability, and social factors related to low levels of education and occupational participation, as well as CT (Dube et al., 2003; European Monitoring Centre for Drugs and Drug Addiction, 2013; The Norwegian Institute of Public Health, 2019; Verhulst et al., 2015). CT may be associated with SUDs development, co-morbidity, and severity (Afifi et al., 2012; Draucker & Mazurczyk, 2013; Dube et al., 2003; Ekinci & Kandemir, 2015; Medrano et al., 2002; Schaefer et al., 2010; Schnieders et al., 2006; Simpson & Miller, 2002; Wu et al., 2010). Research on the prevalence of CT among SUDs patients have varied (Moustafa et al., 2018). Results from the Adverse Childhood Experiences (ACE) study indicated that child abuse increased the likelihood of drug abuse initiation and development by 2 – 4-fold per ACE reported (Dube et al., 2003). A review by Simpson and Miller (2002) reports a 2-fold

increased rate of reported childhood sexual abuse (CSA) in women with SUDs compared to the general population, whereas men reporting CSA showed a higher risk of developing SUDs. CT experiences occurring before 11 years of age were found to be related to higher risk of abusing marihuana, cocaine, prescription drugs, and poly-drug use in a representative sample of US adolescents (Carliner et al., 2016). More CT has been reported for patients with SUDs compared to healthy controls (Ekinci & Kandemir, 2015). There are however some inconsistencies regarding the association between CT and SUDs. A study by Cuomo et al. (2008), found no significant difference on the CTQ-SF total score when comparing prisoners without SUDs to prisoners with SUDs. They did however find higher scores on emotional abuse and physical neglect. A review by Draucker and Mazurczyk (2013) found CSA to be a precursor to various health risk behaviors during adolescence. Across the reviewed studies, CSA was associated with alcohol use/abuse/dependence, nicotine use, cannabis use/abuse/dependence and amphetamine. CSA in relation to illicit drug use was found to be inconclusive.

Studies directly comparing CT in SUDs to SSDs are scarce and findings have yielded inconclusive results. A comparison of CT experiences in SUDs to early onset schizophrenia (EOS) and substance induced psychosis (SIP) found higher rates of and similarities between the EOS and SIP compared to the SUDs groups in terms of psychological trauma and unfavorable life situations (Matzova et al., 2014). Relatedly, more overall CT as well as emotional neglect and emotional abuse were reported by SSDs as compared to SUDs (Khan et al., 2020). However, there were no differences between SSDs and SUDs in terms of exposure to physical neglect and physical abuse, and sexual abuse. In a study of families with multiple members diagnosed with mental illnesses by Someshwar et al. (2020), greater total ACE score was associated with earlier onset of substance dependence, but for not schizophrenia. Thus, CT has been associated with the development of SUDs and substance related problems, as well as being thoroughly researched as a potential risk factor for SSDs. There is however a paucity of research directly comparing the frequency and severity of CT in SUDs to SSDs. Such a comparison is deemed important to clarify whether general or specific CT exposure might differ in clinical groups with severe mental illnesses.

2 Aims

This Ph.D. aimed to examine the severity and frequency of CT in SSDs as compared to SUDs, as well as the role of CT related to clinical features in SSDs. CT was therefore examined in the relation to cognitive impairment in SSDs. A central aim was to elucidate

whether CT could exert a general or differential effect on the antipsychotic treatment effectiveness in routine clinical settings for SSDs patients.

2.1 Research questions

1. Are there differences in the frequency or severity of CT in SSDs patients as compared to patients with SUDs? (Paper I)
2. What are the general and differential effects of CT and CT subtypes on global cognitive performance and specific cognitive domains in SSDs patients? (Paper II)
3. What are the general and differential effects of CT on antipsychotic effectiveness in patients with SSDs? (Paper III)

3 Methods

The studies on which this Ph.D. was based were from two separate research projects. The Bergen-Stavanger-Trondheim-Innsbruck (BeSt InTro) RCT (Paper I, II and III) by the Bergen Psychosis Research group, and the Trauma and adult mental health study by the Trauma Psychology Research group (TPRG) (Paper I).

3.1 The BeSt InTro study

The BeSt InTro study was a pragmatic, naturalistic, semi-randomized and head-to-head, rater-blinded comparison of three atypical antipsychotics (AAPs): amisulpride, aripiprazole and olanzapine. Treatment effectiveness was assessed during and after 52-weeks of follow-up at the following study visits: baseline and weeks 1, 3, 6, 12, 26, 39 and 52. The BeSt InTro study included patients in an observational cohort, from which eligible candidates for the RCT were drawn to ensure representativeness in the SSDs population.

3.1.1 Recruitment and sample

Patients included in BeSt InTro were recruited from Bergen, Stavanger, and Trondheim in Norway and Innsbruck, Austria, from October 2011 to December 2017. Paper I was based on a sample of SSDs (n = 57) which was compared to a sample of SUDs *(*n = 57). The SSDs sample in Paper I was included from Haukeland University Hospital, Bergen, Norway (n = 47); Stavanger University Hospital, Stavanger, Norway (n = 3) and the Medical University of Innsbruck, Innsbruck, Austria (n = 7). Paper II included a SSDs sample (n = 78) from Haukeland University Hospital, Bergen, Norway (n = 60); Stavanger University Hospital, Stavanger, Norway (n = 8) and the Medical University of Innsbruck, Innsbruck, Austria (n = 10). For Paper III the SSDs sample (n = 98) was included from Haukeland University

Hospital, Bergen, Norway (*n* = 78); Stavanger University Hospital, Stavanger, Norway (*n* = 8) and the Medical University of Innsbruck, Innsbruck, Austria (*n* = 12). The recruitment site St. Olav's Hospital, Trondheim, Norway, was also a part of the BeSt InTro study, but did not collect data on CT exposure nor performed cognitive testing and data from this site was not included as part of this thesis.

The total number of participants at baseline in the BeSt InTro RCT at study completion was *N* = 144. See Johnsen et al. (2020) for demographic information and inclusion flow chart for the BeSt InTro study. The overall sample size was reduced as the study progressed during the 52 weeks follow-up: *n* = 130 at 1 week, *n* = 122 at 3 weeks, *n* = 101 at 6 weeks, *n* = 87 at 12 weeks, *n* = 69 at 26 weeks, *n* = 64 at 39 weeks and *n* = 62 at the 52 weeks follow-up. The CTQ-SF was mainly presented at the 6-weeks follow-up (*n* = 94 [96%]), and more rarely at other follow-up points: at one week (*n* = 1 [1%]), 12 weeks (*n* = 1 [1%]), and 26 weeks (*n* = 2 [2%]). At the 6 weeks follow-up, the overall BeSt InTro sample size was reduced to *n* = 101 participants, of which a total of *n* = 98 was assessed with the CTQ-SF. The comprehensive cognitive test battery was conducted at the 12-weeks follow-up, where the total sample size in the RCT was *n* = 87, of which *n* = 70 completed the cognitive testing. An overview of characteristics of the samples from Paper I, II and III is provided in Table 1.

The data used for Paper I was analyzed in 2016 and included *n* = 57 SSDs patients. The CTQ-SF data included *n* = 43 RCT (75.4%) and *n* = 14 (24.5%) cohort patients. The SSDs patients included in Paper II were required to have completed the CTQ-SF assessment as well as the cognitive test battery. A total of *n* = 96 SSDs patients (*n* = 70 RCT, *n* = 26 cohort patients) completed the cognitive testing. The final sample in Paper II (*n* = 78) included *n* = 62 (79.5 %) patients from the RCT and *n* = 16 (20.5 %) patients from the cohort, thus the total sample of SSDs with complete CTQ-SF and cognitive scores were quite large relative to the available pool of SSDs patients. As Paper III examined antipsychotic effectiveness, all patients (*n* = 98) who had data from the CTQ-SF were included from the RCT study.

Table 1 Overall sample characteristics from Paper I, II and III

	Paper 1				Paper 2					Paper 3				
Variables	SSDs n = 57	SUDs n = 57	*U*	*p*	SSDs no CT n = 37	SSDs CT n = 41	Total N = 78	*t*	*p*	SSDs no CT n = 43	SSDs CT n = 55	Total N = 98	*t*	*p*
Age, years	30.24 (11.6)	29.96 (11.3)			29.46 (11.97)	30.20 (12.87)	29.84 (12.37)			31.2 (13.2)	30.8 (12.4)	30.95 (12.68)		
Gender (male)	35 (61.4 %)	35 (61.4 %)			28 (57.14 %)	21 (42.86 %)	49 (62.80 %)			32/43 (74%)	31/55 (56%)	63/98 (64%)		
CTQ-SF sum	45.55 (15.07)	43.85 (11.97)	1587.5	0.834	30.70 (3.99)	51.88 (14.21)	41.83 (15.02)	-8.75	0.001*	31.1 (4.2)	54.3 (13.6)	44.1 (15.6)	-10.812	0.000*
Emotional abuse	10.26 (5.07)	9.99 (3.73)	1561	0.718	6.46 (1.94)	12.85 (5.24)	9.82 (5.13)	-7.00	0.001*	6.4 (1.7)	13.3 (4.7)	10.3 (5.1)	-9.107	0.000*
Physical abuse	7.05 (3.39)	7.07 (3.39)	1607	0.915	5.22 (0.53)	7.24 (3.63)	6.28 (2.83)	-3.37	0.001*	5.3 (0.6)	8.5 (4.1)	7.1 (3.5)	-5.071	0.000*
Sexual abuse	7.33 (4.57)	7.46 (5.05)	1615	0.947	5.05 (0.33)	7.34 (4.25)	6.28 (3.28)	-3.26	0.001*	5.0 (0)	7.4 (4)	6.3 (3.2)	-3.948	0.000*
Emotional neglect	12.12 (4.98)	11.62 (4.67)	1529.5	0.589	7.73 (2.62)	14.95 (5.58)	11.52 (5.71)	-7.18	0.001*	8.1 (2.7)	15.1 (4.6)	12.0 (5.2)	-8.988	0.000*
Physical neglect	8.77 (3.61)	7.72 (2.74)	1349.5	0.114	6.24 (1.46)	9.48 (3.67)	9.95 (3.26)	-5.03	0.001*	6.3 (1.5)	9.9 (3.7)	8.4 (3.5)	-6.041	0.000*
PANSS total	64 (17.15)				70.78 (20.89)	79.83 (14.79)	75.48 (18.43)	-2.21	0.029*	76.2 (18.4)	79.9 (13.5)	78.2 (15.9)	-1.142	0.255
PANSS positive	15.15 (5.6)				18.54 (5.59)	21.38 (5.30)	20.01 (5.59)	-2.28	0.025*	20.7 (4.8)	21.9 (4.9)	21.4 (4.9)	-1.242	0.216
PANSS negative	16.83 (6.3)				15.84 (6.38)	19.05 (6.33)	17.51 (6.51)	-2.22	0.029*	16.6 (6.6)	18 (5.4)	17.3 (5.9)	-1.159	0.249
PANSS general	32.02 (8.28)				36.41 (11.34)	39.40 (7.66)	37.96 (9.66)	-1.37	0.175	38.9 (10.1)	40 (7.2)	39.5 (8.6)	-0.599	0.550

Note. CTQ-SF = Childhood trauma questionnaire short-form. PANSS = The Positive and Negative Syndrome Scale. SSDs = Schizophrenia spectrum disorders. SUDs = Substance abuse disorders. CT = Childhood trauma. Continous variables analyzed using independent samples t-test or Mann-Whitney U, and categorical variables analyzed using $\chi 2$. * significant at $p < .05$.

3.1.2 Inclusion and exclusion

The following criteria was for inclusion to the RCT study. For the cohort there were no requirement for active psychosis or eligibility for medication. All patients were evaluated for study inclusion by their attending physician or psychiatrist. They had to be eligible candidates for oral antipsychotic drug treatment, ≥ 18 years of age and understand the native language (Norwegian or German). Participants were considered for inclusion if they presented with acute psychotic symptoms indicating non-affective psychosis according to the ICD-10 (World Health Organization, 1992) diagnostic section on schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (F20 - F29). All participating patients were considered capable of providing their informed and written consent before study inclusion. The diagnosis within the schizophrenia spectrum was made by means of the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID; Spitzer, Williams, Gibbon, & First, 1992), as well as a score of ≥ 4 on at least one of the items Delusions (P1), Hallucinatory behavior (P3), Grandiosity (P5), Suspiciousness/Persecution (P6), or Unusual thought content (G9) on the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opfer, 1987). The SCID was performed by trained research- or clinical personnell, as early as possible after inclusion to the BeSt InTro. For inclusion to the current thesis, the participants from BeSt InTro also had to have completed the CTQ-SF (Bernstein et al., 2003).

Exclusion criteria were inability to use oral antipsychotics, psychosis due to organic brain disorder, psychoactive substance use, or psychosis due to mania. Candidates were excluded if they were already receiving treatment with clozapine, or if they were pregnant or breast feeding. Further, participants were excluded if hypersensitive to the active substance or excipients of the study drugs, prolactin dependent tumors, phaeochromocytoma, or known risk of narrow-angle glaucoma. Study withdrawal criteria from the clinical trial were pregnancy or serious somatic illnesses or events requiring deviation from study protocol. Changing the antipsychotic medication due to inadequate effects, adverse side effects or safety issues were not considered reason for withdrawal from the BeSt InTro, in line with the pragmatic and naturalistic design of the study. Regular treatment with more than one antipsychotic medication was not permitted in the study.

3.1.3 Treatment

Patients included in the BeSt InTro RCT received oral antipsychotic tablets, either amisulprid, aripiprazole or olanzapine, based on the randomization procedure (described and elaborated upon in Paper III). Clinical decisions related to dosage, combination with other drugs or

change of antipsychotic medication were left at the clinician's discretion in collaboration with the patient. The dosages followed the guidelines and limits as described in the Summary of Product Characteristics, and the dosage intervals were as follows: amisulpride 20 – 1200 mg/day, aripiprazole 5 – 30 mg/day, olanzapine 2.5 – 20 mg/day. As recommended in national and international guidelines, antipsychotic monotherapy was the preferred treatment strategy (National Institute for Health and Care Excellence, 2014; Norwegian Directorate of Health, 2013). In case of inevitable use of regular concomitant antipsychotics, the patient was excluded from the BeSt InTro trial, however no one was excluded based on concomitant antipsychotic medication. Information regarding adherence to medication and dosage was recorded routinely each visit and confirmed by serum measurements of antipsychotic drug level. Dosages of antipsychotic medication were converted to Defined Daily Doses (DDD), which is the assumed daily average maintenance dose (https://www.whocc.no/atc_ddd_index). The conversion to DDD was developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology.

3.2 The trauma and adult mental health study

Paper I included a sample of SUDs (n = 57) from the Trauma and adult mental health project, which was a cross-sectional study aimed at the testing and development of trauma-related assessment instruments, as well as collecting data on the occurrence of CT in high-risk clinical and non-clinical groups. Data collection was performed in collaboration with public mental health care services, substance abuse services, child welfare services, and correctional services. The patients included in the Trauma and adult mental health study all gave written informed consent ahead of study inclusion. The enrollment period was between September 2006 and May 2011.

3.2.1 Recruitment

For Paper I, the patients with SUDs (n = 57) were recruited from either inpatient treatment (n = 19) or outpatient facilities (n = 38) for SUDs in areas in and around Bergen, Norway. Patients included in the SUDs sample primarily received treatment for illegal substance use or dependence and/or alcohol use or dependence. The presence of SUDs was determined by the Norwegian national client mapping system (KKS) (Iversen et al., 2009).

3.2.2 Inclusion and exclusion

Inclusion criteria for the Trauma and adult mental health study was being aged ≥ 15 years, and the ability to give their informed and written consent to participate. The age range

included in the present study was 17 to 65 (M = 30.0 years, SD = 11.1 years). For inclusion to the current project, the participants had to have data on substance abuse collected via the KKS (4th ed., 01.2005, Statens Institutt for Rusmiddelforskning) and to have completed the CTQ-SF screening (Bernstein et al., 2003). Participants were excluded from participation in the Trauma and adult mental health study if inability to complete the screening due to mental or physical disabilities related to severe substance abuse, symptoms of psychosis or psychotic disorder, ongoing risk of suicidality, inappropriate or insufficient language skills, mental retardation, or intoxication at the time of assessment.

3.3 Measurements and clinical variables

3.3.1 Childhood Trauma Questionnaire Short-Form (CTQ-SF)

CT was assessed using the Childhood Trauma Questionnaire Short-Form (CTQ-SF), a self-report 28-item questionnaire examining five subtypes of childhood maltreatment: sexual abuse (e.g., "was touched sexually"), physical abuse (e.g., "punished with a belt or hard objects") and emotional abuse (e.g., "felt hated in the family"), and physical neglect (e.g., "not enough to eat"), and emotional neglect (e.g., "felt important or loved", reverse coded) (Bernstein et al., 1997; Bernstein & Fink, 1998; Bernstein et al., 2003). Each subscale consists of five items scored on a five-point Likert scale ranging from 1 (*never true*) to 5 (*very often true*), summarized into an overall CTQ-SF sum score ranging from 25-125. Three items make up the Minimization-denial subscale, a validation scale, which was not used in this thesis. There are several versions of the CTQ, consisting of 70, 53 and 34 items, including the 28 item CTQ-SF. Baker and Maiorino (2010) therefore recommend reporting mean scores, making it valid to compare and combine data across studies utilizing different versions of the CTQ.

The CTQ-SF has shown good psychometric properties in different samples: internal consistency, test-retest reliability, excellent internal reliability for the total scale, good to excellent internal reliability for the subscales, as well as good sensitivity and specificity (Bernstein et al., 2003; Dovran et al., 2013; Gerdner & Allgulander, 2009). The Norwegian version of the CTQ-SF was found show reasonable fit to the original five-factor structure proposed by Bernstein et al. (2003), as well as satisfactorily to excellent internal consistency (Winje et al., 2004). The reliability estimates are within the range of .78 to .95 (Dovran et al., 2013). The German version of the CTQ-SF has shown satisfactory construct validity and internal consistency, except for physical neglect (Bader et al., 2009; Klinitzke et al., 2012).

3.3.2 Psychotic symptoms

Investigators in the BeSt InTro assessed psychotic symptoms using the Structured Clinical Interview for the Positive and Negative Syndrome Scale for Schizophrenia (SCI-PANSS) (Opler et al., 1999). The assessors were trained and calibrated by the PANSS Institute to ensure sufficient inter-rater reliability. The PANSS has shown good psychometric properties in SSDs (Bell et al., 1992; Kumari et al., 2017; von Knorring & Lindström, 1992), although a five-factor solution has been suggested (Wallwork et al., 2012). The Psychotisism subscale from the Symptom Checklist 90 Revised (SCL-90-R) (Derogatis, 2009) was used in Paper I as a measure of psychotic symptoms in the SUDs group, as the Trauma and adult mental health project did not include a standardized measure of psychosis symptoms such as the PANSS in the BeSt InTro.

3.3.3 Substance abuse

Drugs and alcohol use was in the BeSt InTro screened for using the Alcohol Use Disorders Identification Test (AUDIT) (Bush et al., 1998) and Drug Use Disorders Identification Test (DUDIT) (Berman et al., 2005), found to possess good reliability and validity (Gundersen et al., 2013). The AUDIT is a self-report questionnaire consisting of 10 questions concerning recent alcohol use, alcohol dependence symptoms, and alcohol-related problems (Babor et al., 2001). The DUDIT is similar self-report measure consisting of 11 questions, used to assess aspects of illicit drug use and abuse (Berman et al., 2005). The AUDIT and DUDIT scores were summarized to create a sum scale. The manuals provide the following cut-offs for when to suspect abuse, harmful use, or dependence: DUDIT; males ≥ 6 points, females ≥ 2 points, AUDIT; males ≥ 8 points, females ≥ 6 points. In most cases, higher scores will indicate greater severity of substance related problems, and ≥ 25 points from DUDIT and ≥ 20 points from AUDIT may indicate severe abuse or dependency. For the follow-up period in the BeSt InTro study, the clinician-rater tool Clinical Drug and Alcohol Use Scales was employed (CAUS and CDUS), found to have good validity and reliability in severe mental health disorders (Drake et al., 1990; Mueser et al., 1995). Drug and/or alcohol abuse according to the CAUS and CDUS were rated according to the following categories: 1 (abstinent), 2 (use without impairment), 3 (abuse), 4 (dependence) or 5 (dependence with institutionalization).

Data on substance abuse in the Trauma and adult mental health study was collected using the Norwegian National Client Mapping System (KKS); a standardized method developed by the Bergen Clinics in Bergen, Norway in collaboration with the The Norwegian Institute for Alcohol and Drug research, Norway (Iversen et al., 2009). The KKS included

demographic information, as well as substance related information such as the patient's past (> 6 months) and present (< 6 months) substance use and/or abuse.

3.3.4 Cognitive assessment

Trained research nurses performed the cognitive testing. The BeSt InTro used a comprehensive test battery (2 – 3 hours) administered one time, in addition to a brief test battery repeated at several time points. Both test batteries targeted areas of cognitive performance known to be impaired in many patients with SSDs. The comprehensive test battery provided data for Paper II of this thesis. The following seven domains of cognition were comprehensively assessed: 1) verbal abilities; 2) visuospatial abilities; 3) verbal learning; 4) memory (long-term memory and recognition); 5) attention/working memory; 6) executive abilities and 7) processing speed. The averaged t-scores from the seven domains were used to calculate a measure of global cognitive performance. The study included well-validated and reliable cognitive tests commonly used in studies of cognitive functioning in individuals with SSDs, more details are provided in Paper II. See Table 2 for an overview of the various tests sorted by cognitive domain.

Table 2 Cognitive tests sorted by cognitive domain

Domain	Cognitive test
Verbal abilities	The Wechsler Adult Intelligence Scale III (WAIS III; Wechsler, 1997a) subtests vocabulary and similarities subtests; the D-KEFS verbal fluency test (Delis et al., 2001)
Visuospatial abilities	The block design and digit symbol-coding subtests of WAIS III; the Rey-Osterrieth Complex Figure Test (Shin et al., 2006)
Verbal learning	The California verbal learning test (CVLT; Delis et al., 1987) i.e. trials 1 – 5; the digit span subtest of the WAIS III
Memory	The CVLT (subtests short delay free and cued recall, long delay free and cued recall, and delayed recognition); the Rey-Osterrieth Complex Figure Test (Shin et al., 2006)
Attention and working memory	The Digit vigilance test (Lewis and Rennick, 1979); the CalCAP Continuous performance test subtests sequential reaction time and choice reaction time (Conners, 2002); Trail Making Test (Part B) (Reitan, 1986); the WAIS III subtests digit span and letter-number sequencing; the Wechsler Memory Scale (Wechsler, 1997)
Executive abilities	The Wisconsin Card Sorting test (Heaton, 1981); the Stroop test (Stroop, 1935).
Processing speed	The Trail Making Test (Part A) (Reitan, 1986); the digit symbol-coding subtest of the WAIS III; the Grooved Pegboard Test (Bryden and Roy, 2005); the CalCAP subtest simple reaction time (Conners, 2002)

3.3.5 Other measurements

In the BeSt Intro, symptoms of depression in the SSDs sample were measured using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993). The CDSS is a

clinician-administered 9 item rating scale which has been psychometrically validated and shown to be reliable in distinguishing between negative symptoms and depression in patients with schizophrenia (Addington et al., 1993; Lako et al., 2012). Function and symptom severity was scored at every visit using the Global Assessment of Functioning – Split Version, Functions scale (Pedersen & Karterud, 2012). The Clinical Global Expressions Scale (CGI) (Guy, 1976) was used to assess severity of illness. The CGI is a brief, clinician-rated instrument where the severity of the illness is rated on a Likert scale ranging from 1 – 7 (Guy, 1976). The Trauma and adult mental health project used the SCL-90-R, which is a 90 item self-report questionnaire that broadly assessed psychiatric symptomatology on nine symptom dimensions: somatization, obsessive-compulsive, depression, anxiety, phobic anxiety, hostility, interpersonal sensitivity, paranoid ideation and psychoticism (Derogatis, 1983, 2009). The items are rated on a four-point (0 – 4) Likert scale. A global severity index (GSI) was calculated based on the symptom dimensions. The SCL-90-R has been found to have good psychometric properties in SUDs (Bergly et al., 2014).

3.4 Procedure

The SSDs patients included in the BeSt InTro study were assessed at baseline and weeks 1, 3, 6, 12, 26, 39 and 52 (corresponding to visit 1 to 7) after study inclusion. The CTQ-SF was mainly administered at the 6-week follow-up. The SCI-PANSS was administered at baseline and all following study visits. The comprehensive cognitive test battery was conducted at the 12-week follow-up, when participants were more likely to be in a clinically stable phase, thus increasing assessment validity. Data from the SUDs group was collected by the patients' therapists as part of the daily clinical routine: preferably at treatment initiation, and no later than the fifth treatment session. The therapist received a written report from the screening who informed the patient about the results.

3.5 Statistical analyses

All statistical analyses in Paper I and II were performed in SPSS 22.0 (Corp., 2020) and STATA MP 15 and 16 (StataCorp, 2021). The linear mixed effects models (LME) in Paper III were conducted in R (version 4.0.2) (R Core Team, 2013). Measures are in Paper I, II and III mainly presented as means (*M*) and standard deviations (*SD*), or as number (*n*) and percentages (*%*). Categorical variables such as gender or education were compared using Chi square tests χ^2, whereas continuous variables such as age were compared using independent

samples *t*-test or the non-parametric equivalent Mann-Whitney *U*. A *p*-value of .05 was considered statistically significant.

Statistical power was calculated using LME models in R, and was originally performed for the BeSt InTro study (Johnsen et al., 2020). The analyses indicated that $n = 46$ participants in each group would be sufficient to discover group differences, based on a beta-value of .90 and alpha/*p*-value of .05. Paper III in the present thesis was based on a similar number of participants. Post-hoc power calculations for secondary analyses were not performed, since the results would not change or affect the results found for Paper I and II.

For all three papers, threshold scores from the CTQ-SF manual were used to categorize the CTQ-SF subscale scores into *none*, *low*, *moderate,* and *severe* abuse, or neglect (Bernstein & Fink, 1998). A dichotomous categorical variable grouped none and low levels of CT into a 'no CT group', and moderate and severe levels into a 'CT group'. This variable was used as a cut-off to determine caseness, as studies have found low levels of CT to be common in the general population. Using moderate to severe levels of CT as cut-off might therefore provide more sensitivity in detecting cases when assessing CT effects in patient populations (Baker & Maiorino, 2010).

3.5.1 Paper I – CT in SSDs as compared to SUDs

The SSDs group ($n = 57$) and SUDs group ($n = 57$) were matched for age and gender, to reduce potential selection bias or the influence of age and gender as confounding variables. We compared the CTQ-SF sum scores and subscale scores between the SSDs and SUDs groups using the Mann-Whitney *U* test. Spearman's rho was used for correlational analyses. Pearson correlations coefficient (r) was used to assess effect size, categorized according to Cohen's criteria: small ($r = .10$), medium ($r = .30$), and large ($r = .50$) (Cohen, 1977). Each participant's personal subscale mean was imputed in case of missing data (MD) from the CTQ-SF or the PANSS. Scores were imputed in 12 of 114 cases. None of the participants were excluded from analysis.

3.5.2 Paper II – CT in relation to cognitive functioning in SSDs

The sample of SSDs ($n = 78$) was divided into the CT and no CT group: those reporting none or low CT ($n = 37$) and moderate to severe CT ($n = 41$). Raw test scores from the cognitive test battery were converted to standardized *t*-scores based on the best available norms. We calculated domain mean scores as well as a global cognitive performance score (mean of the domain mean scores). The domains used as dependent variables were verbal abilities,

visuospatial abilities, learning, memory, attention/working memory, executive abilities, and processing speed.

Firstly, the cognitive domains and overall cognitive performance scores were compared by means of independent samples *t*-tests between the CT and no CT SSDs groups. For the main multiple linear regression analyses, the CTQ-SF scores were used as continuous variables as predictors for cognitive performance. The first models included the CTQ-SF subscale scores (physical, sexual, and emotional abuse, and physical and emotional neglect) as predictors for the cognitive performance scores. For the second analyses, antipsychotic medication (DDD), gender, and PANSS positive and negative symptom subscales, were added as covariates in addition to the CTQ-SF subscales. The third models added years of education as covariate. The PANSS total score and the CTQ-SF sum scores were omitted due to multicollinearity with the PANSS positive and negative subscale scores and the CTQ-SF subscale scores, respectively. Mean dosage of antipsychotic medication (DDD) was included as predictor based on previous research showing effect on cognition in SSDs receiving antipsychotic treatment (Johnsen et al., 2013). The goodness of fit as measured by the adjusted R^2 (R^2_a) was assessed as small if ≤ .09, moderate between 0.1 and 0.3 and large effect if ≥ .3 (Mehmetoglu & Jakobsen, 2017). Variables were visually inspected for normality by means of frequency distributions. All regression models were tested for, and adhered to, assumptions underlying linear multiple regression: Homoscedasticity, multicollinearity, normally distributed residuals, correctly specified model, appropriate functional form and influential cases (Mehmetoglu & Jakobsen, 2017). As in Paper I and III, a *p*-level of < .05 was considered statistically significant in Paper II, except for in the regression analyses where we corrected for multiple testing by means of a Bonferroni adjustment (.05/40 = $p < .00125$). MD in the CTQ-SF was handled through imputation based on expectation maximation, and the amount of missing data in the CTQ-SF scale was 0.73 %.

3.5.3 Paper III – CT in relation to antipsychotic effectiveness in SSDs

As in Paper II, the SSDs sample was divided into a no CT group (n = 43) for comparison to a CT group (n = 55). The participants were also grouped according to the medication group to which they were randomized (ITT analyses), and according to the medication that was actually chosen for treatment (PP analyses). LME models were used for both ITT and PP-analyses. LME was chosen for its ability to handle data assumed missing completely at random (all participants were kept in the analyses) and dependencies in the data due to repeated measurements.

The primary analysis examined psychosis symptom change (PANSS total, positive, negative, and general psychopathology) during 52 weeks of antipsychotic treatment in the ITT SSDs CT and no CT group. Secondarily, the analyses were conducted in each medication subgroup (amisulpride, aripiprazole and olanzapine). The following variables were included as fixed effects/covariates in all models: years of education as a proxy for premorbid functioning, sex, age of illness onset, DUP, previous exposure to antipsychotics, antipsychotics DDD, and baseline psychosis symptoms. Due to missing values in some variables for some patients, multiple imputation was used to keep all the 98 patients in the LME analysis. The models were also fitted using no imputed values and removing patients with incomplete data, which did not alter the results.

3.6 Funding, approvals, and ethical considerations

Both the Trauma and adult mental health project and the BeSt InTro study were conducted according to the World Medical Association Declaration of Helsinki (World Medical Association, 2013), and were approved by the Regional Committee for Medical Research Ethics West-Norway: The BeSt InTro (2010-3387), The trauma and adult mental health study (2009–1133), as well as by the Norwegian Social Data Services. The BeSt InTro was registered as a clinical trial 10/03/2011 (NCT01446328) and conducted according to guidelines from the Norwegian Health Research Act (Ministry of Health and Care Services, 2008). As the BeSt InTro study was a drug trial, approval was obtained from the Norwegian Medicines Agency, and the Austrian equivalents: ethics committee at the Medical University of Innsbruck and the Austrian Federal Office for Safety in Health Care. Furthermore, the study was evaluated and conducted according to the Good Clinical Practice guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICHH, 2016). The Department of Research and Development at Haukeland University Hospital in Norway, and the Austrian Clinical Trial Centre at the Medical University Innsbruck were providers of these services.

The BeSt InTro study was funded by the Norwegian Research Council (RCN) #213727 and the Western Norway Regional Health Authority #911820 and #911679 and did not receive financial support nor had other connections to the pharmaceutical industry. The Trauma and adult mental health project was funded by the Department of Clinical Psychology at the University of Bergen and by “The National Program for Integrated Clinical Specialist and Ph.D. Training for Psychologists in Norway”. The present thesis was funded by the

Northern Norway Regional Health Authority #PFP1300-16. The studies were additionally supported by participating universities and hospitals.

4 Results

4.1 Paper I: CT in SSDs as compared to SUDs

There were no statistically significant differences between the SSDs (n = 57) and SUDs (n = 57) groups in terms of clinical or demographic characteristics. Female patients independent of patient group reported higher CTQ-SF sum scores as compared to the male patients (p = .030), as well as more moderate to severe CT as compared to male patients (χ^2 (1) = 8.112, p = .004).

There were no group differences in terms of the CTQ-SF sum scores when comparing the SSDs (M = 45.55, Mdn = 43) and SUDs group (M = 43.85, Mdn = 43; U = 1587.5, p = .834). Comparison of the CTQ-SF subscale scores showed no statistically significant differences between the SSDs and SUDs groups (see Figure 1), and the effect sizes were small: emotional abuse (p = .509, r = -.03), physical abuse (p = .607, r = -.01), sexual abuse (p = .663, r = -.01), emotional neglect (p = .384, r = -.05) and physical neglect (p = .227, r = -.15). There were no statistically significant differences between SSDs and SUDs in terms of CT severity, nor in terms of the number of moderate to severe CT.

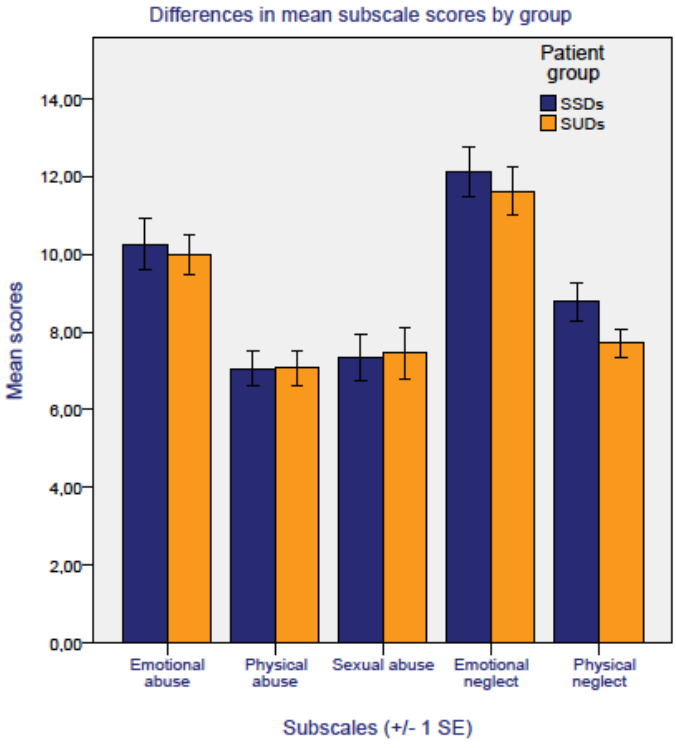

Figure 1 Comparison of mean CTQ-SF subscale scores between the SSDs and SUDs groups

4.2 Paper II: The association of CT and cognitive functioning in SSDs

There were no statistically significant group differences between the SSDs CT (n = 41) and no CT (n = 37) groups in terms of global cognitive performance or any of the domains: verbal abilities, visuospatial abilities, learning, memory, attention/working memory, executive abilities, or processing speed.

The first regression models tested for the effect of the CTQ-SF subtypes (physical, sexual, and emotional abuse, and physical and emotional neglect) on cognitive performance in SSDs (n = 78). After correcting for multiple comparisons, the relation between the CTQ-SF subtypes and cognitive performance was mainly driven by physical neglect on global cognitive performance (β = – 1.288, p = < .00125), visuospatial abilities (β = – 1.560, p = < .00125), memory (β = – 1.243, p = < .00125) and attention/working memory (β = – 1.342, p = < .00125). The second models controlled for gender, psychosis symptoms, and antipsychotic medication (DDD). Physical neglect remained as a statistically significant predictor for attention/working memory abilities in SSDs (β = – 1.082, p = < .00125). The results remained unchanged after years of education was added in the models (β = – 1.082, p = < .00125).

4.3 Paper III: The relation of CT in antipsychotic effectiveness in SSDs

Of those that declined the first offered medication in the ITT-group, a chi square test showed a significant difference between the CT (n = 55) and no CT groups (n = 43) (χ^2 (1) = 4.119, p = .040): Four percent (n = 4) in the no CT group switched medication, compared to 14.29% (n = 14) in the CT group. There were no significant group differences when comparing previous experience with antipsychotics (p = 0.188), the mean level of antipsychotic medication (DDD) (p = 0.838), DUP (p = 0.152), or age of illness onset (p = 0.807). The CT and no CT groups differed in terms of baseline symptoms of depression (p = 0.002).

The ITT and PP analyses showed corresponding results. The first LME model examined differences in change in psychosis symptoms during 52 weeks of antipsychotic treatment between the SSDs CT and no CT groups. There were no significant differences in terms of overall change in psychosis symptoms from baseline to the 52 weeks follow-up (see Figure 2). The LME model estimated an overall difference in change after 52 weeks in PANSS total scores between the CT and no CT group of 4 points, meaning that the CT group showed 4 points less decrease than the no CT group (SD = 4, p = .112). For the PANSS positive subscale scores the difference in change was 2.2 points (SD = 1.2, p = .097), for the PANSS negative subscale scores the difference of change between the CT and no CT groups

was 0.1 point (*SD* = 1.4, *p* = .946), and for the general psychopathology subscale scores the difference of change was 3.6 points (*SD* = 2.1, *p* = .084).

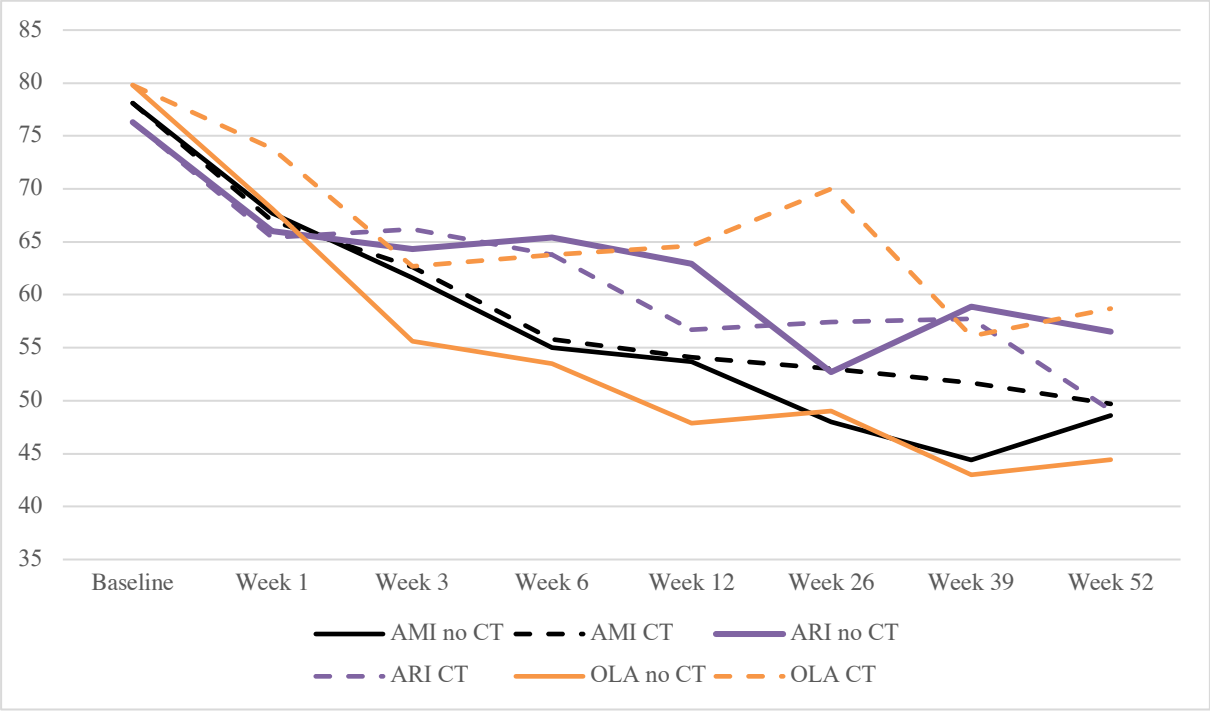

Figure 2 PANSS total scores by CT and no CT groups and type of antipsychotic medication from baseline to 52 weeks

When examining differences in symptom change at specific follow-up points (1, 3, 6, 12, 26, 39 and 52 weeks), the LME models showed less symptomatic decrease for the CT group compared to the no CT group from baseline to several time points: the PANSS total scores at 26 weeks (*p* = .001) and 39 weeks; at 26 (*p* = .005) and 39 (*p* = .035) weeks for the PANSS positive subscale scores, at 12 (*p* = .035) and 26 (*p* = .031) weeks for PANSS negative subscale scores, and at 26 (*p* = .001) weeks for the PANSS general psychopathology subscale scores.

In the amisulprid and aripiprazole subgroups, no statistically significant differences emerged when examining differences in psychosis symptom change in 52 weeks by the ITT-SSDs CT and no CT groups. Figures 3 - 5 shows change in psychosis symptom over time, by the CT and no CT groups within each medication subgroup. In the olanzapine subgroup, the ITT-LME models showed statistically significant differences in psychosis symptom change between the SSDs CT and no CT groups. The CT group showed less decrease in overall psychosis symptoms from baseline to 12, 26, 39 and 52 weeks (*p*-levels .005, .003, 046 and .031, respectively) compared to the no CT group. The CT group showed a total decrease in

overall psychosis symptoms of 21.1 points, whereas the no CT group showed a total decrease of 35.4 points over time (Δ *14.4; p*= .031). Furthermore, there were statistically significant differences in the psychosis symptom domains for those receiving olanzapine: less decrease in positive symptoms for the CT group at 26 weeks, less decrease for the CT group in negative symptoms at 12 weeks, and for general psychopathology symptoms the CT group showed less symptomatic decrease at 6, 12 and 36 weeks.

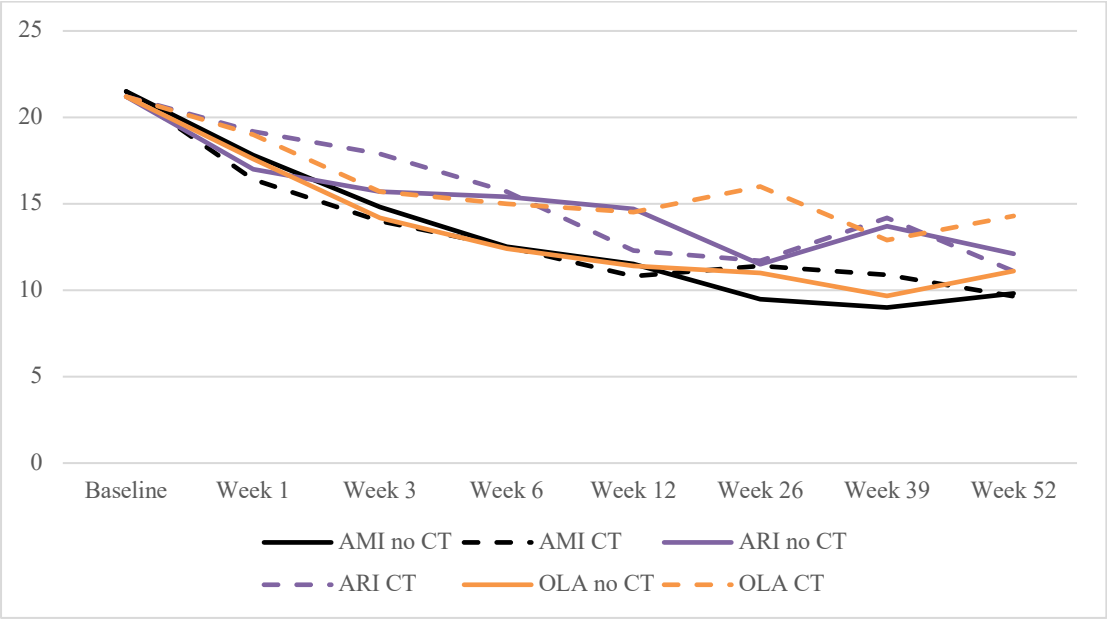

Figure 3 PANSS positive subscale scores by CT and no CT groups and antipsychotic medication

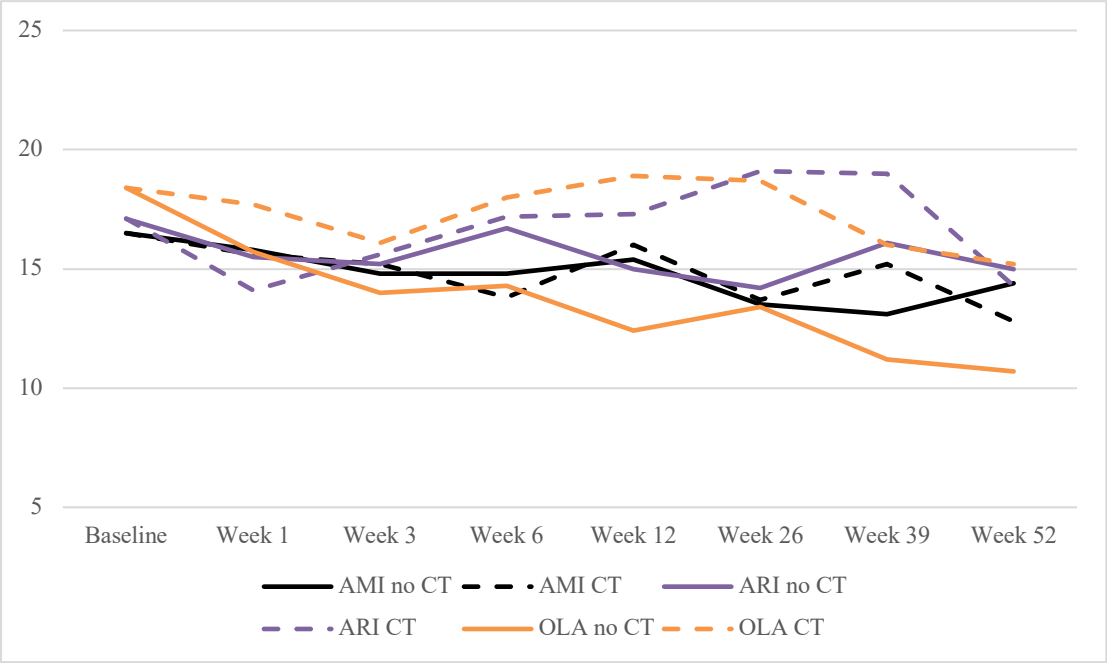

Figure 4 PANSS negative subscale scores by CT and no CT groups and antipsychotic medication

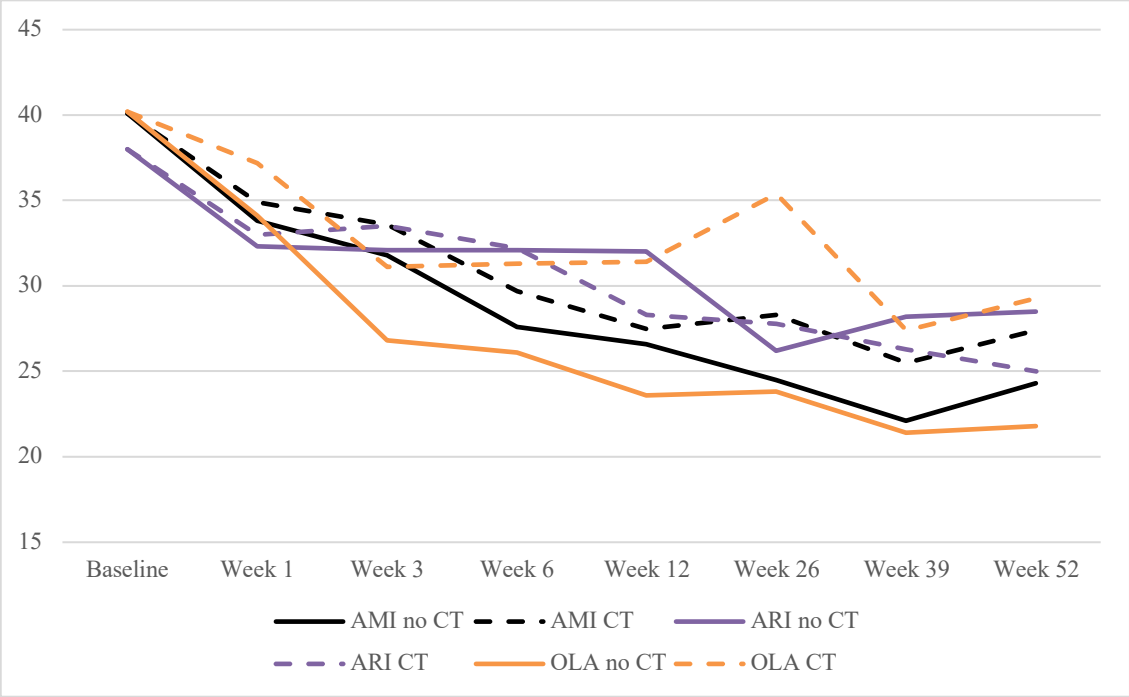

Figure 5 PANSS general psychopathology subscale scores by CT and no CT groups and antipsychotic medication

5 Discussion

5.1 Summary of main findings

The main findings from Paper I, II and III will be briefly summarized in Sections 5.1.1 to 5.1.3, then follows a more thorough discussion in Section 5.2 where findings will be discussed considering existing research and theories.

5.1.1 Paper I: Similarities of CT exposure in SSDs and SUDs

The comparison of the SSDs and SUDs groups in Paper I showed no group differences in terms of overall CT, and CT subtypes (physical, sexual, and emotional abuse, and physical and emotional neglect). There were no group differences between the SSDs and SUDs groups in terms of CT severity and number of CT reported. This indicates that the SSDs and SUDs groups in our study show similarities in self-reported levels of CT exposure, despite being grouped into different diagnostic categories. While there were no significant correlations between substance use measures and CT for the SSDs group, there were significant correlations between psychosis symptoms and CT in the SUDs group. Few previously published studies have investigated and compared levels of CT in SSDs to other severe

mental illnesses, such as SUDs. Our findings indicate that CT should gain clinical attention and be addressed for both SSDs and SUDs in routine clinical settings.

5.1.2 Paper II: Physical neglect predicted reduced attention/working memory abilities in SSDs

The main finding from Paper II was that self-reported levels of childhood physical neglect significantly predicted diminished attentional and working memory abilities in our sample of SSDs. There were no group differences between the CT and no CT groups in terms of general or specific cognitive functioning. No significant relations were found for the CT subtypes physical, emotional, and sexual abuse, and emotional neglect, and the cognitive domains. The analyses controlled for psychosis symptoms, antipsychotic medication (DDD), education, and gender. Our main finding indicates that the inconsistencies observed in the literature on CT and cognitive performance in SSDs may be explained by subtype of CT.

5.1.3 Paper III: CT is associated with a slower and decreased antipsychotic effectiveness in SSDs

There were differences in overall symptomatic change between the SSDs CT and no CT groups when examining specific follow-up points during 52 weeks of antipsychotic treatment, where the CT group showed less symptomatic change from baseline in response to treatment. The difference in psychosis symptom change in the CT and no CT group was however not significant at 52 weeks, but mainly evident at about 26 weeks of receiving antipsychotic medication. Thus, SSDs patients with CT could experience slower symptomatic improvement and less treatment effectiveness compared to SSDs patients with no CT.

For the amisulprid and aripiprazole medication subgroups, no differences in symptom change between the CT and no CT groups were observed at any time point. The SSDs CT group who received olanzapine showed less symptomatic improvement during the course of treatment and at endpoint, compared to the SSDs no CT group, especially for general psychopathology symptoms. The implication of CT on treatment outcomes in SSDs may be differentially related to type of antipsychotic medication received: When treated with olanzapine, SSDs patients with CT experiences could experience a slower symptomatic improvement as compared to SSDs patients with no CT.

5.2 Discussion points

5.2.1 Is CT specific to SSDs?

Firstly, the levels and frequencies of CT found in our SSDs samples are in line with what has been reported previously. In a sample of FEP, Pruessner et al. (2021) found that about 8.6 % reported 4 to 5 CT in the moderate-severe range. Vaskinn et al. (2021) reported comparable CTQ-SF median subscale scores in their Norwegian sample of SSDs, and our results show similarities to the CTQ-SF scores reported in a South African sample of first episode SSDs (Kilian et al., 2020). Over half of our sample reported experiences of more than one CT in the moderate to severe range, which lends support to the possible relevance of CT in SSDs. The past decade, evidence has accumulated to indicate a significant role of CT in increasing the risk for psychosis and SSDs (Varese et al., 2012), as well as influencing the clinical course and outcome, and possibly also a dose-response relationship between severity and number of adversities and severity of SSDs (Mondelli & Dazzan, 2019). Relatedly, statistical analyses have indicated that by removing or preventing occurrences of CT entirely, disorders of psychosis would be reduced by about 33 % (keeping other risk factors constant and assuming causality) (Varese et al., 2012).

Comprehensive theories and hypotheses for the development of SSDs following CT exposure have evolved the past decades as research has advanced across research fields. Psychosocial processes of interest have included insecure attachment style, dissociation, cognitive processes, dysfunctional or less available coping strategies, less social support, and revictimization (Chatziioannidis et al., 2019; Read et al., 2014). Biologically oriented research has focused on stress sensitivity and aberrant HPA-axis dysfunction, neurotransmitters, structural brain abnormalities, gene – environment interactions and psychoneuroimmunology and inflammation (Misiak et al., 2017). The traumagenic neurodevelopmental model launched by Read (2014; 2001) sought to integrate the suggested psychological and biological processes. The model was based on observed similarities between brains of traumatized children and brains of adult individuals with SSDs, such as a HPA-axis dysfunction, aberrant dopamine and/or seretonin functioning, and structural abnormalities (enlarged ventricles, hippocampal damage) (Read et al., 2014; Read et al., 2001). Relatedly, Popovic et al. (2019) outlined three possible pathophysiological pathways from CT to SSDs based on the neurodevelopmental hypothesis, the two hits/several hits model, and the diathesis-stress hypothesis: The neurobiological pathway (aberrations in the HPA-axis and the BDNF), a more genetically based pathway (implicating the COMT genotype, the FKBP5, the 5-

HTTLPR variant, the BDNF), and a pathway based on epigenetically focused evidence and research (hypomethylation of repetitive DNA sequences). Moreover, a unified framework for CT in SSDs was proposed by Misiak et al. (2017), drawing on research from epidemiology, and clinical, neuropsychological, and biological studies, suggesting pathways to psychosis through biologically based dysfunctions, such as DNA hypomethylation, the HPA-axis, the BDNF, various inflammatory mechanisms, structural brain alterations, or psychologically mediated mechanisms (cognitive schemas, affective and dissociative factors, and attachment styles). In sum, the number of research studies, meta-analyses, and reviews, as well as more theoretically oriented papers on CT in SSDs have expanded greatly since the 90s, now providing support for the relation of CT and SSDs, as well as theories on potential pathways underlying this relation. Early conclusions regarding CT in SSDs drawn by Read and colleagues (1997; 2005) were debated and criticized for using early and methodically weak research as a basis for a claim of causality (Bendall et al., 2008; Morgan & Fisher, 2007). The relation between CT in SSDs is probably quite complex, as highlighted by the range of different explanatory pathways and possible factors to consider: the HPA-axis involved in stress regulation, the BDNF neurotropic factor, as well as genetic factors and epigenetics, have been implicated as parts of the biological puzzle underlying the relation of CT in SSDs (Ciufolini et al., 2019; Mondelli et al., 2015; Aas et al., 2019). CT has been found related to positive but not negative psychosis symptoms, perhaps pointing towards interactions with different neurobiological mechanisms (Schalinski et al., 2019). There may be a differential vulnerability of CT by sex, as indicated by findings on male FEP patients exposed to CT who showed no improvement in functioning after two years as compared to female FEP patients (Pruessner et al., 2019).

Furthermore, high rates of CT, child maltreatment or adversities have also been reported for SUDs (Edalati & Krank, 2015; Garami et al., 2019; Lawson et al., 2013; Sacks et al., 2008), as supported by results from Paper I. Individuals with SUDs have reported comparable rates of CT experiences to what was found in our sample of SUDs (Mergler et al., 2018; Schaefer et al., 2010). CT in SUDs has been associated with negative clinical outcomes, such as higher drop-out rates, more comorbidities, and higher rates of relapse (Carliner et al., 2016; Dube et al., 2003; Hyman et al., 2008). The contribution of CT on the development of a vulnerability for SUDs has been reported for both alcohol abuse and illicit drug use (Moustafa et al., 2018). As in the CT – SSDs relation, the underlying explanatory pathways between CT and SUDs are not fully understood. An integrative review by Moustafa et al. (2018) outlined how rodent and human research on acute and chronic stress, such as CT

experiences, have indicated possible adverse effects on dopamine signaling and HPA-axis activity. The CT-associated HPA-axis dysfunction may increase the rewarding effects of drugs (Kreek et al., 2005), thus contributing to substance use. A study of cocaine dependent patients reported that childhood neglect was directly associated with a predisposition towards HPA-axis dysfunction indicated by higher serum cortisol levels, in those addicted compared to healthy controls (Gerra et al., 2008). Building on research indicating an adverse effect of maltreatment on brain development in areas such as the PFC, hippocampus, white and grey matter, and HPA-axis functioning, Edalati and Krank (2015) suggested that the CT – SUDs relation was mediated by cognitive impairments, such as aberrant executive functioning and reasoning abilities triggered by CT as susceptibility factors for SUDs. Furthermore, a vulnerability for SUDs has been associated with behavioral disinhibition in children whose parents were substance users (Kuperman et al., 2005). Growing up with parental SUD has been understood as a type of CT. Furthermore, based on the tension reduction theory, CT may be related to SUDs through emotion and stress regulation to achieve tension reduction, which in turn reinforces drug use (Cappell et al., 1987; Goldstein et al., 2010).

In sum, although CT may increase the risk for psychosis development, not all CT survivors develop SSDs, nor does all SSDs patients report CT experiences. Additionally, CT may be important in relation to other psychiatric disorders such as affective and anxiety disorders and SUDs: one third of the psychiatric disorders worldwide may be attributable to CT (Kessler et al., 2010). Paper I in this thesis indicates quite similar levels of self-reported CT exposure in SSDs and SUDs, which raises the question: Why does some CT-exposed individuals come to develop SSDs whereas others develop SUDs? There is a scarcity of research comparing CT in SSDs to CT in SUDs, and studies have yielded mixed results (Khan et al., 2020; Matzova et al., 2014; Someshwar et al., 2020). The relation of CT and age of onset of several psychiatric disorders, including SSDs and SUDs, was examined in families where several members reported psychiatric disorders (Someshwar et al., 2020). They found that the ACE score was associated with an earlier age of onset for OCD and SUDs, but not for SSDs, in contrast to previous literature. This may be explained by a higher heritability factor for SSDs than SUDs in this sample of affected families (Someshwar et al., 2020). Other studies have been inconclusive (Matzova et al., 2014). There are no existing overreaching explanations or theories delineating the relation of CT in both SSDs and SUDs. Using a latent variable approach, Keyes et al. (2012) examined the relation of CT to underlying internalizing and externalizing psychopathology and specific psychopathology in sample of 34 653 US adults. The CT – psychopathology relation was explained by associations between CT and

latent internalizing (mood disorders, anxiety disorders, PTSD) and externalizing (SUDs, antisocial personality disorder) dimensions rather than specific disorders. Sexual abuse was specifically associated with internalizing disorders, and there were possible differences between CT subtypes and the latent dimensions between men and women (Keyes et al., 2012). Although SSDs were not included in their analyses, it is possible that the internalizing – externalizing framework may shed light on our findings that corresponding rates of CT was reported in our samples of SSDs and SUDs. Moreover, research into CT in SSDs and CT in SUDs draws on research implicating CT in aberrant HPA-axis functioning, neurotransmitter signaling, and brain development (Misiak et al., 2017; Moustafa et al., 2018). Studies have indicated that CT subtypes may exert a differential effect on various aspects of SSDs (Schalinski et al., 2019) as well as in SUDs (Khan et al., 2015), or even interact with a preexisting genetic vulnerability in exacerbating psychopathology (Teicher & Samson, 2013).

Substance use has been commonly reported in SSDs and psychosis may occur in SUDs (Carretta et al., 2021; Degenhardt et al., 2018; Masroor et al., 2021; Nesvag et al., 2015), which could explain our findings. Patients with substance related disorders are prone to psychosis development, which may ultimately lead to SSDs (Niemi-Pynttari et al., 2013; Starzer et al., 2018). Clinical presentations and diagnostic categories are not static entities but prone to change and development, highlighting the complexity of the relation of CT in SSDs and SUDs. Furthermore, there may be clinical aspects related to CT, such as dissociative symptoms, that our study may have overlooked. Dissociative symptoms have been found to mediate the relationship between CT and psychosis symptom severity in clinical and non-clinical populations (Gibson et al., 2017; Schalinski et al., 2019). SSDs patients reported more dissociative symptoms as compared to SUDs patients, and significant correlations were found between measures of CT and dissociation (Khan et al., 2020). Furthermore, there may be differential effects of CT subtypes in SSDs or SUDs, depending on age of exposure, relation to perpetrator, interventions from child protective services, or length of the abuse or neglect, in support of applying a developmental perspective on how CT may contribute to the vast heterogeneity in subsequent psychopathology. A transdiagnostically focused study including SSDs and SUDs as well as mood and anxiety disorders, lend support to the potential importance of type and timing of adversities: more severe symptom load were related to earlier onset and duration of CT. Moreover, the occurrence of neglect between 4 to 5 and 8 to 9 years of age was emphasized as potentially important for a boosted vulnerability for psychopathology (Schalinski et al., 2016). Our results may thus be understood in line with a view of CT as a general vulnerability factor for adulthood psychopathology (Jaffee, 2017),

leaving the specifics for what exactly determines the outcome in terms of type of illness(es) unknown to date.

5.2.2 Physical neglect is involved in cognitive impairments in SSDs

Paper II adds new evidence to the field of CT and cognitive performance in SSDs. Firstly, our findings are in line with extant research, where results have been inconclusive regarding whether CT may be related to general or specific cognitive deficits in SSDs (Dauvermann & Donohoe, 2019; Vargas et al., 2019; Aas, Dazzan, et al., 2014). In a study by Ucok et al. (2015) the significant association between CT subtypes and cognitive domains were no longer evident when examining the CT total scores, which is in line with our findings. Our results are also in line with other research implicating CT in decreased attention and working memory abilities in SSDs (Kasznia et al., 2021; Li et al., 2017; Schalinski et al., 2018).

Our results indicate that parts of the heterogeneity and discrepancy in previous research may be explained by examining specific subtypes of CT such as physical, emotional, or sexual abuse, and physical and emotional neglect. Extant research has varied in terms of focusing on either overall CT or specific CT subtypes in relation to cognitive deficits (Dauvermann & Donohoe, 2019). This differentiation may be of importance. CT subtypes emotional and physical abuse were differentially related to SSDs in comparison to bipolar disorders (Etain et al., 2010), and physical and emotional abuse, and physical neglect, were found to be associated with executive functioning and working memory in ultra-high risk samples (Li et al., 2017; Ucok et al., 2015). The type of CT and timing of exposure have been associated with aberrant brain functioning and psychosis symptom dimensions (Schalinski et al., 2019), as well as aspects of cognitive impairment: physical abuse at 3 years of age was associated with dysfunction in attention, learning and working memory in an exploratory study of SSDs (Schalinski et al., 2018). Our results indicate the potential of childhood physical neglect to influence negatively on the developing brain, as shown by the relation to reduced attentional and working memory performance in adulthood SSDs. Physical neglect as measured by the CTQ-SF concerns not having enough to eat when growing up, wore dirty clothes, parents were ‘high’ or drunk, and not being taken to the doctor (Bernstein et al., 2003). Physical neglect is deemed a commonly reported type of maltreatment (Stoltenborgh et al., 2013), and was in a general community sample associated with increased odds for hallucinations and delusions (Stickley et al., 2021). However, physical neglect was found to be more strongly related to cognitive impairments in bipolar disorder as compared to SSDs in a study by Aas, Steen, et al. (2012), highlighting the potential complexity of the relation.

They did however only control for age, gender, and general IQ, and not for symptom load, antipsychotic medication, or education, which could have influenced the results. Childhood neglect in general as well as its impact on psychoses and SSDs is indeed understudied (De Bellis et al., 2009; Stickley et al., 2021). Neglect may be a marker of parental vulnerability contributing to a diminished ability to provide adequate care for their children (Hornor, 2014). Psychiatric comorbidities, such as mental health disorders (primarily non-psychotic illnesses) and SUDs have been reported in families involved in maltreatment, including childhood neglect (De Bellis et al., 2001). Neglect has further been associated with less financial resources in the family, as well as parental physical health problems and cognitive, mental and substance use related challenges, possibly contributing to an impaired understanding of what constitutes adequate care (Hornor, 2014). Indeed, cognitive impairment in parents was tied to childhood neglect and partially explained by parental non-cooperation with child protective services, mental health issues and low social support (McConnell et al., 2011). Cognitive impairments and substance use have been reported as risk factors for SSDs, and may be understood as potential parental vulnerability factors associated with the risk of neglecting their children, which may ultimately contribute to psychosis liability in some individuals exposed to CT.

The SSDs sample in Paper II performed somewhat better as compared to previously reported cognitive performance in SSDs of about 1 to 2 SD below the population mean (Schaefer et al., 2013). This discrepancy may relate to timing: whether the cognitive testing was conducted at baseline in the acute phase of illness, or as in the present sample three months or later after treatment initiation. The level of cognitive performance in the current sample may thus be understood as related to illness improvement, in line with research indicating that cognitive abilities in SSDs are subject to change throughout the course of illness and may improve as treatment with AAPs is commenced (Anda et al., 2021; Bortolato et al., 2015). Furthermore, we did not have information on parental educational level or cognitive abilities which could have influenced our results. Educational levels in the parents has been found related to education in their children (Ardila et al., 2005). We controlled for the patients' years of education, which has been found related to parental involvement (Huat See & Gorard, 2015) and could be an indicator of childhood neglect. Unfortunately, we were not able to examine the age of exposure to CT, which in previous research was reported as influencing the lower scores on attention in SSDs (Kasznia et al., 2021). The authors also reported a possible differential impact of CT on cognition in SSDs, which is in line with our results. Furthermore, we did not control for illegal substance use, which has been previously

found to influence cognitive performance in SSDs. There were however no significant differences between the two groups when compared on substance abuse measures, which was our main indication for the included covariates.

5.2.3 Should CT influence the choice of antipsychotic medication in the treatment of SSDs?

Our results on CT and APs in SSDs are in line with reports from a recent meta-analysis, where CT was related to treatment outcomes in adulthood SSDs, although the size of the association was small (Thomas et al., 2019). High rates of CT exposure in SSDs have been previously reported as associated with less likelihood of receiving remission (Kilian et al., 2020; Pruessner et al., 2021), in addition to slower improvement rates (Aas et al., 2016). More CT experiences were reported in SSDs patients characterized as treatment resistant as compared to those responding to treatment (Hassan & De Luca, 2015). Our findings are also consistent with research on CT and treatment outcomes in depressive disorders (Nikkheslat et al., 2020).

Considering CT in relation to the treatment of SSDs has been supported by a meta-analysis of recent research (Thomas et al., 2019). However, the contribution of CT to treatment outcomes in SSDs are equivocal, complicating the interpretation of clinical significance. For instance, no significant associations were reported for CT and psychosis symptom improvement, nor was CT related to likelihood of remission in a sample of FEP (Trotta et al., 2016). Further, CT was not related to a differential course of symptoms over three years in a SSDs CT group compared to the no CT group (van Dam et al., 2015). However, information about treatment (psychosocial or pharmacological) was not included nor accounted for and could have influenced the results. Some of the inconsistencies in the literature may relate to challenges in differentiating the impact of CT on general illness outcomes from the impact of CT on the effectiveness of antipsychotic medication more specifically. For instance, CT has been associated with lower levels of education and higher symptom load (Ajnakina et al., 2016; Cotter et al., 2015), as well as earlier age of illness onset (İngeç & Evren Kılıçaslan, 2020) and a longer DUP (Broussard et al., 2013), all of which have also been tied to a less favorable response to antipsychotics (Bozzatello et al., 2019; Cavalcante et al., 2020; Immonen et al., 2017; Penttila et al., 2014). CT was further associated with receiving higher doses of antipsychotic medication which was interpreted as a possible indicator of a reduced effect of antipsychotic medication (Kilian et al., 2020). An increased risk for a less favorable response to treatment may also depend on previous

exposure to antipsychotics (Bozzatello et al., 2019). CT has thus been related to aspects of SSDs associated with worse treatment outcomes. Our analyses accounted for these variables in an effort to disentangle and clarify the relation between CT and antipsychotic effectiveness.

We did however not control for treatment adherence by including serum levels in the analyses and cannot rule out that SSDs patients reporting CT showed less antipsychotic effectiveness due to non-compliance. CT was one of several factors identified as predictors of non-adherence in individuals with early psychosis (Lecomte et al., 2008), and non-adherence was found related to a range of poorer long-term outcomes in SSDs including hospitalizations and suicide risk (Novick et al., 2010). No differences were however identified between participants in the CT and no CT group in our data in terms how long they participated in the study, which was until about 26 weeks, after which there was more uncertainty. Moreover, inconsistencies in the literature may stem from variations in CT assessment instruments and non-standardization of treatment in extant research (Kilian et al., 2020). Our study used the CTQ-SF, which makes our results comparable to studies from other research groups using the CTQ-SF. The AP treatment with either amisulpride, aripiprazole or olanzapine was standardized in a natural setting, and participants were followed at eight time points throughout 52 weeks after treatment initiation ensuring continuity in measures of symptomatic development and change.

To date, most research on antipsychotic medication has been focused on examining antipsychotic effects and side-effects, as well as on comparing the different FGAs and SGAs related to overall psychopathology or symptoms in psychosis and SSDs (Geddes et al., 2000; McCutcheon et al., 2021). Superiority between the different FGAs and SGAs (non-clozapine) has not been adequately resolved, and personalized recommendations for treatment with APs in SSDs are lacking. Consequentially, the potential impact of CT on AP treatment outcomes is understudied, and especially so when considering potential antipsychotic within-group differences. Adding to the scarce literature, the results from Paper III indicate that SSDs patients with CT who received olanzapine experienced reduced antipsychotic effectiveness, as shown by less symptomatic change during the course of treatment. If replicated in larger samples, our findings could be of clinical relevance in the quest for establishing guidelines for personalized treatment recommendations, and in making clinical treatment decisions in SSDs. Personalized medicine is an area in which pharmacological treatment of SSDs has a long way to go as compared to other areas of medicine, such as oncology (Ozomaro et al., 2013). Recognizing that the treatment effectiveness may relate to individual physiology and

vulnerability, and optimizing treatment based on this knowledge, could impact on morbidity and mortality rates in severe mental illnesses such as SSDs (Ozomaro et al., 2013).

In sum, while CT as a risk factor for developing psychosis has been quite extensively researched (Bendall et al., 2008; Varese et al., 2012), the literature on CT in relation to clinical outcomes is less researched and the results have shown inconsistencies. The reason for this discrepancy is unclear. However, SSDs have traditionally been viewed as biologically based mental disorders where environmental factors have played a small role in the etiology and development (Thomas et al., 2019). Furthermore, the methodological quality and scientific rigor of research on CT in SSDs have improved the past decade, which may be one piece of the puzzle. Studies to date have included larger sample sizes, and additionally, more extensive use of validated and reliable CT assessment instruments as compared to the early research. In sum, the scientific quality and possibly also the research interest in the potential contribution of CT in clinical and treatment features in SSDs have increased.

5.3 Methodological considerations

5.3.1 Study design

As compared to the more strict and artificial settings of RCT efficacy trials, the BeSt InTro was designed as a pragmatic trial which sought to examine the AP treatment effectiveness in routine clinical settings. The design included a longer follow-up period and consisted of a more diagnostically heterogenous sample as compared to efficacy trials. The longer follow-up may however have boosted the risk for higher drop-out rates. Recruitment and selection procedures were designed to ensure representativeness by using a two-step inclusion: A diverse sample with acute psychosis or diagnosis within the SSDs were included in an observational cohort, from which eligible candidates for the RCT were selected and offered participation. A total of 359 patients were assessed for eligibility, whereas 144 patients enrolled and were randomly assigned to one of the three study drugs, amisulpride, aripiprazole or olanzapine (Johnsen et al., 2020). The randomized design was a strength of the BeSt InTro study, as potential differences such as medication cross-taper periods or wash-out periods, should be randomly distributed in the three medication subgroups. A further strength was the industry-independent funding of the BeSt InTro trial, limiting bias related to industry sponsorship as SGA trials sponsored by pharmaceutical companies have tended to find the sponsored drug outperform the competitors comparison drugs in almost 90 % of the studies (Heres et al., 2006).

Furthermore, while the study raters were blinded to study drug allocation, the attending physician or psychiatrist initiated the treatment with the assigned study drugs and additional medication (except concomitant antipsychotic drugs) according to standard clinical practice. This may have increased the generalizability of our results to clinical settings, although being associated with scientific disadvantages such as the possibility of the rater being unintentionally informed of the study drug. Although double-blind randomization has been associated with methodological strengths, this would have violated the intended pragmatic design of the BeSt InTro, in addition to being more costly and resource demanding than the rater-blind design. However, in both rater-blind and double-blinded trials, the raters and psychiatrists may guess or deduce the randomized drug based on expected effects or side-effects due to different receptor profiles. Blindness was however ensured as the research team did not assess the medical charts during follow-ups, nor did they observe medication allocation.

Regarding recruitment procedures, there may be a conflict when the therapist or psychiatrist invite the patient to participate, as a therapeutic relation and alliance already exist between the patient and therapist. The patient may feel that participation is mandatory to 'please' the therapist or decline participation due to paranoia towards health care in general or suspiciousness towards the therapist. In the BeSt InTro however, potential study participants were approached by researchers who provided information about study participation and obtained informed consent independent of the therapist in charge of treatment. The therapists ensured patients' competence to understand verbal and written information about the study and to provide informed consent.

The antipsychotic medications chosen for the BeSt InTro were AAPs that differed in terms of pharmacological properties. We did not include an FGA or TA comparison drug(s), which limits the comparison to previous research on FGAs. However, the purpose was to perform a head-to-head comparison, for which the design was well suited. The clinical decisions concerning APs was left to the psychiatrist or attending physician in cooperation with the patient, in line with the pragmatic design. Consequentially, there could be differences in wash-out periods or dosages that could have influenced the results in Paper III, however this should have been randomly distributed. Antipsychotics DDD was controlled for in the primary analyses in Papers II and III, and no significant differences were found when comparing the mean DDD between the CT and no CT groups.

Control group

A limitation in Paper I was the lack of a healthy comparison group, which could have shed light on the differences in CT severity and frequency between clinical groups with severe mental illnesses and the general population. However, as this approach has been quite extensively researched already, we specifically wanted to test two clinical groups with severe mental illnesses not thoroughly researched in terms of CT exposure. A healthy control group could have been useful for Paper II as well, in terms of examining the differential relation of CT to cognitive performance in SSDs relative to healthy controls. However, as the cognitive test scores were converted to standardized t-scores with a population mean of 50, this enabled interpretation of the level of cognitive performance in our sample of SSDs. The BeSt InTro study did not include a placebo control group, which has been described as the gold standard for assessing efficacy and effectiveness. However, this is financially more costly and perhaps ethically questionable since the antipsychotic effect in the acute phase of illness for many patients is highly efficacious. Consequentially, including acutely ill patients and not offering the recommended treatment would be ethically questionable. Finally, including a placebo group would have been at odds with the pragmatic design, as this is not an option in clinical practice. An alternative could have been to include SSDs receiving treatment as usual from a different recruitment site as a control group, but since the most widely used and recommended AAPs were a part of the BeSt InTro drug trial, the potential scientific gains would have been minimal.

5.3.2 Inclusion and exclusion criteria

Inclusion criteria in the BeSt InTro were broad, in line with the pragmatic design, with homogeneity and rigor as a trade-off for increased ecological validity. Differences in inclusion criteria between the projects, for instance that the age limit was 15 years or older in the Trauma and adult mental health study and 18 years or older in the BeSt InTro, could have contributed to unwanted demographic differences in the samples in Paper I. Hence, the matching of age and gender was deemed important. Using the PANSS as assessment of psychosis is considered gold standard in SSDs research. A score of ≥ 4 points on the PANSS used for inclusion in the BeSt InTro study has been widely used as criteria for psychosis threshold in clinical trials.

Moreover, most of the acutely ill patients who were able to provide informed consent and were eligible for receiving oral drugs were offered participation (in addition to adhering to the other inclusion and exclusion criteria described in Section 3.1.2) in the BeSt InTro

RCT. Consequentially, highly ill patients who were not able to provide informed consent or needed depot or long acting injectable or were receiving clozapine, were excluded from the study and thus our results may not be generalizable to this patient group.

Regarding the cognitive testing described in Paper II, patients assessed as too ill to cooperate or suffering from mental retardation were not tested, and the results may not generalize to this group. According to protocol notes, a minority did not complete neuropsychological testing due to mental retardation or inability to cooperate. Also, as research have indicated that more frequent and severe CT may be associated with increased symptom load and more severe disability in SSDs, we may not have captured the true frequency or severity of CT in highly ill SSDs or SSDs with comorbid mental retardation.

Unfortunately, there were no information in the BeSt InTro on cooccurring psychological interventions or psychotherapy such as trauma-focused CBT in addition to treatment with antipsychotic medication, which may have influenced the results. However, this should be evenly distributed among the randomization groups. Also, we do not know whether the included SSDs or SUDs patients experienced interventions from child protective services growing up, which possibly could have influenced the rates of CT exposure.

5.3.3 Sample

Important for the interpretation of the results from Paper I is that the samples were drawn from different research projects, where the diagnostic and assessment procedures differed, except for the CTQ-SF. This precluded a stricter statistical control for potential confounders, and some degree of symptomatic overlap between the samples cannot be ruled out. The SSDs sample may have included individuals with a previous diagnosis of substance induced psychosis or SUD, and the SUDs group included individuals with a psychosis proneness or previous diagnosis within the SSDs. In the absence of corresponding assessment instruments, the SCL-90-R Psychotisism subscale was used to describe psychotic symptoms in the SUDs group, whereas the AUDIT and DUDIT described substance use in the SSDs group, and these measures were correlated with the CTQ-SF scores. While the CTQ-SF scores were unrelated to alcohol and drug abuse in the SSDs group, the SUDs group showed associations between CT scores and psychosis-like symptoms. The psychoticism scale has been criticized for being heterogenous, however possibly capturing psychosis-like experiences (Olsen et al., 2004; Pedersen et al., 2016). Moreover, neither substance abuse nor suicidality were exclusion criteria for inclusion in the BeSt InTro study, which could be a challenge when making comparisons to the SUDs group, but also a strength in increasing the ecological validity from

the BeSt InTro as substance use and suicidality is commonly reported in SSDs (Cassidy et al., 2018; Hunt et al., 2018). A strength in Paper I was that the samples were matched on age and gender to ensure demographic homogeneity in the SSDs and SUDs samples.

There were different reasons for the variation in the SSDs sample sizes in Paper I, II and III. The Paper I SSDs (n = 57) and SUDs (n = 57) study was conducted when the data collection in BeSt InTro was ongoing, hence the number of patients with complete CTQ-SF data to compare to the SUDs group was limited. Additionally, the samples were matched on age and gender, further limiting the sample sizes. The BeSt InTro data collection was completed by December 2018, thus for Paper II and III we had access to a larger pool of potential participants. However, in Paper II, the sample size was constrained by the requirement of data from both the CTQ-SF and the comprehensive cognitive test battery. Both RCT and cohort participants were included in the SSDs samples in Paper I and II to achieve a larger number of participants. In Paper III, the SSDs patients were selected from a total sample of n = 144 RCT participants, of which n = 98 of those had complete CTQ-SF data. A thorough investigation of the data indicate that those with missing CTQ-SF data had no CTQ-SF scores at all. Some seems to have missed out on the 6 weeks visit when the CTQ-SF was administered, whereas others dropped out from the study entirely. We have not identified systematic patterns or reasons underlying the CTQ-SF missingness, suggesting that the data were missing at random or completely at random.

Representativeness

Representativeness of the samples could be debated, which is common in all studies not adhering to random selection. There may be differences between those agreeing or declining participation that could have shed light on the research questions, such as general attitudes towards health care, degree of illness, previous experience with the health care system or antipsychotic medication, or lack of social support from family and friends. Furthermore, the mean age of all samples (see Table 1) was about 30 years, thus limiting knowledge about younger patients with memories of potential abuse or neglect closer in time to the illness debut, as well as older SSDs patients. However, there were no upper age limit for inclusion to any of the studies. Ethnicity was primarily white, ethnic minorities in the BeSt InTro were about 6.7 %, and the majority was male. As inpatients and outpatients from multiple sites in Norway as well as in Austria were included, this ensured representativeness within the sample. Nevertheless, our findings may not generalize to different cultures and low- or middle-income countries.

A strength of the sample selection pertains to the official health care system in Norway such as emergency rooms and acute psychiatric wards, which is free and available to everyone in need of care, limiting potential selection bias related to public and private health care. The samples were recruited from urban catchment areas in Norway and Austria, limiting the knowledge from more rural settings. Possibly, factors such as access to treatment when acutely ill and treatment adherence differs in areas where access to care is limited or distanced from where the patient resides. The gender distribution of about 60% males and 40 % females in all the samples is in line with previous research on SSDs (Ochoa et al., 2012), as well as demographic descriptions from the EUFEST and CATIE trials (Czobor et al., 2015). When grouped by CT and no CT, the gender distribution in the current thesis changed, as shown by the decreased percentage of males in the CT group (42 % in Paper II; 56 % in Paper III). Furthermore, Paper I showed that females irrespective of patient group reported higher CTQ-SF scores as well as more frequent and severe CT experiences as compared to the male patients, again in line with previous research (Felitti et al., 1998).

5.3.4 Drop-out

In the Trauma and adult mental health study, no one dropped out from the initial assessments. The BeSt InTro study suffered from significant drop-out rates, as often occurs in drug trials. Statistical procedures were conducted to keep most participants in the analyses. We do not know whether data from drop-out-patients would have altered the results. Although not allowed for in the BeSt InTro, it would have been interesting to interview those deciding not to further participate in the study. Preferably, information on reasons for dropping out would be included in study notes, however such information was unknown. As dosages, concomitant medications and switching of antipsychotic drugs were decided in cooperation between the psychiatrist and the patient, this may have increased motivation for participation during the study period as compared to more rigorous RCT designs. Also, the BeSt InTro allowed for contact or reminder ahead of scheduled follow-up, to ensure participation. Drop-out may nevertheless be a source of bias. Motivation to participate may have decreased due to illness improvement, absence of improvement and losing faith in the treatment regime, persistent paranoia, persistent drug use or abuse, or illness-unrelated life circumstances.

5.3.5 Assessment

The research personnel and raters were blinded to the allocated study drug in the BeSt InTro. As the Trauma and adult mental health study was cross-sectional, rater blindness was not

relevant. For the BeSt InTro, those performing PANSS assessments attended rater reliability training by the PANSS institute (see https://panss.org/services-training.php for information) and were certified PANSS raters before performing study assessments, ensuring reliability. Valid and reliable diagnostic assessments were ensured in the BeSt InTro by using the SCID based on the DSM-system, which is commonly used as a diagnostic tool in clinical studies. Diagnoses were converted to the ICD-10 equivalents. A limitation is that the diagnostic process used for the SUDs in the Trauma and adult mental health study was left to the therapist's discretion and is unknown. However, using the MINI (Sheehan et al., 1998) or SCID (Spitzer et al., 1992) is routinely used for diagnostic assessments in clinical practice in the official health care system in Norway, making this a reasonable assumption but limiting the diagnostic reliability of the SUDs group in Paper I.

Drug and alcohol use in the BeSt InTro was assessed by self-report using AUDIT or DUDIT (Paper I and II) and clinician-rated using the CAUS and CDUS (Paper III). These measures yield different type of knowledge on self-reported as compared to clinician assessed substance use, abuse, or dependency in the included patients. The AUDIT and DUDIT results as described in Paper I and II indicated levels of self-reported alcohol and substance use that were in the lower range of indications of medium alcohol problems (scores 8 – 15) and below threshold for suspecting substance dependence in high risk groups (scores above 20 to 25) (Babor et al., 2001; Berman et al., 2005). In comparison, the CAUS and CDUS were developed to assess substance abuse and dependency in persons with severe mental illnesses while considering multiple sources of information. The categories in the CAUS and CDUS were based on the diagnostic criteria for substance abuse and dependency in the DSM-III-R (American Psychiatric Association, 1987; Mueser et al., 1995). In Paper III, about 5 % (no CT group) to 13 % (CT group) of the of the sample were rated as alcohol abusers or dependent, and 25 % (no CT group) and 19 % (CT group) were rated as illicit substance abusers or dependent. This was somewhat lower than alcohol and substance use described in the CATIE trial where about 60% were found to use any substances (Swartz et al., 2006), however we did not include substance use without impairment, which probably would have boosted the percentage of alcohol and substance use in our sample. In more strict efficacy trials, substance use often is an exclusion criterion. Allowing comorbid substance use increases the representativeness of the SSDs sample but complicates the interpretation of the CTQ-SF results when compared and contrasted to the SUDs group. A potential limitation was the lack of reliability training for other assessment instruments or cognitive testing besides the PANSS. Symptoms of PTSD or dissociative symptoms were not assessed, which have been

launched as potential mediators in the relation between SSDs and SUDs. Moreover, there are several methodical and ethical challenges defined by using retrospective self-report assessment of CT in SSDs, which is elaborated upon in Section 5.3.6.

Assessment of cognitive functioning were performed by experienced and qualified health personnel, either research nurses or clinical psychologists. The BeSt InTro used a customized neuropsychological test battery, designed to tap into cognitive domains with clinical utility for SSDs, and to be able to obtain an overall neuropsychological profile. All tests included have been commonly used in research on cognitive performance in SSDs and found to possess sound psychometric properties (see Table 2). As an alternative, we could have used a consensus-based test battery, such as the MATRICS Consensus Cognitive Battery (MCCB) (Kern et al., 2011; Nuechterlein & Green, 2006; Nuechterlein et al., 2008). There was however overlap in the included tests used in the BeSt InTro and the MCCB.

5.3.6 Retrospective CT assessment

There are several challenges for research on CT in SSDs. Some questions pertain to the measurement instruments and psychometric properties, in addition to potential obstacles identified at a human level (such as illness-related factors or memory bias). At the study-design level the pros and cons of longitudinal and retrospective studies are frequently debated, often in favor of a prospective and longitudinal design. The knowledge on CT in general and for SSDs, derived from retrospective research, has been and continues to be the object of skepticism and debate. The present thesis has been based on retrospectively collected data on CT in SSDs using the CTQ-SF self-report instrument (Bernstein et al., 2003). One of the challenges in CT research concerns the variability of measures and assessment instruments, making comparisons and aggregation of data between studies quite challenging. The CTQ-SF is to date one of the most widely used tools for assessment of CT worldwide: in general populations (Viola et al., 2016) and in SSDs (Jiang et al., 2018), and by using the CTQ-SF, our data is available for comparison to other research. Clinical interviews are considered a viable option to retrospective questionnaires, and there are several clinical interviews used for CT assessments (Saini et al., 2019). Some respondents may find it easier to answer direct questions from a therapist and being asked questions may elicit cues and aid in remembering (Spinhoven et al., 2014). In research settings with an unknown interviewer disclosure of CT could be more difficult. Incidentally, people have tended to prefer self-report as compared to face-to-face questioning about sensitive subjects (DiLillo et al., 2006). Moreover, the CTQ-SF was found to be more sensitive in detecting maltreatment compared to the CTI, and it has

been recommended to administer a self-report questionnaire to screen for potential CT, followed by a more thorough interview to obtain more details regarding the maltreatment (Spinhoven et al., 2014). In terms of time-constraint and budget, using a less invasive questionnaire as compared to an interview may be favorable in a research setting.

Furthermore, concerns and criticism have been raised about the validity and reliability of retrospective and self-reported information on CT from people with severe mental illnesses (Susser & Widom, 2012). Self-report of CT may be precluded by memory processes (forgetting), lack of awareness and bias due to depression or other affective states (Dube et al., 2004; Tolin & Foa, 2006). Estimates of rates of CT may be prone to uncertainty – are respondents underreporting or overexaggerating childhood adverse events? Overreporting of CT in patients with mental illnesses has been suggested (Colman et al., 2016). However, underreporting of CT is common and possibly a greater risk than overreporting (MacDonald et al., 2016; Maughan & Rutter, 1997; Read et al., 2005). On the other hand, individuals with mental health issues may be prone to search for causes of their suffering, possibly leading to inflated estimates of prevalence (Susser & Widom, 2012). To ensure reliability and validity from retrospective recall of abuse and neglect, efforts have been made to corroborate the information from that of independent records, such as parental reports or official documents (convergent validity) and compare similarities in ratings to a different assessment instruments than the self-report instrument (concurrent validity) (Gayer-Anderson et al., 2020). A study by Fisher, Craig, Fearon, Morgan, Dazzan, Lappin, Hutchinson, Doody, Jones, McGuffin, et al. (2011) found that psychosis patients reports of CT were similar as compared to two different assessment instruments, and the retrospective reports were convergent with that of independent clinical case notes. Further, the reports of abuse or neglect made by psychosis patients were stable over time (test-retest reliability) (Fisher, Craig, Fearon, Morgan, Dazzan, Lappin, Hutchinson, Doody, Jones, & McGuffin, 2011). An investigation of test-retest reliability (i.e., whether responses are consistent in the same individual at two different occasions) found good agreement in a sample of ACE study respondents (Dube et al., 2004).

Concerns have been raised about the impact of mood states and symptoms on the accuracy of CT recall (Brewin et al., 1993; Colman et al., 2016). Patients with SSDs and depression may view their childhood in a more pessimistic manner, compared to patients that do not suffer from comorbid depressive disorder. Although possible, the influence of symptom load on recall was however not supported by the Fisher, Craig, Fearon, Morgan, Dazzan, Lappin, Hutchinson, Doody, Jones, McGuffin, et al. (2011) study, where no impact of current symptom load was found for the reporting of child abuse. Reports of CT was found

to be stable in a sample of FEP with acute psychosis and the subsequent ratings provided when symptoms of psychosis were stabilized after about three months (Simpson et al., 2019). Positive symptoms were not correlated with CTQ-SF scores neither at baseline nor follow-up. Moreover, cognitive impairments, being a core feature of SSDs, may also obfuscate retrospective CT reports (Saykin et al., 1991). However, individuals experiencing lack of inhibition or decreased executive abilities may on the contrary be more likely to disclose such information, as memories of CT may be ridden with shame and efforts to avoid the memories may be great but require vast cognitive resources.

Moreover, there is an ongoing debate concerning study design in CT and SSDs research: why derive knowledge from cross-sectional retrospective studies if there is a possibility for the more ideal prospective and longitudinal study? While prospective measures gather information about CT at the time it actually occurs, retrospective measures involve inquiring about past events (Tajima et al., 2004). Prospective and longitudinal studies are described as preferable to cross-sectional studies using retrospectively collected data (Hardt & Rutter, 2004). Although longitudinal studies are deemed necessary for ensuring temporality in critical events to examine the possibility of causality between CT and psychopathology, the longitudinal design is not without its challenges (Gayer-Anderson et al., 2020). As SSDs are relatively low-frequent, longitudinal research is more costly and time-consuming relative to retrospectively designed research. One would require a large number of individuals to follow up over many years to be able to draw firm conclusions about CT and illness onset (Gayer-Anderson et al., 2020), and it may be challenging to maintain and locate the same individuals at follow up (Tajima et al., 2004). A prospective cohort study would thus aim to target CT exposed and non-exposed individuals at study outset before following the individuals over time (Susser & Widom, 2012). Most likely, children whose abuse or abuser have been identified in childhood, will be subjected to interventions bringing the abuse to a halt and hopefully improving their living conditions preventing further abuse and trauma. More often in CT and SSDs research however, prospective studies have relied on some degree of retrospective recall prior to the assessment of psychopathology (Susser & Widom, 2012). Additionally, asking about ongoing abuse in a family could be prone to difficulties, as the parents may not be aware or afraid of disclosing information in fear of being reported to the child protective services, and the children may be frightened into silence, and thus the accounts could be more or less intentionally inaccurate. In a sample of Norwegian survivors of childhood incest, the mean latency time, namely the time from the abuse started until telling someone about the abuse, was about 17 years (Steine et al., 2016). Furthermore, health

care personnel are ethically and legally obligated to report suspicions of ongoing abuse or neglect of children, thus probably (and hopefully) preventing both long-term massive abuse and more severe psychopathology. To describe and obtain knowledge on the adverse consequences of CT, retrospective data is necessary as the included adult participants often will have experienced a natural course without interventions, as the issue of mandated reporting probably was not raised. A review and meta-analyses identified 16 studies on CT and psychopathology that included both measures, and was able to examine the rate of agreement between prospective and retrospective measures of childhood maltreatment (Baldwin et al., 2019). The authors reported that agreement between the measures indeed was low, although somewhat higher if the retrospective measure was interview-based rather than a self-report questionnaire. About half of those with official records of abuse reported this retrospectively, and about half of the individuals retrospectively reporting of CT did not have documented official records of the abuse. It is possible that only the most severe cases of abuse were documented by official records. Prospective and retrospective measures may thus identify different groups of individuals (Baldwin et al., 2019).

Despite the expanding literature on CT in relation to psychopathology and severe mental illness, obstacles in research and clinical settings are related to the failure of clinicians to inquire about CT (Becker-Blease & Freyd, 2006; Read & Fraser, 1998), and this may especially be relevant for therapists in charge of severely ill individuals such as SSDs (Young et al., 2001). Especially neglect seems to be neglected in research, although probably being quite commonly experienced (Stoltenborgh et al., 2013). The past years, there has been an increasing attention to making inquiries about traumatic events a natural part of routine clinical settings, also for psychoses and SSDs (Norwegian Directorate of Health, 2013). However, what constitutes a trauma, or a traumatic event, may be highly variable and subjective. A traumatic event has by definition a subjective quality, meaning that an objective event such as participating during a war, or experiencing rape or physical abuse, is not necessarily traumatic for everyone. Survivors of sexual abuse may not perceive the sexual actions as traumatic or shameful until puberty or when they realize that such actions were not usually experienced by their peers or normal in other families. Interestingly, agreement between measures of CT was higher for ‘clear cut’ events such as death of a parent, possibly indicative of a subjective interpretation impacting on the heterogeneity of CT reports.

5.3.7 Statistical considerations

Paper I used Mann-Whitney U to compare the CTQ-SF scores, and Chi-square analyses to compare number/severity of CT. These analyses did not control for any confounding variables, thus there is some uncertainty as to what may have influenced the similarities and non-significant results between the two groups. Also, if the sample size was larger, significant group differences might have emerged. However, as sample sizes increases, so does the chance of Type I errors.

Linear multiple regression analyses were the primary analysis strategy used in Paper II, which allowed us to include relevant covariates. As the CTQ-SF sum score (mean of the subscale means) was omitted as predictor, the issue of multicollinearity was avoided. All analyses adhered to predefined requirements and assumptions underlying linear regression analyses, such as homoscedasticity, multicollinearity, normally distributed residuals, correctly specified model, appropriate functional form and influential cases (Mehmetoglu & Jakobsen, 2017). Included covariates were mainly demographic and clinical variables that differed between the CT and no CT groups, however the antipsychotics DDD was included based on the literature. There will always be other relevant factors that were not available to us and that might have influenced the results. The neuropsychological test scores were converted to standardized t-scores to facilitate comparison between the different tests and previously published research. No significant differences emerged when comparing the SSDs CT and no CT groups on the cognitive performance outcomes. Dichotomized CT scores (binary trauma/no trauma) or continuous CT scales have been inconsistently used in previous research (see Vargas et al., 2019). Paper II indicate these two approaches may yield differing results. Possibly, the continuous CT scales may be more sensitive in detecting nuances to cognitive performance scores in SSDs.

In Paper III the LME model were chosen as the primary analysis strategy, as it is well suited for handling missing data and non-independent data as is common in clinical trials. The LME analyses were based on the ITT group, meaning the patients were grouped into medication groups according to the medication they were randomized into and regardless of whether they switched medication or the extent of the treatment they received. MD was in the LME models assumed missing at random. However, whether the randomness was truly random is subject to uncertainty as information about reasons for dropping out is unknown. The high attrition rates in the BeSt InTro study have been thoroughly analyzed, and no systematic between-group differences been found for the APs (Johnsen et al., 2020). The attrition rate peaked at the last follow-up points as the study period stretched for 52 weeks.

The estimated slopes from the last follow-up points should therefore be interpreted with caution. The LME models are well suited for longitudinal studies, accounting for dependency in the data as the same individuals are measured at multiple time points. More complexity and perhaps less intuitive interpretation of the technique are potential limitations of the LME models, as compared to the 'simpler' comparison of means and regression analyses from Papers I and II.

The CTQ-SF

The CTQ-SF scores were categorized into none, low, moderate and severe levels of CT according to predefined cut-offs provided in the CTQ-SF manual by Bernstein and Fink (1998). This categorization was the basis for our CT and no CT groups, where none and low levels of CT was considered 'no CT' as some degrees of CT is commonly reported in the general population (Baker & Maiorino, 2010). By including low levels of CT in the no CT group and defining the CT group according to moderate to severe levels of CT, we aimed to obtain more sensitivity in discovering potential relations between CT and clinical aspects of SSDs. This is not to say that low levels of abuse or neglect are to be ignored, nor to undermine individual experiences of CT occurrences. In clinical settings, we recommend that all reports regarding CT abuse or neglect should be taken seriously and treated with respect. For the purpose of research settings, determining a cut-off could be viable for discovering patterns and relations in the data. Keeping independent variables continuous are however in many cases statistically preferable, and categorization has been associated with several issues (DeCoster et al., 2009). The dichotomization was performed according to recommendations in the CTQ-SF manual by Bernstein and Fink (1998), and since the aim was to examine group differences in SSDs.

There has been some psychometric research on the CTQ-SF where the initial five-factor structure proposed by Bernstein has been confirmed (Dovran et al., 2013; Spinhoven et al., 2014), whereas others advocate for an alternative model primarily based on uncertainty regarding the neglect subscales (Gerdner & Allgulander, 2009). Several studies have indicated that the CTQ-SF physical neglect subscale shows the lowest reliability and internal consistency (Gerdner & Allgulander, 2009; Jiang et al., 2018; Kim et al., 2013), possibly related to a theoretical vagueness related to the physical neglect construct (Spinhoven et al., 2014). Consequentially, physical neglect should be interpreted with some caution. However, most studies do confirm that the CTQ-SF possesses adequate psychometric properties despite some weakness related to the neglect subscales.

Missing data

Paper I, II and III used different techniques for handling missing data (MD). MD in the CTQ-SF in Paper I was handled by imputing each participant's personal subscale mean (PSM). PSM has been used for handling missing values in questionnaires (Peyre et al., 2011). Research has shown that although techniques based on multiple imputation (MI) may be the most accurate, the simpler PSM also performed adequately (Shrive et al., 2006). The CTQ-SF data in Paper II and III was analyzed by Little's Missing Completely at Random (MCAR) test, which indicated that data was missing completely at random. Following the MCAR results, MD was handled by using multiple imputation (MI) based on expectation maximation (EM). EM has been considered superior to listwise or pairwise deletion. Paper III used MI on the demographic and clinical variables included as covariates in the LME models in data to keep all participants in the analyses. Missing PANSS values were not imputed. Both MI and EM have been recommended for handling MD (Schafer & Graham, 2002). The LME models were performed also when participants with incomplete data were excluded, and the results of the analyses (imputed values Vs. not imputed values) did not differ. The different strategies for MD could be explained by an increase in statistical sophistication and progression as well as more knowledge acquired over the years working with the data, culminating in the LME modelling in Paper III. Furthermore, the amount of missing CTQ-SF data was about 0.73 % of all items, making the potential differences between imputation methods less likely to be of substantial influence on the results. An overview of the CTQ-SF data from Paper I, II and III show consistent means and SDs across the SSDs samples, suggesting that imputation techniques have not influenced our results. A more thorough discussion of theories underlying imputation and strategies for handling MD is beyond the scope of the present thesis.

5.3.8 Ethical aspects

Participation in the Trauma and adult mental health and the BeSt InTro was based on informed consent from eligible participants recruited from routine clinical settings. Informed consent lies at the foundation of conducting ethical clinical psychiatric research, and is cardinal especially when involving persons with decreased mental abilities such as cognitive impairments, or an impaired capacity for consent (Gupta & Kharawala, 2012). Obtaining a morally and ethically valid informed consent in persons with SSDs includes information sharing (study design, pros and cons, alternatives, right to withdraw), an assessment of the degree of decisional capacity, and voluntarism (choosing participation in the absence of coercion) (Anderson & Mukherjee, 2007). There is a possibility of diminished decisional

capacity in SSDs due to impaired cognitive abilities in some individuals (Carpenter et al., 2000) or the presence of debilitating psychosis symptoms such as impaired reality testing, paranoia, or disorganization. Capacity for granting informed consent requires an understanding of the information received about study design, risk and benefits, as well as the right to withdraw at any time, the ability to freely and without coercion reason about this information in the decision-making process in addition to communicating their choice (Gupta & Kharawala, 2012). The participants should also be informed about their choice not influencing access to care, which is crucial for ensuring voluntary study enrollment.

Further, capacity for consent may fluctuate (deteriorate or improve) and should thus be continuously evaluated during the research process. In Norway, decisional capacity in severe mental illness is part of routine clinical settings, and a cornerstone in assessment of voluntary or involuntary treatment of SSDs and other severe mental illnesses. Requiring informed consent in individuals with psychoses and SSDs have advantages in ensuring autonomy and motivation for participation, but also poses the risk of excluding the most severely ill whom is of great need of adequate care and thus knowledge about this population is indeed important. The possibility of withdrawing from study participation at any time, albeit being important in ensuring personal autonomy, poses the risk of sample bias, as information about reasons for withdrawal often is not known. This could be solved by allowing the research team to approach these individuals for a short interview about reasons for withdrawing in order to describe whether it was related to personal reasons, study characteristics, or illness related reasons such as paranoia or disorganization. However, being approached by the research team after voluntarily dropping out could also be perceived as distressing for participants.

5.3.9 Trauma research

Conducting trauma research requires ethical considerations related to the potential of inducing unnecessary distress. Trauma research should, as all clinical research, adhere to the principle of 'minimal risk' which describes that distress due to participation should not exceed what is normally encountered in daily life or as part of routine psychological or physiological assessments (Jaffe et al., 2015). Research has indicated that some participants experience immediate, albeit transitory, distress following trauma assessment in research, which often is followed by an experience of personal benefits outweighing the distress (Jaffe et al., 2015). Furthermore, studies using trauma interviews were associated with more distress as compared to self-report questionnaires (Jaffe et al., 2015). Existing research thus suggests that conducting CT assessment is safe and ethical but could have caused a transitory increase in

distress in our participants. Possibly, some may have disclosed information about previous trauma that has been unknown to the health care personnel in charge of treatment. Information on trauma exposure could then preferably be included and integrated in the clinical setting as part of trauma-informed care for individuals with SUDs or SSDs. Furthermore, obtaining evidence-based knowledge of the consequences of CT in relation to severe mental illness is important to ensure an optimal quality of care, and to reduce stigma in trauma survivors. The society's need for knowledge should be in balance with respect and autonomy for the participating individuals. No one dropped out during the assessment period in the Trauma and adult mental health study, where the overall aim was to investigate traumatic experiences in high-risk individuals, indicating that the CTQ-SF was well tolerated. In the BeSt InTro, assessment of CT was secondary to the overall aim of comparing antipsychotic effectiveness and drop-out rates could have been influenced by several reasons not pertaining to the CT assessment.

6 Conclusions and clinical implications

An important clinical take home message and implication from this thesis is that assessment of CT should be of priority in clinical settings. Clinicians should be aware of possible CT exposure in patients with SSDs and SUDs, and that for some patients with SSDs, exposure to CT may have implications for clinical presentations and outcomes. Preferably, inquiring about CT should be considered as a routine part of clinical assessments and case conceptualizations, in line with patient perspectives on the need of therapeutic approaches for framing psychosis symptoms in the context of previous life experiences (Corstens et al., 2014). Furthermore, previous research has indicated that the co-occurrence and interrelatedness of CT subtypes is quite common, which was supported by our studies. The findings from the present thesis underline the importance of broadly assessing subtypes of CT to capture the nuances and severity of exposure, in comparison to single CT measures.

Results from Paper II indicated that SSDs patients with exposure to physical neglect may show decreased cognitive performance in the domains of attention and working memory abilities. Attention is involved in detecting relevant and salient information to be encoded and processed, whereas working memory enables the person to hold a small amount of information in mind while performing a task (Eack, 2012). Thus, in addition to the more general neurocognitive vulnerability often seen in SSDs, CT may add to the burden. In clinical settings, some SSDs patients may profit from additional cognitive aids, such as being aware of repeating important information as often as needed, perhaps obtaining consent to

involve their primary care persons such as family or general practitioner, as well as providing written information about illness and treatment, and making use of smart technology to remember appointments (Norwegian Directorate of Health, 2013).

Moreover, not all SSDs patients respond favorably to antipsychotic medication. As compared to other fields such as oncology, personalized medicine for antipsychotic medication in SSDs has a long way to go. The knowledge gap is vast in terms of predicting which personal, environmental, and physiological factors could influence AP effectiveness. Results from Paper III show preliminary support for the potential role of CT on antipsychotic effectiveness and treatment outcomes in SSDs, and possibly also a differentiated effect depending on type of AAPs. This finding has clinical relevance and importance, as antipsychotic medication is routinely recommended by guidelines and offered as treatment for SSDs in clinical settings (National Institute for Health and Care Excellence, 2014; Norwegian Directorate of Health, 2013). Interestingly, trauma-focused psychosocial interventions such as CBT have been found to improve outcomes in treatment-resistant patients (Sensky et al., 2000). Setting the scene for a focus on CT as part of the treatment strategy for some SSDs patients may augment the medication effectiveness.

To summarize the clinical implications from this thesis, the results are in line with and support recommendations from clinical guidelines that previous trauma should be addressed in SSDs patients (National Institute for Health and Care Excellence, 2014; Norwegian Directorate of Health, 2013). Firstly, an increased focus on trauma-informed care for individuals with SSDs is important considering that a psychotic episode or multiple episodes may in itself be experienced as traumatic (Gianfrancesco et al., 2019). Furthermore, the rates of CT found in our samples indicate the potential and utility for offering trauma-informed or trauma-targeted psychological interventions. Unfortunately, many SSDs patients are not asked about CT experiences in clinical settings, and psychologists and psychiatrists may in fact be less likely to inquire about CT if the patients are diagnosed with SSDs (Young et al., 2001), possibly related to fear of negative clinical side-effects. However, in a study of trauma-treatment in patients with PTSD and psychosis, trauma-focused treatment was neither associated with symptom exacerbation nor revictimization (van den Berg et al., 2016). Furthermore, acknowledging CT, and providing psychoeducation about consequences of traumas such as abuse and neglect in relation to SSDs, may facilitate aspects of the therapeutic alliance, which is a cornerstone in providing adequate treatment. Indeed, patients with SSDs have reported that CT experiences are important for understanding and conceptualizing their disorder, and that failing to assess CT during treatment may lead to

feelings of dissatisfaction (Lothian & Read, 2002). Possibly, the occurrence of comorbid PTSD in individuals with SSDs is underdiagnosed (de Bont et al., 2015), which could have implications for what is the optimal treatment and care. These challenges have been addressed for instance in TRauma-Integrated Psychotherapy for Psychosis (TRIPP), a trauma-informed approach for individuals with psychosis, previous trauma and post-traumatic symptoms (Bendall et al., 2018). The TRIPP model was developed to address trauma in early psychosis services and includes systematic trauma assessments as well as flexible intervention strategies based on evidence-based treatments for PTSD. An investigation of service-users experience of receiving trauma-informed care showed that although initially reluctant to approach traumatic memories, there were also a strong desire for change, and the relation to the therapist was deemed important (Tong et al., 2018). Relatedly, EMDR has been found a safe and viable treatment approach for cooccurring psychosis and PTSD, although more research is needed (de Bont et al., 2013; van den Berg et al., 2015).

6.1 Conclusions

Childhood trauma (CT) was frequently reported in schizophrenia spectrum disorders (SSDs) and substance abuse disorders (SUDs), as almost 65 % of the participants in both groups reported CT experiences in the moderate to severe range. The results from Paper I are in line with previous findings regarding CT in SSDs and CT in SUDs as investigated separately. Childhood physical neglect was in Paper II related to diminished attentional and working memory abilities in SSDs, after controlling for psychosis symptom load, antipsychotic medication, education, and gender. Being neglected by the primary caregivers, whom by nature were assigned a special role in providing the optimal care of which most children is totally dependent and reliant, could possibly have profound effects on the developing brain. Paper III adds to and expands the scarce literature on the role of environmental factors such as CT in antipsychotic treatment effectiveness in SSDs. CT in SSDs patients was related to a slower symptomatic improvement across the medication subgroups and psychosis symptom domains, as compared to SSDs patients not reporting CT. Secondary findings indicate that this was particularly so for SSDs patients with CT who received olanzapine. If replicated in larger samples, this could aid in clinical treatment decisions in SSDs and contribute towards more personalized and tailored antipsychotic treatment strategies for individuals with SSDs.

Overall, our findings indicate that CT and CT subtypes have complex relations to clinical features in SSDs. Although contributing to expanding and nuancing how CT may impact on adulthood psychopathology, the results also underscore the knowledge gap related

to developmental trajectories from CT to SSDs. As we were able to divide our SSDs sample in a group termed 'no CT', we cannot claim that CT is the only or most important factor that characterizes SSDs. Not all patients with SSDs have experienced CT, nor does all CT exposed individuals develop SSDs in adulthood. Possibly, there are subgroups of SSDs based on previous CT exposure and clinical manifestations that could shed light on the inconsistencies (Stevens et al., 2017). Our results should be interpreted within the proposed integrative frameworks, where CT adds to and interacts with other developmental, psychological, biological, and physiological factors implicated in SSDs. The trajectories and pathways from childhood abuse and neglect to SSDs is probably interrelated and complex. Our results should also be considered to counterbalance the importance placed solely on genes and biological aspects related to SSDs. The present thesis communicates the importance of recognizing human suffering as part of complex clinical presentations. The importance of CT should remind clinicians to look beyond the simplifying diagnostic categories and be knowledgeable of the possibility that the overt symptom presentations may represent survivors of abuse and neglect.

6.2 Future research

Vast efforts have been made since the 80s and 90s to examine the relation of CT and SSDs, and the field has come a long way in highlighting the impact of and associations between aspects of CT and SSDs. As a result of working on this thesis, I now advocate that the research field should move forward. Although not necessarily specific to or directly causally related to SSDs, the role of CT in SSDs still needs to be more fully understood and recognized. Firstly, future research should aim to explore and clarify the possible mechanisms and pathways from CT to various psychiatric disorders including SSDs. A question to be answered is this: Why does a trauma-exposed person develop SSDs whereas others engage in illicit substance use? It is possible that knowledge on specific CT subtype constellations, their timing, as well as closeness in relation to the perpetrator could increase our understanding of pathways and outcomes, hopefully arriving at a clearer image of the role of CT in severe mental health disorders. And furthermore, more research is needed to clarify the contribution of CT subtypes in relation to clinical outcomes in SSDs, not only related to cognitive performance, but also related to antipsychotic effectiveness. Advances in personalized medicine for people with severe mental illness could contribute to increase the quality of life, participation in society, decrease stigma associated with mental health disorders, and reducing costs of ineffective therapies. Individuals could be spared for unnecessary 'trial and error'

when faced with the personal struggles related to coping with a severe mental illness. Compared to other areas in medicine, the pharmacological treatment in SSDs is still in many cases a 'one size fits all, if not try Clozapine' treatment strategy. Unraveling the more specific impact of environmental components such as CT in addition to and in interaction with biologically based factors related to (epi)genetics, physiology, and inflammation, could be an interesting venue for future research in SSDs. Especially the field of psychoneuroimmunology seems like an interesting venue for understanding and uniting environmental adversities, physiology, and clinical outcomes.

Although recommended in clinical guidelines, trauma is still not adequately addressed for many individuals with SSDs and psychotic illnesses. Not only have many early experiences of trauma, but the psychotic episode itself as well as aspects related to treatment, such as involuntary hospitalization and medication, may lead to trauma and re-traumatization (Gianfrancesco et al., 2019). Relatedly, PTSD, complex PTSD, and related symptoms such as dissociation, may be significantly underdiagnosed in SSDs. Future research and clinical care should aim at providing evidence for and implementing trauma assessments, as well as providing adequate care based on individual needs, including for those presenting with CT and trauma-related symptomatology in addition to the psychosis.

Lastly, efforts should be made to develop effective preventative strategies for childhood maltreatment and adversities (Bendall et al., 2013). CT has been deemed a modifiable and preventable environmental risk factor (Gianfrancesco et al., 2019), impacting negatively on the mental and physical health, functioning, and participation in society for children and adults. Ultimately, by preventing CT occurrences, mental health disorders around the world could be reduced. Relatedly, assessment of CT should be an integrated part of routine clinical settings, and if confirmed, efforts should be made to provide a trauma-informed or trauma-focused care for individuals with severe mental health disorders such as SSDs and SUDs. Incidentally, programs for targeting trauma in the treatment of psychosis in SSDs have been developed and should be further researched and implemented in clinical settings (Brand et al., 2018).

Needless to say, no children in any parts of the world should experience abuse or neglect growing up. Herein lies some cultural and economic challenges for research, regarding low-income countries as compared to high- and middle-income countries: What do we know about the definition and perception of what constitutes a traumatic childhood event in different cultures? Does physical neglect encompass the same experiences for children growing up in Norway as for children in poorer countries? Our knowledge on the subject is

limited, as most research on trauma and mental health has been conducted in developed and high-income countries. Increasing the research efforts in underdeveloped and low-income countries could potentially aid in informing policy makers responsible for the welfare of children.

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Childhood trauma in schizophrenia spectrum disorders as compared to substance abuse disorders

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ABSTRACT

The prevalence of childhood trauma (CT) in schizophrenia spectrum disorders (SSDs) and substance abuse disorders (SUDs) is high. Direct comparisons of CT in these disorders are lacking, and it is not known whether there are differences in self-reported CT in SSDs as compared to SUDs. We aimed to compare the frequency, severity and types of CT in SDDs and SUDs. Patients with SSDs (n = 57) and SUDs (n = 57) were matched for age and gender. Overall levels of CT and CT subtypes were measured retrospectively by the Childhood Trauma Questionnaire Short-Form (CTQ-SF), and grouped into none/low and moderate/severe levels of CT. Group differences in CTQ-SF sum score and subscale scores, as well as differences in the severity of overall CT and CT subtypes were all non-significant. In both groups, 64.9% reported ≥ 1 subtypes of CT above cut-off. Of those who reported CT above the cut-off, 13.5% in the psychosis group reported ≥ 4 subtypes, as compared to 2.7% in the substance abuse group. We did not find statistically significant differences between SSDs and SUDs in terms of exposure to CT frequency or severity, all effect sizes were small (r < 0.15).

1. Introduction

Maltreated and traumatized children have a greater likelihood of suffering from psychopathology during their life course (Teicher and Samson, 2013). In line with the World Health Organization (WHO) description of childhood maltreatment as abuse and neglect (WHO, 2014), this study understands childhood trauma (CT) as both active abuse, i.e. physical, sexual and emotional abuse, as well as passive abuse, i.e. emotional and physical neglect (Bernstein et al., 2003). A wide body of research supports the influence of CT on the development of schizophrenia spectrum disorders (SSDs) in adulthood (Duhig et al., 2015). Meta-analyses and reviews (Bonoldi et al., 2013; Read et al., 2005; Varese et al., 2012) have identified a high prevalence of CT in adult patients with psychosis in both retrospective (DeRosse et al., 2014; Mørkved et al., 2017; Aas et al., 2016) and prospective studies (Rossler et al., 2014). Studies report more CT in patients with psychosis when compared to in the general population (Bonoldi et al., 2013), and an association between CT and psychosis severity (Sahin et al., 2013). Some authors suggest a dose-response relationship between CT and psychosis (van Dam et al., 2015), indicating that a higher degree of CT is associated with more symptoms of psychosis (Kelleher et al., 2015) and worse cognitive functioning (Ucok et al., 2015). Childhood adversity and trauma has been found to increase the risk of psychosis with an odds ratio of 2.8, suggesting that if this relationship is causal, removal of adversity would reduce the number of people with psychosis by 33% (Varese et al., 2012). Proposed explanations for the influence of

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CT on the development of adult psychosis include affective pathways (van Nierop et al., 2015), neurodevelopmental and epigenetic changes (Green et al., 2014; van Winkel et al., 2013; Aas et al., 2012), and altered physiological and psychological stress mechanisms (Lardinois et al., 2011; Mondelli et al., 2010).

Although CT has been found to be frequent and severe in schizophrenia spectrum disorders (SSDs), CT has also been implicated in various other mental health disorders (i.e. Carr et al., 2013) such as substance abuse disorders (SUDs; Afifi et al., 2012; Dube et al., 2003; Ekinci and Kandemir, 2015; Schaefer et al., 2010; Schnieders et al., 2006; Wu et al., 2010). An investigation of CT and SUDs in a nationally representative sample in the US found that physical, sexual and emotional abuse, and physical and emotional neglect were associated with an increased risk of SUDs (Afifi et al., 2012). Schnieders et al. (2006) reported more frequent CT in patients with SUDs to be related to greater symptom severity and co-morbidity. The Adverse Childhood Experiences (ACE) study indicated that each type of adverse childhood experience was associated with a two to four times greater likelihood of drug abuse initiation and development (Dube et al., 2003). Authors have underscored the need of more research and knowledge of how early experiences, including CT, contribute to substance abuse in adolescence and adulthood (Dube et al., 2003). Proposed explanations for CT in SUDs have focused on e.g. stress-coping (Afifi et al., 2012; Hyman et al., 2007) and tension reduction (Edalati and Krank, 2015).

The comorbidity of illicit substance use in SSDs is well documented, and symptoms of psychosis are often seen in relation to drug abuse (Løberg et al., 2014). However, few studies have investigated CT in SSDs as compared to in SUDs. One study compared the presence of childhood adverse life situations in adolescents with SSDs to adolescents with SUDs (Matzova et al., 2014). They found that 12% of the SUDs group reported neglect and physical aggression towards a child, compared to 4% of the SSDs group. Further, 10% of the SSDs group reported bullying, compared to 4% of the SUDs group. However, more research comparing exposure to CT in SSDs and SUDs is warranted. Thus, in the present study, we aimed to investigate the frequency, severity and types of childhood trauma, as measured by the Childhood Trauma Questionnaire Short-Form (CTQ-SF; Bernstein et al., 2003), in patients with SSDs compared to patients with SUDs.

2. Material and methods

The study is a collaboration between the Bergen Psychosis Project 2 (BP2), Haukeland University Hospital, Bergen, Norway, and the Trauma Psychology Research Group (TPRG) at the Faculty of Psychology, University of Bergen, Bergen, Norway. The sample consisted of 57 patients with SSDs (psychosis group), i.e. F20-29 in the International Statistical Classification of Diseases and Related Health Problems 10 (ICD-10; WHO, 1992), and 57 patients with SUDs (substance abuse group) corresponding to F10-19 in the ICD-10. Each group included 35 males and 22 females (see Table 1 for demographics).

2.1. Psychosis group

The psychosis group was included from BP2, an ongoing independently funded multi-site prospective study. The patients were recruited at the Medical University of Innsbruck, Innsbruck, Austria (n = 7); Stavanger University Hospital, Stavanger, Norway (n = 3); and Haukeland University Hospital, Bergen, Norway (n = 47), and gave informed consent to participate. The mean age in the psychosis group was 30.24 years (SD = 11.6). Patients were included in our sub-project if they had completed a structured assessment of childhood trauma at their 6-week follow-up.

To be included in the BP2 study, the patients had to meet ICD-10 criteria for SSDs (F20-F29; F20 Schizophrenia (n = 30), F21 Schizotypal disorder (n = 1), F22 Persistent delusional disorder (n = 6), F23 Acute and transient psychotic disorders (n = 5), F25 Schizoaffective disorder (n = 5), F28 Other nonorganic psychotic disorder (n = 1), or F29 Unspecified nonorganic psychosis (n = 9)) as determined by the Structural Clinical Interview for Axis I Disorders (SCID; Spitzer et al., 1992), be > 16 years of age, understand the written and spoken native language, and score ≥ 4 on at least one of the following items on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987): Delusions, hallucinatory behavior, grandiosity, suspiciousness/persecution or unusual thought content. Exclusion criteria were organic psychosis, psychosis due to psychoactive substance use, or inability to understand spoken Norwegian or German (Austria). The presence and level of alcohol use was measured by the Alcohol Use Disorder Identification Test (AUDIT), a self-report questionnaire which consist of 10 questions concerning recent alcohol use, alcohol dependence symptoms and alcohol-related problems (Babor et al., 2001). The Drug Use Disorders Identification Test (DUDIT) is similar self-report measure consisting of 11 questions, which was used to assess aspects related to drug use/abuse in the psychosis group

Table 1
Demographic and clinical characteristics by group.

	Psychosis group (n = 57)	Substance abuse group (n = 57)
Age	30.24 (11.6)	29.96 (11.3)
Gender (male)	35 (61.4%)	35 (61.4%)
Marital status		
Single	52 (91.23%)	45 (78.95%)
Married/divorced	4 (7.02%)	11 (19.30%)
Unknown/missing	1 (1.75%)	1 (1.75%)
Education		
Primary school	27 (47.37%)	17 (29.82%)
Further education	30 (52.63%)	39 (68.42%)
Living situation		
Supported housing/institution	21 (36.84%)	19 (33.33%)
Independently	33 (57.89%)	35 (61.4%)
Other	0 (0%)	2 (3.51%)
No residence	1 (1.75%)	0 (0%)
Unknown/missing	2 (3.51%)	1 (1.75%)
Psychosis onset age[a]	24.05 (8.74)	
Duration of psychosis (years)[a]	5.32 (8.96)	
Average time of substance abuse[b]		15.5 (11.2)
Debut drug[b]		
Alcohol		23 (40.4%)
Cannabis		13 (22.8%)
Opiates		1 (1.8%)
Benzodiazepines		4 (7%)
Amphetamines		1 (1.8%)
Polysubstance		12 (21.1%)
DUDIT[c]	11.7 (12.6)	
Male (n = 27)	14.4 (12.6)	
Female (n = 13)	6.2 (11.1)	
AUDIT[d]	8.9 (7.1)	
Male (n = 31)	9.6 (7.0)	
Female (n = 14)	7.4 (7.3)	
PANSS		
Positive symptoms	15.15 (5.6)	
Negative symptoms	16.83 (6.3)	
General psychopathology scale	32.02 (8.28)	
Total	64 (17.15)	
SCL-90-R[e]		
GSI		1.01 (0.69)
Above clinical cutoff		59.6%
Psychoticism		0.51 (0.6)

Note. All numbers = n (%) or M (SD). PANSS = The Positive and Negative Syndrome Scale, SCL-90-R = Symptom Checklist-90-Revised, AUDIT = Alcohol Use Disorder Identification Test, DUDIT = Drug Use Disorder Identification Test, CAUS = Clinician Alcohol Use Scale, CDUS = Clinician Drug Use Scale. n = 57 for all groups, except:

[a] n = 55.
[b] n = 54.
[c] n = 40; Cut-off = ≥ 6 (male), ≥ 2 (female).
[d] n = 45; Cut-off = ≥ 8 (male), ≥ 6 (female).
[e] Cut-off (clinical caseness score) = SCL-90-R GSI t-score > 63 ≥ GSI raw score 0.74 (male) and 0.94 (female). Cut-off psychoticism subscale = male 0,90 (SD = 0,65), female 0,98 (SD = 0,74).

(Berman et al., 2005) (see Table 1). BP2 was approved by the Regional Committee for Medical Research Ethics (2010-3387) and was registered as a clinical trial 10/03/2011 (www.clinicaltrials.gov: NCT01446328).

2.2. Substance abuse group

Data from the SUDs group was collected by TPRG. Patients (n = 57) were recruited from either inpatient (n = 19) or outpatient (n = 38) clinics for SUDs in Bergen, Norway. Mean age was 29.96 years (SD = 11.3). Patients were under treatment for drug and/or alcohol dependence. Presence of substance abuse disorders was determined by the Norwegian national client mapping system (KKS), a standardized method developed by the Bergen Clinics in Bergen, Norway and The Norwegian Institute for Alcohol and Drug research, Norway (Iversen et al., 2009). The KKS is a clinical assessment tool that focuses on the patient's past (> 6 months) and present (< 6 months) substance use/abuse. The sample reported current primary abuse of alcohol (n = 19), cannabis (n = 17), opiates (n = 8), benzodiazepines (n = 4), amphetamines (n = 3), other drugs (n = 2), as well as no current abuse (n = 2). For the purpose of the present study, the level of psychosis symptoms in the SUDs group was assessed by the Psychoticism scale in the Symptoms Check List -90-Revised (SCL-90-R; Derogatis, 1983) (Table 1).

Inclusion criteria were age > 15, and ability to give informed consent to participate. Exclusion criteria were: inability to complete screening, suicidality, presence of a psychotic disorder, mental disability, inappropriate language skills, or intoxication at the time of assessment. The TPRG-study was approved by the Regional Committee for Medical Research Ethics (2009-1133).

2.3. Measurement

CT in both groups was assessed by the Childhood Trauma Questionnaire Short-Form (CTQ-SF), a self-report 28-item questionnaire screening for five subtypes of childhood maltreatment: childhood sexual, physical and emotional abuse, and physical and emotional neglect (Bernstein et al., 1997, 2003; Bernstein and Fink, 1998). Each subscale consists of five items scored on a five-point Likert scale ranging from 1 (*never true*) to 5 (*very often true*), summarized into an overall CTQ-SF sum score ranging from 25 to 125. Three items make up the Minimization-denial subscale, a validation scale, which was not used in the present study. There are several versions of the CTQ, consisting of 70, 53 and 34 items, including the 28 item CTQ-SF. Baker and Maiorino (2010) therefore recommend reporting mean scores, making it valid to compare and combine data across studies utilizing different versions of the CTQ.

The CTQ-SF has shown good internal consistency, test-retest reliability, excellent internal reliability for the total scale and good to excellent internal reliability for the subscales as well as good sensitivity and specificity (Bernstein et al., 2003; Dovran et al., 2013). The Norwegian version of the CTQ-SF has been found to have reasonable fit to the five-factor structure in the original version by Bernstein, as well as satisfactorily to excellent internal consistency (Winje et al., 2004). The reliability estimates are within the range of 0.78–0.95 (Dovran et al., 2013). The German version of the CTQ-SF has shown satisfactory construct validity and internal consistency, except for physical neglect (Bader et al., 2009; Klinitzke et al., 2012).

For the present study, the overall reliability estimate for the CTQ-SF was high: Cronbach's α = 0.89. Subscale Cronbach's α were: Emotional abuse = 0.81, physical abuse = 0.83, sexual abuse = 0.95, emotional neglect = 0.89, and physical neglect = 0.60.

2.4. Procedure

The psychosis group completed the CTQ-SF, PANSS, AUDIT and DUDIT, while the substance abuse group completed the CTQ-SF, SCL-90-R and the KKS, during the first three months of inclusion in the BP2 and TPRG projects respectively. Patients were more likely at this stage to be in a clinically stable phase, thus increasing assessment validity.

2.5. Statistical analysis

Patients from the psychosis group and the substance abuse group were matched for age and gender to reduce potential selection bias and to reduce any influence of age and gender as confounding variables. As initial tests for kurtosis revealed that the CTQ-SF data were not normally distributed, Mann-Whitney U was used for ordinal variables when investigating differences in CTQ-SF sum scores and subscale scores, as well as CTQ-SF scores by gender independent of diagnostic group (SSDs and SUDs). Categorical variables were analyzed using Chi Square tests. Pearson correlations coefficient (r) was used to assess effect size, categorized according to Cohen's criteria (Cohen, 1977). To examine the associations between CT and substance use in the SSD group and between CT and symptoms of psychosis in the SUD group, Spearman's rho was calculated using the CTQ-SF sum scores and subscale scores, the AUDIT, and the DUDIT in the psychosis group, and the CTQ-SF sum scores and subscale scores and the Psychotisism subscale of SCL-90-R in the substance abuse group. A p-value of 0.05 was considered statistically significant for all analyses.

CTQ-SF scores were categorized as *none, low, moderate* and *severe* abuse or neglect according to Bernstein and Fink's threshold scores (Bernstein and Fink, 1998). CTQ-SF scores were dichotomized into a variable of none/low and moderate/severe levels of CT to determine caseness, i.e. whether the patients met the cut-off of moderate to severe levels of CT. This was done in order to maximize sensitivity in detecting potential differences between clinical groups (see Baker and Maiorino, 2010), given the high frequency of low levels of CT in the general population.

In case of missing data (MD) from the CTQ-SF and PANSS, each participant's personal subscale mean was imputed. For demographic data, e.g. the AUDIT and DUDIT, a missing value analysis was performed. However, if MD exceeded 20% of the items in each subscale, the patient's scores were excluded from further analyses. All statistical analyses were carried out using SPSS 22.

3. Results

3.1. Demographic data

There were no significant differences between the psychosis group and substance abuse group in marital status χ^2 (2) = 4.887, p = 0.09, level of education χ^2 (1) = 2.114, p = 0.10, and living situation χ^2 (2) = 3.050, p = 0.22 (see Table 1).

Exploratory analyses of gender independent of patient group indicated a significant gender difference in the CTQ-SF sum score with men (n = 70; *mean (M)* = 41.9, *median (Mdn)* = 40) scoring lower than women (n = 44; M = 49.2, Mdn = 45; U = 1164.5, p = 0.03). Further, 41.4% (n = 29) men and 25% (n = 11) women reported zero CT in the moderate-severe range, whereas 58.6% (n = 41) men and 75% (n = 33) women reported 1 – 5 CT. Of those who reported CT above the cut-off, 100% (n = 41) of the male patients and 81.8% (n = 27) of the female patients reported 1 – 3 CT. None of the male patients reported 4 – 5 CT, compared to 8.1% (n = 6) female patients. This difference was statistically significant χ^2 (1) = 8.112, p = 0.004.

3.2. CTQ-SF scores and subscale scores by groups

Group differences in CTQ-SF sum scores and subscale scores are shown in Table 2. Scores were imputed in 12 of 114 cases. No cases were excluded from analysis. CTQ-SF sum scores and mean scores were not significantly different when comparing the psychosis (M = 45.55, Mdn = 43) and substance abuse (M = 43.85, Mdn = 43; U = 1587.5, p

Table 2
Comparison of CTQ-SF scores and caseness by group.

	Psychosis group		Substance abuse group		Mann-Whitney *U*		Effect Size	CT Caseness			
Measure	*M (SD)*	*Mdn*	*M (SD)*	*Mdn*	*U*	*p*	Pearson's *r*	Psychosis group	Substance abuse group	χ^2	*p*
CTQ sum score	45.55 (15.07)	43	43.85 (11.97)	43	1587.5	0.834	− 0.02				
CTQ mean score	1.82 (0.60)	1.72	1.75 (0.48)	1.72	1587.5	0.834	− 0.02				
Emotional abuse	10.26 (5.07)	9	9.99 (3.73)	10	1561	0.718	− 0.03	12 (21.05%)	15 (26.32%)	0.437	0.509
Physical abuse	7.05 (3.39)	5	7.07 (3.39)	5	1607	0.915	− 0.01	10 (17.54%)	8 (14.04%)	0.264	0.607
Sexual abuse	7.33 (4.57)	5	7.46 (5.05)	5	1615	0.947	− 0.01	15 (26.32%)	13 (22.81%)	0.189	0.663
Emotional neglect	12.12 (4.98)	11	11.62 (4.67)	11	1529.5	0.589	− 0.05	16 (28.07%)	12 (21.05%)	0.757	0.384
Physical neglect	8.77 (3.61)	8	7.72 (2.74)	7	1349.5	0.114	− 0.15	21 (36. 84%)	15 (26.32%)	1.462	0.227

Note. $n = 57$ for all groups. CTQ-SF = Childhood Trauma Questionnaire Short-Form. CT = Childhood trauma. CT caseness = *n* (%) in each group that reported subscale scores in the moderate-severe range.

= 0.834) groups. There were no significant differences between the two groups on the CTQ-SF subscale scores for any of the subscales (see Table 2).

For the SSD and SUD groups respectively, we examined the relationship between CT and psychosis-like symptoms, as well as that between CT and illicit substance and alcohol use. There were no statistically significant correlations between CTQ-SF sum scores, subscale scores and AUDIT (CTQ sum score $r_s = -0.04$, emotional abuse $r_s = 0.06$, physical abuse $r_s = 0.07$, sexual abuse $r_s = 0.13$, emotional neglect $r_s = -0.03$, physical neglect $r_s = -0.02$) and DUDIT (CTQ sum score $r_s = 0.19$, emotional abuse $r_s = 0.15$, physical abuse $r_s = 0.19$, sexual abuse $r_s = 0.12$, emotional neglect $r_s = 0.16$, physical neglect $r_s = 0.23$) in the psychosis group. In the substance abuse group, there were statistically significant correlations between the Psychotisism subscale of SCL-90-R and CTQ sum score ($r_s = 0.42$, $p < 0.05$), emotional abuse ($r_s = .36$, $p < 0.05$), emotional neglect ($r_s = 0.32$, $p < 0.05$) and physical neglect ($r_s = 0.42$, $p < 0.05$), but not for sexual abuse ($r_s = 0.16$) and physical abuse ($r_s = 0.18$).

The groups did not significantly differ in caseness, i.e. whether patients met the cut-off of moderate to severe levels of CT, and there were no statistically significant differences on the following subscales: emotional abuse χ^2 (1) = 0.437, $p = 0.66$, physical abuse χ^2 (1) = 0.264, $p = 0.79$, sexual abuse χ^2 (1) = 0.189, $p = 0.83$, emotional neglect χ^2 (1) = 0.757, $p = 0.51$, and physical neglect χ^2 (1) = 1.462, $p = 0.31$.

The groups were compared on the number of patients who reported 0 – 5 subtypes above the cut-off of moderate/severe level of CT. Analyses showed that 64.9% ($n = 37$) in both groups reported 1 – 5 CT above cut-off, and 35.1% ($n = 20$) in each group reported no CT in the moderate-severe range. Of those who reported ≥ 1 CT, 86.5% ($n = 32$) in the psychosis group and 97.3% ($n = 36$) in the substance abuse group reported 1 – 3 CT. Further, 13.5% ($n = 5$) in the psychosis group and 2.7% ($n = 1$) in the substance abuse group reported 4 – 5 CT. This difference was non-significant χ^2 (1) = 2.902, $p = 0.088$.

3.3. Levels of CT by subtype and group

An overview of the number (%) of patients in the two groups by none/low and moderate/severe levels of subtypes CT are shown in Table 3. The majority of patients reported none/low levels of emotional, physical and sexual abuse, as well as of physical and emotional neglect.

Table 3
Levels of childhood trauma by subtype and group.

Subtype	None/Low *n (%)*	Moderate/Severe *n (%)*	χ^2	*p*
Emotional abuse				
Psychosis group	45 (78.95%)	12 (21.05%)	0.437	0.66
Substance abuse group	42 (73.68%)	15 (26.32%)		
Physical abuse				
Psychosis group	47 (82.46%)	10 (17.54%)	0.264	0.79
Substance abuse group	49 (85.96%)	8 (14.04%)		
Sexual abuse				
Psychosis group	42 (73.68%)	15 (26.32%)	0.189	0.83
Substance abuse group	44 (77.19%)	13 (22.81%)		
Physical neglect				
Psychosis group	36 (63.16%)	21 (36.84%)	1.462	0.31
Substance abuse group	42 (73.68%)	15 (26.32%)		
Emotional neglect				
Psychosis group	41 (71.93%)	16 (28.07%)	0.757	0.51
Substance abuse group	45 (78.95%)	12 (21.05%)		

Note. $n = 57$ for all groups.

4. Discussion

The aim of the present study was to compare the presence of childhood trauma in patients with schizophrenia spectrum disorders and substance use disorders. We found no statistically significant differences in the SSDs and SUDs groups in terms of CTQ sum score or for the five subscales of physical, sexual and emotional abuse, and physical and emotional neglect, and the effect sizes were small. The two groups reported non-significant differences in CT severity. We found no statistically significant correlations between substance use and CTQ sum score and subscale scores in the psychosis group. In the SUDs group, the correlations between the measure of psychosis and CTQ sum score, emotional abuse, emotional and physical neglect, were statistically significant.

The CTQ-SF total scores and subscale scores from the present study replicates the level of trauma as measured by the CTQ-SF scores reported in other studies, such as a studies of patients with early psychosis (Duhig et al., 2015), ultra-high risk psychosis patients (Ucok et al., 2015), SSDs (DeRosse et al., 2014), and in a cocaine dependent SUDs sample (Hyman et al., 2008). When investigating CT by gender across diagnostic groups, our results indicate more frequent and severe CT in women as compared to men, in line with previous research (e.g. Felitti et al., 1998). We found that 58.6% of male and 75% of female patients reported more than one moderate-severe subtype of CT.

Reviewing the literature, the association between CT and psychosis is well established (Varese et al., 2012). Population-based studies have indicated CT as a risk factor for psychosis, and associated with decreased social functioning, lower rates of remission and poorer treatment compliance (Schafer and Fisher, 2011). A recent study by our research group suggest more frequent moderate to severe levels of physical and sexual abuse and physical neglect in patients with psychosis as compared to patients with other mental health disorders. Almost 70% of the patients with SSDs reported more than one CT above the cut-off for moderate-severe levels of CT, compared to 38.5% in the non-psychosis group (Mørkved et al., 2017).

Several authors argue that CT is a risk factor for psychosis. Proposed mechanisms are elevated emotional reactivity to daily stress (Myin-

Germeys and van Os, 2007), alterations of the hypothalamic-pituitary-adrenal axis (Matheson et al., 2013), and abnormal response to stress through gene – CT interactions (Aas et al., 2012). Other authors argue that a genetic vulnerability may augment the effect of CT (van Winkel et al., 2013). However, the design of the present study prevents causal inferences.

Several studies also suggest associations between CT and SUDs (Afifi et al., 2012; Medrano et al., 2002; Schaefer et al., 2010; Schnieders et al., 2006). Afifi et al. (2012) found all five subtypes of CT to be associated with increased risk of all individual SUDs. These results remained significant when adjusting for other Axis I and II mental disorders, with the exception of emotional neglect. Wu et al. (2010) described higher rates of exposure to childhood trauma in adults with SUDs and mental health problems, as compared to a sample from primary health care. Ekinci and Kandemir (2015) found high levels of CT in a sample of patients with SUDs. Theories on the association of CT in SUDs are e.g. the stress-coping model of addiction which states that in the context of high life stress and low healthy coping resources, people might self-medicate with substances in order to improve affect (Afifi et al., 2012). Further, stress might increase vulnerability for substance abuse and relapse in SUD patients, and stress reduction is a potential reinforcing factor in substance abuse (Edalati and Krank, 2015).

Comorbidity of SSDs and SUDs is frequently reported in the literature, with estimates ranging from 20% to 30% (Nesvag et al., 2015). In our present study, psychosis-like symptoms were related to the CTQ-SF sum score and the subscale scores of emotional abuse and emotional and physical neglect in SUDs. Thus, if you have both illicit substance use and psychosis proneness you may have even more experience of CT. Psychosis proneness may also be a marker of drug use severity and drug use onset age (Løberg et al., 2014) in line with previous dose-dependent effects. Also, there is previous research indicating an interaction effect between CT and substance use in the development of SSDs (Konings et al., 2012). However, the associations between CT and alcohol and drug use were small and non-significant in the SSDs group. van Os et al. (2010) have suggested that shared genetic and environmental factors associated with neurodevelopmental alterations might result in a general liability to various dimensions of mental ill-health, such as combinations of affective dysregulation, psychosis, motivational impairment and cognitive alterations.

Co-occurring subtypes of childhood abuse is common (Edwards et al., 2003; Kessler et al., 2010), and found to be associated with poorer mental health (Felitti et al., 1998). We found different subtypes of CT to co-occur, as 64.9% in both groups reported having experienced one or more subtypes of CT above the moderate-severe cut-off, with almost 9% of the psychosis sample reporting more than four subtypes CT above this cut-off. Exposure to one type of CT might also increase the risk of exposure to multiple CT, in line with a dose-response relationship between CT and psychopathology (Varese et al., 2012).

Several limitations should be considered when interpreting these results. Our study is cross-sectional, and causality cannot be inferred. The sample sizes are relatively small, thus increasing the risk for Type II error and limiting generalizability. Suicidality was not assessed using a standardized measure, and could have influenced our results. Further, a healthy control group was not included in the present study. However, previous research has found both SSD and SUD subjects to report more CT as compared to healthy controls (e.g. DeRosse et al., 2014; Ekinci and Kandemir, 2015), and more CT reported in SSDs as compared to other mental health disorders such as anxiety and depression (Mørkved et al., 2017). The SUDs group was not assessed using PANSS. The level of psychotic symptoms in the substance abuse group as measured by the Psychoticism scale of the SCL-90-R (Derogatis, 1983) was below the clinical cut-off, indicating that the SUDs patients was not experiencing symptoms of psychosis at the time of CT assessment. The self-reported levels of alcohol and drug use in the psychosis group as measured by the AUDIT and DUDIT was above the clinical threshold, and might be possible confounders. Moreover, SSDs or SUDs were the respective primary diagnoses at the time of assessment and substance-induced psychoses were not included in the present study.

CT was measured retrospectively by self-report, and the results might be influenced by over-reporting or recall bias. However, research suggests that minimization or underreporting of CT is common (MacDonald et al., 2016), and retrospective ratings by psychosis patients has shown reasonable reliability (Fisher et al., 2011). The CTQ-SF does not measure all possible childhood adversities, or age of CT exposure to investigate the developmental stage of exposure to trauma. Research has however indicated that interpersonal and intentional events, which are well covered by the CTQ-SF, have the most severe consequences (Kessler et al., 2010).

The strengths of this study include the matched design, and the comparison between two clinically distinct patient groups. The present study report results from a comparison between SSDs and SUDs in adulthood in terms of severity and frequency of CT, which is not sufficiently researched. The study includes five subtypes of CT, known to be associated with risk of psychopathology, showing the occurrence of multiple CT in SSDs and SUDs. There were no demographic differences between the groups likely to have affected the results.

In the present study patients with schizophrenia spectrum psychosis and illicit substance use showed similarities in CT frequency and severity. Future research should address the issue of causality and aim at investigating how and why individuals exposed to CT develop a primary SSDs or SUDs. The present finding have clinical implications, CT should be addressed in the treatment of both schizophrenia spectrum psychosis and illicit substance use.

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Declaration of interests

The authors declare that there are no conflicts of interests.

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Paper II

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Does childhood trauma influence cognitive functioning in schizophrenia? The association of childhood trauma and cognition in schizophrenia spectrum disorders.

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ABSTRACT

Childhood trauma (CT) is a risk factor for schizophrenia spectrum disorders (SSDs), and cognitive impairment is a core feature and a vulnerability marker of SSDs. Studies of the relationship between CT and cognitive impairment in SSDs are inconclusive. In addition, few studies have examined differential effects of CT subtypes, e.g. physical, sexual or emotional abuse/neglect, on cognitive functioning. The present study therefore aimed to examine the effects of CT and CT subtypes on cognitive impairment in SSD. Participants (n = 78) with SSDs completed a comprehensive neuropsychological test battery and the Childhood Trauma Questionnaire Short-Form (CTQ-SF). We compared global cognitive performance as well as scores in seven subdomains (verbal abilities, visuospatial abilities, learning, memory, attention/working memory, executive abilities and processing speed) between participants reporting no CT and those reporting CT experiences using independent samples t-tests as well as linear regression analyses to control for possible confounders. CT subtype physical neglect was associated with attention and working memory after controlling for positive and negative psychosis symptoms, years of education, antipsychotics, gender and age, and adjustment of multiple testing. Our results indicate that the observed heterogeneity in cognitive impairment in SSDs, especially attention/working memory abilities, may in part be associated with childhood physical neglect.

Cognitive impairment is both a core feature of schizophrenia spectrum disorders (SSDs; Carrion et al., 2015), a vulnerability marker, and closely related to poor functional outcome and disability in SSDs (Kahn and Keefe, 2013). However, there is great variation in reported cognitive impairments in SSDs, and factors underlying this heterogeneity in cognitive functioning remain poorly understood. Risk factors influencing the development of SSDs may also potentially affect cognitive functioning directly or indirectly, such as illicit substance use which is a risk factor for psychosis, and has been found to influence cognitive vulnerability for psychosis (Løberg et al., 2014).

Childhood trauma (CT), e.g. physical, sexual, emotional abuse and physical and emotional neglect (Bernstein et al., 2003) is another risk factor for SSDs (Mørkved et al., 2017) which may be associated with cognitive impairment. The association between CT and SSDs is evident across study designs and populations, and CT has been found to increase the risk of psychosis with an odds ratio of 2.8 (Varese et al., 2012). CT have been shown to have a detrimental effect on brain development and cognitive functioning in non-psychotic individuals, attributed to disrupted neurodevelopment and stress-regulating brain systems (Pechtel and Pizzagalli, 2011). Understanding the relationship

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between CT and cognition in SSDs may thus aid both its etiological understanding as well as treatment models for psychosis.

A handful of studies have found negative effects of CT on cognition in SSD patients. Shannon et al. (2011) found that CT in SSD predicted greater impairments in working memory and episodic memory as compared to SSD with no history of CT. Quide et al. (2016) reported a negative association between CT and working memory performance in individuals with SSDs. However, some studies have failed to find an association between CT and cognitive impairment in SSDs (e.g. van Os et al., 2017). One study also indicated a positive effect of CT and cognitive abilities in SSDs (Ruby et al., 2017).

One possible explanation for the observed variance of cognitive impairment in SSDs might be differential effects of various types of CT (Schalinski et al., 2016). Li et al. (2017) reported negative effects of physical abuse, neglect and sexual abuse on language and attention. Ucok et al. (2015) found physical CT to have a negative impact on cognitive function in individuals at ultra-high risk of psychosis.

In addition, the mixed findings on CT and cognitive impairment in SSDs could be attributed to discrepancies in the measurement of CT and the use of non-validated self-report questionnaires. The Childhood Trauma Questionnaire Short-Form (CTQ-SF; Bernstein et al., 1997) used in the present study is described as a reliable measure of CT in SSDs (Fisher et al., 2011). Finally, sample differences between studies may also have contributed to the equivocal findings. For example, antipsychotic drug use has been found to improve cognition in SSDs (Johnsen et al., 2013).

In sum, findings on the relation between CT and cognitive impairment in SSDs are inconclusive, and few studies to date have examined whether CT subtypes might differentially affect cognitive functioning in SSDs. The aim of the present study is therefore to investigate possible effects of CT and CT subtypes on global cognitive performance and specific cognitive domains in a clinically representative sample of patients with SSDs.

1. Methods and material

The present study is based on cross-sectional data from the Bergen Psychosis project 2 (BP2), Haukeland University Hospital, Bergen, Norway. The BP2 is an independently funded multi-site prospective study including a randomized, rater-blind, head-to-head comparison of amisulpride, aripiprazole, and olanzapine, approved by the Regional Committee for Medical Research Ethics (2010–3387) and registered as a clinical trial 10/03/2011 (www.clinicaltrials.gov: NCT01446328). Inclusion/exclusion criteria for the BP2 have been described elsewhere (Mørkved et al., 2018). The current sample consisted of 78 patients with SSDs, 49 (63.6%) male, mean age 29.8 years (SD = 12.4 years; Table 1).

Participants were recruited at the Medical University in Innsbruck, Innsbruck, Austria (n = 10); Stavanger University Hospital, Stavanger, Norway (n = 8); and Haukeland University Hospital, Bergen, Norway (n = 60), and gave informed consent to participate.

Participants were required to meet diagnostic criteria for SSDs in the range F20–29 of the ICD-10 (WHO, 1992): F20 Schizophrenia (n = 44), F21 Schizotypal disorder (n = 2), F22 Persistent delusional disorder (n = 7), F23 Acute and transient psychotic disorders (n = 11), F25 Schizoaffective disorder (n = 5), or F29 Unspecified nonorganic psychosis (n = 9), as determined by the Structural Clinical Interview for Axis I Disorders (SCID; Spitzer et al., 1992), be > 18 years of age, be able to read, understand and speak the native language, and score ≥ 4 on at least one of the following items on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987): Delusions (P1), hallucinatory behavior (P3), grandiosity (P5), suspiciousness/persecution (P6) or unusual thought content (G9). Exclusion criteria were organic psychosis or psychosis due to substance use.

2. Measurement

2.1. Childhood trauma

The CTQ-SF is a 28-item self-report questionnaire screening for five subtypes of childhood trauma: childhood sexual, physical and emotional abuse, and physical and emotional neglect (Bernstein et al., 2003). Each subscale consists of five items scored on a five-point Likert scale ranging from 1 (*never true*) to 5 (*very often true*), summarized into an overall CTQ-SF sum score ranging from 25 to 125. Three items make up the Minimization-denial subscale. The CTQ-SF has shown good internal consistency, test-retest reliability, and excellent internal reliability, as well as good sensitivity and specificity (Dovran et al., 2013). For the present study, the overall reliability estimate for the CTQ-SF was high: Cronbach's α = 0.91. Subscale Cronbach's α were: Emotional abuse = 0.88, physical abuse = 0.80, sexual abuse = 0.91, emotional neglect = 0.92, and physical neglect = 0.60.

2.2. Cognitive assessment

Trained research nurses performed the cognitive assessments: a three-hour comprehensive test battery. The following seven domains of cognition were assessed: 1) verbal abilities; 2) visuospatial abilities; 3) verbal learning; 4) memory (long-term memory and recognition); 5) attention/working memory; 6) executive abilities and 7) processing speed.

Verbal abilities were assessed by the Wechsler Adult Intelligence Scale III (WAIS III; Wechsler, 1997) subtests vocabulary and similarities subtests, and the Delis-Kaplan Executive Function System (D-KEFS) verbal fluency test (Delis et al., 2001). Visuospatial abilities were assessed by the WAIS III subtests block design and digit symbol-coding, as well as the Rey-Osterrieth Complex Figure Test (Shin et al., 2006). Learning was assessed by the California verbal learning test (CVLT; Delis et al., 1987) i.e. trials 1–5, and the digit span subtest of the WAIS III. Memory was assessed by the CVLT (subtests short delay free and cued recall, long delay free and cued recall, and delayed recognition) and Rey-Osterrieth Complex Figure Test (Shin et al., 2006). Attention and working memory were assessed by the Digit vigilance test (Lewis and Rennick, 1979), the CALCAP Continuous Performance Test subtests sequential reaction time and choice reaction time (Miller, 1990), Trail Making Test (TMB; Reitan, 1986), the WAIS III subtests digit span and letter-number sequencing, and the Wechsler Memory Scale (Wechsler, 1997). Executive abilities were measured using the Wisconsin Card Sorting test (Heaton, 1981) and the Stroop test (Stroop, 1935). Processing speed was measured using the TMA (Reitan, 1986), the digit symbol-coding subtest of the WAIS III, the Grooved Pegboard Test (Bryden and Roy, 2005), and the CALCAP subtest simple reaction time (Conners, 2002).

The study included well-validated and reliable cognitive measures commonly used in studies of cognitive functioning in individuals with SSDs: The Wechsler Memory Scale (Wechsler, 1997) was found to be a reliable measure of memory deficits in schizophrenia (Gold et al., 1992). The WAIS III is described as having good psychometric properties (Silva, 2008). The Delis Kaplan Executive Function System (D-KEFS) (Delis et al., 2001) was found to have good psychometric properties (Shunk et al., 2006), as did the TMT Part A and B (Bowie and Harvey, 2006; Delis et al., 2001), the Grooved Pegboard Test (Erdodi et al., 2018) and the Rey-Osterrieth Complex Figure Test (Shin et al., 2006). The CVLT (Delis et al., 1987) is described as reliable and valid (Woods et al., 2006). The CALCAP Continuous performance test was found to possess adequate psychometric properties (Miller, 1990). Kopp et al. (2019) report promising reliability data for the Wisconsin Card Sorting test (Heaton, 1981).

Raw scores from cognitive tests were converted to standardized t-scores based on the best available norms (corrected for age, but not for gender and education). Cognitive domain t-scores were calculated as

Table 1
Mean (SD) clinical and demographic characteristics by CT/no CT group.

	No CT (n = 37)	CT (n = 41)	Total (n = 78)	t/χ^2	p-Value
Age	29.46 (11.97)	30.20 (12.87)	29.84 (12.37)	−0.26	0.795
Gender					
Male	28 (57.14%)	21 (42.86%)	49 (62.80%)	4.98	0.026*
Female	9 (31.03%)	20 (68.97%)	29 (37.20%)		
Duration of illness (n = 70)	5.99 (10.71)	5.30 (5.99)	5.63 (8.55)	0.33	0.737
Duration of untreated psychosis (n = 58)	26 (36.87)	83.06 (132.35)	55.52 (101.90)	−2.20	0.032
Antipsychotics DDD	1.18 (0.51)	1.13 (0.80)	1.30 (0.75)	0.34	0.736
Years of education	13 (2.79)	11.88 (2.67)	12.41 (2.76)	1.82	0.073
Education					
Primary	14 (42.42%)	19 (57.58%)	33 (42.3%)	0.73	0.392
Further	23 (52.27%)	21 (47.73%)	44 (57.14%)		
Civil status					
Single	30 (49.18%)	31 (50.82%)	61 (91%)	0.67	0.414
Married/divorced	4 (66.67%)	2 (33.33%)	6 (9%)		
Living situation					
Independently	20 (47.62%)	22 (52.38%)	42 (54.55%)	1.09	0.578
Supported housing/institution	16 (42.11%)	18 (47.37%)	34 (44.16%)		
No residence	1 (100%)	0 (0%)	1 (1.30%)		
PANSS baseline (n = 77)					
Positive symptoms	18.54 (5.59)	21.38 (5.30)	20.01 (5.59)	−2.28	0.025*
Negative symptoms	15.84 (6.38)	19.05 (6.33)	17.51 (6.51)	−2.22	0.029*
General psychopathology scale	36.41 (11.34)	39.40 (7.66)	37.96 (9.66)	−1.37	0.175
Total	70.78 (20.89)	79.83 (14.79)	75.48 (18.43)	−2.21	0.029*
DUDIT (n = 54)	12.73 (12.57)	9.34 (11.92)	10.97 (12.24)	1.02	0.313
AUDIT (n = 68)	9.10 (6.46)	8.19 (6.43)	8.63 (6.41)	0.59	0.559
CTQ-SF					
Emotional abuse	6.46 (1.94)	12.85 (5.24)	9.82 (5.13)	−7.00	0.001*
Physical abuse	5.22 (0.53)	7.24 (3.63)	6.28 (2.83)	−3.37	0.001*
Sexual abuse	5.05 (0.33)	7.34 (4.25)	6.28 (3.28)	−3.26	0.001*
Emotional neglect	7.73 (2.62)	14.95 (5.58)	11.52 (5.71)	−7.18	0.001*
Physical neglect	6.24 (1.46)	9.48 (3.67)	9.95 (3.26)	−5.03	0.001*
Sum	30.70 (3.99)	51.88 (14.21)	41.83 (15.02)	−8.75	0.001*
Cognitive domains					
Verbal abilities (n = 76)	49.35 (9.54)	45.64 (9.13)	47.39 (9.45)	1.73	0.087
Visuospatial abilities	46.73 (10.18)	44.39 (9.78)	45.50 (9.97)	1.03	0.306
Learning	43.63 (7.35)	42.21 (7.50)	42.88 (7.42)	0.85	0.400
Memory	46.03 (6.99)	43.15 (8.84)	44.52 (8.10)	1.58	0.116
Attention/working memory	44.20 (6.47)	42.39 (8.84)	43.25 (7.81)	1.02	0.309
Executive abilities (n = 75)	48.97 (10.99)	45.29 (12.09)	47.05 (11.65)	1.38	0.173
Processing speed	43.59 (8.05)	40.75 (10.03)	42.10 (9.19)	1.37	0.175
Global cognitive performance	46.20 (6.39)	43.45 (7.59)	44.76 (7.13)	1.69	0.095

Note. N = 78 if not stated otherwise. Continuous variables analyzed using independent samples t-test, and categorical variables analyzed using $\chi 2$. Duration of untreated psychosis in weeks, and duration of illness in years. DDD = defined daily dose, PANSS = The Positive and Negative Syndrome Scale, CTQ-SF = Childhood Trauma Questionnaire Short Form, AUDIT = Alcohol Use Disorder Identification Test, DUDIT = Drug Use Disorder Identification Test. * significant at $p < .05$. Verbal abilities: Wechsler Adult Intelligence Scale III (WAIS III; Wechsler, 1997) subtests vocabulary and similarities subtests, and the D-KEFS verbal fluency test (Delis et al., 2001). Visuospatial abilities: Block design and digit symbol-coding subtests of WAIS III, as well as the Rey-Osterrieth Complex Figure Test (Shin et al., 2006). Learning: California verbal learning test (CVLT; Delis et al., 1987) trials 1–5, and the digit span subtest of the WAIS III. Memory: CVLT (subtests short delay free and cued recall, long delay free and cued recall, and delayed recognition) and Rey-Osterrieth Complex Figure Test (Shin et al., 2006). Attention/working memory: Digit vigilance test (Lewis and Rennick, 1979), the CalCAP Continuous performance test subtests sequential reaction time and choice reaction time (Conners, 2002), Trail Making Test (Part B) (Reitan, 1986), the WAIS III subtests digit span and letter-number sequencing, and the Wechsler Memory Scale (Wechsler, 1997). Executive abilities: Wisconsin Card Sorting test (Heaton, 1981) and the Stroop test (Stroop, 1935). Processing speed: Trail Making Test (Part A) (Reitan, 1986), the digit symbol-coding subtest of the WAIS III, the Grooved Pegboard Test (Bryden and Roy, 2005), and the CalCAP subtest simple reaction time (Conners, 2002).

the mean t-score across tests for each domain. A global cognitive performance t-score was calculated by averaging the t-scores from every test.

2.3. Other measurements

The use of antipsychotic drugs at the time of neurocognitive testing was converted to Defined Daily Doses (DDD) as given by the World Health Organization Collaborating Centre for Drug Statistics Methodology at the Norwegian Institute of Public Health (www.whocc.no). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. Adherence with medication was assessed by means of serum level measurements of antipsychotic drugs.

2.4. Procedure

Patients included in BP 2 were assessed at baseline, week 1, 3, 6, 12, 26, 39 and 52. The CTQ-SF was administered at the 6-weeks. The PANSS was measured at week 1, and the cognitive test battery at the 12-week follow-up.

2.5. Statistical analyses

All analyses were carried out using STATA. Measures are presented as means (M) and standard deviations (SD), or as number (n) and percentages (%). A p-level of $< .05$ was considered statistically significant, except for in the regression analyses where we corrected for multiple testing by means of a Bonferroni adjustment ($0.05/40 = p < .00125$). Missing data were handled through imputation based on expectation maximation, and the amount of missing data in

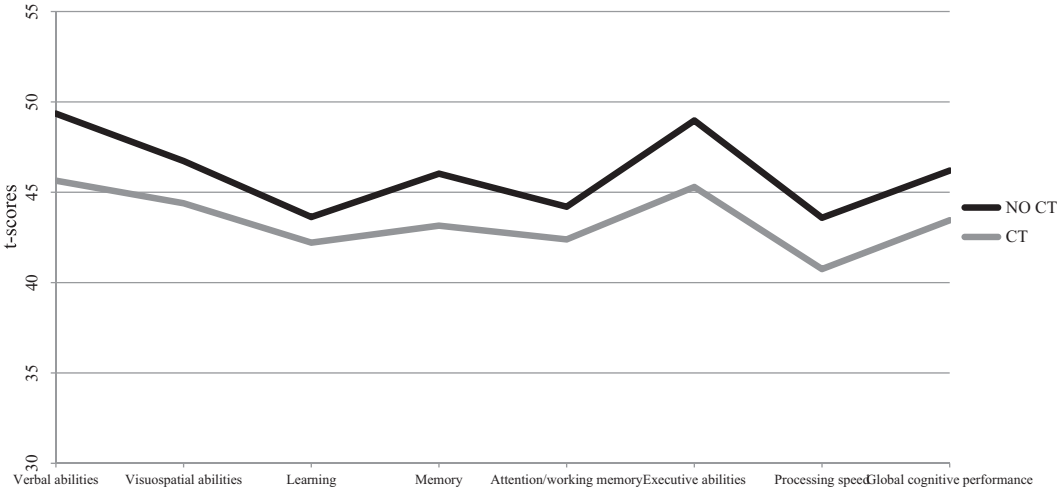

Fig. 1. Cognitive performance by cognitive domain grouped by CT.
Note. $N = 78$, except verbal abilities ($n = 76$) and executive abilities ($n = 75$). CT = moderate to severe childhood trauma. Bonferroni adjusted p-level of .00125. No significant results. Verbal abilities: Wechsler Adult Intelligence Scale III (WAIS III; Wechsler, 1997) subtests vocabulary and similarities subtests, and the D-KEFS verbal fluency test (Delis et al., 2001). Visuospatial abilities: Block design and digit symbol-coding subtests of WAIS III, as well as the Rey-Osterrieth Complex Figure Test (Shin et al., 2006). Learning: California verbal learning test (CVLT; Delis et al., 1987) trials 1–5, and the digit span subtest of the WAIS III. Memory: CVLT (subtests short delay free and cued recall, long delay free and cued recall, and delayed recognition) and Rey-Osterrieth Complex Figure Test (Shin et al., 2006). Attention/working memory: Digit vigilance test (Lewis and Rennick, 1979), the CalCAP Continuous performance test subtests sequential reaction time and choice reaction time (Conners, 2002), Trail Making Test (Part B) (Reitan, 1986), the WAIS III subtests digit span and letter-number sequencing, and the Wechsler Memory Scale (Wechsler, 1997). Executive abilities: Wisconsin Card Sorting test (Heaton, 1981) and the Stroop test (Stroop, 1935). Processing speed: Trail Making Test (Part A) (Reitan, 1986), the digit symbol-coding subtest of the WAIS III, the Grooved Pegboard Test (Bryden and Roy, 2005), and the CalCAP subtest simple reaction time (Conners, 2002).

the CTQ-SF scale was 0.73%.

CTQ-SF scores were categorized into none, low, moderate and severe abuse or neglect, based on threshold scores in the CTQ-SF manual. A dichotomous variable was created, grouping none and low levels of CT (meaning CT absent) on the one hand, and moderate and severe levels (CT present) on the other (Bernstein and Fink, 1998). The sample was divided into two groups: Participants reporting CT ($n = 41$), and participants with no CT experiences ($n = 37$). The relation between demographic variables and CT/no CT-groups was investigated using independent sample t-tests, non-parametric Mann-Whitney U test, or χ^2 tests. Significant results in these tests determined the inclusion of that variable in the regression models to control for confounders. Antipsychotics was included based on previous research showing effect on cognition in SSDs receiving antipsychotic treatment (Johnsen et al., 2013).

For the linear regression analyses, CTQ-SF subscale scores (5–25) were used as predictors for the cognitive performance scores. The first analyses used CTQ-SF subscales as predictors for the cognitive domains. Then, we included gender, PANSS positive and negative symptom scales, and antipsychotic medication (DDD) as confounders. Due to multicollinearity, the PANSS total score was omitted from the analyses. In the last model, we controlled for years of education if this was not already corrected for in the test scoring norms. All scoring norms were corrected for age.

The goodness of fit as measured by adjusted R^2 (R^2_a) is assessed as small if ≤ 0.09, moderate between 0.1 and 0.3 and large effect if ≥ 0.3 (Mehmetoglu and Jakobsen, 2017). We visually inspected frequency distributions of variables for normality. All regression models were tested for, and adhered to, the assumptions underlying linear multiple regression.

3. Results

3.1. Demographic and clinical data

When examining the CTQ-SF, we found that 21 of 78 (26.9%) patients with SSDs reported emotional abuse, 8 of 78 (10.3%) reported physical abuse, 12 of 78 (15.4%) reported sexual abuse, 23 of 78 (29.5%) reported emotional neglect and 20 of 78 (25.6%) reported physical neglect (according to the cut-off of moderate to severe level of abuse and neglect). Further, 37 (47.4%) patients reported no CT, and 41 (52.6%) patients reported 1–5 CT.

We tested for gender differences between CT/no CT groups, and found that the majority of male participants reported no CT, whereas the majority of the female participants reported CT experiences. This difference was statistically significant (Table 1). We also found that the CT group reported significantly higher levels of positive and negative psychosis symptoms compared to the no CT group (Table 1). There were no other significant effects of demographic and clinical data on CT/no CT groups. Further, serum levels generally corresponded well with the antipsychotic drug doses (DDD), indicating satisfactory adherence with medication.

Mean (SD) median, skewness and kurtosis was the following for cognitive domains: Global cognitive performance 44.76 (7.13) 45.26, −0.24 and 2.55; verbal abilities 47.39 (9.45) 46.12, 0.41 and 2.76; visuospatial abilities 45.50 (9.98) 45.88, −0.30 and 2.40; learning 42.89 (7.41) 41.88, −0.02 and 3.51; memory 44.52 (8.10) 43.84, −0.77 and 4.25; attention/working 43.25 (7.81) 42.89, −0.03 and 2.77; executive abilities 47.05 (11.65) 47.5, −0.51 and 3.23; processing speed 42.10 (9.19) 43.25, −0.34 and 3.13. The values were assessed as satisfactory.

3.2. Comparison of cognitive performance in SSDs by CT/no CT groups

We compared cognitive performance in two groups of SSDs patients; one group with no CT, compared to those reporting CT experiences There were no statistically significant differences in global cognitive performance between CT/no CT groups ($p = .095$), nor in verbal abilities ($p = .087$), visuospatial abilities ($p = .306$), learning ($p = .400$), memory ($p = .116$), attention/working memory ($p = .309$), executive abilities ($p = .173$) or processing speed ($p = .175$; Table 1 and Fig. 1).

Table 2
The effects of CTQ-SF subtypes on cognition by cognitive domain.

	Global cognitive performance	Verbal abilities	Visuospatial abilities	Learning	Memory	Attention/working memory	Executive abilities	Visuomotor processing speed
Emotional abuse	−0.134	0.096	0.026	−0.143	0.088	−0.227	−0.222	−0.444
	(−0.58)	(0.30)	(0.08)	(−0.61)	(0.35)	(−0.98)	(−0.57)	(−1.53)
Physical abuse	0.007	−0.483	0.254	0.096	−0.146	0.065	0.747	0.280
	(0.02)	(−0.77)	(0.43)	(0.21)	(−0.31)	(0.15)	(0.99)	(0.50)
Sexual abuse	0.152	−0.0265	0.014	−0.084	0.233	0.021	−0.191	0.242
	(0.48)	(−0.06)	(0.03)	(−0.27)	(0.69)	(0.07)	(−0.36)	(0.62)
Emotional neglect	0.348	−0.0281	0.343	0.416*	0.261	0.511**	0.334	0.444
	(1.84)	(−0.11)	(1.35)	(2.18)	(1.28)	(2.70)	(1.05)	(1.88)
Physical neglect	−1.288***	−1.013*	−1.560***	−1.027**	−1.243***	−1.342***	−1.182*	−1.142**
	(−4.12)	(−2.21)	(−3.72)	(−3.27)	(−3.70)	(−4.31)	(−2.13)	(−2.92)
Constant	50.86	58.40	52.01	47.58	50.01	49.71	51.22	47.14
	(20.21)	(15.91)	(15.40)	(18.82)	(18.50)	(19.81)	(11.57)	(14.97)
N	75	76	78	78	78	78	75	78

Note. Numbers are regression coefficients, and *t*-statistics in parenthesis. Constant = The value of the dependent variable holding all predictors constant. PANSS = The Positive and Negative Syndrome Scale. CTQ-SF = Childhood trauma questionnaire short-form. Unstandardized coefficients are reported due to the independent variables being measured in the same metric.

* $p < .05$.

** $p < .01$.

*** Bonferroni corrected $p < .00125$.

3.3. The association of CT subtypes on cognitive performance

In the first linear regression models, we tested for the effect of CT subtypes on cognitive performance in SSDs. The analyses showed statistically significant effects for the regression models (CT subtypes as predictors) on global cognitive performance, $F(5, 69) = 3.14$, $p = .013$, adjusted R^2 (R^2_a) = 0.13, visuospatial abilities, $F(5, 72) = 2.99$, $p = .016$, $R^2_a = 0.11$, learning, $F(5, 72) = 2.76$, $p = .024$, $R^2_a = 0.10$, memory, $F(5, 72) = 3.32$, $p = .009$, $R^2_a = 0.13$, attention and working memory, $F(5, 72) = 4.90$, $p < .001$, $R^2_a = 0.20$, and processing speed, $F(5, 72) = 2.61$, $p = .031$, $R^2_a = 0.10$. Goodness of fit for the models was small to moderate. No significant effects were found for the CT subtypes and verbal abilities ($p = .131$) and executive functioning ($p = .419$).

After correcting for multiple comparisons (Bonferroni adjustment $0.05/40 = p < .00125$), the results indicated that the association between the predictors and cognitive impairment in SSDs is mainly driven by physical neglect in predicting impairment in global cognitive performance ($p < .001$), visuospatial abilities ($p < .001$), attention/working memory ($p < .001$) and memory ($p < .001$; Table 2).

3.4. The association of CT subtypes on cognitive performance controlling for gender and psychosis symptoms

We tested for the effect of CT subtypes on cognitive performance in SSDs and controlled for gender, positive and negative psychosis symptoms, and antipsychotic medication.

The analyses showed statistically significant effects for the regression models based on the predictors (CT subtypes, gender, psychosis symptoms, antipsychotics) on global cognitive performance, $F(9, 62) = 2.95$, $p = .005$, $R^2_a = 0.19$, visuospatial abilities, $F(9, 65) = 2.67$, $p = .010$, $R^2_a = 0.16$, learning, $F(9, 65) = 2.65$, $p = .011$, $R^2_a = 0.16$, memory, $F(9, 65) = 3.75$, $p < .001$, $R^2_a = 0.25$, and attention and working memory, $F(9, 65) = 3.60$, $p = .001$, $R^2_a = 0.24$, and processing speed, $F(9, 65) = 3.57$, $p < .001$, $R^2_a = 0.24$. Goodness of fit for the models (R^2_a) was assessed as small to moderate. No significant effects were found for the CT subtypes and executive functioning ($p = .636$) and verbal abilities ($p = .122$).

After correcting for multiple comparisons (Bonferroni adjustment $0.05/40 = p < .00125$), the results indicate that the association between the predictors and cognitive impairment in SSDs is mainly driven by the CT subtype physical neglect (see Table 3). Increase in reported physical neglect predicted more impairment in attention/working memory abilities ($p < .001$; Table 3).

Lastly, we performed the analyses including education as a predictor for the cognitive domains. The analyses showed statistically significant effects for the regression models based on the predictors (CT subtypes, gender, psychosis symptoms, antipsychotics and education) on global cognitive performance, $F(10, 61) = 4.59$, $p < .001$, $R^2_a = 0.33$, verbal abilities, $F(10, 62) = 3.42$, $p < .001$, $R^2_a = 0.25$, visuospatial abilities, $F(10, 64) = 5.05$, $p < .001$, $R^2_a = 0.35$, learning, $F(10, 64) = 4.34$, $p < .001$, $R^2_a = 0.31$, memory, $F(10, 64) = 5.85$, $p < .001$, $R^2_a = 0.40$, attention and working memory, $F(9, 65) = 3.60$, $p < .001$, $R^2_a = 0.24$, and processing speed, $F(9, 65) = 3.57$, $p < .001$, $R^2_a = 0.23$. Goodness of fit for the models (R^2_a) was assessed as moderate to large. No significant effects were found for the CT subtypes and executive functioning ($p = .722$).

After correcting for multiple comparisons (Bonferroni adjustment $0.05/40 = p < .00125$), the results indicate that the association between the predictors and cognitive impairment in SSDs is mainly driven by the CT subtype physical neglect (see Table 4). Increase in reported physical neglect predicted more impairment in attention/working memory abilities ($p < .001$; Table 4).

4. Discussion

Reported levels of childhood physical neglect in our sample of SSDs predicted significant impairment in cognitive performance in attention/working memory abilities after adjusting for multiple comparisons, and controlling psychosis symptoms, antipsychotics, years of education, age and gender. In contrast, we found no significant differences in cognitive functioning between CT and no CT groups, nor between any other subtype of CT and the studied cognitive domains. Our findings regarding physical neglect indicate that CT subtypes might differentially influence cognitive abilities.

Half of our sample of patients with SSDs reported experiences of moderate to severe CT. Of those reporting CT, the majority had experienced up to three subtypes of CT. This is in line with previous studies on CT in SSDs (McGrath et al., 2017), and reports of co-occurrence of types of CT (Kessler et al., 2010). Our findings regarding associations between reports of CT and cognitive impairment, are in agreement with previous reports (Quide et al., 2016; Shannon et al., 2011). We did not find all types of CT to predict cognitive impairment in our sample of SSDs. This may in part explain inconsistency in previous research (Dauvermann and Donohoe, 2019): While some studies report associations between CT and cognitive impairment in SSDs (Aas et al., 2014), others, e.g. Ruby et al. (2017), did not find early trauma to

Table 3
The effects of CTQ-SF subtypes on cognition by cognitive domain, controlling for antipsychotics, gender and psychosis symptoms.

	Global cognitive performance	Verbal abilities	Visuospatial abilities	Learning	Memory	Attention/working memory	Executive abilities	Processing speed
Emotional abuse	0.202	0.162	0.428	−0.0389	0.340	0.0355	0.223	0.147
	(0.85)	(0.46)	(1.22)	(−0.16)	(1.27)	(0.14)	(0.49)	(0.50)
Physical abuse	−0.223	−0.772	−0.132	−0.239	−0.502	−0.286	0.615	−0.216
	(−0.54)	(−1.26)	(−0.22)	(−0.56)	(−1.09)	(−0.67)	(0.77)	(−0.43)
Sexual abuse	−0.0505	0.00466	−0.0631	−0.0577	0.231	−0.0457	−0.402	−0.00674
	(−0.17)	(0.01)	(−0.15)	(−0.19)	(0.71)	(−0.15)	(−0.71)	(−0.02)
Emotional neglect	0.198	0.0567	0.184	0.437*	0.239	0.427*	0.0547	0.114
	(1.02)	(0.20)	(0.65)	(2.18)	(1.10)	(2.11)	(0.15)	(0.48)
Physical neglect	−1.001**	−0.797	−1.328**	−0.730*	−0.994**	−1.082***	−1.009	−0.947**
	(−3.31)	(−1.79)	(−3.15)	(−2.44)	(−3.07)	(−3.59)	(−1.74)	(−2.69)
Gender	0.731	2.986	−0.426	1.734	0.145	0.749	−1.031	1.644
	(0.45)	(1.26)	(−0.18)	(1.05)	(0.08)	(0.45)	(−0.33)	(0.84)
PANSS positive	0.109	0.287	0.123	0.0617	−0.0399	0.0721	0.0610	0.145
	(0.78)	(1.38)	(0.59)	(0.42)	(−0.25)	(0.49)	(0.23)	(0.84)
PANSS negative	−0.211	−0.405	−0.227	−0.319*	−0.410**	−0.130	0.0151	−0.00123
	(−1.49)	(−1.94)	(−1.14)	(−2.26)	(−2.69)	(−0.91)	(0.06)	(−0.01)
Antipsychotics DDD	−2.448*	−0.500	−3.435*	−1.594	−1.648	−2.825*	−2.438	−5.129***
	(−2.34)	(−0.32)	(−2.22)	(−1.46)	(−1.39)	(−2.56)	(−1.21)	(−3.98)
Constant	54.76	57.28	57.26	52.06	58.20	53.28	53.25	51.71
	(15.74)	(11.17)	(11.72)	(15.04)	(15.52)	(15.26)	(7.98)	(12.68)
N	72	73	75	75	75	75	72	75

Note. *t*-statistics in parenthesis. *Constant* = The value of the dependent variable holding all predictors constant. *PANSS* = The Positive and Negative Syndrome Scale. *CTQ-SF* = Childhood trauma questionnaire short-form. *DDD* = the assumed average maintenance dose per day for a drug used for its main indication in adults. Unstandardized coefficients are reported due to the independent variables being measured in the same metric.

* $p < .05$.

** $p < .01$.

*** Bonferroni corrected $p < .00125$.

predict cognitive impairment. Our findings indicate that CT subtype physical neglect may in part explain these discrepancies.

Schalinski et al. (2016) suggested that some of the variance in cognitive impairment in SSDs could be explained by subtype of CT, as demonstrated by our findings that physical neglect is more closely associated with poorer cognitive performance. Our findings are in line with reports such as Li et al. (2017), whom in a sample of patients with SSDs found an association between physical neglect and impaired

Table 4
The effects of CTQ-SF subtypes on cognition by cognitive domain, controlling for antipsychotics, education, gender and psychosis symptoms.

	Global cognitive performance	Verbal abilities	Visuospatial abilities	Learning	Memory	Attention/working memory	Executive abilities	Processing speed
Emotional abuse	0.192	0.147	0.432	−0.0360	0.344	0.0355	0.223	0.147
	(0.88)	(0.46)	(1.40)	(−0.16)	(1.42)	(0.14)	(0.49)	(0.50)
Physical abuse	−0.310	−0.909	−0.312	−0.351	−0.631	−0.286	0.615	−0.216
	(−0.82)	(−1.64)	(−0.59)	(−0.91)	(−1.52)	(−0.67)	(0.77)	(−0.43)
Sexual abuse	0.158	0.323	0.301	0.171	0.493	−0.0457	−0.402	−0.00674
	(0.57)	(0.80)	(0.79)	(0.61)	(1.65)	(−0.15)	(−0.71)	(−0.02)
Emotional neglect	0.124	−0.0477	0.0592	0.359	0.149	0.427*	0.0547	0.114
	(0.70)	(−0.18)	(0.24)	(1.95)	(0.76)	(2.11)	(0.15)	(0.48)
Physical neglect	−0.769**	−0.452	−0.994*	−0.520	−0.754*	−1.082***	−1.009	−0.947**
	(−2.72)	(−1.10)	(−2.62)	(−1.87)	(−2.54)	(−3.59)	(−1.74)	(−2.69)
Gender	0.664	3.010	−0.523	1.673	0.0754	0.749	−1.031	1.644
	(0.45)	(1.41)	(−0.25)	(1.11)	(0.05)	(0.45)	(−0.33)	(0.84)
PANSS positive	0.0337	0.168	0.000714	−0.0151	−0.128	0.0721	0.0610	0.145
	(0.26)	(0.89)	(0.00)	(−0.11)	(−0.89)	(0.49)	(0.23)	(0.84)
PANSS negative	−0.149	−0.317	−0.144	−0.267*	−0.350*	−0.130	0.0151	−0.00123
	(−1.15)	(−1.67)	(−0.82)	(−2.07)	(−2.54)	(−0.91)	(0.06)	(−0.01)
Antipsychotics DDD	−2.081*	0.0694	−2.739*	−1.156	−1.147	−2.825*	−2.438	−5.129***
	(−2.17)	(0.05)	(−2.00)	(−1.15)	(−1.07)	(−2.56)	(−1.21)	(−3.98)
Education	0.925***	1.445***	1.570***	0.989***	1.131***			
	(3.72)	(3.99)	(4.42)	(3.81)	(4.08)			
Constant	41.57	36.90	35.47	38.34	42.50	53.28	53.25	51.71
	(8.75)	(5.36)	(5.42)	(8.01)	(8.31)	(15.26)	(7.98)	(12.68)
N	72	73	75	75	75	75	72	75

Note. *t*-statistics in parenthesis. *Constant* = The value of the dependent variable holding all predictors constant. *PANSS* = The Positive and Negative Syndrome Scale. *CTQ-SF* = Childhood trauma questionnaire short-form. *DDD* = the assumed average maintenance dose per day for a drug used for its main indication in adults. Unstandardized coefficients are reported due to the independent variables being measured in the same metric. Years of education is included in the regression models only in domains that did not already have the correction in the cognitive test scoring norms.

* $p < .05$.

** $p < .01$.

*** Bonferroni corrected $p < .00125$.

attention and memory, Traditionally, research has mainly focused on sexual and physical abuse (De Bellis et al., 2009). Although childhood neglect is frequently reported, the neurocognitive effects of neglect are understudied (De Bellis et al., 2009). As neglect entails an inability to meet basic emotional and physical needs, including nutrition and proper medical care during illness, and is related to other forms of abuse, the adverse neurocognitive consequences could be more extensive than for other types of abuse (Wells et al., 2019). Molina et al. (2018) found physical and emotional neglect to be negatively related to cognitive measures and report preliminary evidence for a role of early neglect in disrupted development of prefrontal cortex (PFC) connectivity and disturbed myelination regulation in SSDs. Early neglect at 3 years was found to predict hair cortisol concentration (HCC) in a transdiagnostic group (Schalinski et al., 2019b). HCC indicates cumulative cortisol levels associated with long term stress-reactions, indicating altered HPA-axis biology following inadequate care (Schalinski et al., 2019b). Thus, the absence of a reliable caregiver could be associated with negative impact on the developing brain (De Bellis et al., 2009) due to disrupting normative brain development during sensitive periods (Schalinski et al., 2019a), possibly affecting cognitive functioning in adulthood. Childhood neglect could thus be characterized as an impoverished parent-child relationship, which may in turn be a marker of an inherited cognitive vulnerability compounded by a gene-environment interaction, thus increasing psychopathology (Schalinski et al., 2019a). Maltreated and neglected children are also more likely to have parents who were themselves maltreated or traumatized, indicating intergenerational transmission involving maltreatment and neglect, deficient parenting skills, family stressors and genetic and epigenetic risk (Teicher and Samson, 2013).

When interpreting our findings, our limited sample size should be taken into account, as this boosts the risk of a Type II error. We did not use a control group in the present study, limiting knowledge on how levels of CT and cognitive performance compare to participants without SSDs. We were unable to control for cannabis use, socio-economic status or parental cognitive functioning, known to influence cognitive impairment in SSDs (Wells et al., 2019; Løberg et al., 2014). CT is measured retrospectively and by self-report, which might be associated to problems with validity and reliability. However, retrospective measurement of CT in SSDs is indicated to be valid and reliable (Fisher et al., 2011), albeit afflicted with common problems of retrospective self-reported methods of measuring CT (Baldwin et al., 2019).

Strengths of the study are the large clinical cognitive test-battery used, and the CTQ-SF is a well validated measure of CT, which allowed us to better differentiate between subtypes than much of the previous literature using other measures. Future research could benefit from a longitudinal design, with CT measured more close in time to the trauma and with additional measures to self-report.

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CRediT authorship contribution statement

N. Mørkved:Writing - original draft, Writing - review & editing, Investigation, Visualization, Conceptualization.**E. Johnsen**:Data curation, Writing - original draft, Writing - review & editing, Conceptualization.**R.A. Kroken**:Data curation, Writing - original draft, Writing - review & editing, Conceptualization.**R. Gjestad**:Writing - original draft, Writing - review & editing, Formal analysis, Conceptualization.**D. Winje**:Writing - original draft, Writing - review & editing, Conceptualization.**J. Thimm**:Writing - original draft, Writing - review & editing, Conceptualization.**F. Fathian**:Data curation, Writing - original draft, Writing - review & editing, Conceptualization.**M. Rettenbacher**:Data curation, Writing - original draft, Writing - review & editing, Conceptualization.**L.G. Anda**:Data curation, Writing - original draft, Writing - review & editing, Conceptualization.**E.M. Løberg**:Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Paper III

Impact of Childhood Trauma on Antipsychotic Effectiveness in Schizophrenia Spectrum Disorders: A Prospective, Pragmatic, Semi-randomized Trial

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Abstract

Antipsychotic medications are generally effective in ameliorating psychotic symptoms in schizophrenia spectrum disorders (SSDs). Identifying predictors associated with poor treatment response is important for a personalized treatment approach. Childhood trauma (CT) may have a general and differential effect on the effectiveness of different types of antipsychotics in SSDs. The Bergen-Stavanger-Trondheim-Innsbruck (BeSt InTro) study is a pragmatic, researcher-initiated, semi-randomized trial. The present study aimed to investigate symptom change (the Positive and Negative Syndrome Scale) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment (amisulpride, aripiprazole and olanzapine) by group (CT/no CT). Participants (n = 98) with diagnoses within the schizophrenia spectrum (F20-29 in the International Classification of Diseases – 10th Revision) were randomized to receive amisulprid, aripiprazole or olanzapine, and for this study categorized into groups of none and low CT, and moderate to severe CT according to thresholds defined by the Childhood Trauma Questionnaire Short-Form manual. CT in SSDs predicted an overall slower treatment response and less antipsychotic effectiveness after 26 weeks of treatment, which was statistically nonsignificant at 52 weeks. Secondary analyses showed a differential effect of CT related to type of antipsychotic medication: patients with SSDs and CT who received olanzapine showed less antipsychotic effectiveness throughout 52 weeks of treatment. The intention-to-treat and per-protocol analyses were convergent. Our findings indicate that in patients with SSD and CT, delayed response to antipsychotics could be expected, and a longer evaluation period before considering change of medication may be recommended.

Keywords: atypical antipsychotic*, psychoses, pharmacology, adverse childhood experiences

1. Introduction

Antipsychotic medication is generally effective in ameliorating psychotic symptoms, and is to date the most researched, recommended, and widely used treatment for schizophrenia spectrum disorders (SSDs) (McGregor et al., 2018). However, antipsychotic treatment response shows heterogeneity: about one third of patients treated with first-line (non-clozapine) antipsychotics, did not show a satisfactory response (Demjaha et al., 2017). Identifying predictors associated with poor treatment response in SSDs is important for a more targeted, personalized treatment approach. Previously identified clinical predictors of poor response to antipsychotics has been male sex, younger age at illness debut, longer duration of illness and untreated psychosis, worse premorbid functioning, as well as psychiatric comorbidity, and lack of response to treatment in the early phase of illness (Carbon and Correll, 2014; Cavalcante et al., 2020; Zhu et al., 2017). It has been reported that childhood trauma (CT) can affect the outcome of pharmacotherapy for other mental disorders (Nikkheslat et al., 2020; Williams et al., 2016). Possibly, CT could influence the general and differential response by type of antipsychotic medication in SSDs, although the literature is scarce.

CT, including sexual, physical, and emotional abuse, and physical and emotional neglect, has been found to be associated with factors implicated in treatment-resistant schizophrenia, such as variability in treatment response, and poor adherence to treatment, especially to antipsychotics (Hassan and De Luca, 2015). CT is commonly reported in SSDs: Almost 70 % of patients with SSDs reported moderate to severe CT, as compared to 34 % in patients with other mental health disorders (Mørkved et al., 2016). A dose-response relationship between CT and psychosis symptoms (Sahin et al., 2013) has been shown, and a meta-analysis found CT to be associated with a three-fold risk of developing SSDs (Varese et

al., 2012). Moreover, CT may be associated with worse outcome from psychosis (Trauelsen et al., 2016).

There is however a paucity of research on CT in relation to antipsychotic treatment effectiveness in SSDs. CT was more frequently reported in first episode psychosis (FEP) non-responders to antipsychotic treatment after 12 weeks, as compared to FEP responders (Misiak and Frydecka, 2016). CT exposure in SSDs was associated with a slower treatment response, higher dosages of antipsychotic treatment, and less likelihood of remission compared to those with low CT exposure (Kilian et al., 2020). Misiak et al. (2017) has suggested that the preliminary findings regarding CT and antipsychotics could imply that SSDs patients exposed to CT have a more severe biological dysregulation underlying a less favorable treatment outcome.

Moreover, CT has been suggested to be related to SSDs through sensitization of the dopamine system (Dahoun et al., 2019), elevating central dopaminergic neurotransmission (Valenti et al., 2011). A stress-induced activation of the HPA-axis could lead to dopamine sensitization in mesolimbic areas, and increased stress-induced striatal dopamine release (Van Winkel et al., 2008). Stimulation of D_2 receptors across brain regions are implicated in the pathophysiology of SSDs and has been supported by the observed antipsychotic effect of dopamine receptor antagonists (Popovic et al., 2019). As for older antipsychotic drugs, the newer atypical antipsychotics (AAPs) are functional striatal dopamine D_2 antagonists, however different AAPs are heterogenous in terms of affinity for other dopaminergic and non-dopaminergic receptor systems (Conley and Kelly, 2005). Theoretically, CT could exert a differentiated effect on antipsychotic treatment response depending on which type of AAP is used: Olanzapine has greater affinity for serotonin 5-HT_{2A} than for dopamine D_2 receptors, and amisulpride binds selectively to D_2 and D_3 receptors. Aripiprazole is a partial D_2 agonist, thus functioning as an antagonist during a hyperdopaminergic state and agonistically during

hypodopaminergica, often referred to as a dopamine system stabilizer (Conley and Kelly, 2005).

More knowledge on CT in relation to antipsychotic effectiveness is needed to facilitate a more targeted, personalized treatment approach. This is the first study to investigate CT in relation to SSDs and antipsychotic treatment effectiveness over 52 weeks in three AAPs (amisulpride, aripiprazole, and olanzapine). We aimed to compare symptom change from baseline as a measure of the treatment effectiveness in SSDs with CT and without CT. We further aimed to examine whether CT predicted a differentiated pattern of symptom change depending on type of AAP: amisulpride, aripiprazole and olanzapine.

2. Methods and Material

2.1. Study design

This study is a part of the Bergen, Stavanger, Innsbruck, and Trondheim (BeSt InTro) study, Haukeland University Hospital, Bergen, Norway. The BeSt InTro study is a researcher-initiated, head-to-head, semi-randomized multi-site prospective study comparing amisulpride, olanzapine and aripiprazole in SSDs. The BeSt InTro was approved in Norway by the Regional Committee for Medical Research Ethics (2010-3387) and the Norwegian Medicines Agency, and in Austria by the ethics committee at the Medical University of Innsbruck, and the Federal Office for Safety in Health Care (BASG) and registered as a clinical trial 10/03/2011 (NCT01446328). Clinical monitoring according to ICH-GCP was done by the Department of Research and Development, at the Haukeland University Hospital in Norway, as well as by the Austrian equivalent: Clinical Trial Centre at the Medical University Innsbruck. Participants for the current sub-study were recruited at the Medical University in Innsbruck, Innsbruck, Austria (n = 12); Stavanger University Hospital, Stavanger, Norway (n = 8); and Haukeland University Hospital, Bergen, Norway (n = 78). All gave informed consent to participate.

2.2. Sample

The current sample consisted of 98 patients with SSDs, 63 (64 %) males, mean age 30.9 years (*SD* = 12.7 years). Thirty-four (35 %) were naïve to antipsychotics, meaning no lifetime exposure to antipsychotics before inclusion in the study (demographic and clinical information in Table 1).

Table 1

Participants were required to meet diagnostic criteria for SSDs in the range F20-29 of the ICD-10 (World Health Organization, 1992): F20 Schizophrenia (*n* = 54), F21 Schizotypal disorder (*n* = 2), F22 Persistent delusional disorder (*n* = 13), F23 Acute and transient psychotic disorders (*n* = 14), F25 Schizoaffective disorder (*n* = 7), F 28 Other psychotic disorder (*n* = 1) or F29 Unspecified nonorganic psychosis (*n* = 7), as determined by the Structural Clinical Interview for Axis I Disorders (SCID; Spitzer et al., 1992), be ≥ 18 years of age, be able to understand the native language, and score ≥ 4 on at least one of the following items in the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987): Delusions (P1), hallucinatory behavior (P3), grandiosity (P5), suspiciousness/persecution (P6) or unusual thought content (G9). Exclusion criteria were organic psychosis or psychosis due to psychoactive substance use; however psychoactive substance use was not an exclusion criterion. Hypersensitivity to the active substance or to any of the excipients of the study drugs qualified for exclusion, as did prolactin-dependent tumors, phaeochromocytoma, and concomitant use of medications which could induce torsade de pointes, use of levodopa, and known risk of narrow-angle glaucoma. Suicidal ideation was not defined as reason for exclusion.

2.3. Study drug and randomization

The study participants were randomly assigned to receive orally administered amisulpride (*n* = 37; 37.7 %), aripiprazole (*n* = 34; 34.7 %) or olanzapine (*n* = 27; 27.5 %) (see Table 1 for demographic and clinical information by medication group). Dosages were decided upon by the patient and his or hers attending physician and was within the following ranges: Amisulpride 50 – 1200 mg/d, aripiprazole 5 – 30 mg/d, and olanzapine 2.5 – 20 mg/d.

Study-independent statisticians from the University of Bergen prepared the randomization by means of computer-generated sequences of the three study drugs in random order (Johnsen et al., 2020). Each randomized sequence of study drugs was put in a sealed envelope, and the attending physician offered the first drug in the sequence whenever a new participant was included. If the first study drug was not chosen (tolerability issues or previous inefficacy), the reason was registered and the next study drug in the sequence was offered, and repeated if the second drug was not eligible (Johnsen et al., 2020). Previous experience with the drug was not reason for rejection, due to the pragmatic design. The research team assessing the participants was blind to the randomization, whereas the treatment allocation was open to the patient and the clinical team. The participants were instructed not to reveal the study drug to the research team. The first study drug in the randomized sequence constituted the intention to treat (ITT) group, whereas the drug chosen for treatment was the basis for the per-protocol (PP) analyses.

2.4. Measurement

2.4.1. Childhood trauma

The Childhood Trauma Questionnaire Short-Form (CTQ-SF) is a 28-item self-report questionnaire screening for five subtypes of childhood trauma: childhood sexual, physical, and emotional abuse, and physical and emotional neglect (Bernstein et al., 2003). Each subscale consists of five items scored on a five-point Likert scale ranging from 1 (*never true*) to 5 (*very often true*), summarized into an overall CTQ-SF sum score ranging from 25-125.

Three items make up the Minimization-denial subscale, a validation scale, which was not used in the present study. The CTQ-SF has shown good internal consistency, test-retest reliability, and excellent internal reliability for the total scale, good to excellent internal reliability for the subscales as well as good sensitivity and specificity (Bernstein et al., 2003; Dovran et al., 2013). For the present study, the overall reliability estimate for the CTQ-SF was high: Cronbach's α = .92.

2.4.2. Other measures

The Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS) is a clinician administered clinical interview measuring symptom severity in SSDs (Kay et al., 1987). The PANSS is categorized into the positive, negative, and general psychopathology subscales. The items are scored on a 7-point Likert scale, ranging from 1 (*absent*) to 7 (*extreme*), and the range of PANSS scores is 30 - 210 points. Strong psychometric properties related to reliability, validity and sensitivity have been reported (Leucht et al., 2005). All raters were trained and certified by the PANSS Institute (panss.org)

The Calgary Depression Scale for Schizophrenia (CDSS) was used for rating depression symptoms in our sample of SSDs (Addington et al., 1993). Alcohol and drug use was assessed by means of the Clinician Alcohol Use Scale (CAUS) and Clinician Drug Use Scale (CDUS) (Drake et al., 1990; Mueser et al., 1995). Severity of illness was assessed by means of the Clinical Global Impression – Severity of Illness scale (CGI-S), a brief, clinician-rated instrument where the severity of the illness is rated on a Likert scale ranging from 1 – 7 (Guy, 1976).

3. Procedure

The PANSS was administered at baseline and at all follow-up points: week 1, 3, 6, 12, 26, 39 and 52 corresponding to visit 1, 2, 3, 4, 5, 6, 7 and 8. The CTQ-SF was administered at the 6-weeks follow-up when participants were more likely to be in a clinically stable phase, thus

increasing assessment validity. The SCID diagnostic interview was administered as early as possible to confirm the diagnoses, whereas the other measurements (i.e., CAUS, CDUS) were collected within the first three months of study inclusion.

4. Statistical analyses

Categorical and continuous variables were analyzed by means of chi-square tests and t-tests in STATA. Measures are presented as means (*M*) and standard deviations (*SD*), or as number (*n*) and percentages (*%*). A *p*-level of < .05 was considered statistically significant for all analyses.

The CTQ-SF scores were categorized into none, low, moderate and severe abuse or neglect, according to the threshold scores from the CTQ-SF manual (Bernstein and Fink, 1998). A dichotomous variable was created, grouping none and low levels of CT (no CT group; $n = 43$), for comparison to a group of moderate to severe levels of CT (CT group; $n = 55$) (Bernstein and Fink, 1998), for the purpose of examining SSDs CT and no CT group differences in psychosis symptom change.

Statistical models were fitted using R (version 4.0.2: https://www.r-project.org), and by using the statistical packages mice version 3.1-152 (multiple imputation) and nlme version 3.13.0 (LME-models). The primary analyses were based on the ITT groups, as determined in the pre-study protocol. LME models were chosen for its ability to account for dependency in the data due to repeated measures, and for handling missing data (assumed missing at random). The models were fitted to the PANSS total and subscale scores to examine symptom change from baseline to 52 weeks in the CT and no CT groups. Secondarily, analyses were performed to examine symptom change for the CT and no CT groups within each medication subgroup (olanzapine, amisulpride and aripiprazole). We included years of education, gender, age of illness onset, duration of untreated psychosis (DUP), previous exposure to antipsychotics, dosage of antipsychotic medication, and baseline psychosis symptoms as fixed

effects in all models. A random intercept for each individual was included as a random effect to account for dependencies in the data. Dosages of medication were converted to Defined Daily Doses (DDD), meaning the assumed average maintenance dose per day for a drug used for its main indication in adults (https://www.whocc.no/atc_ddd_index/). Multiple imputation was used on demographic and clinical variables included as covariates in the LME models in data to keep all participants in the analyses. Missing PANSS values were not imputed. Models were also fitted using no imputed values, i.e., removing patients with incomplete data, this did not alter the results. Data on sample size by visit number and medication group is provided in Table 2.

Table 2

5. Results

5.1. Clinical and demographic data

Mean age at baseline was 31.0 years (*SD* = 12.7), and mean age of illness onset was 23.5 years (*SD* = 8.6). The mean DUP was about two years (*M* = 105 weeks, *SD* = 244.2). When examining the CTQ-SF scores, we found that 55 (56.1 %) of the patients reported moderate to severe CT, and 43 (43.9 %) reported none or low CT. The CT and no CT groups were not statistically significantly different in alcohol or illegal substance use, nor did the groups differ in terms of psychosis symptoms at baseline, as shown by PANSS total scores, PANSS positive subscale, negative subscale, and general psychopathology subscale scores. There were no significant group differences in other demographic data, except for baseline symptoms of depression. The groups differed in CDSS scores: the CT group reported more depressive symptoms (*M* = 9.0, *SD* = 5.2) as compared to the no CT group (*M* = 5.7, *SD* = 5.1, *t* = -3.071, *p* = .002).

The randomization medication was accepted by 81.6 % (n = 80), while 18.4 % (n = 18) declined the first medication and was offered next drug in the sequence. Of those that switched medication, 4.1 % (n = 4) were in the no CT group, and 14.3 % (n = 14) in the CT group, which was statistically significant (χ^2 (1), 4.119, p = .040). Mean (SD) [reference range] medication serum level was 610 nmol/L (416) [100 – 1500] for amisulpride, 762 nmol/L (496) [200 – 1300] for aripiprazole and 231 nmol/L (288) [30 – 200] for olanzapine for the Norwegian patients, and the Austrian equivalents were: 203 nmol/L (164) [271 – 866] for amisulpride, 250 nmol/L (136) [223 – 781] for aripiprazole and 66.2 (5.30) [62 – 253] for olanzapine. The mean duration of adherence to antipsychotic treatment during the study was until visit 5, i.e., 26 weeks (SD = 2.07): there were no group differences between the no CT group (M = 5.67, SD = 2.04) and CT group (M = 5.07, SD = 2.08, p = .077).

5.2. Differences in psychosis symptoms change from baseline to 52 weeks in the CT and no CT groups

The results from the analyses using ITT or PP groups were convergent for all LME models (see Tables 3 and 4). The first LME model examined differences in symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by group (CT and no CT; see Figure 1). The following differences in symptom change reached significance: Less change in PANSS total scores for the CT group between baseline and 26 (p < .001) and 39 weeks (p = .030), PANSS positive subscale scores between baseline and 26 (p = .005) and 39 weeks (p = .035), PANSS negative subscale scores between 12 (p = .035) and 26 weeks (p = .031) and PANSS general psychopathology subscale scores between baseline and 26 weeks (p = .001; see Table 3).

Insert Table 3

Insert Figure 1

5.3. Change in psychosis symptoms by the CT and no CT groups within the three medication groups

Separate LME models examining symptom change (PANSS) for the three antipsychotics from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by group (CT and no CT) based on ITT (LME-ITT) and PP (LME-PP), respectively, were performed (see Figures 2 and 3 A-C). No significant differences in symptom change between CT and no CT groups emerged for amisulprid or aripiprazole for the LME-ITT or the LME-PP.

Insert Table 4

Insert Figure 2

Insert Figure 3 A-C

For olanzapine, the LME-ITT models showed less change in the CT group for PANSS total scores from baseline to 12, 26, 39 and 52 weeks (*p*-levels .005, .003, .046 and .031, respectively), less change for the CT group in PANSS positive subscale scores from baseline to week 26 ($p = .027$), less change for the CT group in PANSS negative subscale scores from baseline to week 12 ($p = .007$), and less change for the CT group in PANSS general psychopathology subscale scores from baseline to weeks 12, 26 and 52 (*p*-levels .009, .002, and .028, respectively). The LME-PP model showed statistically significant comparisons of symptom change: The CT group showed less change in PANSS total scores at weeks 12 ($p = .028$) and 26 ($p = .050$), PANSS negative subscale scores at weeks 12 ($p = .006$) and 39 ($p = .026$), and PANSS general psychopathology subscale scores at weeks 6, 12 and 26 (*p*-level .040, .022, and .026, respectively).

6. Discussion

CT in SSDs predicted a slower treatment response and less antipsychotic effectiveness, which was particularly pronounced after 26 weeks, i.e., midway through the treatment. The differences in symptom change between the CT and no CT groups did however converge and was not statistically significant at 52 weeks, thus showing similarities in symptom development over time. Secondary analyses showed a differential effect of CT related to type of antipsychotics: SSDs patients that reported CT and received olanzapine showed less antipsychotic effectiveness compared to SSDs patients with no CT receiving olanzapine. This was not observed for amisulprid or aripiprazole. Our results indicate that type of antipsychotic medication, especially the use of olanzapine for SSDs patients reporting CT, could be of relevance in terms of predicting antipsychotic effectiveness the first year after initiation of a new treatment course. We were able to control for several confounding variables that could have influenced the antipsychotic treatment effectiveness: premorbid functioning (education), sex, age of illness onset, DUP, dosage of antipsychotic medication, previous exposure to antipsychotics, and baseline psychosis symptoms.

Our main result that CT was associated with a slower antipsychotic treatment response in SSDs is in line with findings from a recently published study by (Kilian et al., 2020). CT in SSDs predicted a slower response to treatment, but the CT and no CT groups achieved similar symptom levels after 24 months (Kilian et al., 2020). This study did however use the depot formulation of flupentixol (long-acting injectable), an older antipsychotic drug than the AAPs included in the present study. Also, the researchers did not control for DUP or illness duration. Further, CT was found to be related to antipsychotic non-responders in a sample of FEP after 12-months of treatment (Misiak and Frydecka, 2016). Treatment resistance was predicted by CT in a study by (Hassan and De Luca, 2015), where persons with SSDs reporting four or more adverse experiences, were four times more likely to be treatment

resistant. Illness onset age and DUP, which our study controlled for, were associated with treatment resistance (Hassan and De Luca, 2015). They did however not report information on type of antipsychotic medication.

Secondary analyses indicated that SSDs patients reporting CT who received olanzapine showed less change in psychosis symptoms after 52 weeks of treatment compared to those with no CT who received olanzapine. The lower treatment effectiveness was particularly visible for overall psychosis symptom load, as well as psychosis-related general psychopathology symptoms related to inner tension/anxiety, mannerisms/postures, motor retardation, unusual thought content, difficulties with attention, insight and impulse control, and social avoidance. Our results on CT and the type of antipsychotic is contrary to Misiak and Frydecka (2016) that reported no differences in terms of type of antipsychotics over 12 weeks in FEP medication-responders compared to FEP non-responders who more frequently reported CT. We have not found any other previous research directly comparable to the present study.

Our results indicate that for SSDs individuals with CT, olanzapine might not be an optimal treatment strategy. The study drugs have distinctly different receptor binding profiles, and it could be speculated that the inferiority of olanzapine might be an effect of CT specifically related to olanzapine and its pharmacological profile. There are however no overreaching theories explaining the relation between CT and reduced antipsychotic effectiveness in SSDs. Studies indicate that CT could be associated with the development of psychosis through over-activating the HPA-axis which may lead to increased levels of glucocorticoids (Walker et al., 2008). Glucocorticoids have been linked to dysfunctional monoamine and/or dopamine regulation through activation of the mesolimbic dopaminergic circuit. Further, the effect of antipsychotics is described as proportional to the effect on dopamine receptors (Howes and Kapur, 2009). Various AAPs differ in their receptor affinity

(e.g., dopamine, serotonin), and one may hypothesize that CT could influence antipsychotic treatment outcomes in SSDs possibly due to a more profound biological dopamine-related dysregulation in traumatized individuals. A biological dysregulation could potentially be associated with the negative influence of CT on glucocorticoids and dopamine circuits, and possibly also inflammation (Misiak et al., 2017).

There are limitations to consider when interpreting the results. Our sample size is small, which is related to an increased risk for Type II error and of spurious findings. The study might be under-powered to detect differences between the CT and no CT groups: there might be relations between CT and antipsychotic effects that was overlooked. The CTQ-SF scores were dichotomized to create SSDs groups based on level of exposure to CT, however keeping the CT scores continuous may have had advantages in detecting relations between CT and psychosis symptom change. The CTQ-SF scores corresponding to low levels of CT were included in the no CT group, as low levels of CT have been found to be quite common in the general population. Using moderate to severe levels of CT as cut-off might therefore provide more sensitivity in measuring CT effects in patient populations (Baker & Maiorino, 2010). Further, data missing not at random cannot be ruled out entirely since we were not allowed to follow participants after dropping out of the study. Concerns have been raised regarding the validity and reliability of retrospective measure of CT in SSDs (Susser and Widom, 2012). However, retrospective reports of CT in SSDs have shown good concurrent and convergent validity, and good stability over a 7-year period (Fisher et al., 2011), and CT reports were not influenced by psychosis symptoms (Simpson et al., 2019). Alcohol or illegal substance abuse was not included in our models, the groups did however not differ in substance or alcohol abuse at baseline.

The BeSt InTro study was designed to mimic clinical practice, increasing generalizability and ecological validity providing treatment of SSDs according to national

guidelines (Norwegian Directorate of Health, 2013). The inclusion criteria were broad, and treatment was open label and administered by the psychiatrist in cooperation with the patient. Personnel assessing the patients were uninformed of treatment allocation, ensuring blind rating of effect. Dropout-rates in the BeSt InTro study was comparable to previous research (Johnsen et al., 2020). There is a possibility of treatment discontinuation in SSDs with CT as a consequence of lack of clinically or personally meaningful symptom improvement despite treatment adherence. However, this was not supported by our data, and should be investigated in a larger sample. We investigated the total CTQ-SF scores and not CT subtypes of abuse and neglect, which should be a target for future research (Kilian et al., 2020).

This is, to our best knowledge, the first prospective, pragmatic, and randomized study to investigate the relation between CT and antipsychotic treatment response to three AAPs in SSDs during 52 weeks of treatment. We were able to control for several factors that could have influenced the results. Our results indicated a generally slower antipsychotic treatment response in SSDs exposed to CT compared to those not reporting CT, and SSDs patients with CT showed significantly less treatment effect compared to the no CT SSDs patients when receiving olanzapine. The evidence regarding CT and antipsychotics is to date insufficient to support a specific pharmacological clinical recommendation. We encourage future antipsychotic treatment trials in SSDs to include information on CT exposure and believe that increased knowledge on CT and antipsychotics could be valuable in aiding and facilitating more optimal individualized treatment decision making processes. Our findings indicated that in patients with SSD and trauma experience, delayed response to AAPs could be expected. Given that our results are replicated by other groups, a longer evaluation period before considering change of medication could therefore be in place for patients with CT, compared to those without CT.

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Table 1 Mean (SD) clinical and demographic characteristics by CT and no CT groups and antipsychotic medication subgroups

	No CT group (*n* = 43)	CT group (*n* = 55)	Statistics (*t, f* or chi)	*p* - value	Amisulpride (*n* = 32)	Aripiprazole (n = 31)	Olanzapine (n = 35)	Statistics (*f* or chi)	*p* - value	Total (*n* = 98)
Age, years	31.2 (13.2)	30.8 (12.4)	0.170	0.864	30.5 (11.5)	30.8 (12.8)	31.5 (13.9	0.05	0.964	30.95 (12.68)
Men	32/43 (74%)	31/55 (56%)	3.426	0.064	21/32 (66%)	19/31(61%)	23/35 (66%)	0.177	0.915	63/98 (64%)
Caucasian	35/43 (81%)	45/55 (82%)	0.003	0.957	29/32 (91%)	23/31 (74%)	28/35 (80%)	2.932	0.231	80/98 (81%)
Years of education	12.7 (3)	11.9 (2.7)	1.313	0.192	13.0 (3.1)	11.6 (2.6)	12.1 (2.8)	2.20	0.116	12.2 (2.8)
Living alone (yes) (*n* = 92)	15/43 (35%)	24/55 (44%)	0.693	0.405	15/31 (48%)	9/29 (31%)	15/32 (47%)	2.251	0.324	39/98 (42%)
Employed (yes) (*n* = 93)	14/43 (33%)	12/55 (22%)	1.728	0.189	12/32 (37%)	6/31 (19%)	8/35 (23%)	3.036	0.219	26/98 (28%)
DDD (*n* = 94)	1.10 (.52)	1.08 (.44)	0.204	0.838	1.01 (.47)	1.04 (.54)	1.21 (.38)	1.80	0.170	1.09 (.47)
DUP, weeks (*n* = 53)	40.6 (79.0)	80.9 (121.5)	1.456	0.152	66.1 (118.1)	46.2 (82.4)	74.8 (115.5)	0.32	0.727	63.4 (106.2)
Psychosis onset age, years (*n* = 69)	23.8 (7.1)	23.3 (9.7)	0.244	0.807	24.9 (10)	20.9 (5.6)	24.1 (8.9)	1.26	0.289	23.5 (8.6)
Diagnosis										
Schizophrenia	19/43 (44%)	35/55 (64%)	3.690	0.055	18/32 (56%)	16/31 (52%)	20/35 (57%)	0.228	0.892	54/98 (55%)
Schizotypal	0/43 (0%)	2/55 (4%)	1.596	0.206	1/32 (3%)	0/31 (0%)	1/35 (3%)	0.950	0.622	2/98 (2%)
Delusional disorder	7/43 (16%)	6/55 (11%)	0.604	0.437	3/32 (9%)	5/31 (16%)	5/30 (14%)	0.673	0.714	13/98 (13%)
Brief psychotic disorder	8/43 (19%)	6/55 (11%)	1.167	0.280	8/32 (25%)	2/31 (6%)	4/35 (11%)	4.787	0.091	14/98 (14%)
Schizo-affective disorder	5/43 (12%)	2/55 (4%)	2.323	0.127	2/32 (6%)	4/31 (13%)	1/35 (3%)	2.558	0.278	7/98 (7%)
Other psychotic disorder	1/43 (2%)	0/55 (0%)	1.293	0.256	0/32 (0%)	1/31 (3%)	0/35 (0%)	2.184	0.336	1/98 (1%)
Unspecified psychotic disorder	3/43 (7%)	4/55 (7%)	0.003	0.955	0/32 (0%)	3/31 (10%)	4/35 (11%)	3.731	0.155	7/98 (7%)
Smoking (yes) (*n* = 90)	21/40 (52%)	36/50 (72%)	3.638	0.056	20/30 (67%)	19/29 (65%)	18/31 (58%)	0.574	0.751	57/90 (63%)
CAUS (abuse or dependence) *(n* = 93)	2/40 (5%)	7/53 (13%)	1.175	0.185	3/32 (9%)	5/29 (17%)	1/32 (3%)	3.473	0.176	9/93 (10%)
CDUS (abuse or dependence) (*n* = 93)	10/40 (25%)	10/53 (19%)	0.507	0.476	9/32 (28%)	5/29 (17%)	6/32 (19%)	1.287	0.525	20/93 (21%)
Antipychotics naive	18/43 (42%)	16/55 (29%)	1.736	0.188	10/32 (31%)	13/31 (42%)	11/35 (31%)	1.049	0.592	34/98 (34%)
PANSS total	76.2 (18.4)	79.9 (13.5)	-1.142	0.255	78.1 (17.7)	76.5 (12.4)	79.8 (17.1)	0.35	0.707	78.2 (15.9)
PANSS positive	20.7 (4.8)	21.9 (4.9)	-1.242	0.216	21.5 (4.7)	21.4 (5.3)	21.2 (4.8)	0.03	0.975	21.4 (4.9)
PANSS negative	16.6 (6.6)	18 (5.4)	-1.159	0.249	16.5 (5.5)	17.0 (6.0)	18.4 (6.3)	0.86	0.426	17.3 (5.9)
PANSS general	38.9 (10.1)	40 (7.2)	-0.599	0.550	40.1 (10.2)	38.1 (6.4)	40.2 (8.8)	0.59	0.555	39.5 (8.6)

CGI	5 (0.8)	5.2 (0.7)	-0.992	0.323	5.03 (.93)	5.13 (.62)	5.17 (.78)	0.27	0.086	5.1 (0.1)
GAF (*n* = 97)	35.6 (6.4)	35.7 (9.4)	-0.037	0.970	38 (9.2)	34 (6.4)	35 (8.4)	2.15	0.122	35.6 (8.2)
CDSS (*n* = 91)	5.7 (5.1)	9 (5.2)	-3.071	0.002*	8.2 (5.8)	6.1 (4.4)	7.9 (5.6)	1.38	0.257	7.5 (5.4)
BMI (*n* = 86)	24.4 (4.6)	25.7 (5.7)	-1.192	0.236	24.7 (5.3)	26.3 (5.0)	24.5 (5.3)	1.00	0.372	25.1 (5.2)
CTQ-SF sum	31.1 (4.2)	54.3 (13.6)	-10.812	.000*	41.7 (16.1)	45.5 (16.7)	45.0 (14.4)	0.57	0.566	44.1 (15.6)
Emotional abuse	6.4 (1.7)	13.3 (4.7)	-9.107	.000*	9.7 (5.5)	10.5 (4.9)	10.7 (4.8)	0.38	0.682	10.3 (5.1)
Physical abuse	5.3 (0.6)	8.5 (4.1)	-5.071	.000*	6.3 (2.3)	7.9 (4.6)	6.9 (3.1)	1.87	0.160	7.1 (3.5)
Sexual abuse	5.0 (0)	7.4 (4)	-3.948	.000*	6.3 (2.2)	6.9 (4.6)	5.9 (2.3)	0.95	0.389	6.3 (3.2)
Emotional neglect	8.1 (2.7)	15.1 (4.6)	-8.988	.000*	11.3 (5.5)	12.1 (4.6)	12.6 (5.5)	0.53	0.589	12.0 (5.2)
Physical neglect	6.3 (1.5)	9.9 (3.7)	-6.041	.000*	8.1 (3.5)	8.0 (2.9)	8.9 (3.9)	0.63	0.537	8.4 (3.5)
Other psychofarmaca (*n* = 33)			8.589	0.572				16.416	0.69	
Zopiclone	5 (15.2%)	4 (12.1%)			3 (27%)	4 (36%)	2 (18%)			9 (27.3%)
Diazepam	3 (9.1%)	3 (9%)			2 (18%)	2 (18%)	2 (18%)			6 (18.2%)
Oxazepam	5 (15.2%)	3 (9%)			3 (27%)	1 (9%)	4 (36%)			8 (24.2%)
Setraline	0 (0%)	1 (3%)			0 (0%)	1 (9%)	0 (%)			1 (3%)
Biperiden	0 (0%)	1 (3%)			0 (0%)	0 (0%)	1 (9%)			1 (3%)
Venlafaxin	1 (3%)	1 (3%)			1 (9%)	0 (0%)	1 (9%)			2 (6.1%)
Pregabaline	0 (0%)	1 (3%)			1 (9%)	0 (0%)	0 (%)			1 (3%)
Paroxetine	1 (3%)	0 (0%)			0 (0%)	1 (9%)	0 (%)			1 (3%)
Fluoxetine	0 (0%)	1 (3%)			0 (0%)	1 (9%)	0 (%)			1 (3%)
Lorazepam	0 (0%)	2 (6.1%)			1 (9%)	1 (9%)	0 (%)			2 (6.1%)

Note. N = 98 unless otherwise specified. DDD = Defined daily dose of antipsychotic medication. CT = Childhood trauma. CTQ-SF = Childhood trauma questionnaire short-form. PANSS = positive and negative syndrome scale. CGI = clinical global impression scale. GAF = Global assessment of functioning. CDSS = Calgary depression scale for schizophrenia. BMI = Body mass index. Other psychopharmaca registered at baseline. * *p* level significant at .05.

Table 2 Number of patients in the ITT and PP-groups by visit number

	Medication group	Baseline	week 1	week 3	week 6	week 12	week 26	week 39	week 52
ITT group	Amisulprid	32	30	30	31	25	19	20	19
	Aripiprazole	31	29	28	24	20	17	11	9
	Olanzapine	35	33	33	33	28	19	20	21
	Total	*98*	*92*	*91*	*88*	*73*	*55*	*51*	*49*
PP group	Amisulprid	37	36	35	35	30	24	25	23
	Aripiprazole	34	30	31	28	21	16	11	9
	Olanzapine	27	26	25	25	22	15	15	17
	Total	*98*	*92*	*91*	*88*	*73*	*55*	*51*	*49*

Note. ITT = intention to treat group, PP = per protocol group. ITT constitutes the randomization drug, whereas the PP group shows the medication actually used.

Table 3 LME-ITT models examining symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by SSDs group (CT and no CT)

Antipsychotic medication	Outcome		Baseline [b] (M, SE)	1 week	3 weeks	6 weeks	12 weeks	26 weeks	39 weeks	52 weeks
Overall	PANSS total scores	No CT	78.2 (15.9)	66.7 (4.5)	59.9 (4.5)	56.5 (4.5)	54.1 (4.6)	48.5 (4.7)	47 (4.8)	49 (4.8)
		CT	78.2 (15.9)	69.5 (4.7)	64.1 (4.7)	62.2 (4.7)	60.3 (4.7)	62.3 (4.9)	55.5 (5)	54.9 (5.1)
		Δ [a]	NA	2.8 (3.2) [0.389]	4.2 (3.3) [0.213]	5.7 (3.3) [0.083]	6.2 (3.5) [0.093]	13.8 (3.8) [<0.001]*	8.6 (4) [0.03]*	6 (4) [0.112]
	PANSS positive	No CT	21.3 (4.9)	17.4 (1.4)	14.8 (1.4)	12.9 (1.4)	12.3 (1.5)	10.1 (1.5)	10.1 (1.6)	10.7 (1.5)
		CT	21.3 (4.9)	18.5 (1.5)	16 (1.5)	14.7 (1.5)	13.1 (1.5)	13.5 (1.6)	12.8 (1.6)	12.9 (1.6)
		Δ [a]	NA	1.1 (1) [0.265]	1.3 (1) [0.172]	1.8 (1) [0.077]	0.8 (1.1) [0.484]	3.4 (1.2) [0.005]*	2.7 (1.2) [0.035]*	2.2 (1.2) [0.097]
	PANSS negative	No CT	17.4 (6)	16.2 (1.8)	15.1 (1.8)	15.5 (1.8)	14.8 (1.8)	14.1 (1.9)	13.6 (1.9)	13.8 (1.9)
		CT	17.4 (6)	15.7 (1.9)	15.4 (1.8)	16.3 (1.9)	17.4 (1.9)	17 (1.9)	16 (2)	14 (2)
		Δ [a]	NA	-0.5 (1.1) [0.657]	0.3 (1.1) [0.757]	0.7 (1.1) [0.48]	2.6 (1.2) [0.035]*	3 (1.4) [0.031]*	2.4 (1.4) [0.077]	0.1 (1.4) [0.946]
	PANSS general psychopathology	No CT	39.5 (8.6)	33.1 (2.3)	30 (2.3)	28 (2.3)	27 (2.3)	24.4 (2.4)	23.2 (2.5)	24.5 (2.5)
		CT	39.5 (8.6)	35.2 (2.4)	32.6 (2.4)	31.1 (2.4)	29.7 (2.4)	31.5 (2.5)	26.7 (2.5)	28.1 (2.6)
		Δ [a]	NA	2.1 (1.7) [0.231]	2.7 (1.7) [0.138]	3.1 (1.7) [0.064]	2.8 (1.9) [0.159]	7.2 (2.1) [0.001]*	3.6 (2.1) [0.085]	3.6 (2.1) [0.084]
Amisulprid	PANSS total scores	No CT	78.1 (17.7)	67.7 (7.4)	61.6 (7.4)	55 (7.4)	53.7 (7.5)	48 (7.7)	44.4 (7.6)	48.6 (7.7)
		CT	78.1 (17.7)	67 (6.4)	62.6 (6.5)	55.8 (6.5)	54.1 (6.5)	53 (7.1)	51.7 (7.1)	49.7 (7.1)
		Δ [a]	NA	-0.8 (4.6) [0.866]	1 (4.7) [0.839]	0.7 (4.6) [0.986]	0.5 (4.9) [0.932]	4.9 (5.5) [0.337]	7.2 (5.5) [0.193]	1.1 (5.5) [0.863]
	PANSS positive	No CT	21.5 (4.7)	17.8 (2.2)	14.8 (2.2)	12.5 (2.2)	11.5 (2.2)	9.48 (2.3)	9 (2.3)	9.81 (2.3)
		CT	21.5 (4.7)	16.4 (2)	14 (2)	12.5 (2)	10.8 (2)	11.4 (2.3)	10.9 (2.3)	9.65 (2.3)
		Δ [a]	NA	-1.4 (1.4) [0.327]	-0.8 (1.5) [0.566]	0.1 (1.4) [0.907]	-0.7 (1.6) [0.65]	1.9 (1.8) [0.289]	1.9 (1.8) [0.284]	-0.1 (1.8) [0.945]
	PANSS negative	No CT	16.5 (5.5)	15.8 (4.5)	14.8 (4.5)	14.8 (4.5)	15.4 (4.5)	13.5 (4.5)	13.1 (4.5)	14.4 (4.5)
		CT	16.5 (5.5)	15.6 (3.8)	15.2 (3.8)	13.8 (3.8)	16 (3.8)	13.7 (4)	15.2 (4)	12.8 (4)
		Δ [a]	NA	-0.2 (1.9) [0.903]	0.4 (1.9) [0.892]	-1 (1.9) [0.612]	0.7 (2) [0.792]	0.2 (2.2) [0.919]	2.2 (2.2) [0.34]	-1.6 (2.2) [0.426]
	PANSS general psychopathology	No CT	40.1 (10.2)	33.8 (4.1)	31.8 (4.1)	27.6 (4.1)	26.6 (4.1)	24.5 (4.2)	22.1 (4.2)	24.3 (4.2)
		CT	40.1 (10.2)	34.9 (3.5)	33.6 (3.6)	29.7 (3.6)	27.5 (3.6)	28.3 (4)	25.5 (3.9)	27.4 (3.9)

		Δ [a]	NA	1 (2.5) [0.684]	1.7 (2.6) [0.499]	2.1 (2.5) [0.402]	0.9 (2.7) [0.752]	3.8 (3) [0.235]	3.4 (3) [0.267]	3.1 (3.1) [0.352]
Aripiprazole	PANSS total scores	No CT	76.3 (12.5)	66 (15.4)	64.3 (15.8)	65.4 (15.4)	62.9 (15.5)	52.7 (15.5)	58.9 (15.8)	56.5 (15.5)
		CT	76.3 (12.5)	65.4 (16.4)	66.2 (16.4)	63.8 (16.5)	56.7 (16.4)	57.4 (16.7)	57.7 (16.8)	49.1 (18.1)
		Δ [a]	NA	-0.7 (7.4) [0.93]	1.8 (7.5) [0.804]	-1.7 (7.7) [0.836]	-6.2 (8.1) [0.422]	4.6 (8.4) [0.552]	-1.3 (9.6) [0.912]	-7.4 (11.6) [0.497]
	PANSS positive	No CT	21.2 (5.2)	17 (7.4)	15.7 (7.5)	15.4 (7.4)	14.7 (7.4)	11.5 (7.4)	13.7 (7.5)	12.1 (7.5)
		CT	21.2 (5.2)	19.2 (7.8)	17.9 (7.8)	15.7 (7.8)	12.3 (7.9)	11.7 (7.9)	14.2 (7.9)	11.1 (8.2)
		Δ [a]	NA	2.2 (2.9) [0.465]	2.2 (2.9) [0.427]	0.4 (3) [0.92]	-2.4 (3.2) [0.434]	0.3 (3.3) [0.892]	0.5 (3.5) [0.906]	-1 (4.1) [0.813]
	PANSS negative	No CT	17.1 (6.1)	15.5 (10.1)	15.2 (10.1)	16.7 (10.1)	15 (10.1)	14.2 (10.1)	16.1 (10.1)	15 (10.1)
		CT	17.1 (6.1)	14.1 (10.2)	15.6 (10.2)	17.2 (10.3)	17.3 (10.1)	19.1 (10.2)	19 (10.2)	14.3 (10.7)
		Δ [a]	NA	-1.4 (2.2) [0.537]	0.4 (2.2) [0.857]	0.5 (2.4) [0.865]	2.2 (2.5) [0.372]	4.9 (2.7) [0.067]	2.8 (3.2) [0.382]	-0.8 (4) [0.864]
	PANSS general psychopathology	No CT	38 (6.4)	32.3 (8.3)	32.1 (8.6)	32.1 (8.3)	32 (8.4)	26.2 (8.4)	28.2 (8.6)	28.5 (8.4)
		CT	38 (6.4)	33 (9)	33.5 (9)	32.2 (9.1)	28.3 (9)	27.8 (9.2)	26.3 (9.2)	25 (9.9)
		Δ [a]	NA	0.7 (4.2) [0.877]	1.4 (4.3) [0.766]	0.1 (4.5) [0.979]	-3.7 (4.5) [0.401]	1.6 (4.7) [0.756]	-1.9 (5.3) [0.705]	-3.5 (6.3) [0.548]
Olanzapine	PANSS total scores	No CT	79.8 (17.1)	68.1 (9.4)	55.6 (9.6)	53.5 (9.4)	47.9 (9.4)	49 (10.1)	43 (9.8)	44.4 (9.8)
		CT	79.8 (17.1)	73.8 (8.1)	62.7 (8)	63.8 (8)	64.6 (8)	70 (8.5)	56.1 (8.4)	58.7 (8.3)
		Δ [a]	NA	5.7 (5.5) [0.304]	7.1 (5.6) [0.224]	10.4 (5.7) [0.065]	16.7 (6) [0.005]*	21 (7.4) [0.003]*	13.1 (6.8) [0.046]*	14.4 (6.8) [0.031]*
	PANSS positive	No CT	21.2 (4.9)	17.6 (2.7)	14.2 (2.8)	12.4 (2.7)	11.4 (2.7)	11 (3)	9.67 (2.9)	11.1 (2.9)
		CT	21.2 (4.9)	19 (2.3)	15.7 (2.3)	15 (2.3)	14.5 (2.3)	16 (2.5)	12.9 (2.4)	14.3 (2.4)
		Δ [a]	NA	1.4 (1.7) [0.416]	1.5 (1.7) [0.393]	2.7 (1.8) [0.109]	3.2 (1.9) [0.077]	5 (2.3) [0.027]*	3.3 (2.1) [0.141]	3.2 (2.2) [0.147]
	PANSS negative	No CT	18.4 (6.3)	15.7 (4)	14 (4.1)	14.3 (4)	12.4 (4)	13.4 (4.2)	11.2 (4.1)	10.7 (4.1)
		CT	18.4 (6.3)	17.7 (3.6)	16.1 (3.5)	18 (3.6)	18.9 (3.5)	18.7 (3.7)	16 (3.7)	15.2 (3.6)
		Δ [a]	NA	2 (2.2) [0.344]	2.1 (2.2) [0.31]	3.6 (2.2) [0.092]	6.5 (2.3) [0.007]*	5.2 (2.8) [0.058]	4.7 (2.6) [0.068]	4.4 (2.6) [0.105]
	PANSS general psychopathology	No CT	40.2 (8.8)	34.1 (5.5)	26.8 (5.5)	26.1 (5.5)	23.6 (5.5)	23.8 (5.8)	21.4 (5.6)	21.8 (5.6)
		CT	40.2 (8.8)	37.2 (5.1)	31.1 (5.1)	31.3 (5.1)	31.4 (5.1)	35.4 (5.3)	27.4 (5.3)	29.3 (5.2)
		Δ [a]	NA	3.1 (2.8) [0.267]	4.3 (2.8) [0.123]	5.2 (2.8) [0.068]	7.8 (3) [0.009]*	11.6 (3.7) [0.002]*	6 (3.5) [0.079]	7.4 (3.4) [0.028]*

Note. N = 98. LME = Linear mixed effects model. ITT = intention-to-treat. PANSS = Positive and Negative Syndrome Scale. SSDs = schizophrenia spectrum disorders. CT = childhood trauma. M = estimated mean scores. SE = Standard errror. NA = not applicable. * significant $p < .05$. [a] difference of change from baseline between CT and no CT groups, (standard deviation), [p value]. [b] mean PANSS score as

baseline values are controlled for in the models. Linear mixed effects analyses included the following variables as fixed effects: years of education, gender, age of illness onset, duration of untreated psychosis, previous exposure to antipsychotics, and dosage of antipsychotic medication (defined daily doses) and baseline PANSS values.

Table 4 LME-PP models examining symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by SSDs group (CT and no CT)

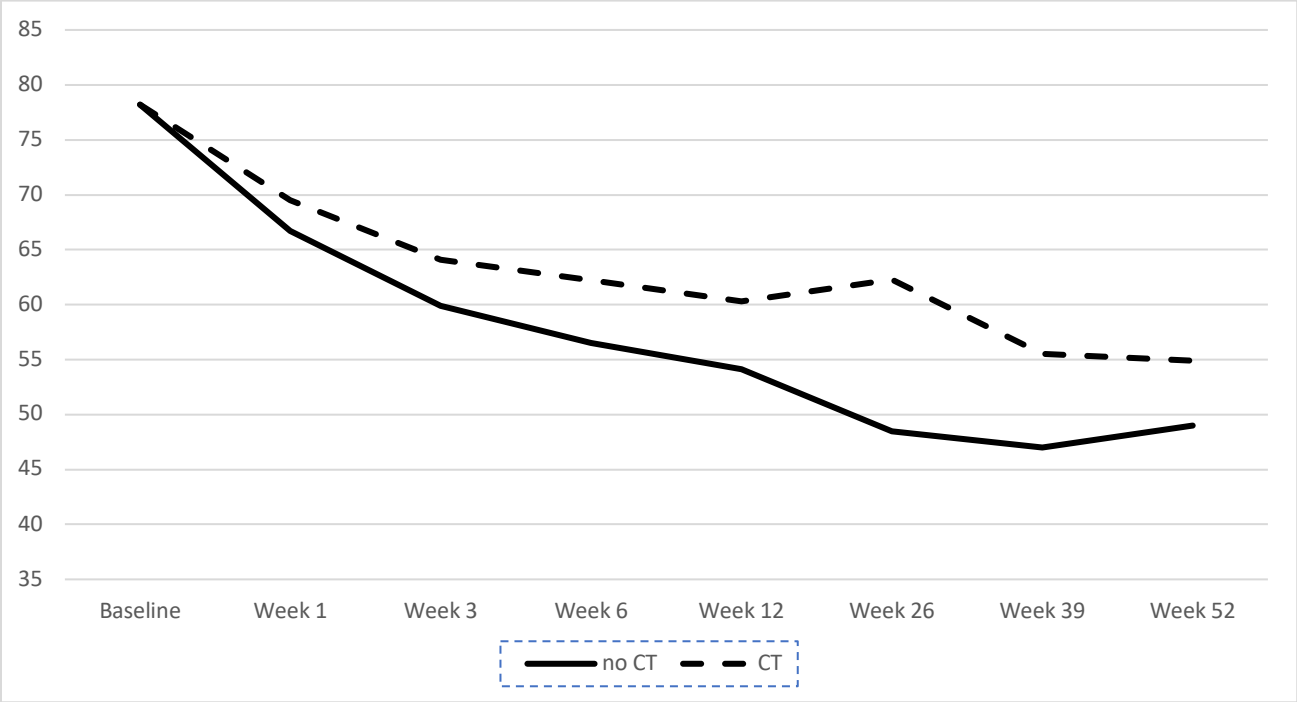
Antipsychotic medication	Outcome		Baseline [b] (M, SE)	1 week	3 weeks	6 weeks	12 weeks	26 weeks	39 weeks	52 weeks
Overall	PANSS total scores	No CT	78.2 (15.9)	66.8 (4.5)	60 (4.5)	56.6 (4.5)	54.1 (4.6)	48.8 (4.7)	47.1 (4.8)	49.1 (4.8)
		CT	78.2 (15.9)	69.2 (4.7)	63.9 (4.7)	61.9 (4.7)	59.7 (4.7)	61.9 (4.9)	55.1 (5)	54.9 (5.1)
		Δ [a]	NA	2.4 (3.3) [0.468]	3.9 (3.2) [0.26]	5.3 (3.3) [0.11]	5.7 (3.5) [0.096]	13.1 (3.8) [0.001]*	8 (4) [0.036]*	5.9 (4.1) [0.129]
	PANSS positive	No CT	21.3 (4.9)	17.5 (1.4)	14.8 (1.4)	13 (1.4)	12.3 (1.5)	10.2 (1.5)	10.2 (1.6)	10.7 (1.5)
		CT	21.3 (4.9)	18.5 (1.5)	15.9 (1.5)	14.7 (1.5)	13 (1.5)	13.5 (1.6)	12.7 (1.6)	12.7 (1.6)
		Δ [a]	NA	1 (1) [0.31]	1.1 (1) [0.244]	1.6 (1) [0.117]	0.6 (1.1) [0.517]	3.2 (1.2) [0.005]*	2.4 (1.3) [0.055]	2 (1.3) [0.106]
	PANSS negative	No CT	17.4 (6)	16.2 (1.8)	15.1 (1.8)	15.6 (1.8)	14.8 (1.8)	14.1 (1.9)	13.7 (1.9)	13.9 (1.9)
		CT	17.4 (6)	15.6 (1.9)	15.5 (1.8)	16.3 (1.9)	17.3 (1.9)	17.1 (1.9)	16 (2)	14 (2)
		Δ [a]	NA	-0.6 (1.1) [0.599]	0.3 (1.1) [0.81]	0.7 (1.1) [0.533]	2.4 (1.2) [0.04]*	3 (1.3) [0.019]*	2.3 (1.4) [0.096]	0.1 (1.4) [0.981]
	PANSS general psychopathology	No CT	39.5 (8.6)	33.2 (2.3)	30 (2.3)	28 (2.3)	27 (2.3)	24.4 (2.4)	23.2 (2.5)	24.5 (2.5)
		CT	39.5 (8.6)	35.2 (2.4)	32.5 (2.4)	31.1 (2.4)	29.4 (2.4)	31.4 (2.5)	26.7 (2.5)	28.2 (2.6)
		Δ [a]	NA	2 (1.7) [0.24]	2.5 (1.7) [0.182]	3.1 (1.7) [0.077]	2.4 (1.8) [0.149]	7 (2) [0.001]*	3.6 (2.1) [0.1]	3.7 (2.2) [0.107]
Amisulprid	PANSS total scores	No CT	81 (17.5)	70.1 (7.1)	63.3 (7.1)	58.5 (7.1)	56.2 (7.4)	48.5 (7.6)	46.7 (7.5)	50.5 (7.6)
		CT	81 (17.5)	67.8 (6.3)	60.4 (6.4)	58.2 (6.5)	56.9 (6.5)	60.5 (6.8)	54.1 (6.8)	57.9 (7)
		Δ [a]	NA	-2.2 (5.3) [0.675]	-2.9 (5.4) [0.621]	-0.3 (5.5) [0.941]	0.7 (5.6) [0.922]	12 (6) [0.056]	7.4 (6.1) [0.282]	7.4 (6.2) [0.277]
	PANSS positive	No CT	21.9 (4.8)	18.4 (2.1)	15.3 (2.1)	13.6 (2.1)	12.4 (2.1)	10.1 (2.2)	10.1 (2.2)	10.7 (2.2)
		CT	21.9 (4.8)	15.9 (1.8)	13.4 (1.9)	12.7 (1.9)	11.6 (1.9)	12.7 (2)	11.8 (2)	12.3 (2)
		Δ [a]	NA	-2.5 (1.6) [0.117]	-1.8 (1.6) [0.248]	-0.8 (1.6) [0.624]	-0.8 (1.7) [0.635]	2.7 (1.8) [0.184]	1.7 (1.8) [0.351]	1.6 (1.9) [0.408]
	PANSS negative	No CT	17.6 (5.9)	16.7 (2.9)	16.1 (2.9)	16.2 (2.9)	16.8 (3)	13.8 (3)	13.6 (3)	14.5 (3)
		CT	17.6 (5.9)	16 (2.5)	15.6 (2.6)	15.4 (2.6)	16.3 (2.6)	16.6 (2.7)	15.6 (2.7)	15 (2.8)
		Δ [a]	NA	-0.7 (1.8) [0.705]	-0.5 (1.8) [0.812]	-0.8 (1.8) [0.64]	-0.5 (2) [0.761]	2.8 (2.1) [0.184]	2 (2.1) [0.355]	0.5 (2.1) [0.788]
	PANSS general psychopathology	No CT	41.5 (8.8)	34.4 (3.9)	31.6 (3.9)	28.7 (3.9)	27.2 (4.1)	24.7 (4.2)	23.1 (4.1)	25 (4.2)

		CT	41.5 (8.8)	35.9 (3.5)	31.4 (3.5)	29.9 (3.6)	29.1 (3.6)	31.2 (3.8)	26.3 (3.8)	30.7 (3.9)
		Δ [a]	NA	1.5 (2.9) [0.611]	-0.2 (2.9) [0.9]	1.2 (2.9) [0.617]	1.9 (3.1) [0.555]	6.6 (3.3) [0.048]*	3.2 (3.3) [0.352]	5.7 (3.4) [0.099]
	PANSS total scores	No								
Aripiprazole		CT	76.5 (13.4)	66.4 (13.7)	63 (13.9)	61.1 (13.7)	59.1 (13.7)	52 (13.8)	55.4 (14.3)	54.7 (14.1)
		CT	76.5 (13.4)	66.9 (20.4)	67 (20.3)	62.2 (20.3)	57 (20.4)	57.4 (20.6)	55.5 (20.6)	43.5 (21.4)
		Δ [a]	NA	0.6 (6.8) [0.934]	4 (6.7) [0.544]	1.1 (6.9) [0.871]	-2.1 (7.4) [0.775]	5.4 (7.8) [0.485]	0.1 (8.8) [0.998]	-11.2 (10.6) [0.295]
	PANSS positive	No								
		CT	21.2 (5.2)	16.6 (5.4)	15.2 (5.5)	13.9 (5.4)	13.9 (5.4)	10.9 (5.5)	12.4 (5.6)	11.2 (5.6)
		CT	21.2 (5.2)	19.9 (7.9)	18.2 (7.9)	15.6 (7.9)	11.9 (7.9)	11.7 (8)	13.3 (8)	8.08 (8.3)
		Δ [a]	NA	3.3 (2.2) [0.146]	3 (2.2) [0.174]	1.7 (2.2) [0.445]	-2 (2.4) [0.392]	0.8 (2.6) [0.779]	0.9 (2.8) [0.752]	-3 (3.5) [0.399]
	PANSS negative	No								
		CT	17 (5.7)	15.7 (5.3)	14.4 (5.4)	15.3 (5.3)	12.7 (5.4)	14.2 (5.4)	15.6 (5.6)	15.3 (5.5)
		CT	17 (5.7)	13.3 (7.5)	14.9 (7.5)	15.8 (7.5)	17.4 (7.5)	17.6 (7.6)	16.5 (7.6)	11.4 (7.9)
		Δ [a]	NA	-2.4 (1.9) [0.222]	0.5 (1.9) [0.813]	0.4 (2) [0.81]	4.7 (2.2) [0.034]*	3.4 (2.4) [0.155]	0.9 (2.8) [0.737]	-3.9 (3.6) [0.276]
	PANSS general psychopathology	No								
		CT	38.3 (8.1)	32.8 (7.5)	32.1 (7.7)	30.5 (7.5)	31.4 (7.6)	26 (7.7)	26.6 (7.9)	27.4 (7.8)
		CT	38.3 (8.1)	34 (11.5)	34.1 (11.5)	31.2 (11.5)	28.2 (11.5)	28.6 (11.6)	26.4 (11.6)	24.8 (12.1)
		Δ [a]	NA	1.2 (3.7) [0.746]	1.9 (3.7) [0.616]	0.8 (3.7) [0.828]	-3.2 (4) [0.394]	2.6 (4.3) [0.519]	-0.3 (4.8) [0.978]	-2.7 (5.9) [0.651]
	PANSS total scores	No								
Olanzapine		CT	76.3 (16.6)	64.7 (13.8)	54.7 (13.9)	51 (13.8)	46.8 (13.8)	49.6 (14.4)	42 (14.1)	43.3 (14.1)
		CT	76.3 (16.6)	73.6 (10)	63.2 (9.8)	64.8 (10)	64.7 (9.8)	66.4 (10.2)	55.2 (10.2)	53.4 (10.1)
		Δ [a]	NA	8.9 (7.3) [0.225]	8.5 (7.8) [0.275]	13.8 (7.6) [0.063]	17.9 (8.3) [0.028]*	16.7 (8.6) [0.05]*	13.2 (8.1) [0.105]	10 (7.9) [0.208]
	PANSS positive	No								
		CT	20.6 (4.7)	17 (5)	14.1 (5)	11.5 (5)	10.8 (5)	11.2 (5.4)	9.24 (5.2)	11.1 (5.2)
		CT	20.6 (4.7)	19.5 (2.7)	15.7 (2.8)	15 (2.8)	14.6 (2.8)	14.9 (3)	12.1 (3.1)	13 (3)
		Δ [a]	NA	2.5 (2.5) [0.323]	1.5 (2.6) [0.597]	3.5 (2.6) [0.239]	3.7 (2.7) [0.199]	3.7 (3.2) [0.267]	2.8 (2.9) [0.39]	1.9 (3) [0.578]
	PANSS negative	No								
		CT	17.6 (6.6)	14.4 (5.3)	13.2 (5.4)	13.1 (5.3)	12.1 (5.3)	13.5 (5.7)	10.8 (5.5)	9.97 (5.5)
		CT	17.6 (6.6)	19.2 (4.6)	16.5 (4.6)	19 (4.7)	20 (4.6)	18.7 (4.7)	17.5 (4.7)	14.9 (4.7)
		Δ [a]	NA	4.9 (2.8) [0.092]	3.4 (2.7) [0.233]	5.9 (2.8) [0.051]	8 (2.9) [0.006]*	5.2 (3.3) [0.126]	6.7 (3.1) [0.026]*	5 (2.9) [0.091]
	PANSS general psychopathology	No								
		CT	38.2 (8.7)	32.4 (7.5)	26.6 (7.5)	25.4 (7.5)	22.9 (7.5)	24 (7.7)	21.1 (7.6)	21.4 (7.6)

CT	38.2 (8.7)	36 (5.9)	31.8 (5.7)	32.1 (5.8)	31.3 (5.7)	33.2 (5.9)	26.9 (5.9)	26.5 (5.8)
Δ [a]	NA	3.5 (3.3) [0.284]	5.2 (3.2) [0.131]	6.7 (3.3) [0.04]*	8.3 (3.4) [0.022]*	9.1 (4.1) [0.026]*	5.8 (3.9) [0.149]	5.1 (3.8) [0.187]

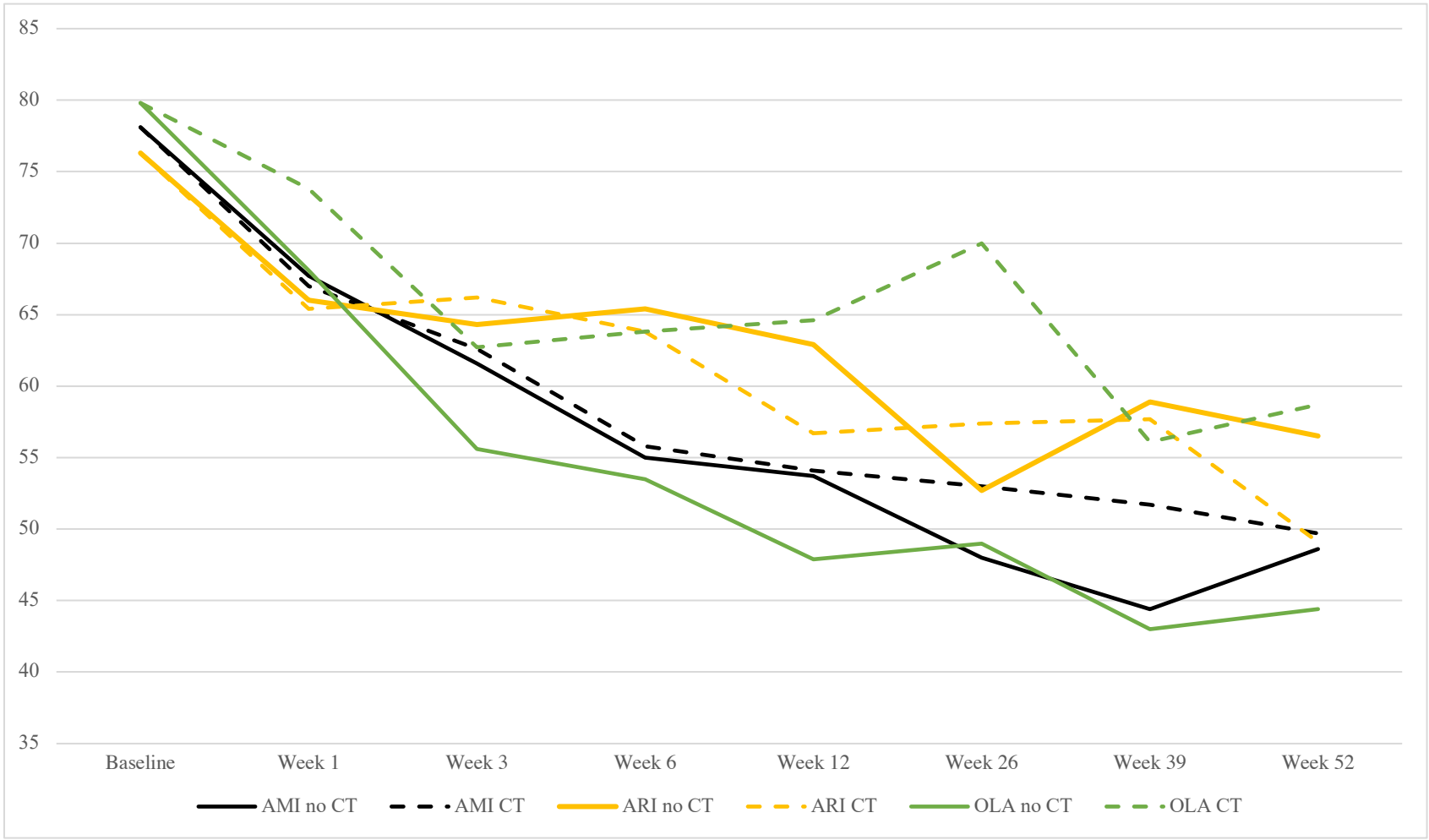
Note. N = 98. LME = linear mixed effects. PP = per protocol. PANSS = Positive and Negative Syndrome Scale. SSDs = schizophrenia spectrum disorders. CT = childhood trauma. M = estimated mean. SE = standard error. NA = not applicable. * Significant $p < .05$. [a] difference of change from baseline between CT and no CT groups, (standard deviation), [*p* value]. [b] mean PANSS score as baseline values are controlled for in the models. Linear mixed effects analyses included the following variables as fixed effects: years of education, gender, age of illness onset, duration of untreated psychosis, previous exposure to antipsychotics, and dosage of antipsychotic medication (defined daily doses) and baseline PANSS values.

Figure 1 PANSS total scores by SSDs CT and no CT groups



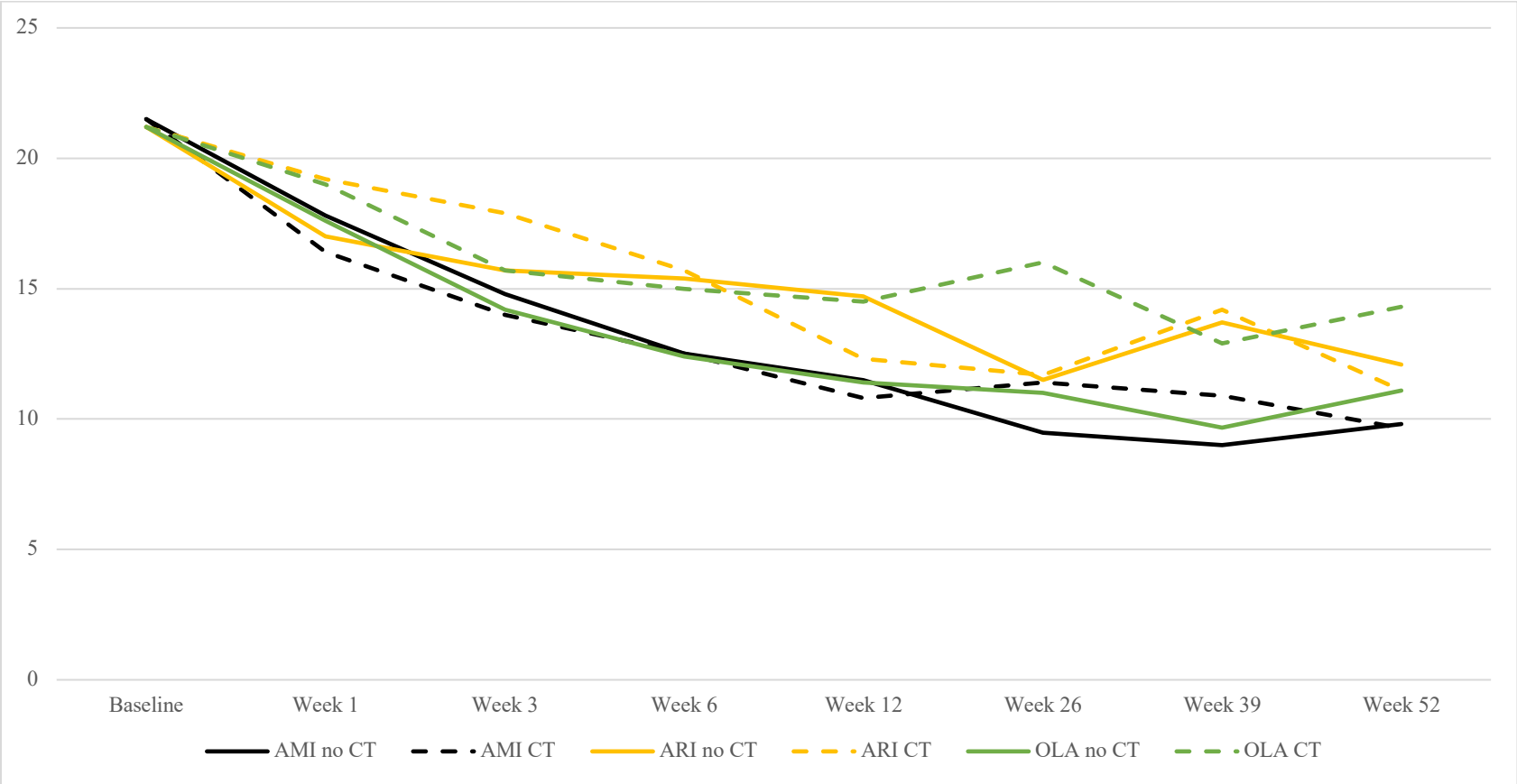
Note. SSDs = Schizophrenia spectrum disorders. PANSS = positive and negative syndrome scale. CT = Childhood trauma. Estimated symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by group (CT and no CT) based on ITT. Aggregated data irrespective of medication subgroup.

Figure 2 PANSS total scores by SSDs CT and no CT groups and type of antipsychotic medication



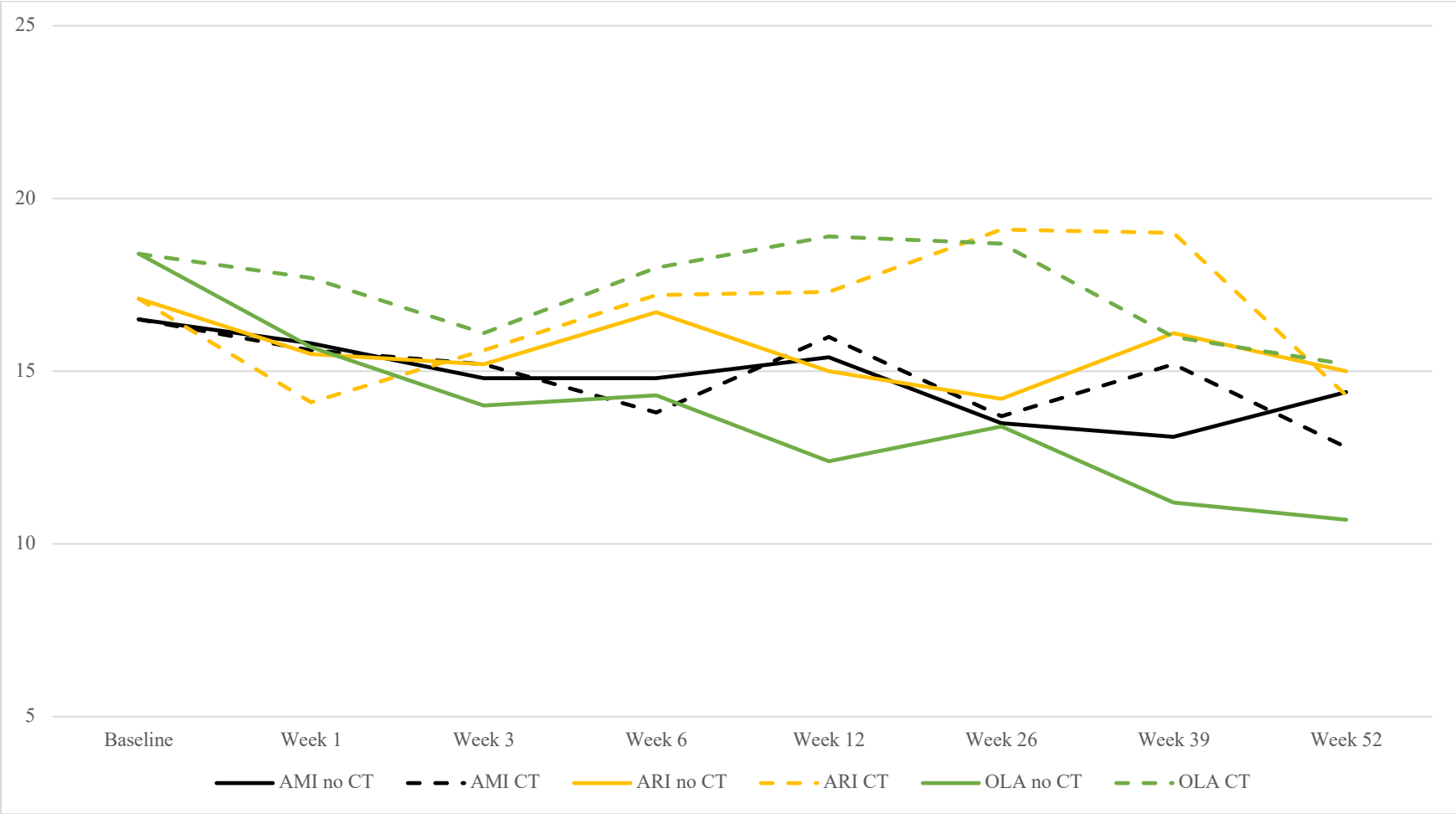
Note. SSDs = Schizophrenia spectrum disorders. PANSS = positive and negative syndrome scale. CT = Childhood trauma. Estimated symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by group (CT and no CT) based on ITT.

Figure 3 A. PANSS positive subscale scores by groups (CT and no CT) and antipsychotic medication



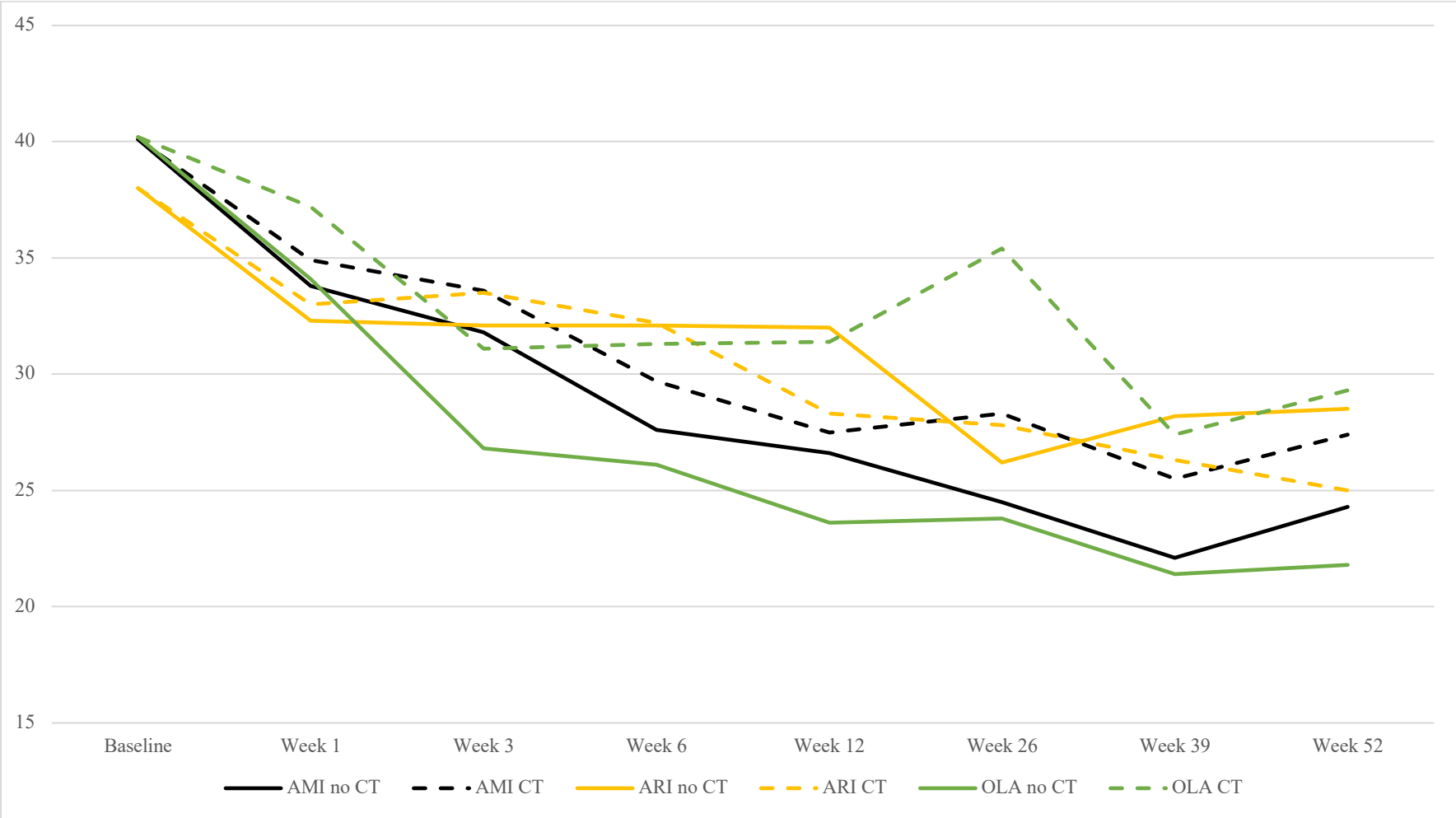
Note. PANSS = positive and negative syndrome scale. CT = Childhood trauma. Estimated symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by group (CT and no CT) based on ITT.

Figure 3 B. PANSS negative subscale scores by groups (CT and no CT) and antipsychotic medication



Note. PANSS = positive and negative syndrome scale. CT = Childhood trauma. Estimated symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by group (CT and no CT) based on ITT.

Figure 3 C PANSS general psychopathology subscale scores by groups (CT and no CT) and antipsychotic medication



Note. PANSS = positive and negative syndrome scale. CT = Childhood trauma. Estimated symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by group (CT and no CT) based on ITT.