Biological correlates of agitation in severe mental disorders

Dissertation for the degree of Philosophiae Doctor (PhD)

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SUMMARY

Schizophrenia and bipolar disorder are severe mental disorders with overlapping clinical presentations and etiology. The course of the disorder varies between individuals, but the burden related to these disorders is high. Agitation is a state of restlessness and excessive psychomotor activity accompanied by anxiety, irritability, and impaired impulse control that constitutes a challenging part of the clinical presentation and often requires intensive psychiatric care. Outside the acute psychiatric setting, agitation has been linked to the quality of life reported by individuals with severe mental disorders that do not achieve remission. Agitation is one of the factors predisposing to aggression, and it represents a clinical construct partly overlapping with aggression and impulsivity. Of note, individuals with severe mental disorders are at increased risk of involvement in an aggressive incident, both as a victim and perpetrator, although the vast majority of individuals with severe mental disorders will never act aggressively. Despite that agitation is a particularly challenging clinical feature associated with quality of life, therapeutic options are limited, and its biological correlates are largely unknown. Thus, the aim of the current thesis was to expand our knowledge of biological correlates of agitation in severe mental disorders, focusing on feasibly accessible blood-sampling based markers with putative links to agitation. The objectives of this work build on indications of a link between agitation-related phenomena and disturbances of the immune system, including immune activation and aberrant inflammasome-related signaling (paper II and III) and on indicated associations between agitation-related phenomena and lower levels of circulating cholesterol (paper I).

In the cross-sectional sample of patients with schizophrenia or bipolar spectrum disorder recruited across inpatient and outpatient clinics through the ongoing Thematically Organized Psychosis study, agitation was assessed using the Positive and Negative Syndrome Scale Excited Component, while impulsivity was measured in a subsample of the patients and among healthy controls using the Barratt Impulsiveness Scale questionnaire. In addition to thorough clinical assessments, the psychopharmacological treatment received by the patients was evaluated. The participants underwent blood sampling, and levels of circulating immune markers were measured using enzyme immunoassays, while levels of circulating cholesterol were analyzed using standard methods. Linear and logistic

regressions were applied to test associations between agitation-related phenomena (measures of agitation, aggression propensity, and impulsivity) and systemic biological status (levels of circulating immune markers and cholesterol). Additionally, associations between impulsivity and psychopharmacotherapy were examined.

A novel finding from the current thesis was an association between agitation and level of circulating interleukin-18 binding protein, while levels of the remaining investigated inflammasome-related immune markers did not show any significant associations to agitation in severe mental disorders. Further, there were no significant associations between transdiagnostic measure of impulsivity and levels of circulating immune markers within the putative pathophysiological pathways (the chemokine Regulated on activation normal T cell expressed and secreted, soluble Tumor necrosis factor receptor 1, and markers within the inflammasome-related pathway). The investigation of circulating cholesterol levels among individuals with severe mental disorders recruited across inpatient and outpatient clinics revealed no significant associations to aggression propensity or impulsivity. Finally, lithium treatment was associated with lower impulsivity, whereas antidepressant treatment was associated with higher impulsivity.

These core findings of the current thesis add to the growing but complex evidence-base of immune system disturbances in severe mental disorders and somewhat challenge the previous indications of links between systemic cholesterol and agitation-related phenomena. Specifically, the findings indicate that interleukin-18 binding protein (i.e., a protein involved in the inflammasome-related interleukin-18 signaling system) is a modest part of the biological correlate of agitation, which warrants future clinical studies to address the source and temporal dynamics of this immune signal. However, the paucity of associations to circulating markers of immune activation suggest that other factors are the major drivers of agitation-related phenomena. Additionally, the observed cross-sectional associations between psychopharmacotherapy and impulsivity warrant further investigation to determine the causal directionality.

SAMMENDRAG PÅ NORSK (SUMMARY IN NORWEGIAN)

Schizofreni og bipolar lidelse er alvorlige psykiske lidelser med overlappende klinisk presentasjon og etiologi. Sykdomsforløpet varierer mellom enkeltindivider, men belastningen knyttet til disse lidelsene er høy. Agitasjon er en tilstand kjennetegnet av rastløshet, uhensiktsmessig psykomotorisk aktivering, angst, irritabilitet og nedsatt impulskontroll som utgjør en utfordrende del av det kliniske bilde og ofte krever intensiv psykiatrisk behandling. Agitasjon er også assosiert med livskvalitet hos pasienter med alvorlige psykiske lidelser som ikke oppnår remisjon. Agitasjon er en risikofaktor for utvikling av aggresjon og representerer et klinisk konstrukt som delvis overlapper med aggresjon og impulsivitet. Individer med alvorlige psykiske lidelser har en forhøyet risiko for å bli involvert i en aggressiv hendelse, både som offer og gjerningsperson, imidlertid de aller fleste med en alvorlig psykisk lidelse kommer aldri til å handle aggressivt. Agitasjon er en spesielt utfordrende del av klinisk presentasjon og er knyttet til livskvalitet. Til tross for dette er behandlingsalternativer begrensede og biologiske korrelater for det meste ukjente. Målet med doktorgradsarbeidet var derfor å utvide vår kunnskap om biologiske korrelater til agitasjon ved alvorlige psykiske lidelser, dette ved å ta i bruk blodprøvetaking som en skånsom og gjennomførbar metode og fokusere på blodprøve-baserte markører med en antydet link til agitasjon. Arbeidet bygger på en antydet link mellom agitasjon-relaterte kliniske fenomener og endringer i immunsystemet, inkludert immunaktivering og forstyrrelse av inflammasom-relatert immunsignalisering (artikkel II og III) og en antydet assosiasjon mellom agitasjon-relaterte fenomener og lavere nivå av systemisk kolesterol (artikkel I).

I et tverrsnittsutvalg av pasienter med schizofreni og bipolart spektrum lidelser rekruttert på tvers av poliklinikker og sykehusavdelinger gjennom studien Tematisk Organisert Psykose ble agitasjon målt med en skala basert på klinisk intervju og observasjon, mens impulsivitet ble målt ved bruk av et spørreskjema i underutvalget av pasienter og hos friske kontrollpersoner. I tillegg til detaljert klinisk evaluering ble pasientenes bruk av psykofarmaka kartlagt. Studiedeltakere avga en blodprøve, og systemisk kolesterol samt immunmarkører ble analysert. Assosiasjoner mellom agitasjon-relaterte fenomener (agitasjon, aggresjon, impulsivitet) og systemisk biologisk status (nivåer av kolesterol og

immunmarkører) ble testet med lineære og logistiske regresjoner. I tillegg ble assosiasjoner mellom impulsivitet og psykofarmakoterapi undersøkt.

Et nytt funn i dette doktorgradsarbeidet var en assosiasjon mellom agitasjon og nivået av systemisk interleukin-18 bindende protein, mens nivåer av resterende undersøkte inflammasom-relaterte markører viste ingen signifikante assosiasjoner til agitasjon ved alvorlige psykiske lidelser. Videre fant man ingen signifikante assosiasjoner mellom et transdiagnostisk mål på impulsivitet og nivåer av systemiske immunmarkører med en antatt rolle i impulsivitet (kjemokin RANTES, løselig tumor-nekrosefaktor reseptor 1 og inflammasom-relaterte immunmarkører). Undersøkelse av systemisk kolesterol på tvers av inneliggende og polikliniske pasientgrupper med alvorlige psykiske lidelser viste ingen signifikante assosiasjoner til aggresjon eller impulsivitet. I tillegg var litium-medikasjon assosiert med lavere impulsivitet, mens antidepressiv medikasjon var assosiert med høyere impulsivitet.

Disse hovedfunnene utvider den voksende dog komplekse evidensbasen for immunforstyrrelser ved alvorlige psykiske lidelser og utfordrer til en viss grad tidligere antydet sammenheng mellom systemisk kolesterol og agitasjon-relaterte fenomener. Funnene indikerer interleukin-18 bindende protein som en beskjeden del av det biologiske korrelatet til agitasjon og det kan derfor være nyttig å undersøke hva som ligger bak dette immunsignalet i fremtidige kliniske studier. Imidlertid tyder den begrensede mengden av assosiasjoner med systemiske immunmarkører på at andre faktorer er hoved-drivere av agitasjon-relaterte fenomener. Dessuten peker observerte assosiasjoner mellom psykofarmakoterapi og impulsivitet på at det kan være nyttig med videre forskning for å avklare kausalitet.

LIST OF STUDIES

Study I

Disentangling the relationship between cholesterol, aggression, and impulsivity in severe mental disorders

Gabriela Hjell, Lynn Mørch-Johnsen, René Holst, Natalia Tesli, Christina Bell, Synve H. Lunding, Linn Rødevand, Maren C. F. Werner, Ingrid Melle, Ole A. Andreassen, Trine V. Lagerberg, Nils Eiel Steen, Unn K. Haukvik

Brain and Behavior (2020); 10: e01751

Study II

Interleukin-18 signaling system links to agitation in severe mental disorders

Gabriela Hjell, Attila Szabo, Lynn Mørch-Johnsen, René Holst, Natalia Tesli, Christina Bell, Thomas Fischer-Vieler, Maren C. F. Werner, Synve H. Lunding, Monica B. E. G. Ormerod, Ingrid T. Johansen, Ingrid Dieset, Srdjan Djurovic, Ingrid Melle, Thor Ueland, Ole A. Andreassen, Nils Eiel Steen, Unn K. Haukvik

Psychoneuroendocrinology (2022); 140: 105721

Study III

Impulsivity across severe mental disorders: a cross-sectional study with focus on immune markers and psychopharmacotherapy

Gabriela Hjell, Jaroslav Rokicki, Attila Szabo, René Holst, Natalia Tesli, Christina Bell, Thomas Fischer-Vieler, Maren C. F. Werner, Synve H. Lunding, Monica B. E. G. Ormerod, Ingrid T. Johansen, Srdjan Djurovic, Thor Ueland, Ole A. Andreassen, Ingrid Melle, Trine V. Lagerberg, Lynn Mørch-Johnsen, Nils Eiel Steen, Unn K. Haukvik

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ABBREVIATIONS

AUDIT	Alcohol Use Disorders Identification Test
BBB	Blood-brain barrier
BD	Bipolar spectrum disorder
BIS-11	Barratt Impulsiveness Scale
BMI	Body mass index
CDSS	Calgary Depression Scale for Schizophrenia
CRP	C-reactive protein
CVD	Cardiovascular disease
DAMP	Damage-associated molecular pattern
DDD	Defined daily dose
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	The fourth revision of Diagnostic and Statistical Manual of Mental Disorders
DUDIT	Drug Use Disorders Identification Test
ELISA	Enzyme-linked immunosorbent assay
GAF	Global Assessment of Functioning Split Version
GWAS	Genome-wide association study
HDL	High density lipoprotein
HDL-C	HDL cholesterol
HLAS	Group with higher levels of agitation or aggression symptoms
IL	Interleukin
IL-1RA	IL-1 receptor antagonist
IL-18BP	IL-18 binding protein
IL-18R1	IL-18 receptor 1
IL-18RAP	IL-18 receptor accessory protein
INF	Interferon
LDL	Low density lipoprotein
LDL-C	LDL cholesterol
MHC	Major histocompatibility complex

MLAS	Group with minimal level of agitation or aggression symptoms
NAS	Group with no agitation or aggression symptoms
NLR	Nucleotide-binding oligomerization domain-like receptor
NLRP3	NLR pyrin-containing protein 3
NOS	Not otherwise specified
PANSS	Positive and Negative Syndrome Scale
PANSS-EC	PANSS Excited Component
PRR	Pattern-recognition receptor
RANTES	Regulated on activation normal T cell expressed and secreted
RCT	Randomized controlled trials
SCID-I	Structured Clinical Interview for DSM-IV axis I disorders
SCZ	Broad schizophrenia spectrum disorder
sTNFR1	Soluble TNF receptor 1
TC	Total cholesterol
TGF	Transforming growth factor
T_H1	T helper 1
T_H17	T helper 17
TNF	Tumor necrosis factor
TOP	Thematically Organized Psychosis
VLDL	Very low density lipoprotein
WHO	World Health Organization
YMRS	Young Mania Rating Scale

1. BACKGROUND

1.1 Severe mental disorders

1.1.1 Epidemiology and burden

The World Health Organization (WHO) highlights that mental health is an intrinsic component of health, which can be described as a state of "well-being that enables people to cope with the stresses of life, realize their abilities, learn well and work well, and contribute to their community" (1). The WHO also points out that mental health and mental disorders exist on a continuum. Mental disorders are accompanied by distress or impaired functioning and involve disturbances in cognition, emotional regulation, and behavior (2). Mental disorders such as schizophrenia and bipolar disorder, typically requiring intensive psychiatric care and leading to marked impairments in functioning, are often referred to as severe mental disorders (3). In this thesis, severe mental disorders are defined as broad schizophrenia and bipolar spectrum disorders.

The onset of severe mental disorders usually occurs in the early adulthood (4, 5). The prevalence is approximately 2% for bipolar and 1% for schizophrenia spectrum disorders (6, 7, 8, 9). These disorders often affect quality of life (10, 11) and interfere with functioning (12), although the course of the disorder varies substantially between individuals (13). Despite the relatively low prevalence, severe mental disorders constitute one of the leading causes of disability (14, 15). In turn, the burden related to severe mental disorders represents a major cause of health loss for the affected individuals (16) and a major cause of costs to the society (17). Individuals with severe mental disorders are at increased risk of multiple adverse outcomes (18). People with severe mental disorders have about 10 to 20 years shorter life expectancy compared to the general population, mainly due to suicide, accidents, and somatic comorbidities such as respiratory and cardiovascular diseases (CVDs) (19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29). Moreover, comorbid mental disorders as well as comorbid substance use disorders are also common (30, 31).

1.1.2 Diagnosis and symptomatology

Current diagnostic systems of mental disorders are based on descriptive classifications of the complex symptomatology. The WHO has created a framework of International Classification of Diseases (32). Another diagnostic system broadly used in research and clinical practice is the Diagnostic and Statistical Manual of Mental Disorders (DSM) (33). This thesis builds on diagnostic criteria described in the fourth revision of DSM (DSM-IV) (34).

Severe mental disorders have heterogeneous and overlapping clinical presentations, which may involve positive psychotic symptoms, as well as negative, cognitive, and affective symptoms (35, 36). Positive psychotic symptoms are characterized by excessive or altered perception, thought, or behavior and refer to hallucinations, delusions, and disorganized behavior and speech. Negative symptoms are characterized by a reduction of normal mental processes, including diminished emotional expression, social interactions, and motivation. Positive psychotic symptoms are a prominent feature in schizophrenia (37) and also commonly occur in bipolar disorder (38). Similarly, affective symptoms are the key feature of bipolar disorder (39) and are also prevalent in schizophrenia (40, 41, 42). Moreover, cognitive dysfunction may accompany both disorders, although, on a group level, it is more pronounced in schizophrenia (43).

According to the DSM-IV, an individual is diagnosed with schizophrenia if the following criteria A-F are fulfilled (34). Criterion A is met upon presence of at least two symptom categories defined as delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms. Criterion A is also met in case of bizarre delusions or auditory hallucinations with either multiple voices conversing or a voice keeping up a running commentary on the individual's behavior or thoughts. Criterion B is met if the individual experiences social or occupational dysfunction. Criterion C is defined as a duration for at least six months. Criteria D and E are met when the disturbance cannot be accounted for by mood disorder, schizoaffective disorder, substance use, or general medical conditions. Criterion F states that comorbid schizophrenia and autism or other pervasive developmental disorders can be diagnosed only if prominent delusions or hallucinations are present. Clinical presentations of schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, and psychotic disorder not otherwise specified

(NOS) are related to schizophrenia symptoms, with a spectrum of symptomatologic overlap (34). According to the DSM-IV, these disorders have the following diagnostic criteria. Schizophreniform disorder is diagnosed if an individual fulfills criteria for schizophrenia except for that the duration is between one and six months. Schizoaffective disorder is diagnosed if the following criteria A-D are met. Criteria A and B are fulfilled in case of an uninterrupted episode that consists of a major depressive episode, a manic episode, or a mixed episode concurrent with symptoms that meet the criterion A for schizophrenia (criterion A) and delusions or hallucinations present for at least two weeks in absence of prominent affective symptoms (criterion B). Criterion C states that the affective symptoms are present for a substantial portion of the episode. Criterion D is met when the disturbance cannot be accounted for by substance use or general medical conditions. Delusional disorder is diagnosed in case of delusions when the criterion A for schizophrenia is not met. Brief psychotic disorder is diagnosed in case of psychotic symptoms present for less than one month. In case of lacking or contradictory information, psychotic symptoms lead to psychotic disorder NOS diagnosis.

The DSM-IV diagnostic criteria state that bipolar I disorder diagnosis requires an occurrence of at least one manic or mixed episode and that the disturbance cannot be accounted for by schizoaffective disorder, substance use, or general medical conditions (34). A manic episode is defined as an elevated or irritable mood leading to psychotic features, hospitalization, or marked impairment in social or occupational functioning that lasts for at least one week (or shorter in case of hospitalization) and that includes at least three of the listed symptoms (inflated self-esteem, decreased need for sleep, increased talkativeness, racing thoughts, distractibility, increase in motor or goal-directed activity, excessive involvement in pleasurable activities that have a high potential for negative consequences) or at least four of the symptoms if the mood is only irritable. When the elevated or irritable mood involves the same range of symptoms and lasts for at least four days but leads to neither severely impaired functioning, hospitalization, nor psychotic symptoms, it is classified as a hypomanic episode. A major depressive episode is characterized by reduced mood, interest, and pleasure lasting for at least two weeks and leading to distress or impaired functioning. A mixed episode is defined as a period with disturbed mood that fulfills criteria for both the manic and major depressive episode. According to the DSM-IV, bipolar II disorder diagnosis

requires at least one major depressive episode and one hypomanic episode, and the disturbance cannot be accounted for by bipolar I disorder, schizoaffective disorder, substance use, or general medical conditions. In case of lacking or contradictory information, occurrence of bipolar features leads to bipolar disorder NOS diagnosis. Further, a major depression with psychotic features might be grouped alongside bipolar disorders (44, 45).

1.1.3 Agitation and related clinical phenomena

1.1.3.1 Conceptualization

Agitation constitutes a particularly challenging part of the symptomatology of severe mental disorders (46). Agitation, aggression, and impulsivity can be conceptualized as distinct but partly overlapping clinical phenomena (46, 47, 48, 49) (**Figure 1**).

Figure 1. Agitation, aggression, and impulsivity conceptualized as overlapping phenomena

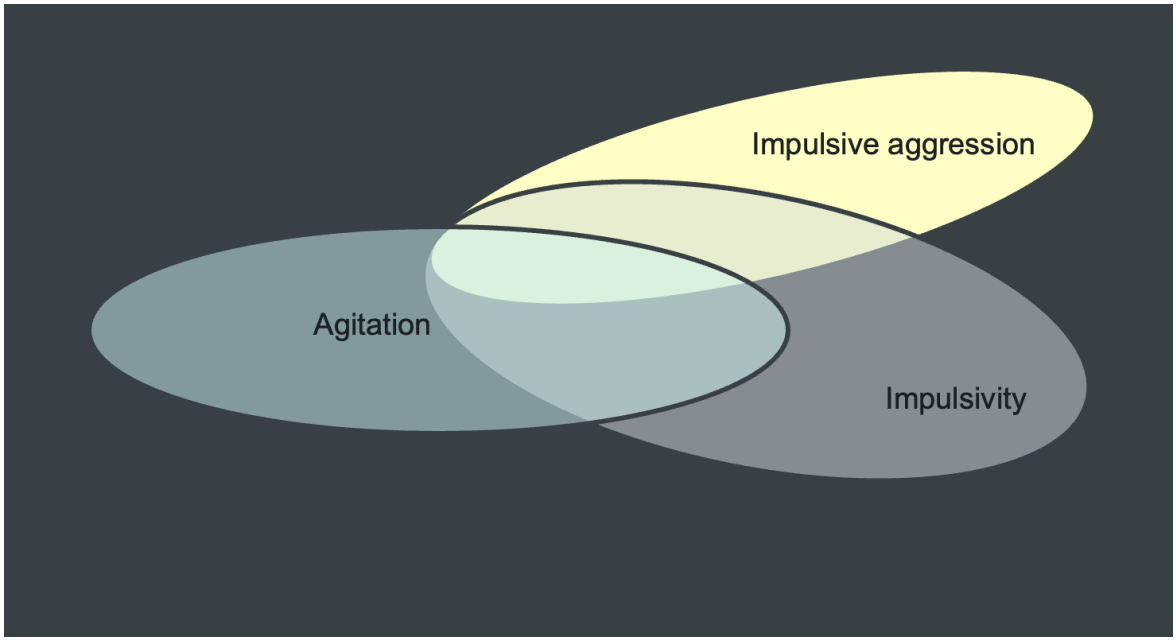


Illustration by Gabriela Hjell

Agitation is a state of restlessness and excessive movement or speech accompanied by anxiety, irritability, and impaired impulse control (46, 50). The DSM describes agitation as an

"excessive motor activity associated with a feeling of inner tension" (33). Aggression might be defined as "hostile, injurious, or destructive behavior" (51), and impulsivity refers to a tendency to react without considering the consequences (52).

1.1.3.2 Agitation

Agitation is typically seen across severe mental disorders, as well as in major depressive disorder, personality disorders, substance use disorders, and dementia (47, 53, 54, 55). The prevalence of agitation in emergency psychiatric settings ranges between 4% and 10%, although the estimates are largely based on conflated conceptualizations of agitation and aggression (46). Agitation often requires intensive psychiatric care (53, 56), and it has been described as one of the factors predisposing to aggression (57, 58). Thus, successful management of agitation, typically using verbal de-escalation techniques and psychopharmacotherapy, is among priorities in acute psychiatric and emergency department settings (46, 56, 59, 60, 61). Furthermore, agitation may also be a part of the clinical presentation encountered outside the acute psychiatric setting (62), and it has been linked to the quality of life reported by individuals with severe mental disorders that do not achieve remission (63).

1.1.3.3 Aggression

Aggression comprises verbal threats or threating gestures and verbal or physical acts leading to destruction or harm (47). Violence is an extreme form of physical aggression that imposes risk of severe harm to the assaulted individual (64, 65). Aggression can be looked at as an essential component of the normal spectrum of social behaviors in most species (66). However, violence and pathological forms of human aggression represent a substantial social concern and a challenge to public health, as well as to everyday psychiatric clinical practice (67, 68, 69). Aggression is typically characterized as impulsive or instrumental, although features of both aggression types also often co-occur (65, 67). Impulsive aggression usually manifests as a response to perceived provocation or threat and is often accompanied by anger, while instrumental aggression is typically initiated by the offender in search of a personal gain (67). Additionally, based on a clinical perspective, psychotic aggression motivated by positive psychotic symptoms has emerged as a third

phenomenological category (70, 71, 72, 73). Of note, psychotic aggression has been described as the least prevalent type of aggression in severe mental disorders, while impulsive aggression has been indicated as the most prevalent type (72). Importantly, the vast majority of individuals with severe mental disorders will never exhibit aggression or act violently, although having a severe mental disorder constitutes a risk factor (18, 74, 75, 76, 77), alongside male gender, young age, history of early life adversities, antisocial personality traits, and alcohol and illicit substance use (78, 79, 80, 81, 82, 83).

1.1.3.4 Impulsivity

Impulsivity may be conceptualized as a behavioral and personality construct that reflects a tendency to react without considering the consequences (52). Elevated impulsivity has been shown across severe mental disorders, as well as in attention-deficit hyperactivity disorder, and in borderline and antisocial personality disorders (84, 85, 86, 87). Impulsivity in severe mental disorders has been linked to severe clinical manifestations such as early onset of the disorder, suicidality, and aggression (48, 86, 88, 89). It has been proposed that, regardless the diagnostic boundaries, patients with high impulsivity levels might benefit from prevention and treatment efforts focusing on impulsivity (86, 88).

1.2 Biological underpinnings of severe mental disorders

1.2.1 Biological insights

The current knowledge suggests that the etiology of severe mental disorders is multifactorial and involves a complex interplay between genetic and environmental factors (90, 91). The pathophysiological models propose that environmental risk factors such as early life adversities interact with genetic susceptibility, to affect neurodevelopment and brain functioning (90, 91, 92). Still, the exact pathophysiological mechanisms underlying severe mental disorders are largely unknown.

Seminal biological insights originate from the discovery of psychopharmacotherapeutic agents and from neurochemical studies (93, 94). The observation that the clinical antipsychotic potency across early antipsychotics such as chlorpromazine and haloperidol strongly correlates with the affinity to the dopamine D2 receptor has implicated alterations

of the dopamine signaling in schizophrenia (95). Similarly, there is evidence for an involvement of dopaminergic disturbances in bipolar disorder (96). However, dopamine antagonism is not sufficient to successfully treat all clinical aspects of severe mental disorders (e.g., cognitive, negative, and depressive symptoms), and the superior antipsychotic agent clozapine has low dopamine D2 receptor affinity (97). The observation that the N-methyl D-aspartate glutamate receptor antagonism caused by phencyclidine induced psychosis has led to consideration of a role for the glutamate signaling dysfunction in severe mental disorders (98). The current models of neurotransmission in severe mental disorders suggest complex disturbances across dopaminergic and glutamatergic systems (97), complemented by involvement of several other signaling systems such as serotonin and gamma-aminobutyric acid (99, 100, 101, 102).

Another important line of biological insight is derived from genome-wide association studies (GWASs) (103). Genetic information is encoded on double strings of deoxyribonucleic acid (DNA), and the polynucleotide chains of DNA comprise in total over three billion base pairs. Above 99% of the genetic information in the human genome is identical across individuals, while common genetic variants account for unique traits and susceptibility to complex disorders. The most abundant common genetic variants are variations in a single base pair that are relatively frequent in a population (frequency above 1%) (104, 105). Severe mental disorders are highly heritable (106), with a substantial share of the heritability explained by common genetic variants (107, 108). Thus, part of the etiological complexity of severe mental disorders can be attributed to the numerous common genetic variants involved, which form the polygenic architecture of severe mental disorders (103). While some of the common genetic variants have been linked specifically to schizophrenia or bipolar disorder, a substantial proportion of the variants underlie the polygenic overlap between severe mental disorders (109, 110, 111). Of note, multiple mental disorders display overlapping polygenic architectures, which are largely separate from other disorders of the brain such as neurological disorders (112). Collaborative research efforts have facilitated a continuously advancing discovery of common genetic variants associated with severe mental disorders through GWASs (113). Common genetic variants that have been linked to severe mental disorders point to an involvement of biological processes implicated in neurodevelopment,

synaptic functioning (e.g., excitatory glutamatergic neurons and inhibitory interneurons), neuronal excitability (e.g., calcium signaling), and the immune system (107, 108, 114, 115).

1.2.2 The immune system

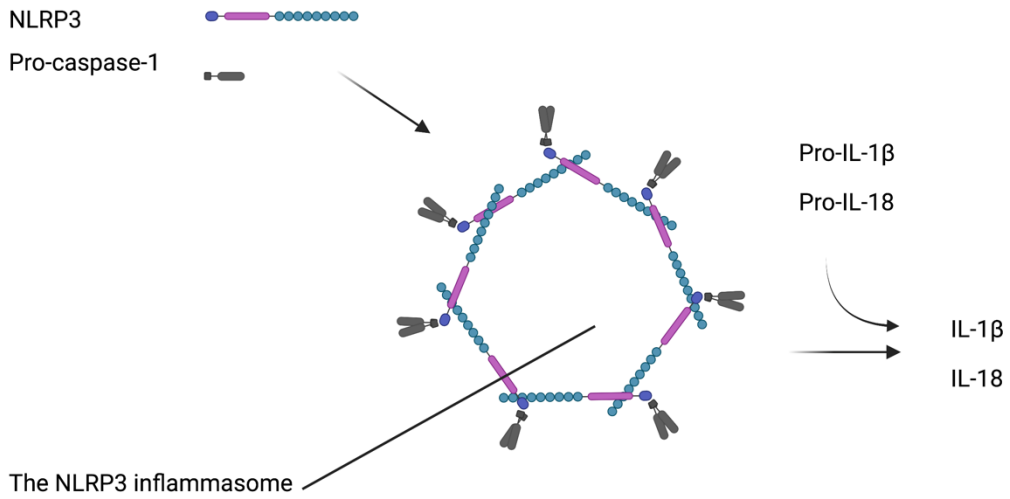
1.2.2.1 Overview of the immune responses

The immune system protects the body from pathogens and related threats to its integrity. This essential physiological system comprises a complex network of effector cells and molecules involved in the innate and adaptive immune responses. The innate immune system provides immediate unspecific defense. In contrast, the adaptive system is highly specific, but its response can take several days to build up (116).

Phagocytic and sensory cells such as macrophages, neutrophils, and dendritic cells initiate the innate immune response. These cells express pattern-recognition receptors (PRRs), which recognize pathogen-associated molecular patterns and damage-associated molecular patterns (DAMPs). PRRs encompass transmembrane proteins such as the toll-like receptors and cytoplasmic proteins such as the nucleotide-binding oligomerization domain-like receptors (NLRs), retinoic acid-inducible gene-I-like receptors, and cyclic guanosine monophosphate-adenosine monophosphate synthase stimulator of interferon genes. The activation of PRR can lead to phagocytosis. Importantly, activated PRRs propagate the immune response by inducing secretion of signaling proteins called cytokines (117). Cytokines then regulate immune activity and orchestrate further inflammatory response. Cytokines comprise different types of proteins such as interleukins (ILs), interferons (INFs), and chemokines, which together serve a wide range of interconnected functions. IL-1β and tumor necrosis factor (TNF) represent typical inflammatory cytokines. One of the cytoplasmic PRR proteins that react to cellular stress signals is the NLR pyrin-containing protein 3 (NLRP3), part of the NLRP3 inflammasome. The NLRP3 inflammasome is an intracellular multiprotein complex that activates the enzyme caspase-1, which then results in the release of IL-1β and IL-18 (118) (**Figure 2**). Another part of the innate immune system is the complement. The complement consists of several circulating proteins produced mainly by the liver, which are arranged in different activation cascades triggered by the proteins with PRR properties. The complement acts directly on the pathogen or facilitates

phagocytosis and inflammation (117, 119). Further, natural killer cells react to exposure to cellular stress or viral infection, and innate lymphoid cells serve as a source of inflammatory cytokines in peripheral tissues. Dendritic cells play an important role in bridging the innate and adaptive part of the immune system. Following phagocytosis, dendritic cells process the pathogen to present antigens and induce the adaptive immune response (117).

Figure 2. Activation of the NLRP3 inflammasome



IL-1β, Interleukin-1β; IL-18, Interleukin-18; NLRP3, Nucleotide-binding oligomerization domain-like receptor pyrin-containing protein 3

Illustration created by Gabriela Hjell using BioRender.com

The adaptive immune response involves B and T lymphocytes, each with specialized functions. Collectively, these lymphocytes express a huge variety of specific antigen receptors. Most circulating lymphocytes are immunologically inactive. However, once they encounter the specific antigen that binds to the specific antigen receptor expressed on their surface, they differentiate into effector lymphocyte cells. Antigens presented together with major histocompatibility (MHC) molecules stimulate the differentiation of T lymphocytes into effector T cells and memory T cells. Following the ubiquitous MHC class I processing and presentation of antigen, CD8 cytotoxic effector T cells serve elimination of compromised cells. Following the MHC class II antigen processing and presentation by dendritic cells, CD4 T cells can differentiate into several types of effector cells that affect

further development of the immune response through cytokine signaling patterns. Cytokines such as IL-12, IL-18, and IFN-γ induce differentiation into T helper 1 (T_H1) cells, which in turn produce IFN-γ and activate macrophages. IL-4 induces differentiation into T helper 2 cells, which lead to IL-4, IL-5, and IL-13 mediated activation of eosinophils and basophils. Transforming growth factor (TGF)-β, IL-6, and IL-23 stimulate differentiation into T helper 17 (T_H17) cells, which produce IL-17 and IL-22 and act on neutrophils. Combination of TGF-β and IL-2 induce differentiation into T regulatory cells, which dampen T cell activation trough production of TGF-β and IL-10. Finally, T follicular helper cells produce IL-21, which stimulate proliferation of B cells (120). Immunoglobulins are the antigen recognition proteins of B cells. Membrane-bound immunoglobulins function as receptors. Upon antigen recognition, B lymphocytes differentiate into plasma cells that produce antibodies (i.e., secreted form of immunoglobulins) as well as into memory B cells. Ultimately, repeated exposure to the same antigen triggers a faster specific immune response of the adaptive immune system (117).

1.2.2.2 Interplay between the immune system and the brain

Although once believed the opposite, the brain operates in a close bi-directional interplay with the peripheral immune system (121). A commonly experienced consequence of such interplay is the phenomenon of sickness behavior, a state of impaired mood and irritability, sleepiness, disturbed cognition, hyperalgesia, and decreased appetite that occurs during systemic inflammatory response to bacterial or viral infections (121, 122). Several complex finetuned mechanisms are in place to maintain the communication between the periphery and the brain and vice versa, including neuroimmune interactions (123) and endocrine signaling (124). These communication pathways make it possible for the immune system to engage the rest of the body in battling the infection and reciprocally allow the brain to adjust the peripheral immune responses (121). Importantly, the blood-brain barrier (BBB) restricts and regulates the passage of signaling molecules and immune cells between the circulation and the brain (125, 126). The molecular arm of these communication pathways involves areas at circumventricular organs that lack the BBB (127). Moreover, the BBB endothelium is involved (126), and it has been suggested that sustained exposure of the BBB to inflammatory factors may lead to increase in BBB permeability and further

propagation of the inflammatory signaling to the brain (128). The cellular communication pathway involves a recruitment of circulating immune cells through the BBB (129). Additionally, meningeal components of the immune system have been shown to communicate with the cerebrospinal fluid, cerebral interstitial fluid and peripheral lymph nodes (130, 131). Finally, the neuronal pathway consists of immune signals conveyed by the autonomic nerve fibers (123).

Microglia are the resident immune cells of the brain, which have surveillance, phagocytic and cytokine-producing properties (132). Under physiological conditions, microglia constantly scan the surrounding environment, maintain homeostasis, and participate in the synapse remodeling (133). During the neurodevelopment, microglia also play a role in the synaptic pruning (134). In similarity with peripheral macrophages, microglia exert a fast response to a broad range of DAMPs. This response is hallmarked by prominent morphological changes and is referred to as the microglial activation, due to enhanced phagocytosis and cytokine production (132). Peripheral inflammation and psychological stress are examples of the stimuli that have been linked to the microglial activation (132, 134). Of note, in addition to microglia, several other cell types such as astroglia and neurons participate in the production of immune signaling molecules in the brain (135). Intriguingly, immune signaling molecules exhibit many functional similarities with neurotransmitters and hormones (121). There is accumulating evidence concerning production of immune signaling molecules in the brain and their roles in signal transduction to neurons and glial cells (136). This notion, together with the expanding knowledge about bi-directional interplay between the brain and systemic immune responses, opens exciting opportunities for non-invasive studies of immune disturbances in mental disorders.

1.2.2.3 Immune disturbances in severe mental disorders

Accumulating evidence point toward an involvement of the immune system in severe mental disorders. Common genetic variants linked to severe mental disorders have indicated the immune system as one of the pathophysiological candidates (107, 108). The implicated immune signals comprise the GWAS signal at the extended MHC region as well as signals related to the biology of the adaptive immune response (107, 108, 114, 137, 138, 139, 140). In addition to MHC molecules, the extended MHC region codes for several other

components of the immune system such as TNF cytokine family and the complement (138). Intriguingly, complement component 4 has been indicated as the key driver of the association between the extended MHC region and schizophrenia (141, 142), while a membrane protein has been proposed to drive the association between the extended MHC region and bipolar disorder (107).

Transcriptome-wide approach in human brain tissue has also provided support for a role of immune pathways in severe mental disorders (143). Complementary to the evidence based on GWASs, analyses at the transcriptome level have implicated a dysregulation of neuronal, glial, and endothelial pathways with distinct temporal patterns. This dysregulation encompasses the nuclear factor κ B pathway with downstream transcription factor targets and upstream activators such as IL-1 and TNF cytokine families (143).

Further indications of the immune system ’s involvement in severe mental disorders have emerged based on epidemiological studies. These include an increased risk of developing a severe mental disorder related to conditions with altered immune activation such as autoimmune disorders or infections (144, 145, 146, 147, 148, 149, 150). Autoimmune mechanisms with inadequate control and elimination of self-reactive lymphocytes can lead to excessive tissue damage (117). Individuals diagnosed with an autoimmune disorder have a higher risk of developing a severe mental disorder and vice versa (151, 152). Interestingly, autoimmune disorders with suspected brain-reactive antibodies convey even higher risk of developing a severe mental disorder than autoimmune disorders in general (144, 145), and some autoimmune disorders such as systemic lupus erythematosus, multiple sclerosis, and autoimmune encephalitis manifest neuropsychiatric symptoms (153, 154, 155). Infections lead to states of immune activation, while a dysregulated immune system may also exhibit an underlying vulnerability to pathogens (117, 156). Indeed, a substantial genetic pleiotropy between propensity to infections and severe mental disorders has been suggested (157). Moreover, maternal infections, particularly during pregnancy, but also outside the pregnancy period have been associated with increased risk of developing a mental disorder (158, 159).

A broad line of evidence based on investigations of immune marker levels in blood and cerebrospinal fluid has shown low-grade inflammatory aberrations in severe mental

disorders (160, 161, 162, 163, 164, 165, 166). Observations across psychotic, manic, and depressive symptoms have indicated immune activation with changes in inflammatory signaling (e.g., IL-6, TNF, IL-1, and IL-18 pathways) (160, 163, 167, 168, 169). Two of the upstream inflammatory pathways that have been linked to severe mental disorders are NLRP3 inflammasome-related (118). The inflammasome-related IL-1β and IL-18 pathways have been suggested as a link between immune activation and processes such as neurodevelopment, synaptic remodeling, neurotransmission, and neuronal excitability (170, 171, 172). Cytokines and receptors of the IL-1 family signaling pathways are primarily involved in innate immune responses (173). These pathways include immune markers such as IL-1β, IL-1 receptor antagonist (IL-1RA), IL-18, IL-18 binding protein (IL-18BP), IL-18 receptor 1 (IL-18R1), and IL-18 receptor accessory protein (IL-18RAP) (174). The NLRP3 inflammasome activates the enzyme caspase-1, which then results in the release of IL-1β and IL-18 (118) (**Figure 2**). Mechanistically, IL-1RA interferes with IL-1β action by binding to IL-1 receptor 1 (173). In clinical studies, circulating levels of IL-1RA are shown to reliably reflect the activity within IL-1 system (175). IL-18 plays an important role in the T_H1 response (173). IL-18 binds to IL-18R1, and IL-18RAP contributes to formation of a high-affinity signaling complex (173). Upregulation of IL-18BP, which typically follows elevations of IL-18, functions as a negative feedback loop within the regulatory signaling system (176). The TNF superfamily represents another typical upstream inflammatory pathway that has been implicated in severe mental disorders (160, 177). Cytokines and receptors of the TNF superfamily play important roles in the propagation of the inflammatory process and regulation of innate and adaptive immune responses (178, 179). Immune markers such as TNF and soluble TNF receptor 1 (sTNFR1) are broadly used indicators of the activity within the TNF pathway, and sTNFR1 in particular is considered as a reliable surrogate marker (180).

There are multiple theoretical models of how components of the immune system may contribute to the development and clinical presentations of severe mental disorders. In parallel with the general pathophysiological models of severe mental disorders, these models include elements of an interplay between genetics and environment, a role for neurodevelopment, and the diathesis-stress concept (181). A role of genetic susceptibilities to develop inadequate immune responses that may manifest both in the brain and the

periphery has been suggested (181). Complement component 4 has been indicated as the key driver of the genetic association between the extended MHC region and schizophrenia (141). Given that complement component 4 has been implicated in neurodevelopment and synaptic pruning, it represents a plausible pathophysiological candidate that might play a part in the development of schizophrenia (142, 182). Across severe mental disorders, influence of neuroinflammation with altered microglial responses (e.g., chronically activated and primed microglia) has been proposed, potentially interfering with neurodevelopment and affecting brain circuits involved in cognition, mood regulation, and behavior (135, 170, 183, 184, 185). Further, it has been suggested that cytokines exerting neuromodulatory effects in the brain may play a role in the development of psychopathologies seen across severe mental disorders (136, 186). Moreover, influence of the peripheral inflammation on the brain has been proposed, resembling the link seen between the peripheral immune response and the sickness behavior (122, 187, 188). Observations that therapeutic use of IL-2 as well as IFN-α in conditions such as renal malignities and viral hepatitis often lead to transient psychopathologies support the suggested involvement of the peripheral immune response in mental health and illness (189, 190). Furthermore, the kynurenine pathway model propose that cytokine induced shift in tryptophan metabolism can influence glutamate and monoaminergic neurotransmission and result in psychotic, affective, and cognitive symptoms (191, 192).

1.2.2.4 Immune disturbances and agitation-related phenomena

Observations across psychotic, manic, and depressive symptoms suggest immune activation with aberrations in inflammatory signaling such as the IL-1, IL-18, TNF, and IL-6 pathways (160, 167, 168). Interestingly, immune activation has also been indicated in agitation and related clinical phenomena such as aggression and impulsivity, both in the general population (193) and across mental disorders (194, 195, 196, 197). Elevated IL-6 has been linked to hostility in healthy individuals (193) and to impulsive aggression in intermittent explosive disorder (197), while immune activation reflected by increased levels of C-reactive protein (CRP) has been indicated in aggression among individuals with personality disorders (198) and schizophrenia (199). An association between T_H17 related cytokines and agitation in individuals with schizophrenia has been suggested (200), and elevation of TNF has been

reported in agitated patients in psychiatric emergency settings (194). Further, elevation of IL-1β has been observed in agitated individuals with dementia (201). Experimental animal models of agitation have indicated a role of IL-2, TNF, IL-1, and IL-18 signaling pathways (202, 203, 204, 205, 206). Moreover, the chemokine Regulated on activation normal T cell expressed and secreted (RANTES), IL-1 family, and TNF pathways have been suggested as pathophysiological candidates of impulsivity based on studies among individuals with alcohol dependence (207) and suicidal behavior (195), as well as on rodent models (208). In addition to the suggested interplay of the IL-1 family and TNF signaling pathways with neurotransmission and neuronal excitability (186), the inflammatory chemoattractant RANTES has also been proposed to play a neuromodulatory role (209, 210).

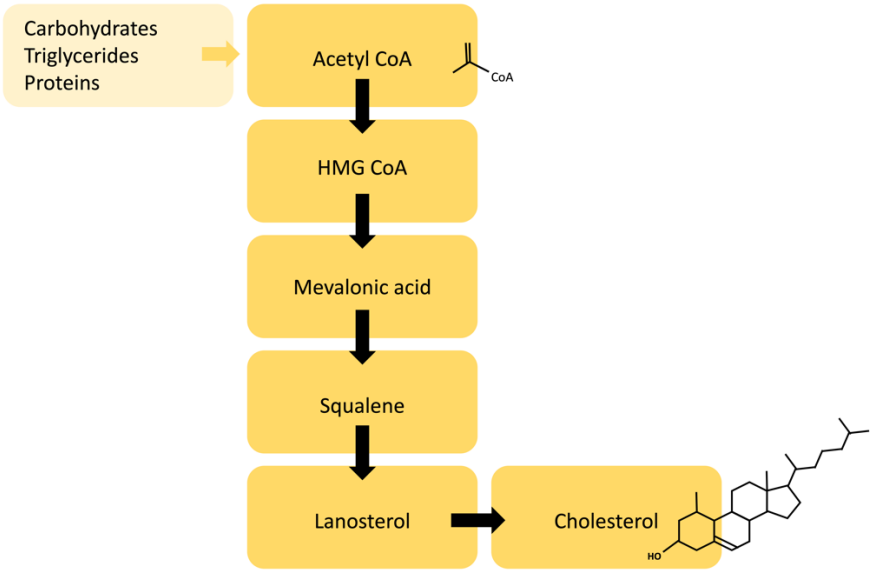
1.2.3 Cholesterol

1.2.3.1 Physiological roles and metabolism

Cholesterol is a lipid compound that is essential for proper cellular structure and functioning. It plays an important role in signaling at the cellular membrane and in fluidity of the membrane. Moreover, it serves as a precursor for steroid hormones and bile acids (211).

The brain is particularly rich in cholesterol. It contains approximately 20% of the total pool of cholesterol, while representing about 2% of the body mass (212). The brain cholesterol is involved in key physiological functions such as neurotransmission as well as in the myelination of neuronal axons by oligodendroglia (213, 214). The brain cholesterol is almost entirely synthetized de novo from acetyl coenzyme A (**Figure 3**) locally in the brain (215, 216). The metabolic pathway of the brain cholesterol is separated from the metabolism and transport of cholesterol in the periphery by the BBB. Following hydroxylation of cholesterol in neurons, the cholesterol metabolite 24-hydroxycholesterol diffuses through the BBB and is eliminated by the liver after conversion into bile acids (217).

Figure 3. A simplified presentation of the cholesterol synthesis



Acetyl CoA, acetyl coenzyme A; HMG CoA, 3-hydroxy 3-methyl glutaryl coenzyme A

Illustration by Gabriela Hjell

The circulating cholesterol can originate either from de novo synthesis from acetyl coenzyme A (**Figure 3**), which occurs mainly in the liver, or from absorption of dietary cholesterol. In the circulation, cholesterol is transported as a part of lipoprotein particles, due to its hydrophobic properties. Lipoprotein particles undergo dynamic changes, which can be divided into the exogenous lipoprotein pathway, the endogenous lipoprotein pathway, and the reverse cholesterol transport. Reflecting their decreasing size and increasing density, the different types of lipoprotein particles can be classified as chylomicrons, chylomicron remnants, very low density lipoproteins (VLDLs), intermediate density lipoproteins, low density lipoproteins (LDLs), and high density lipoproteins (HDLs) (218) (**Figure 4**).

Figure 4. Examples of the structure of lipoprotein particles

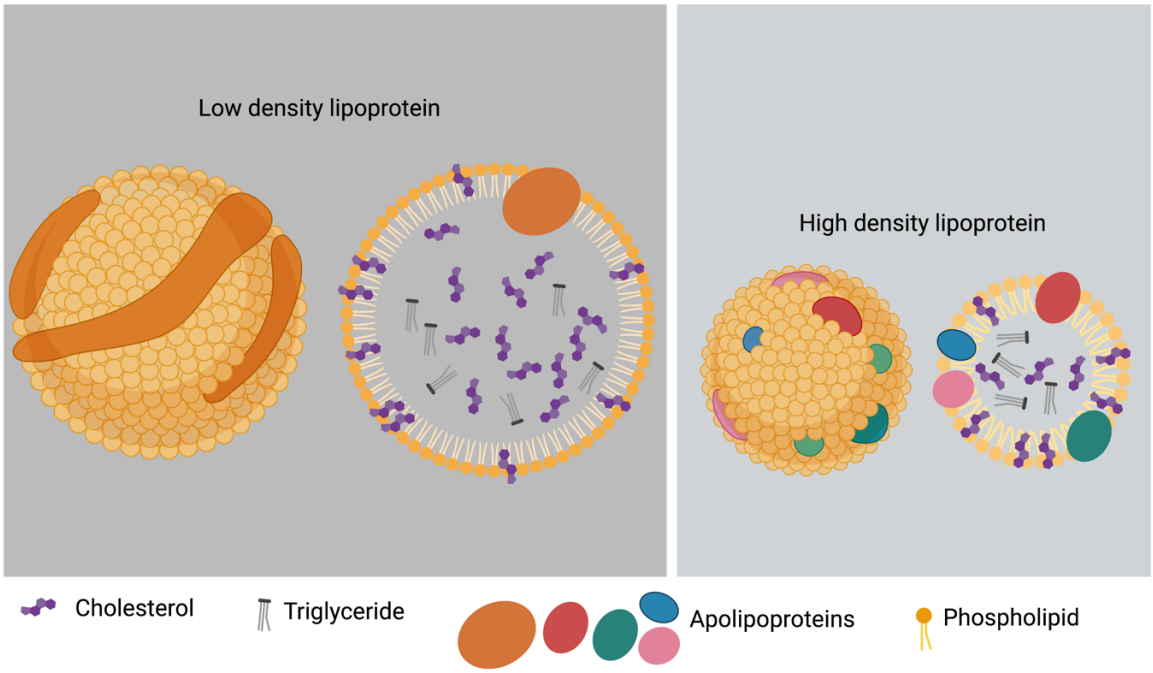


Illustration created by Gabriela Hjell using BioRender.com

The exogenous lipoprotein pathway starts when hydrolyzed lipids, including fatty acids, monoglycerides, and cholesterol, form micelles, which are then transported into enterocytes. In enterocytes, monoglycerides are converted to triglycerides, and a portion of cholesterol is esterified. These lipids are then, together with phospholipids and apolipoprotein B48, secreted as chylomicrons to lymphatic vessels and further into the circulation. Once in the circulation, chylomicrons interact with HDL and receive apolipoprotein E. Fatty acids from hydrolyzed triglycerides are absorbed by muscle and fat tissue, resulting in chylomicron remnants. Further, apolipoprotein E binds to hepatic receptors, and chylomicron remnants are internalized by hepatocytes (218).

The endogenous lipoprotein pathway is initiated in the liver, where VLDL particles are assembled from apolipoprotein B100, triglycerides, de novo synthesized cholesterol, as well as cholesterol from chylomicron remnants. VLDL is secreted into the circulation, where it interacts with HDL and receives apolipoprotein E. Interactions with endothelial cells transform VLDL to intermediate density lipoproteins, which, in turn, can be absorbed by the liver or transformed into LDL. LDLs are cholesterol-rich particles, representing the majority

of the circulating cholesterol. Eventually, LDL binds to LDL receptors either on hepatocytes or on cells in the peripheral tissues, to supply the tissue with cholesterol (218, 219).

The liver eliminates cholesterol together with bile acids via the biliary tract. The reverse cholesterol transport serves to facilitate cholesterol elimination. HDL, which contains apolipoprotein A-I, as well as other apolipoproteins such as apolipoprotein E, is secreted mainly by the liver. In the circulation, HDL receives triglycerides from chylomicrons and VLDL. Up on binding of apolipoprotein A-I, HDL receives phospholipids and unesterified cholesterol from peripheral tissues. Finally, HDL particles containing cholesterol return to the liver (218, 220).

1.2.3.2 Impact on CVD risk

Cholesterol transport in the circulation is a physiological process. However, the cumulative exposure to cholesterol-rich LDLs drives atherosclerosis, the key pathophysiological concept in the development of CVD. CVDs such as atherosclerotic disease of the coronary arteries and stroke are amongst the leading causes of death (221). Randomized controlled trials (RCTs) have demonstrated a robust protective effect of cholesterol-lowering on CVD mortality (222). Cholesterol-lowering strategies constitute one of the keystones in CVD prevention. Cholesterol management guidelines currently advise a stratified approach based on calculation of CVD risk and shared decision making (223, 224). The cholesterol-lowering preventive and therapeutical measures include adherence to a healthy lifestyle, pharmacological treatment with statins, and add-on pharmacotherapy with ezetimibe or proprotein convertase subtilisin kexin type 9 inhibitors (221).

1.2.3.3 Putative links to psychopathology

Implementation of cholesterol-lowering as a CVD primary prevention strategy has drawn attention to possible psychological effects of cholesterol-lowering (225). An early meta-analysis of cholesterol-lowering RCTs in the primary CVD prevention setting in the general population has indicated a link between the cholesterol-lowering and an increase in violent deaths caused by accident, homicide and suicide (225). However, these findings were not

replicated (226), and cholesterol-lowering pharmacotherapy with statins has gained a substantial record of safety (227, 228).

Psychological effects of cholesterol-lowering have not been specifically addressed in individuals with mental disorders. However, a number of smaller to medium scaled cross-sectional studies in the psychiatric settings have assessed the associations between agitation-related phenomena and circulating cholesterol levels (229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240). Several of these studies have shown negative associations between circulating levels of total cholesterol (TC) and aggression (229, 233, 238, 239, 240) or impulsivity (234, 236), while some of the studies have reported no significant associations between TC and aggression (230, 231, 232, 236, 237) and impulsivity (230). Negative associations between LDL cholesterol (LDL-C) and aggression (238, 239) or impulsivity (236) have also been shown. Evidence based on the studies that have investigated HDL cholesterol (HDL-C) (234, 236, 237, 238, 239) varies from positive (239), to negative (237), to non-significant (234, 236, 238) associations with aggression. Taken together, despite indications of an association between lipid profile with low TC and agitation-related phenomena, the evidence is conflicting.

Genetic susceptibility affecting the cholesterol synthesis pathway may underlie the possible link to agitation-related phenotypes, given that GWASs have implicated a role of cholesterol metabolism in severe mental disorders (241, 242). Alternatively, possible indirect effects of circulating cholesterol on the brain might be mediated by cholesterol metabolites (217, 243) or by an interplay with the endocrine system (244). Indeed, experimental animal studies have suggested that TC levels twice as high as the physiological range may have protective effects against aggression (245, 246). Furthermore, even though use of statins in the general population has gained a substantial record of safety (227, 228), and studies from psychiatric settings linking TC and agitation-related phenomena have been mainly conducted among statin non-users (229, 238, 239), lipophilic statin agents have also been suggested as a potential factor that may contribute to this link (247). Ultimately, the indications of an inverse relationship between cholesterol levels and agitation-related phenomena, regardless the unclear underpinnings, might in some cases influence the clinical decision-making about cholesterol management (248).

2. AIMS, OBJECTIVES, AND HYPOTHESES

2.1 The overarching goal

Agitation is a particularly challenging clinical feature associated with quality of life among individuals with severe mental disorders. However, biological correlates of agitation and related clinical phenomena are largely unknown. Despite methodological advances facilitating feasible acquisition of blood-sampling based markers with putative links to agitation, the relationships between the immune system, cholesterol, and pathophysiology of agitation-related phenomena and severe mental disorders are unclear. Thus, the aim of this thesis was to identify systemic biological correlates of agitation-related phenomena in severe mental disorders, focusing on feasibly accessible blood-sampling based markers that reflect disturbances of the immune system and cholesterol metabolism.

2.2 Knowledge gaps, objectives, and hypotheses

2.2.1 Study I

Given the increased CVD risk, individuals with severe mental disorders are often in the target group for cholesterol-lowering. However, associations between lower systemic cholesterol levels in mental disorders and agitation-related phenomena have been indicated, although there are substantial limitations to the study designs that underpin this indication. The inconsistencies in findings and the previous focus on the inpatient psychiatric settings call for an investigation in a large representative sample to expand our insight into the relationships between cholesterol and agitation-related phenomena.

Therefore, the objective of study I was to investigate associations between systemic cholesterol levels and agitation-related phenomena in a large sample of in- and outpatients with severe mental disorders. It was hypothesized that systemic cholesterol levels (TC, LDL-C, and HDL-C) among patients with severe mental disorders would be negatively associated with aggression propensity and impulsivity.

2.2.2 Study II

The inflammasome activation has been linked to severe mental disorders, and aberrant inflammasome-related immune signaling has been implicated in animal models of agitation and observed across agitation-related phenomena. However, our knowledge regarding inflammasome-related immune pathways in agitation among individuals with severe mental disorders is limited.

Thus, the objective of study II was to investigate the links between agitation and circulating inflammasome-related immune markers in severe mental disorders. It was hypothesized that agitation across the spectrum of severe mental disorders would be associated with immune activation reflected by circulating levels of the inflammasome-related immune markers (IL-1RA, IL-18, IL-18BP, IL-18R1, IL-18RAP). Further, it was hypothesized that agitation would be associated with the immune marker levels independently of core symptoms of illness exacerbation (i.e., psychotic, manic, and depressive symptoms). Moreover, the neuroendocrine influence on the relationship between agitation and immune activation was explored.

2.2.3 Study III

In similarity with agitation, impulsivity is a transdiagnostic feature linked to severe clinical expression, which has largely unknown biological correlates. Involvement of inflammatory signaling in impulsivity has been indicated, including RANTES, inflammasome-related, and TNF pathways. However, these potential links between immune signaling and impulsivity, with their possible impacts on psychopathology in severe mental disorders, are yet to be determined. In addition, impulsivity is a potential target for psychopharmacological strategies, and animal models have revealed impulsivity-lowering effect of lithium with a putative association to the immune system. Still, the relationships between impulsivity in severe mental disorders and psychopharmacological treatment regimens have been sparsely investigated.

Hence, the objectives of study III were (1) to assess the links between impulsivity and circulating immune markers in a large cross-sectional sample of individuals with and without a severe mental disorder and (2) to explore associations between impulsivity and

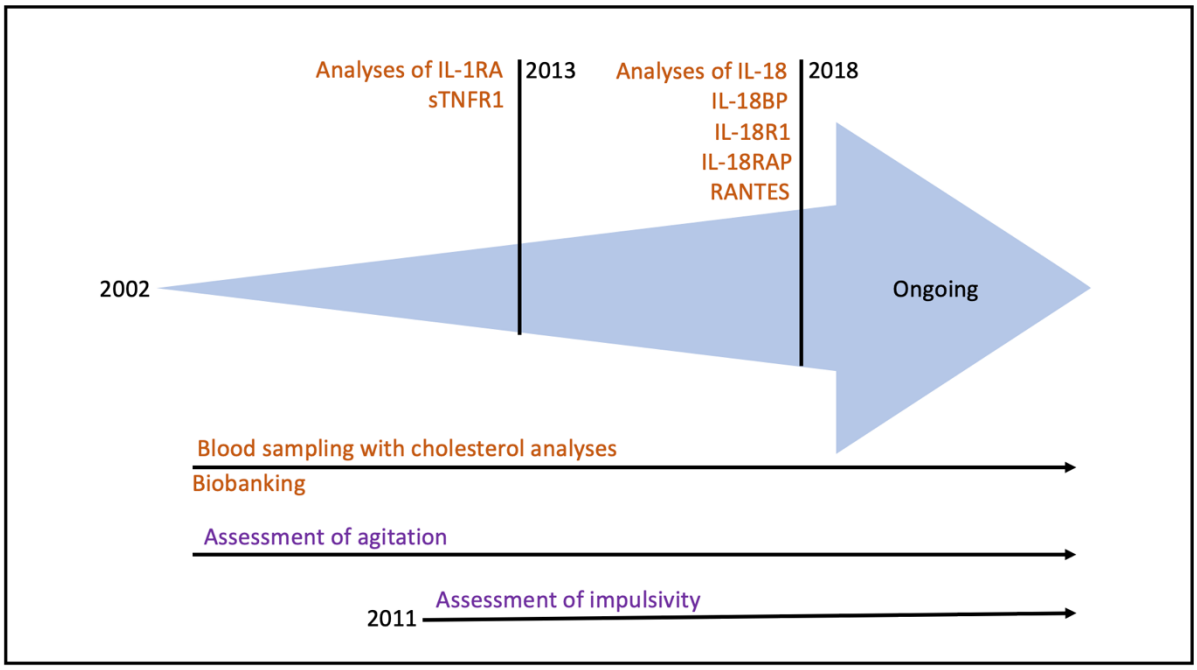
psychopharmacological treatment in a naturalistic sample of individuals with severe mental disorders. It was hypothesized that (1) circulating levels of RANTES, IL-1RA, IL-18, IL-18BP, and sTNFR1 would be positively associated with impulsivity across the diagnostic categories and that (2) antipsychotic, anticonvulsant, and lithium treatment would be negatively associated with impulsivity in severe mental disorders. Given the sparsity of evidence concerning the relationship between antidepressants and impulsivity in severe mental disorders, the respective part of the study was explorative.

3. METHODS

3.1 Study design and ethics

This thesis builds on cross-sectional study designs. All participants were recruited through the ongoing Thematically Organized Psychosis (TOP) study at the Norwegian Center for Mental Disorders Research, Oslo, Norway. The overall aim of the TOP study is to improve our insight into development and course of severe mental disorders. Since 2002, the TOP study has been enrolling patients with severe mental disorders referred from psychiatric inpatient and outpatient clinics. The TOP study also recruits age- and catchment area matched control subjects randomly selected from the national population registry. The study is approved by the Regional Ethics Committee, the Norwegian Directorate of Health, and the Norwegian Data Protection Authority. All study participants have given written informed consent and can withdraw from participation at any time. The research work was conducted in accordance with ethical standards articulated in the Declaration of Helsinki.

Figure 5. Chronological overview of relevant elements in the study protocol



IL-1RA, Interleukin-1 receptor antagonist; sTNFR1, Soluble tumor necrosis factor receptor 1; IL-18, Interleukin-18; IL-18BP, Interleukin-18 binding protein; IL-18R1, Interleukin-18 receptor 1; IL-18RAP, Interleukin-18 receptor accessory protein; RANTES, Regulated on activation normal T cell expressed and secreted.

Illustration by Gabriela Hjell

3.2 Research protocol

The TOP study protocol is comprehensive and forms a large database that serves different specific sub-studies. Thus, the participants underwent thorough characterization, including self-report questionnaires, neurocognitive testing, blood sampling, magnetic resonance imaging, and electroencephalography. The patient group was assessed by trained psychologists and physicians, whom had access to medical records and conducted systematic interviews such as the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) (249). To ensure validity and reliability of the assessments, the interviewers were trained according to the standardized course adapted from a training and quality assurance program developed at the University of California Los Angeles (250). Moreover, the interviewers were supervised by a psychiatrist with extensive clinical and academic experience. Symptom dimensions, including psychotic symptoms, were assessed using the Positive and Negative Syndrome Scale (PANSS) (251). Affective symptoms were quantified using the Young Mania Rating Scale (YMRS) (252) and the Calgary Depression Scale for Schizophrenia (CDSS) (253). Level of functioning was estimated according to the Global Assessment of Functioning Split Version (GAF) (254). The healthy participant group was assessed using the Primary Care Evaluation of Mental Disorders (255), following psychiatric and somatic history-taking. An overview of the relevant elements in the study protocol throughout the recruitment period is shown in **Figure 5.**

3.3 Subject samples

Subject samples in the three studies that are part of this thesis were drawn from the TOP database. The general inclusion criteria in the TOP patient group are a broad schizophrenia (SCZ) or bipolar spectrum disorder (BD) diagnosis assigned according to the DSM-IV (34), age between 18 and 65 years, and the capacity to give informed consent. Healthy participants are included in the TOP study if there is no presence or history of a severe mental disorder among the participants themselves or their first-degree relatives. The overall exclusion criteria comprise a severe somatic illness that interferes with brain functioning, history of severe head trauma, pronounced cognitive deficit with IQ scores below 70, and insufficient skills to communicate in Norwegian.

Table 1. Subject samples in the three studies

	Study I N=1001	**Study II** N=660	**Study III** N=657
SCZ	N=601	N=388	N=116
	Schizophrenia	Schizophrenia	Schizophrenia
	Schizophreniform disorder	Schizophreniform disorder	Schizophreniform disorder
	Schizoaffective disorder	Schizoaffective disorder	
	Delusional disorder	Delusional disorder	
	Brief psychotic disorder Psychotic disorder NOS	Brief psychotic disorder Psychotic disorder NOS	
BD	N=400	N=272	N=159
	Bipolar I disorder	Bipolar I disorder	Bipolar I disorder
	Bipolar II disorder	Bipolar II disorder	Bipolar II disorder
	Bipolar disorder NOS	Bipolar disorder NOS	Bipolar disorder NOS
	MDD with psychotic features	MDD with psychotic features	
HC			N=382

BD; broad bipolar spectrum disorders; HC, healthy participants; MDD, major depressive disorder; NOS, not otherwise specified; SCZ, broad schizophrenia spectrum disorders.

The subject sample in study I consisted of 1001 patients recruited between 2002 and 2017. The sample in study II included 660 patients recruited between 2002 and 2018 that had their plasma immune markers measured and that were not excluded due to use of immunomodulatory agents, immunological comorbidity, or current infection (indicated by medical records, self-report, medication use, or serum CRP level above 10 mg/L). Study III comprised 657 participants (275 patients and 382 healthy subjects) recruited between 2011 and 2018. The objectives of study III focused on impulsivity, a behavioral and personality construct with known diagnosis-specific differences (84). Thus, in addition to healthy subjects, only patients with schizophrenia, schizophreniform, or bipolar disorder were

included, while the exclusion criteria applied to study II were also followed. Diagnoses that constitute the subject samples in the three studies are displayed in **Table 1.**

3.4 Measurements

3.4.1 Agitation

Agitation constituted the main measure of interest in study II. The agitation measure was based on the PANSS assessment, which is a commonly used instrument for symptom evaluation in psychotic disorders (251). The PANSS consists of 30 interviewer-rated items, each reflecting a current symptom on a scale from 1 (no symptom) to 7 (severe symptom). The inter-rater reliability of the PANSS assessment in the TOP study has been repeatedly documented as good, achieving intraclass correlation coefficient above 0.7 (256, 257). Agitation score was calculated as the sum of the PANSS item P4-Excitement, item P7-Hostility, item G4-Tension, item G8-Uncooperativeness, and item G14-Poor impulse control. These five items constitute the PANSS Excited Component (PANSS-EC), a validated (50) and commonly used measure of agitation (258) derived from a five factor PANSS model (259).

3.4.2 Aggression propensity categories

In study I, agitation scores were used to define categories reflecting level of aggression propensity. The unifactorial structure of the PANSS-EC (50) and PANSS rating criteria (251) guided the definition of the cut-offs. Accordingly, PANSS-EC score of 5 represented a group with no agitation or aggression symptoms (NAS). PANSS-EC ranging from 6 to10 represented a group with minimal level of agitation or aggression symptoms (MLAS), and PANSS-EC greater than 10 represented a group with higher levels of agitation or aggression symptoms (HLAS). Thus, the first group NAS was defined by the absence of all PANSS-EC symptoms, the second group MLAS comprised suspected pathology, and PANSS-EC scores indicative of more certain and expressed pathology were categorized into the third group HLAS.

3.4.3 Impulsivity

Barratt Impulsiveness Scale (BIS-11) (260) was used as the main measure of interest in study III. The BIS-11 is a self-report of behavioral and personality constructs of impulsivity scored on a 4-point Likert scale. It consists of 30 items. The total score ranges from 30 to 120, with higher total scores reflecting higher levels of impulsivity. Internal consistency of the total score has been repeatedly found to be acceptable (52, 260, 261, 262, 263).

3.4.4 Cholesterol

Venous blood samples were collected in the morning after an overnight fast. Serum levels of TC, LDL-C and HDL-C were analyzed at Oslo University Hospital on routine instruments (Roche Diagnostics Cobas Integra 800, Roche Diagnostics Cobas 8000 e602/e801) using standard methods controlled by internal and external quality control samples. Until 2012, LDL-C was calculated by the Friedewald formula (264). From 2012 onwards, it was analyzed by an enzymatic colorimetric method.

3.4.5 Immune markers

Following venipuncture, blood was drawn using EDTA vials. Plasma was isolated the next working day and stored at -80 °C in the biobank. The cumulative storage time in the freezer was recorded (265). Immune marker levels were measured using enzyme-linked immunosorbent assay (ELISA) methods. Some key immune markers such as IL-1β or TNF have relatively short biological half-life and circulate at levels close to detection limit of commercially available assays. Thus, in addition to measurements of RANTES and IL-18 system markers (i.e., IL-18, IL-18BP, IL-18R1, IL-18RAP), IL-1 and TNF systems were assessed using robust markers that are known to reflect the activity of these systems (i.e., sTNFR1, IL-1RA) (175, 180). The antibodies used in the assays are described in **Table 2.**

Table 2. Antibodies used in the immunoassays

	Manufacturer	Assay sensitivity
IL-18	R&D Systems (Stillwater, MN, USA), Cat# DY318-05	22 pg/mL
IL-18BP	R&D Systems (Stillwater, MN, USA), Cat#DY119	25 pg/mL
IL-18R1	Sino Biological (Beijing, China), Cat#11102	25 pg/mL
IL-18RAP	Sino Biological (Beijing, China), Cat#SEK10176	10 pg/mL
IL-1RA	PeproTech (Cranbury, NJ, USA), Cat#900K474	25 pg/mL
sTNFR1	R&D Systems (Stillwater, MN, USA), Cat#DY225	20 pg/mL
RANTES	R&D Systems (Stillwater, MN, USA), Cat#DY278	20 pg/mL

The assays were run in duplicate in a 384-well format, assisted by a pipetting robot (SELMA, Analytik Jena, Jena, Germany) and a washer dispenser (BioTek, Winooski, VT, USA). Absorption was read by ELISA plate reader (BioTek, Winooski, VT, USA) at 450 nm with 540 nm wavelength correction. Intra-assay and inter-assay coefficients of variation were less than 10 % for all analyses. Levels of IL-1RA that were under the detection limit (9 samples in study II (2%) and in 1 sample in study III (0.4 %)) were set to 25 pg/mL. Similarly, levels of RANTES were under the detection limit in 10 samples in study III (1.5 %) and thus set to 20 pg/mL.

3.4.6 Psychotropic medication

Information about psychopharmacological treatment was retrieved from medical records and via interview. Currently used doses of antipsychotics, anticonvulsants, lithium, and antidepressants were recorded and expressed according to the defined daily dose (DDD) method, following guidelines from the WHO Collaborating Center for Drug Statistics Methodology (266).

3.4.7 Additional measurements

Serum cortisol level and several demographical (sex, age) and clinical measures (body mass index (BMI), inpatient versus outpatient status, psychotic and affective symptoms, alcohol and illicit substance use) were also part of the analyses (267, 268, 269). Serum cortisol was analyzed using a competitive luminescence immunoassay (Immulite 2000xpi, Siemens

Healthineers, Erlangen, Germany) at the Hormone Laboratory at Oslo University Hospital. Calculations of BMI, expressed as kg/m², were based on weight and height measurements. Substance use was assessed using the Drug Use Disorders Identification Test (DUDIT) (270) and the Alcohol Use Disorders Identification Test (AUDIT) (271), in addition to self-reported information about use of cannabis and stimulants, smoking status (smoking daily versus non-smoker), and number of alcohol units during the two-week period prior the assessment.

3.5 Statistical analyses

3.5.1 General statistical approach

Statistical analyses were conducted using IBM SPSS Statistics for Windows Version 25.0 software package (study I) and R software package versions 4.1.1 and 4.2.1 (study II and III). All analyses were two-tailed, and the general statistical significance level operationalized throughout the thesis was set at 0.05. Normality was evaluated using Kolmogorov-Smirnov tests and inspection of Q-Q plots and histograms. Descriptive characteristics were assessed using chi-squared tests, independent samples t-tests, one-way ANOVAs, Wilcoxon rank-sum tests, and Kruskal-Wallis tests. Associations between systemic biological status (circulating cholesterol and immune markers) and agitation related phenomena were analyzed using linear and logistic regressions.

3.5.2 Study I

In study I, the multinomial logistic regression model was applied to analyze the associations between cholesterol (TC, LDL-C, HDL-C) and the three levels of aggression propensity (NAS, MLAS, HLAS), with cholesterol as the independent variable, adjusting for sex, age, and diagnostic group (SCZ versus BD). The analyses were repeated in a subsample (N = 689) that was available for additional adjustments (BMI, inpatient versus outpatient status, alcohol use (AUDIT scores), illicit substance use (DUDIT scores), and psychotropic medication (antipsychotics, antidepressants, anticonvulsants, and lithium expressed in DDDs)). The associations between cholesterol (TC, LDL-C, HDL-C) and impulsivity (BIS-11 total score) were assessed using the linear regression model with impulsivity as the dependent variable

and cholesterol as the independent variable, adjusting for sex, age, and diagnostic group. Subanalyses (N = 259) with the additional adjustments (BMI, inpatient versus outpatient status, alcohol use, illicit substance use, and psychotropic medication) were also conducted. Additionally, interactions between cholesterol levels and sex, inpatient versus outpatient status, and diagnostic group were tested.

3.5.3 Study II

Before proceeding to main analyses in study II, plasma levels of IL-1RA, IL-18, IL-18BP, and IL-18R1 were logarithmically transformed and outliers outside 3 standard deviations were removed (3.2% of IL-1RA, 0.0% of IL-18, 2.9% of IL-18BP, 0.9% of IL-18R1) to comply with the test assumptions. The associations between agitation (PANSS-EC score) and immune signaling (IL-1RA, IL-18, IL-18BP, and IL-18R1) were assessed using the linear regression model with the immune marker as the dependent variable and agitation as the independent variable, adjusting for sex, age, BMI, smoking status (smoking daily versus non-smoker), diagnostic group (SCZ versus BD), psychotropic medication (antipsychotics, antidepressants, anticonvulsants, and lithium expressed in DDDs), alcohol (number of alcohol units), illicit substance use (cannabis and stimulants as dichotomous variables), and freezer storage time. Bootstrapping approach with 2 000 replicates was applied to check the stability of regression coefficients. IL-1RA analysis was performed in a subsample of participants (N = 405) (**Figure 5**). Due to a highly skewed distribution, IL-18RAP was dichotomized based on the median value and analyzed using the logistic regression model. Interaction between agitation and diagnostic group was tested using the same models. The models from main analyses were applied to investigate the influence of psychotic and affective symptoms on any significant association between agitation and the immune marker, using adjustment for psychotic (sum of PANSS Positive Component items: P1, P3, P5, G9, G12), manic (YMRS scores), and depressive symptoms (CDSS scores). To assess the influence of stress hormone levels, the main analyses were repeated in a subsample with available cortisol measurements (N=463 for the IL-18 system markers, N=356 for IL-1RA), followed by an additional adjustment for serum cortisol level.

3.5.4 Study III

Before proceeding to main analyses in study III, the BIS-11 total scores (measure of impulsivity) were logarithmically transformed to achieve normality. Further, immune marker values exceeding the first or third quantile by three interquartile ranges or more were removed (1.4% of RANTES, 3.8% of IL-1RA, 0.5% of IL-18, 1.7% of IL-18BP, and 0.4% of sTNFR1). The associations between immune signaling (plasma levels of RANTES, IL-1RA, IL-18, IL-18BP, and sTNFR1) and impulsivity were analyzed using the linear regression model with impulsivity as the dependent variable and the immune marker as the independent variable, adjusting for sex, age, and diagnosis (healthy individuals, SCZ, and BD coded as dummy variables). IL-1RA and sTNFR1 analyses were conducted in a subsample of participants (N=240) (**Figure 5**). The associations between psychopharmacological treatment and impulsivity were assessed in the patient group. The linear regression model with DDD of antipsychotics, anticonvulsants, lithium, and antidepressants as independent variables and impulsivity as the dependent variable was employed, while controlling for sex, age and diagnosis (SCZ versus BD). Follow-up analyses were carried out to assess the influence of the current affective state (YMRS and CDSS scores).

3.5.5 Test assumptions and multiple testing

Variance inflation factors, standardized residuals, and Cook's distances were evaluated to ensure no violation of the test assumptions (normality, homoscedasticity, and absence of multicollinearity and influential cases).

The general statistical significance level operationalized in this thesis was 0.05. Bonferroni method was applied throughout the three studies to correct for multiple testing, yielding significance level at 0.017 (0.05/ 3) for the associations between agitation related phenomena and cholesterol fractions in study I, at 0.01 (0.05/5) for the associations between agitation related phenomena and immune markers in study II and III, and at 0.0125 (0.05/4) for the associations between impulsivity and psychotropic medications in study III.

4. RESULTS

4.1 Study I

The sample consisting of inpatients and outpatients with schizophrenia- or bipolar spectrum disorders revealed no significant associations between cholesterol levels and aggression propensity or impulsivity. There were no significant interactions between cholesterol and diagnostic group, inpatient versus outpatient status, or sex. Controlling for BMI as well as use of psychotropic medication, illicit substances, and alcohol did not affect the findings.

4.2 Study II

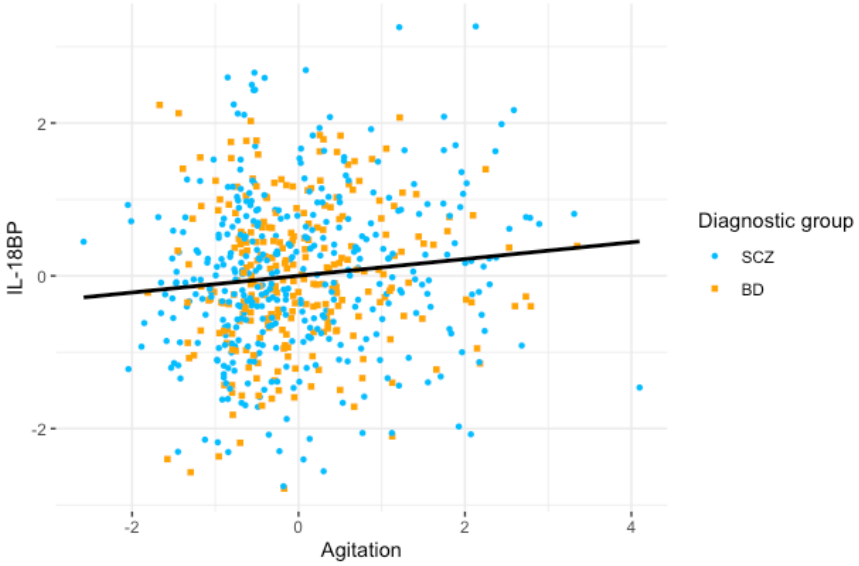
Agitation was significantly positively associated with IL-18BP (β=0.13, t=3.41, p=0.0007) after controlling for confounders, and adjustment for psychotic, manic, and depressive symptoms did not affect the findings (**Figure 6**). The stability of regression coefficients was confirmed by the bootstrapping approach. There were no significant associations between agitation and the other investigated immune markers (IL-1RA, IL-18, IL-18R1, IL-18RAP). Further, there were no significant interactions between agitation and diagnosis. Additional adjustment for cortisol did not substantially alter the results (association between agitation and IL-18BP (β=0.17, t=3.69, p=0.0003)).

4.3 Study III

The sample of individuals with and without a severe mental disorder revealed no significant associations between the immune marker levels (RANTES, IL-1RA, IL-18, IL-18BP, sTNFR1) and impulsivity independent of diagnosis. Among patients, impulsivity was negatively associated with lithium treatment (β=-0.16, t=-2.68, p=0.008) and positively associated with antidepressant treatment (β=0.16, t=2.78, p=0.006), while there were no significant associations between impulsivity and antipsychotics or anticonvulsants. Additional adjustment for the current affective state (YMRS and CDSS scores) did not substantially influence the results (association between impulsivity and lithium (β=-0.19, t=-3.00, p=0.003), association between impulsivity and antidepressants (β=0.16, t=2.58, p=0.011)).

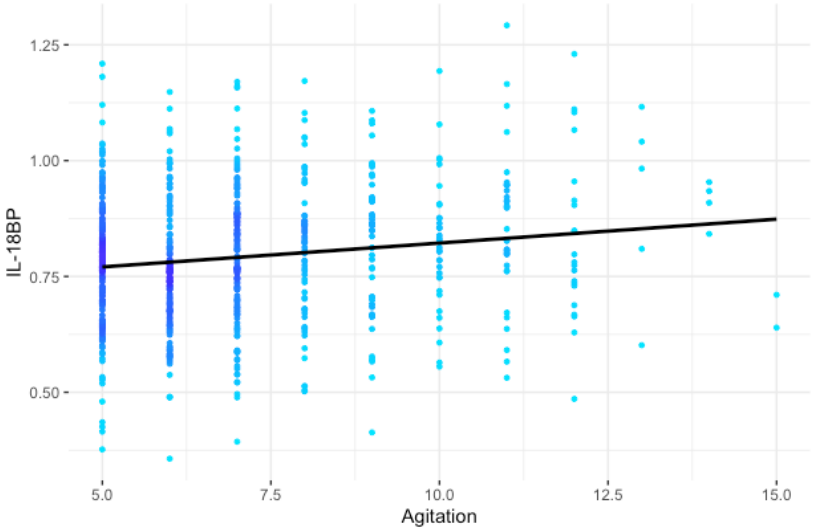
Figure 6. Association between agitation and IL-18BP

5) After correction for multiple confounders and symptom dimensions



X axis: Z-scores (standardized residuals) of PANSS-EC (Positive and Negative Syndrome Scale Excited Component) obtained from a regression model with PANSS-EC as dependent and sex, age, BMI, smoking, diagnosis, medication, alcohol use, substance use, freezer storage time, psychosis, mania, and depression as independent variables, Y axis: Z-scores (standardized residuals) of log-transformed interleukin-18 binding protein (IL-18BP) levels (ng/ml) obtained from a regression model with IL-18BP as dependent and sex, age, BMI, smoking, diagnosis, medication, alcohol use, substance use, freezer storage time, psychosis, mania, and depression as independent variables. BD, Affective disorders; SCZ, Psychotic disorders.

b) Raw data



X axis: PANSS-EC (Positive and Negative Syndrome Scale Excited Component), Y axis: Log-transformed interleukin 18 binding protein (IL-18BP) plasma levels (ng/ml). Shading represents the density of observations.

5. DISCUSSION

5.1 Main findings

Aiming at identification of systemic biological correlates of agitation-related phenomena in severe mental disorders, the main findings of current thesis can be summarized as follows.

- A novel finding of positive association between agitation and level of circulating IL-18BP, while levels of the remaining investigated inflammasome-related immune markers did not show any significant associations to agitation in severe mental disorders.

- No significant associations between transdiagnostic measure of impulsivity and levels of circulating immune markers within the putative pathophysiological pathways (the chemokine RANTES, sTNFR1, and inflammasome-related markers).

- The investigation of circulating cholesterol levels among individuals with severe mental disorders recruited across inpatient and outpatient clinics revealed no significant associations to aggression propensity or impulsivity.

These core findings add to the accumulating, yet complex, evidence of immune system disturbances in severe mental disorders and somewhat challenge the previous indications of links between systemic cholesterol and agitation-related phenomena. In addition, there was a negative association between impulsivity and lithium treatment as well as a positive association between impulsivity and antidepressant treatment, warranting future investigations to determine the causal directionality.

5.2 Circulating immune marker levels and agitation-related phenomena

Immune activation, including aberrant inflammasome-related signaling, has been previously indicated across agitation-related phenomena (193, 194, 197, 198, 199, 201), and the inflammasome-related, TNF, and chemokine signaling pathways have been suggested as pathophysiological candidates of impulsivity (195, 207, 208). Expanding on these previous

indications, the positive association between agitation and level of circulating IL-18BP represents a novel finding from the current thesis, derived from a large well-characterized sample of patients with severe mental disorders. IL-18BP is a protein involved in inflammasome-related signaling and regarded as a reliable marker of immune activation (176). The current finding of a link between agitation and level of circulating IL-18BP may indeed reflect immune activation, with parallels to the previously reported immune activation in agitated states (194, 199, 201) and agitation-related conditions (197). Of note, the positive association between agitation and circulating IL-18BP levels was independent of psychotic, manic, and depressive symptoms. Thus, this finding lends support to the notion that agitation is a phenomenon linked to immune disturbances independently of core symptoms of illness exacerbation (160). IL-18BP is a major regulatory protein within the inflammasome-related IL-18 pathway (176). Phagocytic and sensory immune cells express NLRP3 proteins that react to cellular stress signals and form the NLRP3 inflammasomes (117). The NLRP3 inflammasomes than propagate the immune response by inducing secretion of IL-1β and IL-18 (118), while components of these inflammasome-related pathways interact in a complex way to ensure a fine-tuned coordination of the immune responses (173). Typically, upregulation of IL-18BP follows elevations of IL-18 and forms a negative feedback loop (176). The present finding of an association between agitation and levels of circulating IL-18BP is in line with indicated links between aberrant inflammasome-related signaling, severe mental disorders (163, 272), and animal models of agitation (203). However, the current comprehensive study of circulating inflammasome-related immune markers, IL-18 included, did not reveal any other significant associations to agitation in severe mental disorders. This raises the question about the specific origins of the immune signal underlying the IL-18BP elevation. Importantly, IL-18BP elevations can be a sum of several immune signals. Besides the negative feedback loop with IL-18, IL-18BP can also be upregulated by immune factors such as IFN-γ and IFN-α (176) (**Figure 7**). Indeed, elevation of circulating IL-18BP has been demonstrated as a part of the response to IFN-α treatment of viral hepatitis (273). Intriguingly, indices of a causal involvement of the immune system in agitation may be drawn from RCTs showing substantially higher rates of side effects in form of agitation in the IFN-α treatment arm of hepatitis as compared to IFN-α-free treatment (190, 274). Furthermore, a porcine model of agitation has indicated a potentiating effect of inflammatory stimulation with lipopolysaccharide, with somewhat conflicting evidence

regarding the effect on IFN-γ levels in the brain tissue (275, 276). Further, chronic viral infection in the rodent brain tissue has been shown to lead to increased motor activity and low-grade inflammatory changes, including upregulated IFN-γ (277). Finally, additional line of evidence linking interferon signaling and agitation-related phenomena builds on the observation of upregulated transcriptional activity within the interferon signaling pathway among individuals prone to impulsive aggression in the context of intermittent explosive disorder (278).

Figure 7. Regulatory interplays of IL-18BP

IFN-α, interferon-α; IFN-γ, interferon-γ; IL-18BP, Interleukin-18 binding protein

Illustration by Gabriela Hjell

Agitation and impulsivity can be conceptualized as related and partly overlapping clinical phenomena (46, 48, 49). However, agitation typically denote a state of restlessness accompanied by impaired impulse control (50), while impulsivity may be defined as a personality and behavioral trait (52). In contrast to agitation across severe mental disorders, the investigation of transdiagnostic measure of impulsivity revealed no significant association to circulating IL-18BP level. Thus, despite that agitation and impulsivity are two clinically related constructs, this discrepancy in the current findings may point toward somewhat distinct biological correlates underlying their presentations. Moreover, multiple lines of evidence have indicated positive association between agitation, impulsive aggression, and interferon signaling known to affect IL-18BP levels (190, 274, 278), while no corresponding robust specific indices linking interferon signaling with impulsivity trait have been reported (279, 280). Further, the current novel assessment of the link between impulsivity and circulating IL-18 revealed no significant association, in parallel with the absence of significant association between IL-18 and agitation.

Neuroimmune interactions and endocrine signaling serve as important modes of bidirectional communication between the brain and the periphery (121). Acute psychological stress stimuli are known to lead to activation of both the inflammatory signaling pathways (281) and the hypothalamic-pituitary-adrenal axis with elevations of cortisol (124). Similarly, emotional states such as anger (282) and hostility (283) have been reported to lead to immune activation. However, adjustment for cortisol levels in the analysis of agitation and IL-18BP did not influence the current findings, suggesting that other mechanisms than acute psychological stress underpin the observed link between agitation and level of circulating IL-18BP. In accordance, immune alterations distinct from those linked to stress-related disorders have been reported in impulsive aggression (278). Of note, the relation between agitation and immune alterations following chronic psychological stress is unknown (284).

A role of the inflammasome-related IL-1 signaling pathway has been previously indicated in agitation among individuals with dementia (201) as well as in animal models of agitation (202, 206) and impulsivity (208). In contrast, the current investigation of circulating IL-1RA levels in relation to agitation and impulsivity revealed no significant associations. A feline model of agitation has shown regionally specific effects of cytokines (204), including potentiating effects of IL-1β in midbrain periaqueductal gray (202) and medial hypothalamus (285). In line with the current findings, a recently reported rodent model of agitation has shown no link between phenotype characterized by reactive aggression and circulating IL-1β levels (286). The same rodent model has indicated a role of IL-1β signal transduction in dorsal raphe nucleus in the midbrain and transient elevations of circulating inflammatory immune markers, including IL-1β, following a stressful encounter (286). This might point to occurrence of temporally specific systemic inflammatory response to social stress related to agitated and aggressive behavior, which was not captured in the present sample of individuals with severe mental disorders. The current assessment revealed no link between circulating IL-1RA levels and impulsivity, contrasting the previously reported parallel reductions in impulsivity and circulating IL-1β in rodents (208). These parallel reductions in impulsivity and circulating IL-1β have been observed in specific conditions following administration of lithium, which might possibly explain the discrepancy. In line with the current findings, a previous report assessing level of circulating IL-1β messenger

ribonucleic acid (mRNA) has shown no significant correlation to impulsivity among individuals with suicidal ideation or behavior, multiple testing taken into an account (195).

There were no significant associations between impulsivity and levels of circulating sTNFR1 or RANTES, contrasting previous findings of a link to circulating TNF mRNA levels in individuals with suicidal ideation or behavior (195) and links to circulating levels of RANTES in individuals with alcohol dependence (207) and in rodents (208). These inconsistencies may indicate relationships specific to certain populations, characterized by high substance use, suicide risk, or other distinct clinical features. Furthermore, the methodological choice of markers that reflect the immune pathway activity and their disparate expression patterns may also play a part in the discrepancies across the literature (175, 180). Taken together, the present paucity of associations linking agitation and related clinical phenomena to circulating markers of immune activation suggest that other factors are the major drivers of agitation-related phenomena in severe mental disorders.

5.3 Circulating cholesterol levels and agitation-related phenomena

The present assessment of circulating cholesterol levels in a large sample of individuals with severe mental disorders recruited across inpatient and outpatient clinics revealed no significant associations to aggression propensity or impulsivity. These null findings are in contrast with the previous smaller to medium scaled studies reporting negative associations between TC and agitation-related phenomena (229, 233, 234, 236, 238, 239, 240). On the other hand, the present findings are in accordance with several previous observations that have not detected significant associations to agitation-related phenomena (230, 231, 232, 236, 237). The evidence regarding links between systemic cholesterol levels and agitation-related phenomena among individuals with mental disorders is indeed conflicting. A recent systematic review within psychosis spectrum disorders has described a pattern with negative or nonsignificant associations between TC and aggression (287). Given that the evidence-base consists of observational studies, the findings might represent reverse causality and thus be prone to influence by clinical characteristics of the psychiatric populations investigated. It has been shown that clinical characteristics may drive the association to cholesterol level, and the importance of exploring potential confounding

factors in this context has been highlighted (288). Most of the previous study designs were adjusted for sex and age, whereas the current assessment accounted also for a wide range of other potential confounding factors, including diagnosis, medication, BMI, and substance use. Further, the vast majority of the previous research has been conducted in the inpatient psychiatric setting, while the current assessment was done in a sample recruited in naturalistic broad clinical settings across outpatient and inpatient clinics. Hence, contrasting some of the previous research, the present null findings are based on a well-adjusted assessment among patients within a range of illness stages and severity, which might explain some of the discrepancies. Of note, the current findings are also in line with the null findings from RCTs in the general population assessing agitation-related phenomena and cholesterol-lowering (226).

Interestingly, findings linking low TC with aggression are based on studies that have recorded aggressive behavior over a longer period (229, 233, 239, 240), whereas studies that have used recordings acquired over a shorter period (230, 231, 232, 236), the current findings included, do not show this link. This indicate that the previously reported link between cholesterol level and aggression might be related to the trait properties, possibly reflecting antisocial personality traits rather than act of aggression itself (289, 290).

Building on previous indications of links between agitation-related phenomena and systemic biological components, the studies in the current thesis investigated hypotheses based on the anticipated inverse relationship between agitation-related phenomena and circulating cholesterol levels and the anticipated positive relationship between agitation-related phenomena and immune activation. The studies revealed a positive association between agitation and level of circulating IL-18BP but no significant associations to circulating cholesterol levels. It has been robustly demonstrated that a metabolic profile with hypercholesterolemia, high BMI, and large deposits of adipose tissue is linked to development of a systemic low grade inflammatory response (291), and cholesterol crystals have been implicated in the NLRP3 inflammasome activation (118). Of note, only weak correlations between circulating cholesterol and elements of the inflammasome-related IL-18 system in severe mental disorders have been shown (163), indicating that the relationships between lipid metabolism and immune responses are likely complex. Intriguingly, lack of microglial physiological functions in the adult brain tissue has been

shown to affect cholesterol metabolism in oligodendrocytes, lead to increase in brain cholesterol, hypermyelination, and consecutive demyelination (292), while disruptions of white matter integrity have been linked to antisocial traits among individuals with a history of aggression (293).

5.4 Psychotropic medication and impulsivity

Impulse control impairments are frequently part of the clinical expression during illness exacerbations such as psychotic or manic episodes, and these can be treated with antipsychotics, anticonvulsants, or lithium (60, 294, 295). Moreover, adjunctive psychopharmacotherapy with antidepressants is often initiated in clinical practice across severe mental disorders (296, 297). As such, impulsivity may constitute a target for psychopharmacological strategies, although the relationships between impulsivity in severe mental disorders and psychopharmacological treatment have been sparsely investigated (298, 299, 300). Thus, these relationships were cross-sectionally addressed in study III.

In line with evidence based on rodent models showing impulsivity-lowering properties of lithium (208, 301, 302), there was a negative association between lithium treatment and impulsivity. Further, impulsivity-lowering effects of psychopharmacotherapy with lithium have been seen in the context of manic episodes (300) and comorbid pathological gambling (299) among patients with bipolar disorder. Interestingly, impaired impulse control has been identified as one of the major factors in suicidality (303), and lithium has shown protective effects on suicide risk in mood disorders (304, 305, 306). While the molecular mechanisms of lithium effects are incompletely understood, inhibition of glycogen synthase kinase-3 as well as of inositol monophosphatase and subsequent interactions with cellular signaling and neurotransmission have been proposed to play a role (307, 308, 309, 310). Of note, a link between clinical characteristics and lithium prescription practice (311) might also underlie the observed association between impulsivity and lithium treatment.

Study III showed a positive association between antidepressant treatment and impulsivity. This association may indicate a causal effect of antidepressants on impulsivity or a more intensive antidepressant prescription practice applied to impulsive patient populations. Indeed, the antidepressant prescription practice has been proposed to be affected by

clinical characteristics of the patients. Specifically, deflections from the standard first-line treatment of major depressive disorder in more severely ill patient populations at higher suicide risk have been demonstrated (312). Somewhat in parallel, a large register-based observational study has shown an increased risk of suicide attempt repetition among patients that were prescribed antidepressants, which was not apparent after accounting for the baseline risk of suicide attempt repetition based on demographic and clinical characteristics (313). On the other hand, meta-analyses of RCTs of antidepressants have indicated an increase in suicidality among adolescents (314) and young adults (315), while no significant increase was reported in the adult population (315). Of note, it has been suggested that impulsivity may be particularly related to suicide risk among younger adults (316). Importantly, antidepressants typically target serotonergic signaling, but the effects beyond relief of depressive symptoms (317) and exhaustive mechanisms of action remain elusive and likely complex (318, 319).

No significant associations between antipsychotic or anticonvulsant treatment and impulsivity were detected, which is in line with decrease in impulsivity in rodents exposed to lithium but not in those exposed to anticonvulsants such as carbamazepine or valproate (301, 302). In contrast, previous clinical studies have indicated an inverse relationship between impulsivity and psychopharmacotherapy with valproate (300) as well as with antipsychotics (298). The inconsistencies may be partly explained by differences in the conceptualization of impulsivity, distinct characteristics of the patient populations, or pharmacological heterogeneity within the medication groups (320).

5.5 Methodological considerations

5.5.1 Internal validity

Consideration of potential methodological challenges is an important aspect of planning a study and drawing scientific conclusions. A variety of steps in the process of generating new knowledge may lead to bias, a systematic error in the way data is collected, analyzed, interpreted, and published (321). Bias can in turn compromise the internal validity of a study, i.e., the capacity to generate valid findings (321).

Ethically sound acquisition of scientifically accurate data constitutes a common and important challenge in research. The use of minimally invasive methods for data acquisition throughout this thesis (i.e., psychometric assessments and blood sampling) has allowed analyses of systemic biological correlates in large samples. Consequently, this thesis builds on analyses restricted to the systemic biological measures (i.e., circulating cholesterol and immune markers), which inherently prevents direct inferences about processes in the brain. Still, the similarities in brain and blood gene expression profiles (322) as well as the production of immune signaling molecules in the brain (121) and the bi-directional immuno-psychoneuroendocrinological interplays (121) suggest that investigation of systemic biological correlates may contribute to advancements in our understanding of metabolic profiles and immune responses in mental health and illness. Importantly, the cross-sectional observational design prevents inferences about causal directions.

This thesis comprises analyses of markers with putative links to agitation, including circulating markers that reflect immune activation and aberrant inflammasome-related signaling (paper II and III) and cholesterol metabolism (paper I). The blood samples that formed basis for study I and II were drawn in the morning after an overnight fast. In contrast, adherence to acquisition of morning samples after overnight fast was not feasible in case of study III. Hence, bias due to variation of the diurnal and fasting status of blood samples forming basis of study III cannot be ruled out. Similarly, despite that cortisol levels in study II were measured in the morning, the blood draws were not timed according to individual circadian rhythms (323). While the serum samples for cholesterol analyses were analyzed using pipelines and methods complying with the standards for clinical use, immediate plasma isolation and freezing of the samples for immune marker analyses was not feasible. Since the plasma was isolated and frozen the next working day, a risk of bias due to handling of the blood samples cannot be dismissed (324). To minimize this risk, analyses of immune markers with longer biological half-life were chosen (180). Further, some key markers within the immune pathways of interest such as IL-1β and TNF circulate at levels close to the detection limit of commercially available assays. In the current thesis, less than 2% of the samples showed a value below the detection limit for any given marker analyzed (IL-1RA, IL-18, IL-18BP, IL-18R1, IL-18RAP, sTNFR1, RANTES). Thus, on the one hand, robust markers known to reflect activity within the immune pathways of interest

were used (175, 180), on the other hand, the activity of IL-1 and TNF systems was assessed solely by the surrogate markers (i.e., IL-1RA, sTNFR1). Furthermore, the uncertainty regarding origins of extreme values of the immune marker levels also represents a potential bias. To handle the potential undue influence of these values, extreme values were removed before proceeding to main statistical analyses. The immune marker levels were measured using ELISA, which is a commonly used and well-established method. However, in similarity with other analytical methods, both false positive (e.g., detection of a protein structurally resembling the immune marker) and false negative readings (e.g., masking or sequestration of the immune marker or competition with endogenous antibodies) may occur (325). To monitor reliability of the measurements, intra- and inter-assay coefficients of variation were calculated and were all below 10 %.

Similar hypotheses were postulated about the relationships between immune markers and both trait and state measures of agitation-related phenomena. In general, immune marker levels show large heterogeneity (326). The exact patterns of immune marker variability over time are unclear, even though both elements of stability over time and phasic differences have been indicated in severe mental disorders (327, 328). The blood samples were not always acquired during the same session as the measures of agitation and impulsivity. Still, the clinical assessments and blood sampling were conducted in a reasonable temporal proximity, i.e., within one month, median 9 days, and interquartile range up to 13 days.

The scope of the current thesis comprised biological correlates of agitation as well as of related clinical phenomena such as aggression propensity and impulsivity. Measures of agitation and aggression propensity were based on the interviewer-rated PANSS assessment. To minimize potential interviewer-related bias and to facilitate validity and reliability of the PANSS assessments (251), the interviewers were trained according to a standardized course and supervised by a psychiatrist with extensive clinical and academic experience. The measure of impulsivity was questionnaire-based. The BIS-11 is a self-report of behavioral and personality constructs of impulsivity scored on a Likert scale, which has an acceptable internal consistency of the total score (52, 260, 261, 262, 263). However, the risk of bias due to oversimplification cannot be excluded, since the total BIS-11 scores may not fully reflect the multifaceted construct of impulsivity (86).

The well-characterized sample enabled the focus on associations with psychopharmacological treatment in study III. Still, use of a proxy of the exposure to the psychotropic agent (the prescribed and self-reported medication expressed as DDD) prevented adjustments for the treatment non-compliance (329), which represents risk of bias that should be considered when interpreting the results.

The thorough characterization of the clinical samples allowed, in addition to standard demographic variables such as sex and age, adjustments for other relevant potential confounding factors (study I and II) including diagnosis, medication, substance use, and BMI (267, 268, 269). Of note, even though several potential confounders were taken into an account, residual confounding cannot be ruled out.

The current thesis reported elevated impulsivity levels across schizophrenia and bipolar spectrum disorders as compared to healthy control population. Considering potential selection bias, validity of this finding relies on representativeness of the samples, the control sample in particular. Of relevance, the median values of impulsivity in the current healthy control group correspond to the values acquired among customers of 23andMe consumer genetics company, which represents a control population recruited based on reciprocal interests, as opposed to the traditional public health and academic recruitment procedures (263).

5.5.2 External validity

Generalizability is dependent on the representativeness of the study samples (321). Occurrence of systematic differences between characteristics of individuals that participate in a study and remaining individuals from the population of interest leads to limited generalizability of research findings. Mismatch between interpretation of study results and actual generalizability of the study findings may compromise the external validity of the study (321). An important factor strengthening the representativeness of the current study samples of individuals with severe mental disorders is the publicly funded health care in Norway, facilitating equal availability of the mental health care for patients across socioeconomic backgrounds. Further, representativeness of the combined inpatient and outpatient settings may have contributed to a broader external validity of the findings,

which was of particular relevance for objectives of study I investigating circulating cholesterol levels. However, because of the relatively comprehensive study protocol and, implicitly, inclusions mainly in sub-acute or non-acute phase, there was a sparsity of high agitation levels in the current samples. Thus, the findings must be interpreted with caution in term of generalizability to the acute psychiatric setting. Further concerns regarding representativeness might also be raised, since the study inclusion relies on the participant's capacity to consent and on the participant's willingness to volunteer to take part in research. It has been previously indicated that some sociodemographic and clinical characteristics differ between study participants and psychiatric inpatients that do not participate in research (330). Different theoretical explanations for a potential non-representativeness of the current study samples may be constructed, e.g., the most severely ill patients might not participate as often due to preoccupancy with the symptoms of the illness and, concurrently, the patients with the mildest functional impairment might not participate due to personal preference to prioritize work or family over research. Substantial efforts have taken place in attempt to minimize this risk of non-representativeness, including reaching out and maintaining regular contact with clinicians across the inpatient and outpatient clinics, holding lectures, giving feedback on findings from the TOP studies, refreshing the study referral procedures, offering clinical assessments and blood-sampling at the most convenient location for the patient, and offering transport for participants that have difficulties to travel.

5.5.3 Random error

Random error reflects variation of the studied phenomena that happens by chance and can be reduced by increasing sample size (331). The use of minimally invasive methods in the current thesis facilitated investigation of systemic biological correlates in large samples. Consequently, the analytical power opened the opportunity to target even small effect sizes. The stringent statistical approach with Bonferroni correction for multiple testing applied throughout the thesis minimized the risk of false positive results, while the risk of false negative results cannot be fully dismissed.

5.6 Conclusions, implications, and future directions

The current thesis adds to the growing but complex evidence-base of immune system disturbances in severe mental disorders and somewhat challenge the previous indications of links between systemic cholesterol and agitation-related phenomena.

Study II showed a novel link between agitation and circulating IL-18BP levels, suggesting the IL-18 system as one of the biological correlates of agitation in severe mental disorders and thus expanding the biological knowledge base of a particularly challenging clinical feature. In contrast, study III revealed no links between impulsivity and circulating RANTES, TNF-, or inflammasome-related immune markers, highlighting the complexity of the accumulating evidence regarding immune system disturbances in severe mental disorders. The previously indicated inverse relationships between cholesterol levels and agitation-related phenomena in mental disorders, although based on designs with substantial limitations, might influence the clinical decision-making about cholesterol management in this patient group. No links between systemic cholesterol levels and aggression propensity or impulsivity were detected in study I. Thus, these null findings based on a large representative sample constitute a valuable enrichment of the knowledge base relevant for this clinical decision-making process.

The large clinical heterogeneity of severe mental disorders and involvement of small effect sizes in combination with cross-sectional observational design challenge interpretation on the individual level and translation into direct clinical implications. Efforts to replicate and complement the observed link with IL-18 signaling system, for instance, in acute psychiatric settings are warranted, before taking a step forward to neurobiological models and potentially clinical trials. Alternatively, another interesting way forward is to zoom out and focus on immune aberrations across symptom domains or in relation to the severity of the impairment, including longitudinal data acquisition and multimodal measurements (332). Moreover, particularly intriguing but challenging is the question of disentangling the involvement of neurodevelopmental and direct pathways between the immune system and mental health. Additionally, this thesis captured a negative link between impulsivity and lithium treatment as well as a positive link to antidepressant treatment. Given that impulsivity is a potential target for psychopharmacological strategies, the current cross-

sectional observations call for future pragmatic clinical studies with randomized designs to determine the causal directionality and assess the potential for development of optimized treatment strategies.

The current thesis conveyed subtle but potentially valuable advancements to the research field of systemic biological correlates of agitation-related phenomena in severe mental disorders. Specifically, the findings indicate that interleukin-18 binding protein is a modest part of the biological correlate of agitation. However, the paucity of associations to circulating markers of immune activation suggest that other factors are the major drivers of agitation-related phenomena. The thesis contributes to the evidence basis that may serve future neurobiological studies and, ultimately, development of optimized treatment strategies in severe mental disorders.

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Study I-III

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ORIGINAL RESEARCH

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Disentangling the relationship between cholesterol, aggression, and impulsivity in severe mental disorders

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Abstract

Objective: Low total cholesterol has been linked with adverse mental symptoms such as aggression and impulsivity in severe mental disorders (SMDs). This putative association may affect the clinician's decision making about cholesterol lowering in this patient group. Here, we investigated the associations between cholesterol levels, aggression, and impulsivity in a large representative sample of in- and outpatients with SMD.

Methods: Patients with schizophrenia- or bipolar spectrum disorders (N = 1 001) underwent thorough clinical characterization and blood sampling (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol). Aggression was characterized by the Positive and Negative Syndrome Scale Excited Component. Impulsivity was measured with the Barratt Impulsiveness Scale in a subsample of patients (N = 288). We used a multinomial logistic regression model to analyze the association between cholesterol and aggression and a multiple linear regression model to analyze the association between cholesterol and impulsivity, while controlling for confounders.

Results: We found no significant associations between cholesterol levels and aggression or impulsivity. There were no significant interactions between cholesterol and diagnostic group or inpatient versus outpatient status. Controlling for medication use, body mass index, alcohol or illicit substance use did not affect the results.

Conclusion: In this large sample of patients with schizophrenia- and bipolar spectrum disorders, we found no associations between cholesterol levels and aggression or impulsivity. This has clinical implications as patients with SMD are at increased CVD risk and currently undertreated with statins.

KEYWORDS

aggression, bipolar disorder, cardiovascular disease, cholesterol, schizophrenia

1 | SIGNIFICANT OUTCOMES

- A large representative sample of patients with schizophrenia- and bipolar spectrum disorders revealed no significant associations between cholesterol levels and aggression or impulsivity.

2 | LIMITATIONS

- Despite the comprehensive range of variables accounted for in our analysis, the process of controlling for potential confounders was limited by the observational design.
- The highest levels of aggression were scarcely represented among the study participants.

3 | INTRODUCTION

Patients with severe mental disorder (SMD) such as schizophrenia and bipolar disorder are at increased risk of adverse outcomes including aggressive behavior, suicide, and premature mortality (Fazel et al., 2015; Fazel, Wolf, Palm, & Lichtenstein, 2014; Fleischman, Werbeloff, Yoffe, Davidson, & Weiser, 2014; Hayes, Miles, Walters, King, & Osborn, 2015; Walter et al., 2019). Cardiovascular diseases (CVDs) are among the leading causes of death in patients with SMD (Olfson, Gerhard, Huang, Crystal, & Stroup, 2015; Swaraj et al., 2019; Tanskanen, Tiihonen, & Taipale, 2018). Cholesterol lowering has strong protective effect on CVD mortality (Benjamin et al., 2018; Boekholdt et al., 2014), and the current cholesterol management guidelines (Grundy et al., 2019; Piepoli et al., 2016) advise initiation of statin therapy based on calculations of CVD risk. As a step toward personalized cholesterol management, the excessive CVD risk in SMDs (Laursen et al., (2013)) has been taken into account in the development of CVD risk assessment tools (Hippisley-Cox, Coupland, & Brindle, 2017; Osborn et al., 2015). Low total cholesterol (TC) has, however, been linked with adverse mental symptoms such as aggression and impulsivity in SMDs (Tomson-Johanson and Harro, (2018)). As such, the recommendations regarding cholesterol management may risk potentiating aggressive dispositions. Although most patients with SMD will never be aggressive, aggression and violent acts challenge everyday psychiatric clinical practice. Establishing the association between cholesterol and aggression and impulsivity in patients with SMD is therefore of high clinical relevance for personalized CVD prevention.

Psychological effects of cholesterol lowering have been robustly addressed in the general population (Collins et al., 2016). Even though an early meta-analysis of primary CVD prevention randomized controlled trials (RCTs) linked decrease in TC to an increase in violent deaths caused by accident, homicide, and suicide (Muldoon, Manuck, & Matthews, 1990), subsequent research did not show adverse psychological effects of cholesterol lowering in the general public (Golomb et al., 2015; Muldoon, Manuck, Mendelsohn, Kaplan, & Belle, 2001). An explicit or implicit exclusion of individuals with SMD in these RCTs may limit our knowledge about psychological effects of cholesterol lowering in SMD patient group (Rothwell, 2005). Moreover, individuals with SMD might be particularly susceptible to potential adverse psychological effects of low TC. Genome-wide association studies implicate a role of cholesterol metabolism in SMDs (Andreassen et al., (2013)). Cholesterol has been shown to interact with serotonin (Kaplan et al., 1994; Vevera et al., 2016), which is central in the pathophysiology of mental disorders (Lucki, 1998) and aggression (Coccaro, Fanning, Phan, & Lee, 2015; Klasen et al., 2019). Despite the protective role of the blood–brain barrier against direct effects of circulating levels of cholesterol on the brain, indirect mechanisms mediated by cholesterol metabolites have been demonstrated (Olsson et al., 2017).

Cholesterol and adverse mental symptoms have been investigated over the past three decades in a number of smaller-to-medium scaled studies in psychiatric settings (Apter et al., 1999; De Berardis et al., 2013; Eriksen, Bjorkly, Lockertsen, Faerden, & Roaldset, 2017; Huang & Wu, 2000; Kavoor, Mitra, Kumar, Sisodia, & Jain, 2017; Mufti, Balon, & Arfken, 1998; Roaldset, Bakken, & Bjorkly, 2011; Steinert, Woelfle, & Gebhardt, 1999; Suneson et al., 2019; Troisi, 2011; Wu et al., 2016), often showing inverse associations between TC and degree of aggression, impulsivity, or suicidality. Moreover, low TC has been associated with more frequent acts of aggression in forensic psychiatric populations (Hillbrand, Spitz, & Foster, 1995; Paavola, Repo-Tiihonen, & Tiihonen, 2002). A meta-analysis of the relationship between cholesterol and suicidality has shown inverse association between TC and suicidality (Wu et al., 2016). Several studies have shown inverse associations between TC and aggression (Hillbrand et al., 1995; Mufti et al., 1998; Paavola et al., 2002; Roaldset et al., 2011; Suneson et al., 2019) or impulsivity (Kavoor et al., 2017; Troisi, 2011), whereas other studies have reported no significant associations between TC and aggression (Apter et al., 1999; Eriksen et al., 2017; Huang & Wu, 2000; Kavoor et al., 2017; Steinert et al., 1999) or impulsivity (Apter et al., 1999). Findings among those studies that have investigated high-density lipoprotein cholesterol (HDL-C) (Eriksen et al., 2017; Kavoor et al., 2017; Paavola et al., 2002; Suneson et al., 2019; Troisi, 2011) vary from positive (Paavola et al., (2002)), to inverse (Eriksen et al., (2017)), to nonsignificant (Troisi, (2011); Kavoor et al., 2017; Suneson et al., 2019) associations with aggression. Additionally, inverse associations between low-density lipoprotein cholesterol (LDL-C) and aggression (Paavola et al., 2002; Suneson et al., 2019) or impulsivity (Kavoor et al., 2017) have been reported. Taken together, the body of evidence appears to be split into suggestions of lipid profile with low cholesterol (TC, LDL-C) and suggestions of no distinct lipid profile pattern related to aggression. These substantial inconsistencies in findings and a focus restricted to inpatient settings call for an investigation of the association between cholesterol and aggression in a large representative sample of patients with SMD.

The aim of the present study was to determine the associations between cholesterol levels and aggression and impulsivity by investigating a large sample of in- and outpatients with schizophrenia or bipolar disorder. We hypothesized that cholesterol levels

(TC, LDL-C) would be negatively associated with aggression and impulsivity in patients with SMD. For completeness, we aimed to provide insight into how HDL-C contributes to the hypothesized TC associations. Hence, we postulated that HDL-C also would be negatively associated with aggression and impulsivity in patients with SMD.

4 | MATERIAL AND METHODS

4.1 | Participants

The present study is part of the Thematically Organized Psychosis (TOP) study, which recruits patients with SMD from psychiatric in- and outpatient clinics of the major hospitals in Oslo, Norway (Rodevand et al., 2019). The main inclusion criterion was a diagnosis within the schizophrenia- or bipolar spectrum. Further inclusion criteria were age between 18 and 65 years, ability to give informed consent, and Norwegian language skills sufficient for valid assessments. Exclusion criteria comprised marked cognitive deficit (IQ scores below 70), neurological disorder, and history of severe head trauma. The study participants were recruited between the years 2002 and 2017. Patients (N = 1 001) were classified in the following diagnostic groups according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) (American Psychiatric Association, 1994): schizophrenia spectrum disorders (N = 601), including schizophrenia (N = 360), schizophreniform disorder (N = 31), schizoaffective disorder (N = 96), delusional disorder (N = 36), and psychotic disorder not otherwise specified (NOS) (N = 78); bipolar spectrum disorders (N = 400), including bipolar I disorder (N = 229), bipolar II disorder (N = 112), bipolar disorder NOS (N = 21), and major depressive disorder with psychotic features (N = 38).

4.2 | Clinical measures

All participants were thoroughly assessed by trained psychologists and physicians. The diagnostic evaluation was based on the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) (First, Spitzer, Gibbon, & Williams, 1995), including a review of medical records. The inter-rater diagnostic agreement has been estimated to a satisfying level of 82% with overall $\kappa = 0.77$ (95% CI: 0.60–0.94) (Rodevand et al., 2019). General psychiatric symptom load was evaluated using the Global Assessment of Functioning Split Version (GAF) (Pedersen, Hagtvet, & Karterud, 2007). Affective symptoms were assessed with the Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978) and the Calgary Depression Scale for Schizophrenia (CDSS) (Addington, Addington, & Schissel, 1990). The Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) was used to rate current psychotic symptoms, achieving inter-rater reliability of intraclass correlation coefficient at 0.82 (Rodevand et al., 2019). The PANSS consists of 30 items, each scored from 1 (no symptoms) to 7 (severe symptoms).

A measure of aggression among patients was obtained using the PANSS Excited Component (PANSS-EC) (Montoya et al., 2011), which is a part of the Five Factor PANSS Model (White, Harvey, Opler, & Lindenmayer, 1997). The PANSS-EC was calculated as a sum of the following items: P4-excitement, P7-hostility, G4-tension, G8-uncooperativeness, and G14-poor impulse control (Lindenmayer et al., 2004). The PANSS-EC is commonly used as a primary outcome measure in RCTs targeted at agitation and aggressive behavior in emergency psychiatric settings (Citrome, 2007; Zeller et al., 2017). Due to the distribution of PANSS-EC scores in our sample, PANSS-EC was grouped into the following categories reflecting the level of aggression: PANSS-EC = 5 represents a group with no aggression symptoms (NAS), PANSS-EC ranging from 6 to 10 represents a group with minimal level of aggression symptoms (MLAS), and PANSS-EC > 10 represents a group with higher levels of aggression symptoms (HLAS). The unifactorial structure of the PANSS-EC (Montoya et al., 2011) and PANSS rating criteria (Kay et al., 1987) were used as a background for the establishment of the cutoffs. Thus, the first group NAS was defined by the absence of all PANSS-EC symptoms, the second group MLAS spanned from outer end of the normal range to suspected pathology, and PANSS-EC scores indicative of more certain and expressed pathology were categorized into the third group HLAS. The PANSS assessment was conducted within one month of the blood sampling (median 9 days, interquartile range 9 days).

Impulsivity was measured with the Barratt Impulsiveness Scale (BIS-11) (Patton, Stanford, & Barratt, 1995) questionnaire among a subgroup of patients (N = 288). The BIS-11 consists of 30 items scored on a 4-point Likert scale. Hence, the total score ranges from 30 to 120, with higher scores reflecting higher levels of impulsivity. Internal consistency of the BIS-11 total score has been repeatedly reported as acceptable (Lindstrom, Wyller, Halvorsen, Hartberg, & Lundqvist, 2017; Patton et al., 1995; Reise, Moore, Sabb, Brown, & London, 2013; Stanford et al., 2009).

The Alcohol Use Disorders Identification Test (AUDIT) (Babor et al.,) and the Drug Use Disorders Identification Test (DUDIT) (Voluse et al., 2012) questionnaires were used to evaluate alcohol and illicit substance use. Information about psychopharmacological treatment was collected from medical records and by interview. Current dose in use relative to the defined daily dose (DDD) was calculated in line with the guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (https://www.whocc.no/atc_ddd_index/). Body mass index (BMI) (kg/m^2) was calculated based on weight and height measurements.

4.3 | Serum analyses

Venous blood samples were collected in the morning after an overnight fast of at least 8 hr. Levels of TC, LDL-C, and HDL-C were measured at the Department of Medical Biochemistry, Oslo University Hospital, on routine instruments (Roche Diagnostics Cobas Integra 800, Roche Diagnostics Cobas 8000 e602/e801) using standard

methods controlled by internal and external quality control samples. Until 2012, LDL-C was calculated by the Friedewald formula (Martin et al., 2013), thereafter analyzed by an enzymatic colorimetric method.

4.4 | Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. The TOP study has approvals from the Regional Ethics Committee, the Norwegian Data Inspectorate, and the Norwegian Directorate of Health.

4.5 | Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows version 25.0 software package. Normality was assessed by Kolmogorov–Smirnov tests and Q-Q plots. Differences in demographic and clinical characteristics across the aggression categories were investigated using chi-squared tests, one-way ANOVAs with post hoc *t* tests, or Kruskal–Wallis tests with post hoc Mann–Whitney U tests. All descriptive analyses were two-tailed, with a significance level at 0.05.

We used a multinomial logistic regression model to analyze the association between cholesterol (TC, LDL-C, HDL-C) and the three levels of aggression (NAS, MLAS, HLAS), with cholesterol levels as the independent variable, adjusting for age, sex, and diagnostic group (schizophrenia- versus bipolar spectrum disorders). Then, we repeated the analyses with additional adjustments (BMI, inpatient versus outpatient status, alcohol use (AUDIT scores), illicit substance use (DUDIT scores) and use of psychotropic medication (dose relative to DDD) including antipsychotics, antidepressants, mood stabilizers, and lithium) in a subsample with all the covariates available ($N = 689$). Variation inflation factors (VIFs) were used to assess multicollinearity. Interactions between cholesterol levels (TC, LDL-C, HDL-C) and diagnostic group, inpatient versus outpatient status, and sex were tested. We applied the Bonferroni method to correct for multiple testing (three consecutive analyses with TC, LDL-C, and HDL-C as independent variable), with a significance level set at 0.017 (0.05/ 3).

The association between cholesterol (TC, LDL-C, HDL-C) and impulsivity (BIS-11 total score) was assessed with a multiple linear regression model with impulsivity scores as the dependent variable, cholesterol levels as the independent variable and age, sex, and diagnostic group (schizophrenia- versus bipolar spectrum disorders) as covariates. Then, subanalyses ($N = 259$) with the additional covariates (BMI, inpatient versus outpatient status, alcohol use, illicit substance use, and use of psychotropic medication) were conducted. Multicollinearity was assessed using VIFs. Assumption of normality and presence of outliers were investigated by inspection of standardized residuals and Cook's distances. Interactions between cholesterol levels and diagnostic group, inpatient versus outpatient status, and sex were tested. We used the Bonferroni method to correct for multiple testing (analyses with TC, LDL-C, and HDL-C as independent variable), with a significance level at 0.017 (0.05/ 3).

5 | RESULTS

5.1 | Descriptive analyses

Demographic and clinical characteristics of the sample with aggression outcome are summarized in Table 1. There were significant differences in age ($p < .001$), education level ($p < .001$), and symptom load (GAF ($p < .001$), PANSS total score ($p < .001$), CDSS ($p < .001$), YMRS ($p < .001$) between the three aggression groups, with age decreasing and symptom load increasing gradually with increasing levels of aggression. Schizophrenia spectrum disorders were significantly more frequent than bipolar spectrum disorders in the HLAS group compared to the remaining groups ($p = .009$). There were no significant differences in uncorrected cholesterol levels across the three groups.

Demographic and clinical characteristics of the subsample with impulsivity outcome are summarized in Table 2.

5.2 | Aggression

The raw data are presented in Figure 1. As shown in Table 3 and Table S1, there were no significant associations between TC, LDL-C, or HDL-C and aggression category when controlled for other covariates. There were no significant interactions between cholesterol levels (TC, LDL-C, HDL-C) and diagnostic group, inpatient versus outpatient status, or sex. Age was significantly negatively associated with aggression level (HLAS versus NAS ($p < .001$). There were no significant associations of sex, inpatient versus outpatient status, BMI, alcohol use, illicit substance use, or psychotropic medication with aggression category when controlled for other covariates. The total sample ($N = 1\,001$) and the subsample with all covariates available ($N = 689$) yielded the same results, with two exceptions. Firstly, there was a significant association of diagnostic group with the HLAS versus NAS status in the total sample ($p = .006$), as opposed to no significant association of diagnostic group in the subsample. Secondly, the subsample showed an additional negative association of age with MLAS versus NAS status ($p = .011$).

5.3 | Impulsivity

Scatterplots of cholesterol levels (TC, LDL-C, HDL-C) and impulsivity (BIS-11 total score) are presented in Figure 2. As shown in Table 4 and Table S2, there were no significant associations between TC, LDL-C, or HDL-C and impulsivity when controlled for other covariates. There were no significant interactions between cholesterol levels (TC, LDL-C, HDL-C) and diagnostic group, inpatient versus outpatient status or sex. Illicit substance use was significantly positively associated with impulsivity ($p < .001$). There were no

TABLE 1 Demographic and clinical characteristics of the sample with aggression outcome

	NAS (*N* = 270)	MLAS (*N* = 618)	HLAS (*N* = 113)	NAS versus MLAS	NAS versus HLAS	MLAS versus HLAS
	N (%)	*N* (%)	*N* (%)	*p*	*p*	*p*
Male	139 (51.5)	329 (53.2)	57 (50.4)	NS	NS	NS
Caucasian	221 (81.9)	511 (82.7)	85 (75.2)	NS	NS	NS
Schizophrenia spectrum disorder	151 (55.9)	368 (59.5)	82 (72.6)	NS	**.002**	**.009**
Bipolar spectrum disorder	119 (44.1)	250 (40.5)	31 (27.4)	NS	**.002**	**.009**
Outpatient[a]	160 (70.2)	381 (68.2)	64 (60.4)	NS	NS	NS
Currently smoking[a]	122 (46.4)	334 (55.2)	66 (59.5)	**0.017**	**.021**	NS
Use of statins	8 (2.9)	8 (1.3)	0 (0)	NS	NS	NS
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	*p*	*p*	*p*
GAF-S	54.4 (14.5)	48.3 (12.4)	38.9 (10.6)	**<.001**	**<.001**	**<.001**
GAF-F[a]	52.8 (13.5)	48.7 (12.9)	40.3 (10.7)	**<.001**	**<.001**	**<.001**
PANSS total score[a]	45.6 (12.3)	57.3 (14.1)	73.5 (16.6)	**<.001**	**<.001**	**<.001**
TC in mmol/l	5.14 (1.07)	5.08 (1.07)	4.99 (0.98)	NS	NS	NS
LDL-C in mmol/l	3.20 (0.97)	3.16 (0.95)	3.10 (0.90)	NS	NS	NS
HDL-C in mmol/l	1.41 (0.41)	1.40 (0.42)	1.34 (0.44)	NS	NS	NS
	Median (IQR)	Median (IQR)	Median (IQR)	*p*	*p*	*p*
Age	30.0 (15)	29 (15)	25 (11)	**.016**	**.002**	**<.001**
Years of education	13 (3)	12 (3)	12 (2)	**<.001**	**<.001**	**<.001**
PANSS-EC	5 (0)	7 (2)	12 (2)	**<.001**	**<.001**	**<.001**
CDSS[a]	3 (6)	5 (7)	7 (9)	**<.001**	**<.001**	**.001**
YMRS[a]	1 (4)	2 (8)	8 (9)	**< 0.001**	**<.001**	**<.001**
AUDIT[a]	5 (9)	4 (8)	6 (10)	NS	NS	NS
DUDIT[a]	0 (3)	0 (2)	0 (4)	NS	NS	NS
Antipsychotics[a,b]	0.75 (1.23)	0.75 (1.50)	0.67 (2.00)	NS	NS	NS
Lithium[a,b]	0 (0)	0 (0)	0 (0)	NS	**.017**	NS
Mood stabilizers[a,b]	0 (0)	0 (0)	0 (0)	NS	NS	NS
Antidepressants[a,b]	0 (0.27)	0 (1.00)	0 (0.47)	**.008**	NS	NS
BMI[a]	25.7 (5.6)	25.1 (5.8)	24.1 (6.7)	**.042**	**.028**	NS

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; BMI, body mass index; CDSS, Calgary Depression Scale for Schizophrenia; DUDIT, Drug Use Disorders Identification Test; GAF-F, Global Assessment of Functioning Split Version-Function; GAF-S, Global Assessment of Functioning Split Version-Symptoms; HDL-C, high-density lipoprotein cholesterol; HLAS group with higher levels of aggression symptoms; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MLAS, group with minimal level of aggression symptoms; NAS, group with no aggression symptoms; NS, nonsignificant; PANSS, Positive and Negative Syndrome Scale; PANSS-EC, Positive and Negative Syndrome Scale Excited Component; *SD*, standard deviation; TC, total cholesterol; YMRS, Young Mania Rating Scale.

[a]Information about inpatient versus outpatient status available for *N* = 893, about smoking status for *N* = 979, about GAF-F for *N* = 999, about PANSS total score for *N* = 996, about CDSS for *N* = 697, about YMRS for *N* = 885, about AUDIT for *N* = 814, about DUDIT for *N* = 822, about antipsychotics for *N* = 982, about lithium *N* = 988, about mood stabilizers *N* = 988, about antidepressants *N* = 988, and about BMI for *N* = 964.

[b]Psychotropic medications as current daily dose relative to defined daily dose.

$p \leq .05$ in bold.

significant associations of sex, diagnosis, BMI, inpatient versus outpatient status, alcohol use, or use of psychotropic medication with impulsivity when controlled for other covariates. The total sample (*N* = 288) and the subsample with all covariates available (*N* = 259) yielded the same results, with exception of age being significantly negatively associated with impulsivity in the subsample ($p = .016$) as opposed to nonsignificant association in the total sample.

6 | DISCUSSION

The main finding of this study was an absence of significant associations between cholesterol levels and aggression or impulsivity in a large naturalistic sample of patients with schizophrenia- and bipolar spectrum disorders. This is to date the largest clinical study of cholesterol and aggression or impulsivity in SMDs, expanding the

TABLE 2 Demographic and clinical characteristics of the sample with impulsivity outcome

	N = 288
	N (%)
Male	146 (50.7)
Caucasian	232 (80.8)
Schizophrenia spectrum disorder	157 (54.5)
Bipolar spectrum disorder	131 (45.5)
Outpatient	207 (72.9)
Currently smoking	145 (50.9)
Use of statins	1 (0.3)
	Mean (*SD*)
BIS−11 total score	68.6 (10.8)
GAF-S	53.5 (13.6)
GAF-F	52.7 (13.6)
PANSS total score	52.2 (13.8)
TC in mmol/L	4.88 (0.95)
LDL-C in mmol/L	3.06 (0.85)
HDL-C in mmol/L	1.43 (0.44)
	Median (IQR)
Age	27 (13)
Years of education	12 (3)
PANSS-EC	6 (3)
CDSS[a]	4 (7)
YMRS[a]	2 (4)
AUDIT[a]	5 (8)
DUDIT[a]	0 (4)
Antipsychotics[a,b]	0.75 (1.50)
Lithium[a,b]	0 (0)
Mood stabilizers[a,b]	0 (0)
Antidepressants[a,b]	0 (0.17)
BMI[a]	25.2 (6.2)

Abbreviations; AUDIT, Alcohol Use Disorders Identification Test; BIS-11, Barratt Impulsiveness Scale; BMI, body mass index; CDSS, Calgary Depression Scale for Schizophrenia; DUDIT, Drug Use Disorders Identification Test; GAF-F, Global Assessment of Functioning Split Version-Function; GAF-S, Global Assessment of Functioning Split Version-Symptoms; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; PANSS, Positive and Negative Syndrome Scale; PANSS-EC, Positive and Negative Syndrome Scale Excited Component; *SD*, standard deviation; TC, total cholesterol; YMRS, Young Mania Rating Scale.

[a]Information about inpatient versus outpatient status available for *N* = 287, about smoking status for *N* = 285, about GAF-F for *N* = 286, about PANSS total score for *N* = 285, about CDSS for *N* = 285, about YMRS for *N* = 234, about AUDIT for *N* = 283, about DUDIT for *N* = 286, about antipsychotics for *N* = 272, about lithium *N* = 276, about mood stabilizers *N* = 276, about antidepressants *N* = 275, and about BMI for *N* = 282.

[b]Psychotropic medications as current daily dose relative to defined daily dose.

scope of investigations to the outpatient psychiatric population. We found no significant interactions between cholesterol levels and diagnostic group or inpatient versus outpatient status on aggression or impulsivity.

In contrast to our hypothesis, lower cholesterol levels were not associated with higher levels of aggression or impulsivity. The literature on cholesterol and aggression in psychiatric populations is conflicting. Several studies have shown inverse associations between TC and aggression (Hillbrand et al., 1995; Mufti et al., 1998; Paavola et al., 2002; Roaldset et al., 2011; Suneson et al., 2019) or impulsivity (Kavoor et al., 2017; Troisi, 2011), whereas other studies have reported no significant associations between TC and aggression (Apter et al., 1999; Eriksen et al., 2017; Huang & Wu, 2000; Kavoor et al., 2017; Steinert et al., 1999) or impulsivity (Apter et al., 1999). Importantly, these were observational studies, and the findings may represent reverse causality with cholesterol levels reflecting the severity of distress among specific psychiatric populations. The negative findings in the current study are based on investigations among patients within a wide range of illness stages and severity, which may explain some of the discrepancy. As previously published (Gohar et al., 2019), an overlapping sample revealed no significant associations between TC and suicidal behavior. Considering the relationship between cholesterol levels and adverse mental symptoms in general, the meta-analytic investigation of the relationship between TC and suicidality showing an inverse association is of importance (Wu et al., 2016). Since this meta-analysis was based on cross-sectional designs, causality remains unelucidated. Moreover, the need of exploring confounding variables has been highlighted in this context (Bartoli et al., 2017). Our results are more in line with results from RCTs in the general population which have not indicated adverse psychological effects of cholesterol lowering (Collins et al., 2016; Golomb et al., 2015; Muldoon et al., 2001). Experimental animal studies (Haagensen et al., 2014; Kaplan, Manuck, & Shively, 1991;) suggest that very high TC levels (above double the high end of the normal range) might indeed have protective effects against aggressive behavior. Interestingly, a negative association between prepubertal TC and adulthood impulsivity has been reported in healthy men (Tomson-Johanson, Kaart, Kiivet, Veidebaum, & Harro, 2019). As aggression is a highly complex phenomenon, the possibility that unmeasured confounders overshadow weak associations between cholesterol levels and aggression cannot be ruled out. However, all lines of evidence taken together, findings do not suggest clinically significant adverse effects of cholesterol lowering on aggression in adults with SMDs.

Some studies, the present study included, aimed at estimating the association between exposure (i.e., cholesterol levels) and outcome (i.e., aggression), while other studies aspired prediction of the outcome using range of available covariates including variables such as history of violence or involuntary hospitalization (Roaldset et al., 2011). As such, complexity of the literature may be partly explained by these different methodological approaches motivated by different aims (Pearl, 2000). Despite extensive methodological

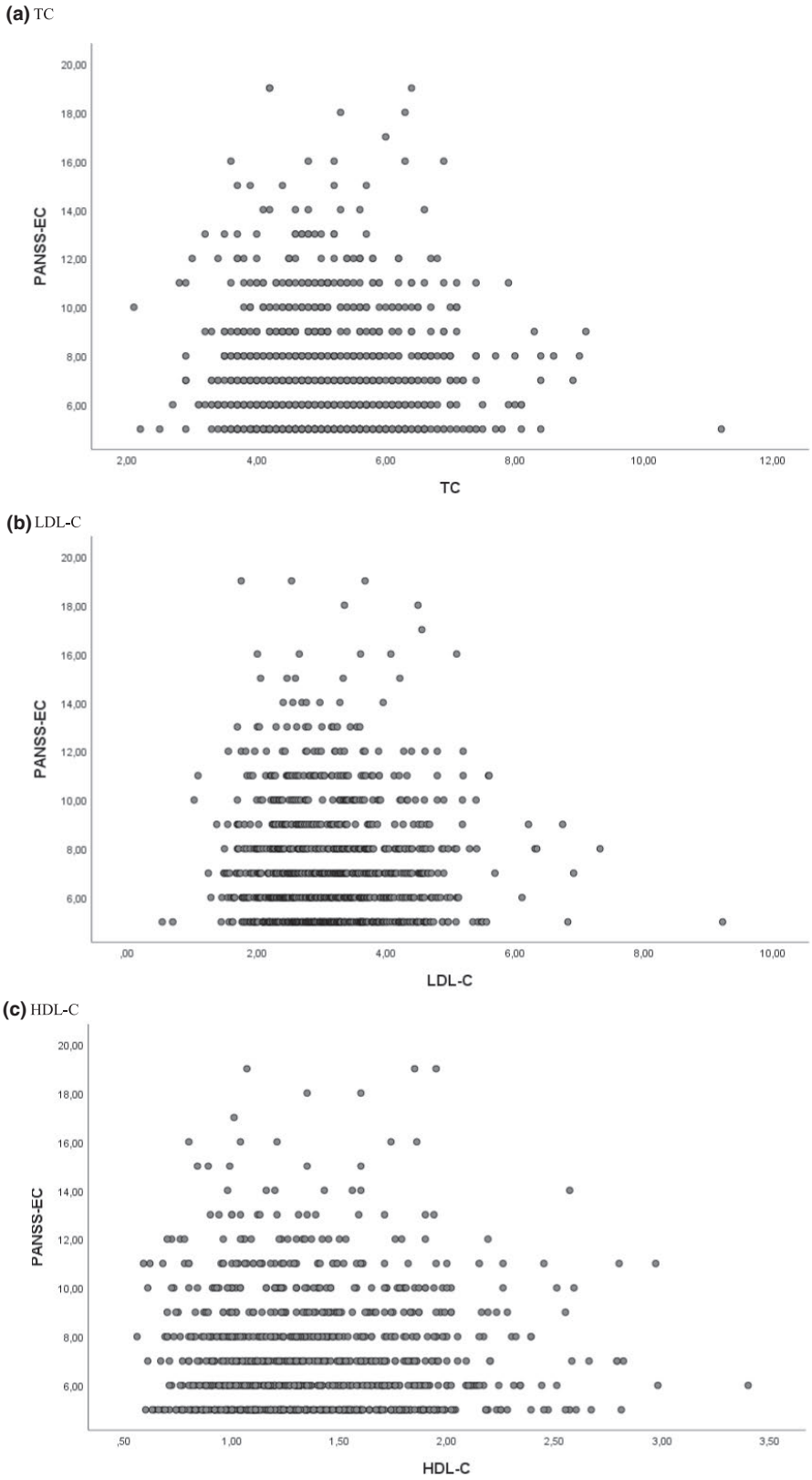

FIGURE 1 Aggression by cholesterol levels: (a) TC, (b) LDL-C, (c) HDL-C. Aggression measured by PANSS-EC (y-axis). Cholesterol levels in mmol/l (x-axis). HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PANSS-EC, Positive and Negative Syndrome Scale Excited Component; TC, total cholesterol

heterogeneity, there are some common aspects of the previous research. Several previous studies have limited sample size (Kavoor et al., 2017; Mufti et al., 1998; Suneson et al., 2019). Many of the previous study designs involve testing for multiple cholesterol fractions (Eriksen et al., 2017; Kavoor et al., 2017; Paavola et al., 2002; Suneson et al., 2019; Troisi, 2011). However, none of these studies apply correction for multiple testing, implying a risk of false-positive results. In terms of potential confounding, most of the previous study designs controlled for demographic variables such as sex and age, whereas the current study accounted also for

TABLE 3 Multinomial logistic regression with aggression categories as dependent and TC as independent variable

	B (SE)	Wald	*p*	OR (95% CI)
HLAS versus NAS, total sample (*N* = 1001)				
TC	0.00 (0.12)	0.00	.971	1.00 (0.80 to 1.26)
Age	−0.05 (0.01)	13.37	**<.001**	0.95 (0.93 to 0.98)
Gender = male	−0.23 (0.23)	0.94	.332	0.80 (0.51 to 1.26)
Diagnosis = schizophrenia spectrum disorder[a]	0.70 (0.25)	7.69	**.006**	2.01 (1.23 to 3.29)
MLAS versus NAS, total sample (*N* = 1001)				
TC	−0.01 (0.07)	0.02	.895	0.99 (0.86 to 1.15)
Age	−0.01 (0.01)	3.00	.083	0.99 (0.97 to 1.00)
Gender = male	0.03 (0.15)	0.05	.823	1.03 (0.77 to 1.39)
Diagnosis = schizophrenia spectrum disorder[a]	0.11 (0.15)	0.55	.458	1.12 (0.83 to 1.51)
HLAS versus NAS, subsample (*N* = 689)				
TC	0.04 (0.16)	0.07	.796	1.04 (0.77 to 1.42)
Age	−0.05 (0.02)	9.52	**.002**	0.95 (0.92 to 0.98)
Gender = male	−0.33 (0.30)	1.22	.270	0.72 (0.40 to 1.30)
Diagnosis = schizophrenia spectrum disorder[a]	0.51 (0.35)	2.13	.144	1.67 (0.84 to 3.33)
Inpatient versus outpatient status = inpatient	−0.32 (0.34)	0.89	.346	0.73 (0.37 to 1.42)
BMI	−0.02 (0.03)	0.53	.467	0.98 (0.92 to 1.04)
AUDIT	0.03 (0.02)	1.79	.181	1.03 (0.99 to 1.08)
DUDIT	−0.00 (0.02)	0.04	.836	1.00 (0.96 to 1.04)
Antipsychotics	−0.05 (0.17)	0.10	.755	0.95 (0.68 to 1.32)
Antidepressants	−0.05 (0.19)	0.07	.798	0.95 (0.66 to 1.38)
Mood stabilizers	−0.15 (0.47)	0.10	.752	0.86 (0.35 to 2.15)
Lithium	−0.39 (0.53)	0.55	.459	0.68 (0.24 to 1.91)
MLAS versus NAS, subsample (*N* = 689)				
TC	0.02 (0.10)	0.03	.859	1.02 (0.84 to 1.24)
Age	−0.02 (0.01)	5.69	**.017**	0.98 (0.96 to 1.00)
Gender = male	0.08 (0.19)	0.17	.680	1.08 (0.75 to 1.57)
Diagnosis = schizophrenia spectrum disorder[a]	0.10 (0.22)	0.23	.630	1.11 (0.73 to 1.70)
Inpatient versus outpatient status = inpatient	−0.08 (0.22)	0.12	.730	0.93 (0.60 to 1.44)
BMI	−0.02 (0.02)	1.49	.223	0.98 (0.94 to 1.02)
AUDIT	−0.02 (0.02)	0.95	.329	0.99 (0.96 to 1.02)
DUDIT	−0.00 (0.02)	0.00	.955	1.00 (0.97 to 1.03)
Antipsychotics	−0.04 (0.11)	0.14	.711	0.96 (0.78 to 1.19)
Antidepressants	0.19 (0.11)	2.99	.084	1.21 (0.98 to 1.49)
Mood stabilizers	0.11 (0.25)	0.19	.660	1.12 (0.68 to 1.84)
Lithium	−0.32 (0.25)	1.71	.191	0.73 (0.45 to 1.17)

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; BMI, body mass index; CI, confidence interval; DUDIT, Drug Use Disorders Identification Test; HLAS group with higher levels of aggression symptoms; MLAS, group with minimal level of aggression symptoms; NAS, group with no aggression symptoms; OR, odds ratio; SE, standard error; TC, total cholesterol.

[a]Diagnosis variable: schizophrenia spectrum disorder versus bipolar spectrum disorder.

$p \leq .017$ in bold.

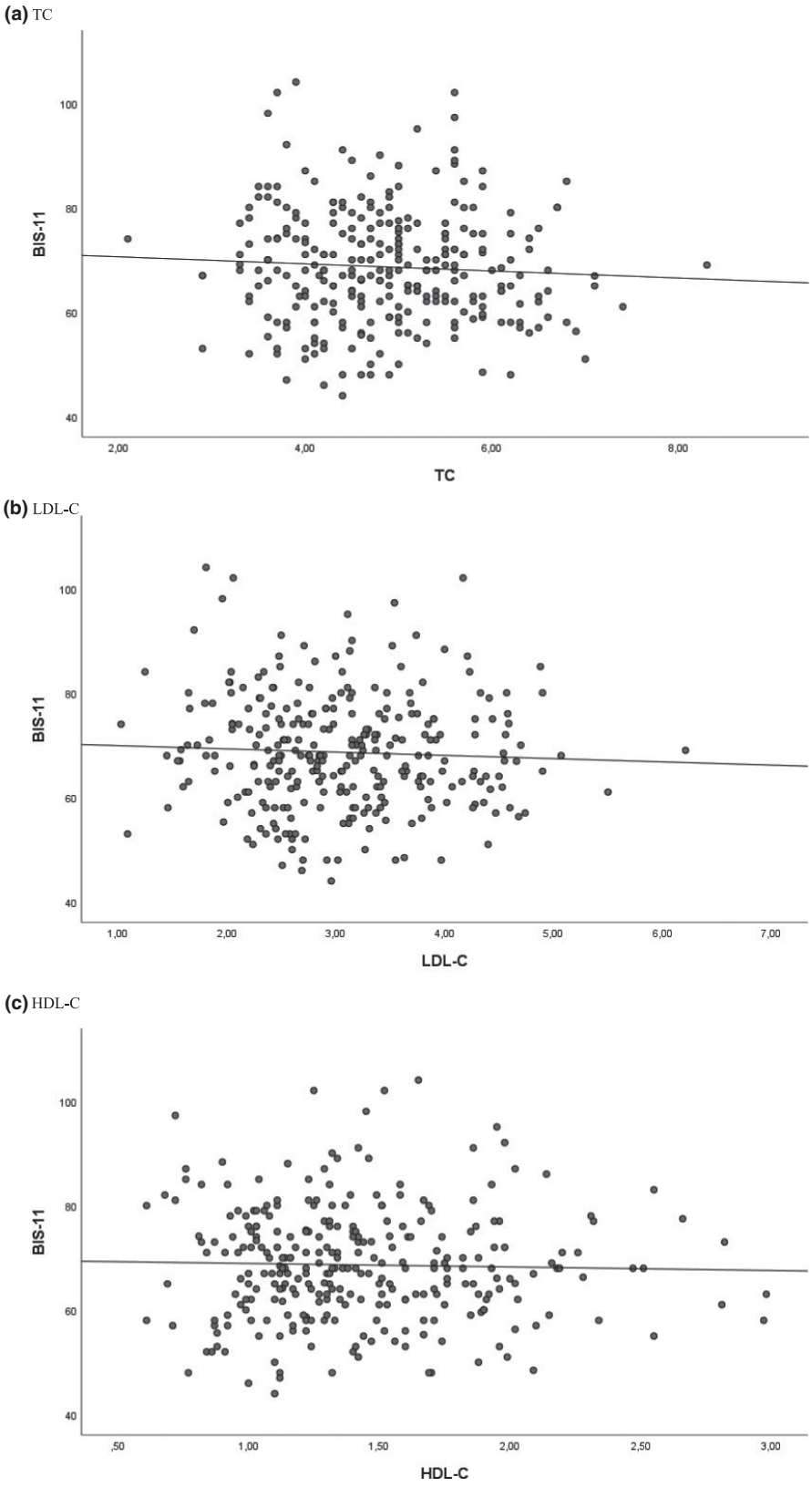

FIGURE 2 Scatterplot of cholesterol levels and impulsivity: (a) TC, (b) LDL-C, (c) HDL-C. Impulsivity measured by BIS-11 total score (y-axis). Cholesterol levels in mmol/l (x-axis). Abbreviations: BIS-11, Barratt Impulsiveness Scale; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol

diagnosis, medication, BMI, and substance use. These issues are addressed in the current study by the large sample size and stringent statistical approach. Moreover, a variety of aggression outcome measures are applied in the field. Findings linking low TC with aggressive behavior are based on studies that have operationalized registrations of aggressive behavior over a longer time period (Hillbrand et al., 1995; Mufti et al., 1998; Paavola et al., 2002; Roaldset et al., 2011), whereas studies that have used registrations acquired over a shorter time period (Apter et al., 1999; Huang & Wu, 2000; Kavoor et al., 2017; Steinert et al., 1999) do not show

TABLE 4 Multiple linear regression with impulsivity scores as dependent and TC as independent variable

	B (SE)	β	*p*	95% CI for B
Total sample (*N* = 288)				
TC	−0.06 (0.72)	−0.01	.932	−1.48 to 1.36
Age	−0.15 (0.07)	−0.14	.025	−0.28 to −0.02
Gender[b,a]	−0.13 (1.31)	−0.01	.924	−2.70 to 2.45
Diagnosis[a,b]	−1.71 (1.33)	−0.08	.200	−4.33 to 0.91
Subsample (*N* = 259)				
TC	−0.30 (0.75)	−0.03	.688	−1.79 to 1.18
Age	−0.11 (0.07)	−0.10	.132	−0.25 to 0.03
Gender[b,a]	0.99 (1.34)	0.05	.464	−1.66 to 3.63
Diagnosis[a,b]	−2.20 (1.54)	−0.10	.154	−5.24 to 0.83
BMI	0.15 (0.14)	0.07	.263	−0.12 to 0.43
Inpatient versus outpatient status[b,c]	−1.94 (1.63)	−0.08	.234	−5.15 to 1.26
AUDIT	0.22 (0.13)	0.12	.083	−0.03 to 0.47
DUDIT	0.41 (0.11)	0.26	**<.001**	0.19 to 0.62
Antipsychotics	−0.10 (0.70)	−0.01	.893	−1.48 to 1.29
Antidepressants	1.99 (0.99)	0.12	.045	0.04 to 3.93
Mood stabilizers	−1.38 (1.87)	−0.05	.463	−5.06 to 2.31
Lithium	−2.64 (2.03)	−0.08	.195	−6.64 to 1.36

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; B, unstandardized coefficient; BMI, body mass index; CI, confidence interval; DUDIT, Drug Use Disorders Identification Test; SE, standard error; TC, total cholesterol; β, standardized coefficient.

[a]Gender variable: male = 0, female = 1.

[b]Diagnosis variable: bipolar spectrum disorder = 0, schizophrenia spectrum disorder = 1.

[c]Inpatient versus outpatient status: outpatient = 0, inpatient = 1.

$p \leq .017$ in bold.

this link. This may suggest that trait properties of aggression implicated in this link can be descriptive of antisocial personality traits rather than of acts of aggression itself. This is supported by findings from criminal settings (Virkkunen, 1979) and general population (Freedman et al., 1995). Two outcome measures with different properties were used to assess aggression-related behavior (Garcia-Forero, Gallardo-Pujol, Maydeu-Olivares, & Andres-Pueyo, 2009) in our study design. As such, aggression and impulsivity were addressed using both state (PANSS-EC) and trait (BIS-11) measures, encompassing both interviewer-rated and questionnaire-based approaches to outcome measure acquisition.

The main strengths of our study are representativeness of inpatient- and outpatient settings, thorough characterization of the sample, large sample size, and thus the opportunity of applying a stringent statistical approach. We controlled for potential confounding factors such as BMI, medication, and substance use, and we adjusted for multiple comparisons. These are methodological aspects targeting the key challenges in the field such as external validity and risk of false-positive findings.

The present study also has some noteworthy limitations. Despite adjustments for a comprehensive range of variables, residual confounding cannot be ruled out. Moreover, as a consequence of the naturalistic study design, the highest levels of aggression were scarcely represented among the study participants. Exploratory plots presented in the current study did not indicate nonlinear associations between cholesterol and aggression or impulsivity; thus, no comprehensive investigations targeted at nonlinearity (Sedgwick, Young, Das, & Kumari, 2016) were conducted.

As of relevance for CVD risk management, the median age of patients in our sample was 29 years, which is below the recommended age of 40 years for initiation of systematic CVD risk evaluation and consecutive statin therapy initiation. As such, our sample with only 16 statin users was not suitable to investigate specific associations between statin use and adverse mental symptoms. Studies from psychiatric settings linking TC and aggression have been mainly conducted among statin nonusers (Mufti et al., 1998; Paavola et al., 2002; Suneson et al., 2019). There are neither findings from SMD populations (Leppien, Mulcahy, Demler, Trigoboff, & Opler, 2018) nor robust findings from the general population (Collins et al., 2016) supporting the concept of aggression as a side effect of statin use, independent of cholesterol levels.

7 | CONCLUSION

We found no associations between cholesterol levels and aggression or impulsivity in this representative large sample of patients

with schizophrenia- and bipolar spectrum disorders. This has clinical implications as CVDs are among leading causes of substantially reduced life expectancy in SMDs (Laursen et al., 2013), and patients with SMD are currently undertreated with statins (Mitchell, Lord, & Malone, 2012). An undertreatment of CVD risk in patients with comorbid SMD is a complex clinical challenge contributing to high morbidity and mortality rates in SMDs, implicating health care in both psychiatry and general practice (Jones, Howard, & Thornicroft, 2008; Leucht, Burkard, Henderson, Maj, & Sartorius, 2007; Woodhead et al., 2016).

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CONFLICT OF INTEREST

Ole Andreas Andreassen has received consultancy fees from HealthLytix and speaker's honorarium from Lundbeck. All other authors report no conflict of interest.

AUTHOR CONTRIBUTION

GH, NES, and UKH designed the study with help from LMJ, RH, IM, OAA, and TVL. GH, NT, CB, SHL, LR, and MCFW participated in data collection and quality control. GH performed the statistical analyses. GH, LMJ, NES, and UKH wrote the first draft, and all authors critically revised and approved the manuscript.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/brb3.1751.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy and ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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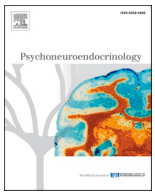

Interleukin-18 signaling system links to agitation in severe mental disorders

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ABSTRACT

Objective: Agitation is a challenging clinical feature in severe mental disorders, but its biological correlates are largely unknown. Inflammasome-related abnormalities have been linked to severe mental disorders and implicated in animal models of agitation. We investigated if levels of circulating inflammasome-related immune markers were associated with agitation in severe mental disorders.

Methods: Individuals with a psychotic or affective disorder (N = 660) underwent blood sampling and clinical characterization. Plasma levels of interleukin (IL)-18, IL-18 binding protein (IL-18BP), IL-18 receptor 1 (IL-18R1), IL-18 receptor accessory protein (IL-18RAP), and IL-1 receptor antagonist (IL-1RA) were measured. Agitation levels were estimated with the Positive and Negative Syndrome Scale Excited Component. Multiple linear- and logistic regression were used to investigate the associations between agitation and the immune markers, while controlling for confounders. The influence of psychotic and affective symptoms was assessed in follow-up analyses.

Results: Agitation was positively associated with IL-18BP ($\beta = 0.13$, $t = 3.41$, $p = 0.0007$) after controlling for multiple confounders, including BMI, smoking, medication, and substance use. Adjustment for psychotic, manic, and depressive symptoms did not affect the results. There were no significant associations between agitation and the other investigated immune markers (IL-1RA ($\beta = 0.06$, $t = 1.27$, $p = 0.20$), IL-18 ($\beta = 0.05$, $t = 1.25$, $p = 0.21$), IL-18R1 ($\beta = 0.04$, $t = 1.01$, $p = 0.31$), IL-18RAP (odds ratio = 0.96, $p = 0.30$)). In a subsample (N = 463), we also adjusted for cortisol levels, which yielded unaltered results.

Conclusion: Our findings add to the accumulating evidence of immune system disturbances in severe mental disorders and suggest the IL-18 system as a part of the biological correlate of agitation independent of affective and psychotic symptoms.

1. Introduction

Severe mental disorders such as schizophrenia and bipolar disorder are among the leading causes of morbidity (GBD 2019 Diseases and Injuries Collaborators, 2020), with a profound influence on affected individuals and high societal costs (Owen et al., 2016). These disorders

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have heterogeneous and overlapping clinical presentation, which can involve alterations of perception, thought, emotion, and behavior, including agitation. Agitation is a challenging clinical feature (Volicer et al., 2017) closely related to aggression (Volavka and Citrome, 2011) and linked to the self-reported quality of life (Gardsjord et al., 2018). Despite the extensive impacts of agitation, therapeutic options are limited (Paris et al., 2021), and the biological correlates are largely unknown.

The complex etiology of severe mental disorders involves overlapping polygenic architectures (Smeland et al., 2020) in interplay with environmental factors (Guloksuz et al., 2019). The immune system has emerged as a pathophysiological candidate supported by genetic (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Mullins et al., 2021) and epidemiological studies (Benros et al., 2011, 2013). Moreover, immune activation with dysregulation of pro-inflammatory signaling such as the interleukin (IL)-1, IL-18, tumor necrosis factor (TNF), and IL-6 pathways has been observed across psychotic, manic, and depressive symptoms (Goldsmith et al., 2016; Wedervang-Resell et al., 2020). Intriguingly, similar dysregulation has been indicated in agitation-related conditions in the general population and across mental disorders. Elevated IL-6 has been linked to hostility in healthy individuals (Marsland et al., 2008) and to impulsive aggression in intermittent explosive disorder (Coccaro et al., 2014). Elevation of TNF-α has been reported in agitated patients in psychiatric emergency settings (Larsen et al., 2019) and elevation of IL-1β has been observed in agitated individuals with dementia (Higuchi et al., 2010). Furthermore, experimental animal models of agitation have suggested a role of IL-1β and IL-18 (Bhatt et al., 2008; Lisboa et al., 2018). The NLRP3 inflammasome is an intracellular complex that activates caspase-1, resulting in the subsequent release of IL-1β and IL-18 (Strowig et al., 2012). The inflammasome-related IL-1β and IL-18 pathways have been proposed to link immune activation and behavior-relevant processes such as neurotransmission, neuronal excitability, and synaptic remodeling (Herman and Pasinetti, 2018; Kaufmann et al., 2017). However, our insight into the role of these inflammasome-related pathways in agitation is limited and the relationship between the IL-18 system and human agitation remains unexplored.

Hence, we investigated the inflammasome-related systems and agitation in a well-characterized sample of patients with severe mental disorders. We focused on circulating soluble inflammasome-related immune markers, including IL-1 receptor antagonist (IL-1RA), IL-18, IL-18 binding protein (IL-18BP), IL-18 receptor 1 (IL-18R1), and IL-18 receptor accessory protein (IL-18RAP). We hypothesized that agitation across the spectrum of severe mental disorders would be associated with immune activation reflected by levels of the inflammasome-related immune markers. Further, we hypothesized that agitation would be associated with the immune marker levels independently of core symptoms of illness exacerbation (i.e., psychotic, manic, and depressive symptoms). Finally, we explored the neuroendocrine influence on the relationship between agitation and immune activation.

2. Material and methods

2.1. Study setting and participants

Participants in the present study (N = 660) were recruited between the years 2002 and 2018 through the ongoing Thematically Organized Psychosis (TOP) study at the NORMENT research center, Oslo, Norway. An overview of the recruitment years is shown in Fig. S1. The TOP study enrolls patients with severe mental disorders referred from psychiatric inpatient and outpatient clinics. The inclusion criteria of the present study were a psychotic or affective disorder diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) (American Psychiatric Association, 1994), age between 18 and 65 years, and the ability to give informed consent. The exclusion criteria comprised use of any immunomodulatory agents, immunological disorder or current infection (indicated by medical records, self-report, medication use, or C-reactive protein (CRP) level above 10 mg/L), neurological disorder, history of severe head trauma, and pronounced cognitive deficit (IQ scores below 70). The work was conducted in accordance with the Declaration of Helsinki, and all participants have given written informed consent. The TOP study is approved by the Regional Ethics Committee, the Norwegian Directorate of Health, and the Norwegian Data Protection Authority.

2.2. Clinical assessment

All participants underwent thorough assessments with review of medical records, general physical examination, and clinical interviews, including the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) (First et al., 1995). Following the assessment, participants were assigned one of the diagnoses within psychotic disorders (SCZ, N = 388), including schizophrenia (DSM-IV 295.1, 295.3, 295.6, or 295.9, N = 216), schizophreniform disorder (DSM-IV 295.4, N = 30), schizoaffective disorder (DSM-IV 295.7, N = 51), delusional disorder (DSM-IV 297.1, N = 27), brief psychotic disorder (DSM-IV 298.8, N = 8), and psychotic disorder not otherwise specified (DSM-IV 298.9, N = 56) or affective disorders (BD, N = 272), including bipolar I disorder (DSM-IV 296.0, 296.4, 296.5, 296.6, 296.7, N = 161), bipolar II disorder (DSM-IV 296.89, N = 81), bipolar not otherwise specified (DSM-IV 296.80, N = 12), and major depressive disorder with psychotic features (DSM-IV 296.24, 296.34, N = 18). Level of functioning was quantified using the Global Assessment of Functioning Split Version (GAF-F) (Pedersen et al., 2007). Psychotic symptoms were evaluated according to the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and derived from the positive component (P1-Delusions, P3-Hallucinatory behavior, P5-Grandiosity, G9-Unusual thought content, and G12-Lack of judgment and insight) of a five factor PANSS model (Kay and Sevy, 1990). Affective symptoms were evaluated with the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990). Current dose of psychopharmacological medication (antipsychotics, antidepressants, anticonvulsants, and lithium) relative to the defined daily dose (DDD) was calculated in line with the guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (https://www.whocc.no/atc_ddd_index/). Self-reported information about the use of alcohol (number of alcohol units) and illicit substance use during the two-week period prior the assessment was recorded. Information about smoking status was based on a self-report of daily tobacco smoking. BMI (kg/m^2) was calculated using weight and height measurements.

2.3. Agitation scores

A measure of agitation was obtained using the PANSS Excited Component (PANSS-EC), which is calculated as a sum of the following PANSS items: P4-Excitement, P7-Hostility, G4-Tension, G8-Uncooperativeness, and G14-Poor impulse control (Montoya et al., 2011). The PANSS-EC is a part of a five factor PANSS model (Kay and Sevy, 1990) and is commonly used as a primary outcome measure in randomized controlled trials targeted at agitation (Citrome, 2007). The PANSS consists of 30 interviewer-rated items, each evaluating a current symptom on a scale from 1 (no symptom) to 7 (severe symptom). The PANSS assessment was conducted in temporal proximity of the blood sampling (median 9 days, interquartile range 13 days) and with a good inter-rater reliability (intraclass correlation coefficient above 0.7) (Ringen et al., 2008).

2.4. Blood sampling, cortisol, and immune markers

Venous blood samples were drawn in the morning after an overnight fast. Serum cortisol level was measured using a competitive

luminescence immunoassay (Immulite 2000xpi, Siemens Healthineers, Erlangen, Germany) at the Hormone Laboratory, Department of Medical Biochemistry, Oslo University Hospital, Norway. Plasma was collected using EDTA vials, isolated the next working day, and stored at − 80 °C in the biobank. Information about the cumulative freezer storage time of the sample was recorded (Enroth et al., 2016). Immune markers were analyzed with enzyme-linked immunosorbent assay (ELISA) methods. We used antibodies from R&D Systems (Stillwater, MN, USA) to measure levels of IL-18 (Cat# DY318–05) and IL-18BP (Cat# DY119), antibodies from Sino Biological (Beijing, China) to measure levels of IL-18R1 (Cat#11102) and IL-18RAP (Cat#SEK10176), and antibodies from PeproTech (Cranbury, NJ, USA) to measure IL-1RA (Cat#900K474). Samples were analyzed in duplicate in a 384-well format using a pipetting robot (SELMA, Analytik Jena, Jena, Germany) and a dispenser (BioTek, Winooski, VT, USA). Absorption was read by ELISA plate reader (BioTek, Winooski, VT, USA) at 450 nm with 540 nm wavelength correction. IL-18, IL-18BP, IL-18R1, and IL-18RAP were analyzed in 2018, while IL-1RA was analyzed in a subsample of participants (N = 405) in 2013. The assay sensitivity was 22 pg/mL for IL-18, 25 pg/mL for IL-18BP, 10 pg/mL for IL18-RAP, 25 pg/mL for IL-18R1, and 25 pg/mL for IL-1RA. In 9 samples (2%), levels of IL-1RA were under the detection limit and were set to 25 pg/mL. Intra- and inter-assay coefficients of variation were below 10% for all analyses. To ensure compliance with the exclusion criteria, the samples were screened for serum CRP levels above 10 mg/L, using particle-enhanced immunoturbidimetric methods from Roche Diagnostics (Indianapolis, IN, USA) at the Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway.

2.5. Statistical analyses

Statistical analyses were performed using R software package version 4.1.1 (www.R-project.org). Descriptive characteristics were compared across diagnostic categories using chi-squared-, Wilcoxon rank-sum-, and independent samples t-tests. Normality was assessed by inspection of Q-Q plots and histograms. Based on inspection of immune marker distributions and standardized residuals, plasma levels of IL-1RA, IL-18, IL-18BP, and IL-18R1 were logarithmically transformed, and outliers outside 3 standard deviations were removed (3.2% of IL-1RA, 0.0% of IL-18, 2.9% of IL-18BP, 0.9% of IL-18R1). The association between agitation and immune activation was analyzed using multiple linear regression, with immune markers (IL-1RA, IL-18, IL-18BP, and IL-18R1) as the dependent variable and agitation scores (PANSS-EC) as the independent variable, while controlling for sex, age, BMI, smoking status (smoking daily versus non-smoker), diagnosis (SCZ versus BD), medication (antipsychotics, antidepressants, anticonvulsants, and lithium quantified as DDDs), alcohol use (number of alcohol units), illicit substance use (cannabis and stimulants as dichotomous variables), and freezer storage time. Stability of regression coefficients was checked using bootstrapping approach with 2 000 replicates. Due to a highly skewed distribution, IL-18RAP was dichotomized based on the median value and analyzed with logistic regression. Interaction between agitation and diagnosis was tested using the same models. The influence of psychotic and affective symptoms on any significant association between agitation and the immune marker was investigated in follow-up analyses. We used the same model as in the main analysis and additionally adjusted for psychotic (sum of PANSS Positive Component items: P1, P3, P5, G9, G12), manic (YMRS scores), and depressive symptoms (CDSS scores). To explore the influence of stress hormone levels, main analyses were repeated in a subsample with available cortisol measurements (N = 463 for the IL-18 system markers, N = 356 for IL-1RA), followed by an additional adjustment for serum cortisol level. Inspection of standardized residuals, Cook's distances, and variation inflation factors was used to ensure no violation of the test assumptions. We applied the Bonferroni method to correct for multiple testing (5 consecutive analyses with IL-1RA, IL-18, IL-18BP, IL-18R1, and IL-18RAP). All analyses were two-tailed, with a significance level at 0.05 for the descriptives and at 0.01 (0.05/5) for the main, follow-up, and cortisol subsample analyses.

3. Results

3.1. Descriptive characteristics

Demographic and clinical characteristics are presented in Table 1. The patients in the SCZ group were more frequently male and less frequently of European ethnicity than the patients in the BD group. The patients in the SCZ group had lower level of functioning (GAF-F), higher psychotic symptom load (PANSS positive component), as well as higher level of agitation (PANSS-EC) compared to the BD group. The patients in the SCZ group were also more frequently smokers and used more antipsychotic medication, less lithium, less anticonvulsants, and less alcohol two weeks before the assessment. The levels of immune markers across patient groups are presented in Table 1. The patients in the SCZ group had higher levels of IL-1RA, IL-18, IL-18BP, and IL-18R1. Descriptive characteristics of the IL-1RA and cortisol subsamples are shown in Tables S1 and S2.

3.2. Agitation and immune markers

The results are summarized in Table 2. The association between agitation and IL-18BP is shown in Fig. 1. As presented in Table 3, agitation was significantly positively associated with IL-18BP after controlling for confounders. Adjustment for psychotic, manic, and depressive symptoms did not affect the results (outlined in Tables 4 and S3). We found no significant associations between agitation and the other investigated immune markers and there were no significant

Table 1
Descriptive characteristics of participants.

Total N = 660	SCZ N = 388	BD N = 272
Demographic and clinical characteristics		
Male (%)	59.5*	41.2
Age (median (IQR))	27 (12)	29 (16)
European ethnicity (%)	79.1*	86.0
GAF-F (mean ± SD)	46.4 ± 12.7*	55.0 ± 13.1
CDSS (median (IQR))	4 (7)	4 (7)
YMRS (median (IQR))	2 (8)	2 (4)
PANSS Positive Component (median (IQR))	12 (6)*	6.5 (4)
PANSS-EC (median (IQR))	7 (3)*	6 (3)
BMI (mean ± SD)	26.1 ± 5.1	25.7 ± 4.6
Smoking (%)	46.4*	36.8
Antipsychotics (%)	83.2*	49.3
Antidepressants (%)	26.0	31.6
Lithium (%)	2.3*	17.3
Anticonvulsants (%)	7.2*	32.4
Alcohol units last 2 weeks (median (IQR))	0 (4)*	2 (8)
Cannabis (%)	6.4	8.8
Stimulants (%)	2.8	2.9
Immune markers		
IL-1RA** (median (IQR))	234 (292)*	174 (272)
IL-18 (median (IQR))	1 088 (1 641)*	819 (1 383)
IL-18BP (median (IQR))	6 433 (3 029)*	5 806 (2 534)
IL-18R1 (median (IQR))	898 (473)*	838 (420)
IL-18RAP (median (IQR))	46 (18)	48 (17)

SCZ, Psychotic disorders; BD, Affective disorders. CDSS, Calgary Depression Scale for Schizophrenia; GAF-F, Global Assessment of Functioning Split Version; PANSS, Positive and Negative Syndrome Scale; PANSS-EC, Positive and Negative Syndrome Scale Excited Component; YMRS, Young Mania Rating Scale. IL-1RA, Interleukin-1 receptor antagonist (pg/mL); IL-18, Interleukin-18 (pg/mL); IL-18BP, Interleukin-18 binding protein (pg/mL); IL-18R1, Interleukin-18 receptor 1 (pg/mL); IL-18RAP, Interleukin-18 receptor accessory protein (pg/mL). SD, Standard deviation; IQR, Interquartile range.

* $p < 0.05$.

** IL-1RA subsample (N = 405, N_{SCZ}=264, N_{BD}=141).

Table 2
Associations between agitation and inflammasome-related immune markers.

	Coefficient (95% confidence interval)	Standardized coefficient β	t	p
IL-1RA	0.010 (−0.006 to 0.026)	0.06	1.27	0.20
IL-18	0.009 (−0.005 to 0.024)	0.05	1.25	0.21
IL-18BP	0.009 (0.004 – 0.015)	0.13	3.41	0.0007
IL-18R1	0.003 (−0.003 to 0.009)	0.04	1.01	0.31
	Odds ratio (95% confidence interval)			**p**
IL-18RAP	0.96 (0.89 – 1.03)			0.30

IL-1RA, Interleukin-1 receptor antagonist; IL-18, Interleukin-18; IL-18BP, Interleukin-18 binding protein; IL-18R1, Interleukin-18 receptor 1; IL-18RAP, Interleukin-18 receptor accessory protein.

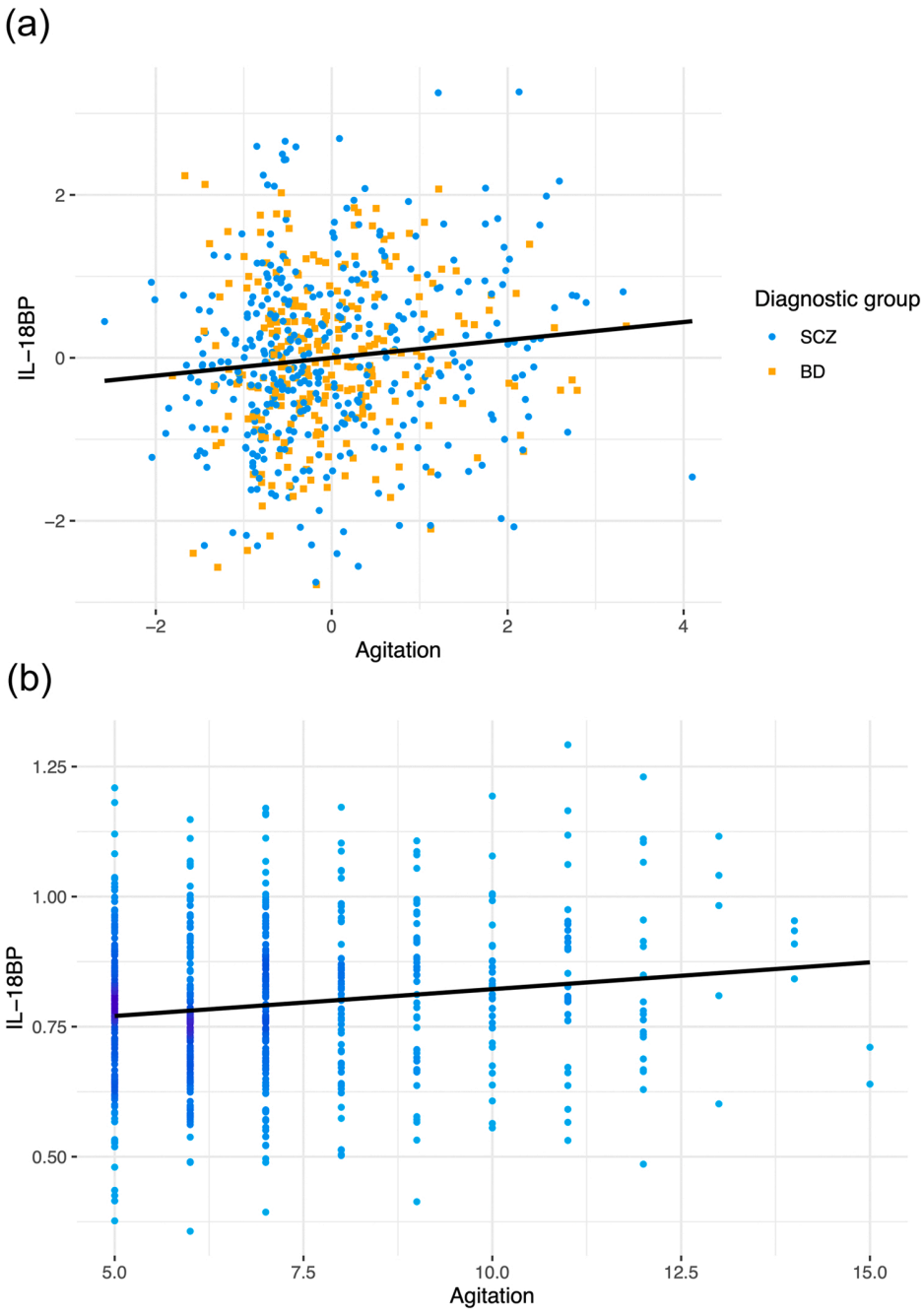

Fig. 1. Association between agitation and IL-18BP. a) After correction for multiple confounders and symptom dimensions. X axis: Z-scores (standardized residuals) of PANSS-EC (Positive and Negative Syndrome Scale Excited Component) obtained from a regression model with PANSS-EC as dependent and sex, age, BMI, smoking, diagnosis, medication, alcohol use, substance use, freezer storage time, psychosis, mania, and depression as independent variables, Y axis: Z-scores (standardized residuals) of log-transformed interleukin-18 binding protein (IL-18BP) levels (ng/mL) obtained from a regression model with IL-18BP as dependent and sex, age, BMI, smoking, diagnosis, medication, alcohol use, substance use, freezer storage time, psychosis, mania, and depression as independent variables. BD, Affective disorders; SCZ, Psychotic disorders. b) Raw data. PANSS-EC (Positive and Negative Syndrome Scale Excited Component), Y axis: Log-transformed interleukin 18 binding protein (IL-18BP) plasma levels (ng/mL). Shading represents the density of observations.

Table 3
Association between agitation and IL-18BP in a multiple linear regression model.

	Coefficient (95% confidence interval)	Standardized coefficient β	t	p	R^2
					0.135
Agitation	0.009 (0.004 – 0.015)	0.13	3.41	0.0007	
Sex[a]	0.051 (0.028 – 0.074)	0.17	4.43	0.00001	
Age	0.002 (0.001 – 0.004)	0.17	4.21	0.00003	
BMI	0.003 (0.001 – 0.006)	0.11	2.88	0.004	
Smoking	0.0004 (−0.023 to 0.024)	0.001	0.03	0.97	
Diagnosis[b]	0.039 (0.012 – 0.066)	0.13	2.88	0.004	
Freezer time	0.002 (−0.002 to 0.005)	0.03	0.90	0.37	
Antipsychotics	0.002 (−0.012 to 0.016)	0.01	0.30	0.77	
Antidepressants	0.015 (0.002 – 0.028)	0.08	2.21	0.03	
Lithium	0.020 (−0.009 to 0.049)	0.05	1.35	0.18	
Anticonvulsants	0.005 (−0.027 to 0.037)	0.01	0.31	0.76	
Alcohol	-0.0003 (−0.001 to 0.001)	-0.03	-0.69	0.49	
Cannabis	0.020 (−0.024 to 0.065)	0.04	0.90	0.37	
Stimulants	0.042 (−0.026 to 0.110)	0.05	1.20	0.23	

[a] Female coded as 0, Male coded as 1.
[b] Affective disorders coded as 0, Psychotic disorders coded as 1.

Table 4
Association between agitation and IL-18BP after adjustment for symptom dimensions.

	Coefficient (95% confidence interval)	Standardized coefficient β	t	p	R^2
Agitation, corrected for psychosis[a]	0.008 (0.002 – 0.014)	0.12	2.82	0.005	0.137
Agitation, corrected for mania[a]	0.009 (0.004 – 0.015)	0.13	3.34	0.001	0.135
Agitation, corrected for depression[a]	0.009 (0.004 – 0.015)	0.13	3.34	0.001	0.135
Agitation, corrected for psychosis, mania, and depression[a]	0.008 (0.002 – 0.014)	0.11	2.78	0.006	0.137

[a] Also controlled for sex, age, BMI, smoking, diagnosis, medication, alcohol use, substance use, and freezer storage time.

interactions between agitation and diagnosis. The bootstrapping approach confirmed stability of regression coefficients, converging on 95% confidence interval of 0.004 – 0.015 for association between agitation and IL-18BP. The cortisol subsample yielded the same results, apart from subtle changes in effect sizes (association between agitation and IL-18BP (β = 0.17, t = 3.73, p = 0.0002), IL-1RA (β = 0.05, t = 1.04, p = 0.30), IL-18 (β = 0.08, t = 1.85, p = 0.07), IL-18R1 (β = 0.06, t = 1.29, p = 0.20), IL-18RAP (odds ratio = 0.95, p = 0.25)), and the results remained unaltered after the additional adjustment for cortisol (association between agitation and IL-18BP (β = 0.17, t = 3.69, p = 0.0003), presented in Table S4).

4. Discussion

We conducted a comprehensive study of circulating inflammasome-related immune markers and agitation in a well-characterized sample of patients with severe mental disorders. The main finding of the study was a significant positive association between agitation and IL-18BP levels, which was independent of psychotic, manic, and depressive symptoms. The current findings add to the accumulating evidence of immune system disturbances in severe mental disorders.

Our finding of an association between agitation and IL-18BP levels was not driven by depressive, manic, or psychotic symptoms. Further, we also controlled for other factors known to affect the immune system such as sex, age, BMI, smoking, medication, and substance use (Baumeister et al., 2016; Haack et al., 1999; Lippai et al., 2013). Thus, agitation seems to be a clinical phenomenon linked to immune disturbances independently of psychotic and affective symptoms, in line with previous findings from the general population (Marsland et al., 2008).

Components of the inflammasome-related pathways interact in a complex way to ensure coordinated immune responses (Dinarello, 2018). IL-18BP is a major signaling protein within the IL-18 system and is regarded as a stable marker of immune activation (Dinarello et al., 2013). Specifically, upregulation of IL-18BP following elevations of IL-18 forms a negative feedback loop and, as such, serves as a part of the regulatory signaling system. Given the regulatory role of IL-18BP, our findings may suggest a compensatory upregulation of IL-18BP reflective of a state of immune activation. This is consistent with previous indices of immune activation in agitated states (Barzilay et al., 2016; Higuchi et al., 2010; Larsen et al., 2019) and agitation-related conditions (Coccaro et al., 2014). The present findings support a link between altered IL-18 system signaling and clinical features in severe mental disorders. A compensatory alteration of systemic IL-18 signaling has previously been indicated in individuals with schizophrenia (Palladino et al., 2012), which is also in line with previously reported case-control differences based on a subject sample overlapping with the current (Szabo et al., 2022). In contrast, we found no association between agitation and circulating levels of IL-18, which raises the question about the specific source of the immune signal underlying IL-18BP elevation.

Of note, IL-18BP elevations can be a sum of multiple immune signals. Besides the negative feedback loop with IL-18, IL-18BP can be also upregulated by inflammatory factors such as interferon (IFN)-γ or IFN-α (Dinarello et al., 2013). Interestingly, elevation of circulating IL-18BP has been described as a part of the response to IFN-α treatment (Kaser et al., 2002), a treatment regime linked with agitation (Renault et al., 1987). Substantially higher rates of side effects in form of agitation following IFN-α treatment of hepatitis as compared to IFN-α-free treatment provide an indication of a causal involvement of the immune system in human agitation (Lawitz et al., 2013). Upregulated transcriptional activity within the interferon signaling pathway has been observed in impulsive aggression (Coccaro et al., 2021). Moreover, a potentiating effect of inflammatory stimulation with lipopolysaccharide on aggression in pigs has also been reported, with somewhat conflicting evidence regarding effect on IFN-γ levels in a porcine brain (Veit et al., 2020). Taken together, this may point toward some possible mechanisms underpinning the observed association between agitation and IL-18BP.

No significant associations were found between agitation and levels of IL-1RA. This could represent a true null finding, in line with findings

of no differences in levels of circulating IL-1β in a mouse model (Takahashi et al., 2021). Given the previous findings implicating a role of the IL-1 system in agitation (Bhatt et al., 2008; Friedman et al., 1996; Higuchi et al., 2010), further investigation of agitation and the IL-1 signaling pathway may be warranted.

Inflammatory signaling pathways are known to be upregulated following acute psychological stress, which is also accompanied by activation of hypothalamic-pituitary-adrenal (HPA) axis (Marsland et al., 2017). Similarly, anger (Pesce et al., 2013) and hostility (Kiecolt-Glaser et al., 2005) have been reported to lead to activation of the immune system. Activation of the HPA axis with elevations of cortisol constitutes a part of the complex network of neuro-immune signaling pathways that engage in a bidirectional crosstalk (Dantzer, 2018). There was no influence of the adjustment for cortisol levels in our analysis, which indicates that other mechanisms than acute psychological stress may underlie the association between agitation and levels of circulating IL-18BP. Interestingly, immune alterations distinct from those linked to stress-related disorders have been observed in impulsive aggression (Coccaro et al., 2021). However, it is unknown how agitation symptoms relate to immune alterations following chronic psychological stress (Weber et al., 2017).

The main strength of our study lies in the novelty of addressing the relationship between elements of the inflammasome-related signaling pathways and human agitation. Moreover, the well-characterized clinical sample allowed us to control for relevant potential confounding factors and the large sample size enabled us to target even small effect sizes. However, the study also has some limitations. Due to the relatively comprehensive study protocol and, implicitly, the participant enrollment mainly in non-acute phase, there is a sparsity of high agitation levels in our sample. Thus, efforts to complement our findings with an investigation of the phenomenon in acute psychiatric settings might be warranted. Moreover, IL-1RA and cortisol were analyzed in subsamples. Furthermore, since IL-1β, in contrast to IL-1RA, often circulates at levels just above the detection limit of commercially available assays (Arend, 2002), the IL-1 system's activity was assessed solely by IL-1RA in our study. In general, our analyses were also restricted to the secreted circulating elements of the inflammasome-related signaling systems. Finally, despite adjustments for a wide range of potential confounders, residual confounding cannot be ruled out and the cross-sectional observational design prevents inferences about causal directions.

5. Conclusions

Taken together, our results suggest the IL-18 system as a significant, yet modest, part of the biological correlate of agitation in severe mental disorders, independent of affective and psychotic symptoms. The findings add to the growing body of evidence that implicates immune system disturbances in severe mental disorders. Future clinical studies should address the source and the temporal dynamics of the immune signal underlying IL-18BP elevation linked to agitation and related clinical states.

Declaration of interest

Ole A. Andreassen is a consultant for HealthLytix and received speaker's honorarium from Lundbeck and Sunovion. All other authors report no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105721.

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Study III

Title:

Impulsivity across severe mental disorders: a cross-sectional study with focus on immune markers and psychopharmacotherapy

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Abstract:

Background

Impulsivity is a transdiagnostic feature linked to severe clinical expression and a potential target for psychopharmacological strategies. Biological underpinnings are largely unknown, but involvement of immune dysregulation has been indicated, and the effects of psychopharmacological agents vary. We investigated if impulsivity was associated with circulating immune marker levels and with a range of psychopharmacological treatment regimens in severe mental disorders.

Methods

Impulsivity was assessed in a sample (N=657) of patients with schizophrenia or schizophreniform disorder (SCZ) (N=116) or bipolar disorder (BD) (N=159) and healthy participants (N=382) using the Barratt Impulsiveness Scale (BIS-11) questionnaire. Plasma levels of systemic immune markers (RANTES, IL-1RA, IL-18, IL-18BP, sTNFR-1) were measured by enzyme immunoassays. Patients underwent thorough clinical assessment, including evaluation of psychotropic medication. Associations were assessed using linear regressions.

Results

Impulsivity was positively associated with SCZ ($p<0.001$) and BD ($p<0.001$) diagnosis and negatively associated with age ($p<0.05$), but not significantly associated with any of the circulating immune markers independently of diagnostic status. Among patients, impulsivity was negatively associated with lithium treatment ($p=0.008$) and positively associated with antidepressant treatment ($p=0.006$) after controlling for diagnosis and psychotropic co-medications.

Conclusions

We report elevated impulsivity across SCZ and BD but no associations to systemic immune dysregulation based on the current immune marker selection. The present study reveals associations between impulsivity in severe mental disorders and treatment with lithium and antidepressants, with opposite directions. Future studies are warranted to determine the causal directionality of the observed associations with psychopharmacotherapy.

Keywords: Impulsiveness, Cytokines, Interleukin-1, Tumor necrosis factor, Chemokine CCL5, Psychopharmacology, Lithium, Antidepressants, Schizophrenia, Bipolar disorder

Main text:

Background

Schizophrenia and bipolar disorder are severe mental disorders with overlapping clinical presentations, environmental risk factors, and polygenic architectures (1, 2). The development of a severe mental disorder affects quality of life and functioning, although illness course varies substantially between individuals (3). Impulsivity can be conceptualized as a tendency to react without considering the consequences (4). Elevated impulsivity has been demonstrated in bipolar and schizophrenia spectrum disorders as well as in a range of other mental disorders such as attention-deficit hyperactivity disorder, borderline and antisocial personality disorders, and intermittent explosive disorder (5, 6, 7). Impulsivity has been linked to severe clinical expression, including suicidality, aggression, and early onset of the disorder (7, 8, 9). Thus, it has been proposed that patients across psychiatric diagnostic categories that express high impulsivity levels may benefit from preventive and therapeutic strategies targeting impulsivity (7, 8). However, the biological underpinnings of impulsivity are largely unknown, which imposes limitations to the development of optimized treatment and prevention of adverse outcomes.

A growing body of evidence points to involvement of the immune system in mental health and illness. Clinical genome-wide association studies and transcriptome-wide approach in human brain tissue have suggested a role of immune pathways across severe mental disorders (10, 11). Furthermore, elevations of circulating inflammatory immune markers have been demonstrated in schizophrenia, bipolar, as well as major depressive disorder (12). Intriguingly, impulsivity and overlapping clinical phenomena such as agitation and aggression have been linked to disturbances in inflammatory pathways, both in the general population (13) and across mental disorders (14, 15, 16, 17, 18, 19). Specifically, the chemokine Regulated on activation normal T cell expressed and secreted (RANTES), interleukin (IL)-1 family, and tumor necrosis factor (TNF) pathways have been proposed as pathophysiological candidates of impulsivity based on studies among individuals with alcohol dependence (20) and suicidal behavior (21), as well as on rodent models (22). The IL-1 family signaling pathways include immune markers such as IL-1β, IL-1 receptor antagonist (IL-1RA), IL-18, and IL-18 binding protein (IL-18BP), while markers such as TNF and soluble TNF receptor 1 (sTNFR1) belong to the TNF superfamily. The IL-1 family and TNF signaling pathways are involved in the coordination of innate immune responses and have potent pro-inflammatory properties (23, 24). As ligands in these immune marker superfamilies circulate at levels just above the detection limit of commercially available assays, use of surrogate stable markers such as IL-1RA and sTNFR1 can be employed to reliably reflect the activity within IL-1 and

TNF systems (25, 26). Interestingly, the IL-1 family and TNF signaling pathways have been proposed to interplay with neurotransmission and neuronal excitability (27). Likewise, the inflammatory chemoattractant RANTES has been suggested to play a neuromodulatory role (28, 29). However, potential links between these immune pathways and impulsivity, with their possible impact on psychopathology in severe mental disorders, are yet to be determined.

Impulse control impairments are often seen in the context of illness exacerbations such as psychotic or manic episodes, which can be treated with antipsychotics, anticonvulsants, and lithium (30, 31, 32). Intriguingly, animal models have shown impulsivity-lowering effect of lithium (33, 34), paralleled by anti-inflammatory effects (i.e., decrease of RANTES and IL-1β levels in plasma and brain tissue) (22). However, reports that focus on links between psychopharmacological treatment and specifically defined measures of impulsivity in severe mental disorders are sparse (35, 36, 37). In particular, despite that adjunctive psychopharmacotherapy with antidepressants is broadly used in clinical practice across bipolar and schizophrenia spectrum disorders (38, 39), its relationship to impulsivity in severe mental disorders has not been assessed.

The aim of the present study was to (1) investigate associations between impulsivity and plasma levels of immune markers in a large cross-sectional sample of individuals with and without severe mental disorder and (2) explore links between impulsivity and psychopharmacological treatment in a naturalistic setting. We hypothesized that plasma levels of RANTES, IL-1RA, IL-18, IL-18BP, and sTNFR1 would be positively associated with impulsivity across the diagnostic categories. Further, we hypothesized that antipsychotic, anticonvulsant, and lithium treatment would be negatively associated with impulsivity. Given the sparsity of evidence regarding the relationship between antidepressants and impulsivity in severe mental disorders, the corresponding part of our study was explorative.

Methods

Study design and participants

The present study is a cross-sectional investigation of impulsivity in a sample (N=657) of participants recruited between the years 2011 and 2018 through the ongoing Thematically Organized Psychosis (TOP) study at the NORMENT research center, Oslo, Norway. The TOP study enrolls patients with severe mental disorders referred from psychiatric inpatient and outpatient clinics and age- and catchment area matched healthy controls randomly selected from the national population registry. In the patient group (N=275), the main inclusion criterion was a schizophrenia or schizophreniform disorder diagnosis (SCZ) or a bipolar disorder diagnosis (BD)

assigned according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) (40). Further inclusion criteria were age between 18 and 65 years and the ability to give informed consent. The exclusion criteria consisted of pronounced cognitive deficit (IQ scores below 70), history of severe head trauma, neurological disorder, immunological condition, current infection (indicated by medical records, self-report, medication use, or C-reactive protein (CRP) level above 10 mg/L), and use of any immunomodulatory agents. In the healthy participant group (N=382), the presence or history of a severe mental disorder among the participants or their first-degree relatives constituted an additional exclusion criterion.

Clinical assessment

Participants in the patient group underwent general physical examination, review of medical records, and clinical interviews, including the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) (41). The assessments resulted in assigning one of the following diagnoses; SCZ (N=116): schizophrenia (DSM-IV 295.1, 295.3, 295.6, 295.9, N=103), schizophreniform disorder (DSM-IV 295.4, N=13) or BD (N=159): bipolar I (DSM-IV 296.0, 296.4, 296.5, 296.6, 296.7, N=90), bipolar II (DSM-IV 296.89, N=59), bipolar not otherwise specified (DSM-IV 296.80, N=10). Symptom load was evaluated with the Positive and Negative Syndrome Scale (PANSS) (42), the Young Mania Rating Scale (YMRS) (43), and the Calgary Depression Scale for Schizophrenia (CDSS) (44). The level of functioning was measured according to the Global Assessment of Functioning Split Version (GAF-F) (45). In addition to a comprehensive review of somatic and psychiatric history, healthy participants were assessed using the Primary Care Evaluation of Mental Disorders (46).

Impulsivity scores

Impulsivity was measured using the Barratt Impulsiveness Scale (BIS-11) questionnaire (47). The BIS-11 is commonly used to assess behavioral and personality constructs of impulsivity across general- and patient populations (48). The BIS-11 consists of 30 items, which are self-evaluated on a 4-point Likert scale. The total score ranges from 30 to 120, with higher scores reflecting higher levels of impulsivity. Internal consistency of the total score has been reported as acceptable (4, 47, 48, 49, 50).

Psychotropic medication

All patients were interviewed about their current pharmacological treatment, and medical records were used to validate the information. The psychopharmacological agents were sorted into the following groups: antipsychotics (olanzapine, risperidone, paliperidone, amisulpride, aripiprazole, clozapine, quetiapine, zuclopenthixol, perphenazine, ziprasidone, chlorprothixene, levomepromazine), anticonvulsants (valproate, lamotrigine, carbamazepine), lithium, and antidepressants (escitalopram, fluoxetine, sertraline, paroxetine,

venlafaxine, mirtazapine, mianserin, bupropion). The current dose relative to the defined daily dose (DDD) was calculated for the antipsychotics, anticonvulsants, lithium, and antidepressants, according to the guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (https://www.whocc.no/atc_ddd_index/).

Immune markers

Blood samples were collected using venipuncture and EDTA vials. Plasma was isolated the next working day and stored at -80 °C in the biobank. Plasma concentrations of immune markers were measured with enzyme-linked immunosorbent assay (ELISA) methods, using IL-1RA antibodies (Cat#900K474) from PeproTech (Cranbury, NJ, USA) and IL-18 (Cat#DY318-05), IL-18BP (Cat#DY119), sTNFR1 (Cat#DY225), and RANTES antibodies (Cat#DY278) from R&D Systems (Stillwater, MN, USA). RANTES, IL-18 and IL-18BP were analyzed in 2018, while IL-1RA and sTNFR1 were analyzed in a subsample of participants (N=240) in 2013. All analyses were conducted in duplicate in a 384-well format, using a pipetting robot (SELMA, Analytik Jena, Jena, Germany) and a washer dispenser (BioTek, Winooski, VT, USA). Absorption was read by ELISA plate reader (BioTek, Winooski, VT, USA) at 450 nm with 540 nm wavelength correction. The assay sensitivities were: 20 pg/mL for RANTES, 25 pg/mL for IL-1RA, 22 pg/mL for IL-18, 25 pg/mL for IL-18BP, and 20 pg/mL for sTNFR1. In 10 samples (1.5 %), levels of RANTES were under the detection limit and were set to 20 pg/mL, while level of IL1-RA was under the detection limit in 1 sample (0.4 %) and thus set to 25 pg/mL. Intra- and inter-assay coefficients of variation were below 10 % for all analyses. To ensure compliance with the exclusion criteria, samples were screened for serum CRP levels above 10 mg/L, using particle-enhanced immunoturbidimetric methods from Roche Diagnostics (Indianapolis, IN, USA) at the Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway.

Statistical analyses

Data were analyzed using the R software package version 4.2.1 (www.R-project.org). Differences in Descriptive characteristics were compared across diagnostic categories using Wilcoxon rank-sum tests, Kruskal-Wallis tests with post hoc pair-wise comparisons, or chi-squared tests. Before further analyses, the BIS-11 total scores (measure of impulsivity) were successfully log-transformed to attain normality. Following inspection of the immune marker distributions, extreme values exceeding the first or third quantile by three interquartile ranges or more were removed prior to entry into analyses (1.4% of RANTES, 3.8% of IL-1RA, 0.5% of IL-18, 1.7% of IL-18BP, and 0.4% of sTNFR1). Linear regressions with one immune marker at a time as the independent variable and impulsivity as the dependent variable were employed, while controlling for sex, age,

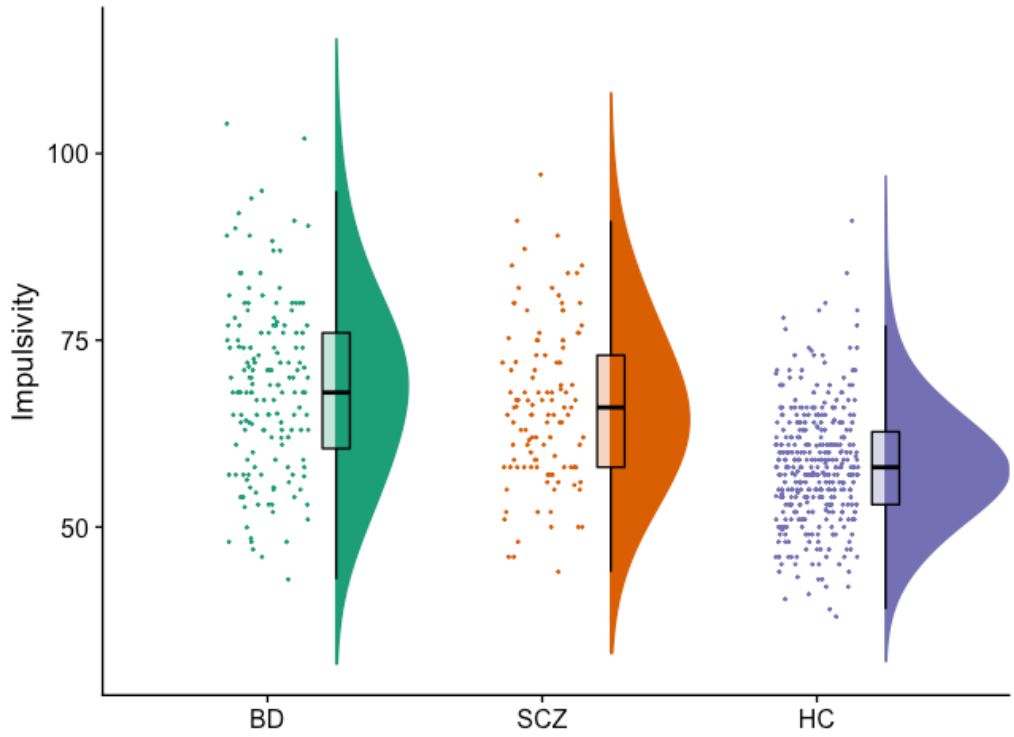
and diagnosis (healthy individuals, SCZ, and BD coded as dummy variables). Next, associations between psychopharmacological treatment and impulsivity were investigated in the patient group. We ran a linear regression with DDD of antipsychotics, anticonvulsants, lithium, and antidepressants as independent variables and impulsivity as the dependent variable, while controlling for sex, age and diagnosis (SCZ versus BD). Influence of the current affective state (YMRS and CDSS scores) was assessed in follow-up analyses. Standardized residuals, variance inflation factors, and Cook's distances were inspected to ensure no violation of the model assumptions. All analyses were two-tailed, with a general significance level at 0.05. Based on Bonferroni correction for multiple testing, significance level was set at 0.01 (0.05/5) for the immune marker analyses and at 0.0125 (0.05/4) for the analyses of psychopharmacotherapy.

Results

Descriptive characteristics

The median of the BIS-11 total score was 66 in the SCZ group, 68 in the BD group, and 58 in the healthy participant group. The BIS-11 total scores were higher in both the SCZ ($p<0.001$) and the BD ($p<0.001$) group, compared to the healthy participants, while there were no significant differences in the BIS-11 total scores between the patient groups ($p=0.09$) (Figure 1). Patients in the BD group were more often female and had a higher level of functioning, more depressive symptoms, and lower total PANSS scores than patients in the SCZ group. Compared to patients in the SCZ group, patients in the BD group also less often used antipsychotics and more often used anticonvulsants and lithium. Descriptive characteristics are presented in more detail in Table 1 and Table S1.

Fig. 1 Impulsivity across individuals with severe mental disorders and healthy individuals



BD bipolar disorder; SCZ, schizophrenia or schizophreniform disorder; HC, healthy participant group.
Impulsivity displayed as total scores on Barratt Impulsiveness Scale 11.

Table 1 Demographic and clinical characteristics

	SCZ	**BD**	**HC**	Group differences[a]
Total N=657	N=116	N=159	N=382	
N (%)				
Male	78 (67)	63 (40)	221 (58)	SCZ, HC > BD
Antipsychotics	104 (90)	72 (45)	NA	SCZ > BD
Anticonvulsants	9 (8)	43 (27)	NA	BD > SCZ
Lithium	5 (4)	27 (17)	NA	BD > SCZ
Antidepressants	21 (18)	35 (22)	NA	NS
Median (IQR)				
Age	28 (14)	30 (17)	31 (13)	NS
BIS-11 total score	66 (15)	68 (16)	58 (10)	SCZ, BD > HC
PANSS total score	62 (18)	42 (11)	NA	SCZ > BD
CDSS	3 (5)	4 (7)	NA	BD > SCZ
YMRS	2 (4)	2 (4)	NA	NS
GAF-F	42 (16)	60 (19)	NA	BD > SCZ

SCZ, schizophrenia or schizophreniform disorder; BD bipolar disorder; HC, healthy participant group.
BIS-11, Barratt Impulsiveness scale; CDSS, Calgary Depression Scale for Schizophrenia; GAF-F, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale.
NA, not applicable; NS, nonsignificant; IQR, interquartile range.
[a]$p < 0.05$; based on chi-squared-, Wilcoxon rank-sum-, or Kruskal-Wallis tests with post hoc pair-wise comparisons.

Associations between impulsivity and the immune markers

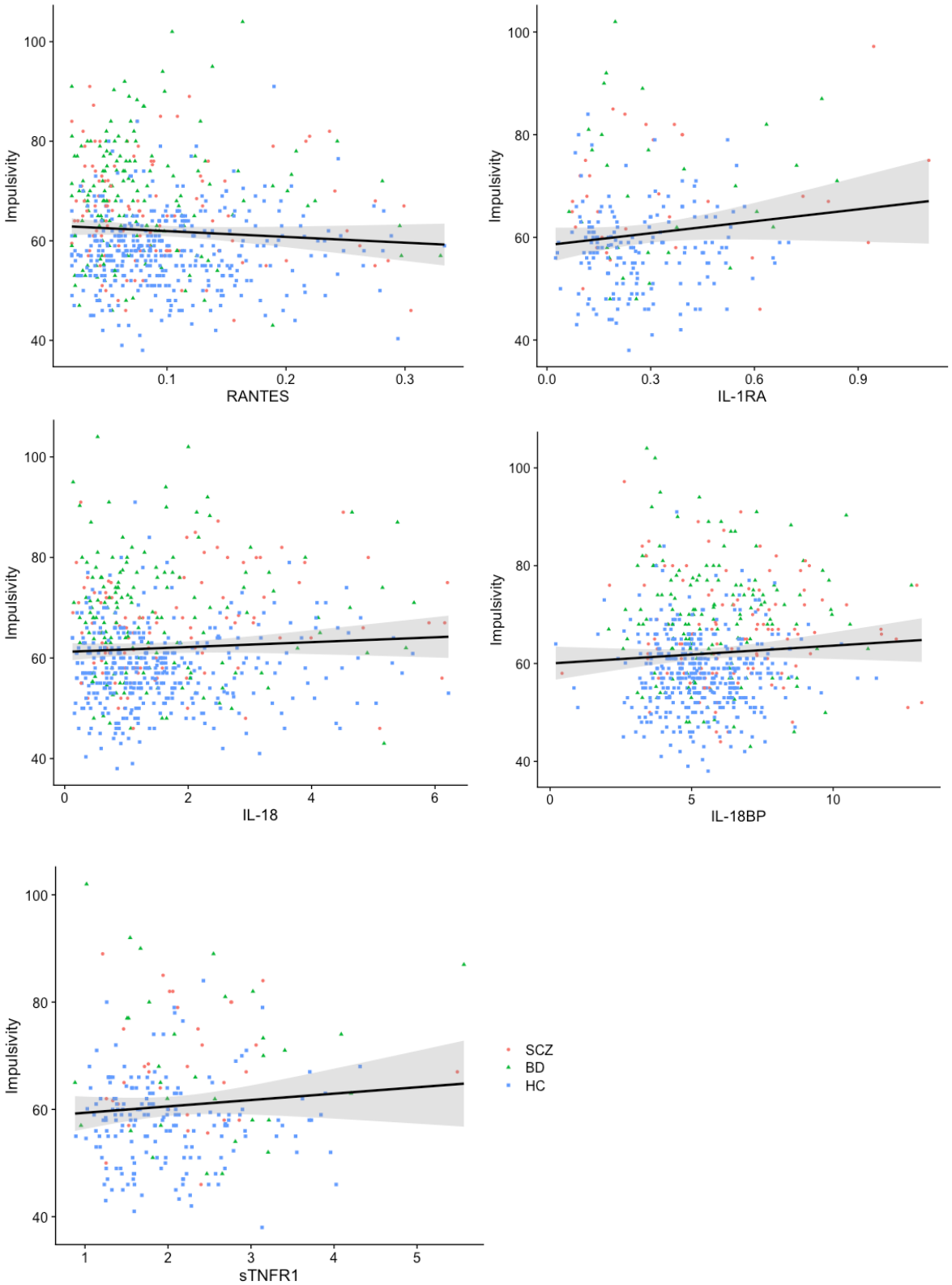
In the full model, impulsivity was positively associated with SCZ ($p<0.001$) and BD ($p<0.001$) diagnosis and negatively associated with age ($p<0.05$), while there was no significant association with sex. As shown in Table 2, there were no significant associations between the immune markers and impulsivity independent of diagnostic status. Visualization of the relationships between the immune markers and impulsivity is presented in Figure 2.

Table 2 Linear regressions of associations between circulating immune markers and impulsivity*

	Coefficient estimate (95% CI)	**Standardized coefficient β**	**t**	**p**
RANTES	-0.07 (-0.25 to 0.12)	-0.03	-0.74	0.46
IL-1RA	0.07 (-0.04 to 0.18)	0.07	1.21	0.23
IL-18	0.01 (-0.004 to 0.01)	0.04	1.13	0.26
IL-18BP	0.001 (-0.01 to 0.01)	0.01	0.18	0.85
sTNFR1	-0.001 (-0.03 to 0.02)	-0.01	-0.12	0.91

CI, confidence interval
RANTES, Regulated on activation normal T cell expressed and secreted; IL-1RA, Interleukin-1 receptor antagonist; IL-18, Interleukin-18; IL-18BP, Interleukin-18 binding protein; sTNFR1, Soluble tumor necrosis factor receptor 1.
*Also controlled for sex, age, and diagnosis.

Fig. 2 Associations between circulating immune marker levels and impulsivity



X axis: Plasma level of the immune marker (ng/mL). Y axis: Barratt Impulsiveness scale 11, total score.
RANTES, Regulated on activation normal T cell expressed and secreted ; IL-1RA, Interleukin-1 receptor antagonist; IL-18, Interleukin-18; IL-18BP, Interleukin-18 binding protein; sTNFR1, Soluble tumor necrosis factor receptor 1.
SCZ, schizophrenia or schizophreniform disorder; BD bipolar disorder; HC, healthy participant group.

Associations between impulsivity and psychopharmacological treatment

Among the patients, impulsivity was negatively associated with DDD of lithium (β=-0.16, t=-2.68, p=0.008) and positively associated with DDD of antidepressants (β=0.16, t=2.78, p=0.006) after controlling for sex, age, diagnosis, and other psychotropic medications (Table 3). There were no significant associations between impulsivity and DDD of antipsychotics (β=0.03, t=0.49, p=0.63) or anticonvulsants (β=-0.11, t=-1.80, p=0.07). Controlling for the current affective state (YMRS and CDSS scores) did not influence the significant associations between impulsivity and lithium (β=-0.19, t=-3.00, p=0.003) or antidepressants (β=0.16, t=2.58, p=0.011) (Table S2).

Table 3 Linear regression model of associations between psychopharmacotherapy and impulsivity among patients with severe mental disorders

	Coefficient estimate (95% CI)	**Standardized coefficient β**	**t**	**p**	**R^2**
					0.08
Diagnosis[a]	-0.06 (-0.11 to -0.01)	-0.17	-2.39	0.02	
Sex[b]	0.01 (-0.03 to 0.05)	0.02	0.33	0.75	
Age	-0.002 (-0.004 to -0.0001)	-0.12	-2.03	0.04	
Antipsychotics, DDD	0.01 (-0.02 to 0.03)	0.03	0.49	0.63	
Anticonvulsants, DDD	-0.05 (-0.10 to 0.004)	-0.11	-1.80	0.07	
Lithium, DDD	-0.08 (-0.13 to -0.02)	-0.16	-2.68	0.008	
Antidepressants, DDD	0.04 (0.01 to 0.06)	0.16	2.78	0.006	

CI, confidence interval, DDD, defined daily dose.
[a]Bipolar disorder coded as 0, Schizophrenia and schizophreniform disorder coded as 1
[b]Female coded as 0, Male coded as 1

Discussion

We investigated links between impulsivity and circulating immune markers within putative pathophysiological pathways, and we examined associations between impulsivity and psychopharmacotherapy in severe mental disorders. The main findings were (1) no significant associations between circulating levels of RANTES, TNF, or IL-1 family immune markers and impulsivity, (2) a negative association between impulsivity and lithium treatment, and a positive association between impulsivity and antidepressant treatment.

We found a negative association between lithium treatment and impulsivity, which is in line with reported impulsivity-reducing properties of lithium in rodent models (22, 34). While the exact molecular mechanisms that may underlie lithium effects are not fully understood, inhibition of glycogen synthase kinase-3 as well as of inositol monophosphatase and subsequent interplay with cellular signaling and neurotransmission

have been identified as the main candidates (51, 52, 53, 54). Impulsivity-reducing properties of lithium treatment have also been described among patients with bipolar disorder in the context of manic episodes (37) or comorbid pathological gambling (36). Moreover, impaired impulse control has been indicated as one of the major factors in suicidality (55), and lithium has shown protective effects on suicide risk in mood disorders (56, 57, 58). On the other hand, a link between clinical characteristics and the lithium prescription practice (59) may also underlie the observed association between impulsivity and lithium treatment.

We found a positive association between antidepressant treatment and impulsivity. This association might reflect a causal effect of antidepressants on impulsivity or a more intensive antidepressant prescription practice in impulsive patient populations. Indeed, clinical characteristics have been suggested to affect the antidepressant prescription practice, with deflections from the standard first-line treatment of major depressive disorder in more severely ill patient populations at higher suicide risk (60). A large register-based observational study has shown an increased risk of suicide attempt repetition in individuals prescribed antidepressants, which was not apparent after accounting for the baseline risk of suicide attempt repetition (61). However, meta-analyses of randomized controlled trials of antidepressants have indicated an increase in suicidality among adolescents (62) and young adults (63), while no significant increase was detected across the adult population (63). Interestingly, it has been proposed that impulsivity may be particularly related to suicide risk among younger adults (64). Importantly, antidepressants typically target serotonergic signaling, but the effects beyond reduction of depressive symptoms (65) and exact mechanisms of action remain elusive and likely complex (66, 67).

There were no significant associations between anticonvulsant or antipsychotic treatment and impulsivity. This is in line with impulsivity reductions in rodents exposed to lithium but not in those exposed to anticonvulsants such as valproate or carbamazepine (33, 34). However, clinical studies have previously indicated an inverse relationship between impulsivity and treatment with valproate (37) as well as antipsychotics (35). These inconsistencies might reflect differences in the conceptualization of impulsivity, distinct characteristics of the patient populations, or pharmacological heterogeneity within the medication groups (68).

We tested the hypothesized associations between immune signaling and impulsivity across a broad spectrum of impulsivity levels, including impulsivity variance among healthy participants. While the current study captured elevated impulsivity across BD and SCZ disorders, no significant associations to the immune marker levels independent of diagnostic status were detected. This result is in contrast to earlier findings of links between the plasma level of the chemokine RANTES and impulsivity in individuals with alcohol

dependence (20) and changes in impulsivity in rodents (22). The rodent model of impulsivity has also shown parallel reductions in plasma IL-1β and impulsivity (22), but we found no corresponding associations between systemic signaling within IL-1 family, as reflected by IL-1RA, and impulsivity in the present study. Moreover, circulating levels of sTNFR1 were not significantly associated with impulsivity, in contrast to previous findings of a positive association between circulating TNF mRNA levels and impulsivity among individuals with suicidal behavior (21). These disparities may indicate a relationship specific to certain populations, characterized by high substance use, suicide risk, or other distinct clinical features. Since some key immune markers such as IL-1β or TNF often circulate at levels just above the detection limit of commercially available assays and have relatively short biological half-life, we assessed the activity of IL-1 and TNF systems by using robust markers that are known to reflect the activity of these systems (i.e., sTNFR1, IL-1RA, IL-18, and IL-18BP) (25, 26). However, the observed discrepancy may also be due to disparate sources (e.g., leukocytes, activated vascular endothelium, or fibroblasts) and expression patterns of these immune markers.

One of the strengths of the present study is a large well-characterized sample, which facilitated well-powered analyses of impulsivity levels across diagnostic categories and enabled the focus on associations with psychopharmacological treatment. Moreover, with a hypothesis-driven approach, we investigated candidate immune markers that have emerged across the clinical and experimental research fields. The current study should, however, be interpreted in light of its limitations. The cross-sectional observational design prevents inferences about causal directions, and the effects of confounding factors cannot be ruled out. We only studied one single measure of impulsivity (i.e., the total score of the BIS-11), which may not fully reflect the multifaceted construct of impulsivity (7). Furthermore, we used the prescribed dose of psychotropic medication as a proxy of the exposure to the psychotropic agent and thus were not able to account for possible pharmacokinetic influences or treatment non-compliance.

Conclusions

We show elevated impulsivity across BD and SCZ disorders but no significant associations between impulsivity and circulating immune markers within TNF and IL-1 superfamilies or RANTES. Interestingly, we found a significant negative relationship between impulsivity and lithium and a positive association with antidepressant treatment. Future investigations in clinical settings are warranted to determine the causal mechanisms of the observed associations between lithium and antidepressants and impulsivity.

Declarations

Ethics approval and consent to participate

The work was carried out in accordance with the Declaration of Helsinki, and all participants have given written informed consent. The TOP study is approved by the Regional Ethics Committee, the Norwegian Directorate of Health, and the Norwegian Data Protection Authority.

Consent for publication

Not applicable. The current study does not display any individual person's data.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

Competing interests

OAA is a consultant for HealthLytix and received speaker's honorarium from Lundbeck and Sunovion. All the other authors declare that they have no competing interests.

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Authors' contributions

GH, UKH, NES, and LMJ designed the study with help from JR, RH, and NT. UKH, OAA, IM, and TVL acquired the funding. GH, AS, CB, TFV, MCFW, SHL, MBEGO, ITJ, SD, and TU participated in data collection including analyses of biological samples. GH performed the statistical analyses. GH wrote the first draft with help from UKH, NES, and LMJ. All authors critically revised and approved the manuscript.

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List of abbreviations

BD: bipolar disorder diagnosis

BIS-11: Barratt Impulsiveness Scale

CDSS: Calgary Depression Scale for Schizophrenia

CRP: C-reactive protein

DDD: defined daily dose

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition

ELISA: enzyme-linked immunosorbent assay

GAF-F: Global Assessment of Functioning Split Version

IL: Interleukin

IL-1RA: Interleukin-1 receptor antagonist

IL-18BP: IL-18 binding protein

PANSS: Positive and Negative Syndrome Scale

RANTES: Regulated on activation normal T cell expressed and secreted

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

SCZ: schizophrenia or schizophreniform disorder diagnosis

sTNFR1: soluble TNF receptor 1

TNF: Tumor necrosis factor

TOP: Thematically Organized Psychosis

YMRS: Young Mania Rating Scale

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