UPPSALA UNIVERSITET

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1793

Immunometabolic patterns in psychiatric disease

MIKAELA SYK

ACTA UNIVERSITATIS UPSALIENSIS UPPSALA 2021

ISSN 1651-6206
ISBN 978-91-513-1351-1
URN urn:nbn:se:uu:diva-459466

Dissertation presented at Uppsala University to be publicly examined in Humanistiska teatern, Engelska parken, Thunbergsvägen 3, Uppsala, Thursday, 20 January 2022 at 09:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English. Faculty examiner: Professor Brenda Penninx (Amsterdam UMC).

Abstract

Syk, M. 2021. Immunometabolic patterns in psychiatric disease. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1793. 74 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-1351-1.

Many forms of immune system dysregulation are linked to psychiatric disorders. This thesis examines specific types of immune dysregulation in broad cohorts with psychiatric disease. The first section focuses on adipokines and other immunometabolic biomarkers and their interaction with state vs. trait symptoms. Direct-acting autoantibodies are an increasingly recognized mechanism for causing psychosis and obsessive-compulsive disorder, but it is unclear how prevalent this patient group is. To identify which patients to investigate more extensively, superior methods are needed. Therefore, the second section addresses the value of clinical red flags in predicting elevated central nervous system (CNS) damage biomarkers and other CNS pathology.

In paper I-III, a psychiatric cohort of young adults was examined for plasma immunometabolic biomarkers, depressive symptom severity, bulimia nervosa and neurotic traits. Psychiatric diagnoses were based on diagnostic interviews while depressive symptom severity was assessed with the self-rating version of the Montgomery-Åsberg Depression Rating Scale. Personality traits were evaluated using the Swedish universities Scales of Personality. Young adults with higher leptin levels self-reported more severe depressive symptoms (paper I) and leptin levels were independently linked to neuroticism (paper III). Neuroticism was also linked to other immunometabolic alterations. Women with bulimia nervosa had elevated plasma adiponectin levels that remained stable over time (paper II), suggesting long-term metabolic changes.

In paper IV, a psychiatric patient cohort enriched for clinical signs of suspected autoimmune psychiatric disease was investigated for psychiatric symptoms, neurological findings and signs of CNS pathology in radiological, neurophysiological, blood and CSF analyses. In this cohort, 27% had CSF signs of CNS tissue damage and 21% had CSF signs of neuroinflammation or blood-brain barrier dysfunction. Six percent had known anti-neuronal autoantibodies in serum and 2% in CSF. CNS damage biomarkers in CSF were also linked to red flags and specific psychiatric features.

In summary, the thesis confirms different patterns of immunometabolic biomarkers and associations with trait and state symptoms in a psychiatric patient cohort that may have important implications for the future health of young adults with psychiatric morbidity. The final study supports clinical red flags in previous guidelines, indicating that a more comprehensive inclusion of patients with diverse psychiatric symptoms (not restricted to purely psychosis) is necessary to find all psychiatric patients requiring further investigation for immune system involvement.

Keywords: Psychiatry, Human, Autoimmunity, Cytokines, Inflammation, Adiponectin, Leptin, CNS damage, NfL, Tau, GFAp, Biomarkers, Depression, Neuroticism, Bulimia nervosa

Mikaela Syk, Department of Neuroscience, Cervenka: Psychiatry, Akademiska sjukhuset, ingång 10, Uppsala University, SE-75185 Uppsala, Sweden.

ISSN 1651-6206
ISBN 978-91-513-1351-1
URN urn:nbn:se:uu:diva-459466 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-459466)

“Sometimes, the answers we need don’t match the questions we’re asking.”
— *Brandon Sanderson, Skyward*

To my family

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Syk, M., Ellström, S., Mwinyi, J., Schiöth, H.B., Ekselius, L., Ramklint, M., Cunningham, J.L. (2018) Plasma levels of leptin and adiponectin and depressive symptoms in young adults. *Psychiatry Research*, 272, 1-7.

II. Syk, M., Ramklint, M., Fredriksson, R., Ekselius, L., Cunningham, J.L. (2017) Elevated total plasma adiponectin is stable over time in young women with bulimia nervosa. *European Psychiatry*, 41, 30-36.

III. Syk, M., Isaksson, J., Rasmusson, A.J., Ekselius, L., Cunningham, J.L. (2021) Neuroticism is positively associated with leptin/adiponectin ratio, leptin and IL-6 in young adults. *Scientific Reports*, 11, 9690.

IV. Syk, M. and Malmström, E., Gallwitz, M., Fällmar, D., Amandusson, Å., Rothkegel, H., Danfors, T., Thurlin, M., Rasmusson, A.J., Cervenka, S., Bodén, R., Nilsson, B.M., Burman, J., Cunningham, J.L. Biological markers for CNS damage in a patient cohort with suspected autoimmune psychiatric disease. *Manuscript*.

Scientific papers not included in the thesis

1. Söderquist, F., Syk, M., Just, D., Kurbalija Novicic Z., Rasmusson, A.J., Hellström, P.M., Ramklint, M., Cunningham, J.L. (2020) A cross-sectional study of gastrointestinal symptoms, depressive symptoms and trait anxiety in young adults. *BMC Psychiatry*, 20:535.

2. Bhandage, A.K., Cunningham J.L., Jin, Z., Shen, Q., Bongiovanni, S., Korol, S.V., Syk, M., Kamali-Moghaddam, M., Ekselius, L., Birnir, B. (2019) Depression, GABA and Age Correlate with Plasma Levels of Inflammatory Markers. *International Journal of Molecular Sciences*, 20 (24).

Contents

Abbreviations

α	Alpha
AdipoR	Adiponectin receptor
AgRP	Agouti-related protein
AMPAR	α-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid receptor
AMPK	AMP-activated protein kinase
AQ	Albumin quotient
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
BFCRS	Bush Francis Catatonia Rating Scale
BMI	Body mass index
BPRS-E	Brief Psychiatric Rating Scale-Expanded
CART	Cocaine- and amphetamine-regulated transcript
CGI	Clinical Global Impression
CNS	Central nervous system
CRP	C-reactive protein
CSF	Cerebrospinal fluid
DSM	Diagnostic and Statistical Manual of Mental Disorders
EDE-Q	Eating Disorder Examination Questionnaire
EEG	Electroencephalogram
ELISA	Enzyme-linked immunosorbent assay
GABA	Gamma-aminobutyric acid
GFAp	Glial fibrillary acidic protein
GLzM	Generalized linear model
HMW	High molecular weight
HPA-axis	Hypothalamic-pituitary-adrenal axis
IDO	Indoleamine 2,3-dioxygenase
IFN	Interferon
IL	Interleukin
L/A	Leptin/adiponectin
LGI1	Leucine-rich Glioma Inactivated 1
LMW	Low molecular weight
M.I.N.I.	Mini International Neuropsychiatric Interview
MADRS-S	Montgomery-Åsberg Depression Scale (self-rating version)
MAPK	Mitogen-activated protein kinase
MDD	Major depressive disorder
MHC	Major histocompatibility complex

MMW	Middle molecular weight
MRI	Magnetic resonance imaging
NfL	Neurofilament light protein
NLRP3	NLR family pyrin domain containing protein 3
NMDAR	N-methyl-D-aspartate receptor
NPY	Neuropeptide Y
OCBs	Oligoclonal bands
OCD	Obsessive-compulsive disorder
POMC	Proopiomelanocortin
PPAR	Peroxisome proliferator-activated receptor
PRR	Pattern recognition receptor
RIA	Radioimmunoassay
SCID-I	Structural Clinical Interview for DSM IV axis I disorders
SLE	Systemic lupus erythematosus
SSP	Swedish universities Scales of Personality
STAT	Signal transducer and activator of transcription
t-Tau	Total Tau
TNF	Tumor necrosis factor
T2DM	Type 2 diabetes mellitus
UIP	Uppsala Immunopsychiatry cohort
UPP	Uppsala Psychiatric Patient samples
VGKC	Voltage gated potassium channel
WAT	White adipose tissue
WBC	White blood cell count
5-HT	5-hydroxytryptamine (Serotonin)

Introduction

Contemplating psychiatric disease

"What is psychiatric disease?" This is a simple yet important question without a straightforward answer. As is implied in the name (*psyche*; soul/mind/spirit), psychiatric disorders are commonly defined as disorders of the mind. However, this statement immediately invokes the follow-up question: what is the mind? And is the mind really a separate entity unconnected to the physical body? Historically, there has been disagreement in psychiatry on whether psychiatric disorders should be characterized as disorders of the mind or the brain. However, another common viewpoint is that they are actually both – disorders of the mind and the brain (1).

One definition of the mind is the part of intellect and consciousness that we experience as thoughts, cognitive processes, perception, memory, emotion, will and imagination (2). Because these complex functions could be considered vital aspects of our very beings, as well as fundamental for our ability to interact and adapt to the world, it makes sense that dysfunction of mental processes can result in severe suffering and impairment. In fact, psychiatric disease is one of the most common causes for years lived with disability. Moreover, it contributes significantly to premature morbidity and mortality (3).

From a neuroscientific perspective, it is difficult to explain mental processes apart from neural processes. Therefore the mind is often regarded as an epiphenomenon arising from the complex signaling and organization of the central nervous system (CNS) (1). Neuroscientific evidence shows that alterations to the CNS can influence a person's mental state (2). For example, it is well known that traumatic and neurodegenerative damage to the CNS can have far-reaching effects on our mental processes: from how we think and feel to how we perceive and interact with the world. Similarly, psychotropic substances (e.g., antipsychotic medication or psychedelic drugs) can alleviate and cause psychiatric symptoms (e.g., hallucinations). Conversely, primarily mental experiences such as exposure to psychologically traumatic events can alter neural circuits in the brain (1).

Despite the many scientific advancements, the causes of psychiatric disorders remain largely unknown. In more developed areas of medicine, objective tests are used to identify the cause of a specific disease state (3). In contrast, our current lack of insight into the etiology and pathophysiology of

psychiatric disease and the lack of biomarkers, means that psychiatric disorders remain syndrome diagnoses based on a collection of symptoms (3). This lack of knowledge leads to a catch 22 situation for psychiatric research in the sense that we need accurate and specific diagnostic criteria to find precise biomarkers/tests and precise biomarkers/tests to establish accurate and specific diagnostic criteria. So, at which end do we begin? With the biological correlate or the psychopathology?

Either way, the complexity of psychiatric disease makes psychiatric research both daunting and inspiring. Still, we must continue to face its challenges to find better treatment options and preventive measures for psychiatric disorders.

Homeostasis

For our body to remain healthy and functional, its internal environment needs to be kept in balance. That is to say, the conditions inside the body (e.g., our temperature or blood sugar levels) need to be kept relatively stable around a physiologically optimal set-point. The active maintenance of this stability is called homeostasis.

Like a pendulum, the internal conditions of our body can be temporarily moved away from their optimal set-point as an adaptive response to environmental disturbances. However, the system should then be capable of resetting, or we risk illness or death. For example, our blood pressure should increase in response to acute stress to improve our capacity to fight or escape danger. However, when the threat is over, blood pressure should return to normal physiological levels, or it may cause damage to the body.

Because of its importance for survival, homeostasis is tightly controlled by regulatory mechanisms such as negative feedback loops. For example, high blood sugar levels will trigger the pancreas to release insulin into the blood. Insulin will make the cells take up more sugar from the blood, decreasing blood sugar levels until they return to normal.

If the regulatory mechanisms fail or become too strong, homeostasis cannot be maintained. For example, in individuals with type 2 diabetes mellitus (T2DM), the cells become less responsive to insulin, subsequently allowing blood sugar levels to continue rising instead of returning to normal. In contrast, too much insulin will cause dangerously low blood sugar levels (hypoglycemia). Typically, too little or too much of an internal variable (e.g., blood sugar levels) can damage the body if maintained over time. This thesis will focus on the imbalance in inflammatory and metabolic homeostasis as it pertains to psychiatric disease.

Inflammation

Inflammation is a defensive mechanism that can be defined as the body's immune response to various stimuli (e.g., pathogens or tissue damage). The primary purpose of inflammation is to protect the body from internal and external threats such as invading pathogens and injury. The immune system has a broad spectrum of functions, including localizing and eliminating the threat, removing the damaged debris and mediating tissue repair.

Inflammation is orchestrated and regulated by cytokines and chemokines. Cytokines are soluble messenger molecules involved in cell-to-cell communication, usually connected to the immune response. Cytokines bind to receptors on the membranes of target cells, triggering signaling pathways that subsequently change key enzyme activity and gene expression. The release of these soluble messenger molecules creates gradients that guide cell navigation. The temporal production of different molecules in combination also induces shifts in cell phenotypes and functions. Inflammation involves a cascade of cytokine signaling that leads to the activation of innate and adaptive immune cells as well as changes to the endothelial cells lining the interior surface of blood vessels. This cytokine signaling enables the rapid recruitment of activated immune cells to the invaded or damaged area.

The inflammatory response is normally brief and resolves after the danger has been averted. However, when the mechanisms regulating the inflammatory response are defective, or its ability to clear the damaged tissue or foreign materials is impaired, the inflammatory response can be prolonged and cause damage to cells and tissue. An inflammatory response lasting for a prolonged period, sometimes months or years, is usually referred to as chronic inflammation. Chronic inflammation is typically characterized by continuously elevated levels of pro-inflammatory cytokines that can damage the body.

Autoimmunity

Sometimes the immune system mounts a defensive response against the organism itself and its healthy tissues or cellular components. This is referred to as autoimmunity. Typically, autoimmunity is an adaptive immune response involving self-reactive T cells and autoantibodies (made by B cells) that target normal elements of an organism (autoantigens). The autoimmune response can range from the manifestation of low levels of circulating autoantibodies without clinical consequences to pathogenic autoimmunity, where the immune system attacks the organism in a way that causes disease.

Immunometabolic interactions

Metabolism provides the body with essential building blocks (proteins, lipids, carbohydrates etc.) and the energy required to run cellular processes. In turn, the immune system defends our bodies against tissue damage and pathogen invasion (4). Considering their essential functions, it is not surprising that various immune and metabolic response pathways and their interactions have been evolutionarily conserved (4).

Overall, the key regulators of immune and metabolic functions in mammals have evolved from shared ancestral structures (4). It has likely been a potent evolutionary advantage to have a strong defence against pathogens, which in turn requires access to energy reserves. As a consequence, immune response and metabolic regulation are highly integrated (4).

White adipose tissue (WAT) is a central site for crosstalk between the immune and metabolic response systems (5). In addition to its role in energy storage and mobilization, WAT is an endocrine and immunological organ that contains various cell types, including resident immune cells (5). White adipocytes produce a large number of adipocyte-specific signaling molecules (adipokines), including but not limited to leptin and adiponectin (5). Adipokines regulate metabolic homeostasis by autocrine and paracrine signaling in the adipose tissue and endocrine signaling with distal organs (e.g., the brain, the liver and skeletal muscle) (5). Many adipokines also have immunoregulatory effects (5).

Integration of the immune and metabolic signaling transpires at various levels, including gene expression, the organelles, the receptors and the kinase pathways (4). In general, many metabolic and immune signaling molecules have both immune and metabolic responses (4).

As an example of the integration between immune and metabolic signaling, pattern recognition receptors (PRRs) are expressed in both innate immune cells and metabolic cells such as hepatocytes and adipocytes (6). PRRs are essential for the function of the innate immune system as they detect pathogens and endogenous stress signals (6). When activated, the PRRs promote local and systemic inflammation as well as insulin resistance (6). In line with this, septic shock is associated with severe insulin resistance (6).

Another example of immunometabolic interactions is the NLR family pyrin domain containing 3 (NLRP3) inflammasome (6). The NLRP3 inflammasome can be activated by pathogen components as well as metabolic stressors. When activated, the inflammasome cleaves pro-IL-1β and pro-IL-18 into their bioactive forms, which initiates an inflammatory response. In addition to its pro-inflammatory effects, bioactive IL-1β contributes to insulin resistance (6).

Recent studies further indicate a link between obesity and alterations to the adaptive immune system. For example, a positive association between regulatory T cells and insulin sensitivity is described in rodent obesity models. Obese mice and humans also have an influx of CD4+ and CD8+ T cells in the

adipose tissue (4). Obesity is also associated with abnormal B lymphocyte function and the production of pathological immunoglobulins and autoantibodies (4, 7, 8). In line with these findings, epidemiological studies indicate obesity is a risk factor for autoimmune disease (7, 9).

Overall, dysfunctional cooperation between the immune and metabolic systems can lead to chronic inflammation and metabolic dysregulation (e.g., insulin resistance), which can, in turn, contribute to the development of metabolic disorders (e.g., obesity, T2DM) and cardiovascular disease (4).

Neuro-immune communication

Immune cells regulate the microenvironment homeostasis of the CNS, which is essential for its functionality. Dysregulation of the microenvironment homeostasis can impact aspects often affected in individuals with psychiatric disorders, such as mood, stress responses, cognitive function and behavior (10).

Under physiological conditions, immune cells in the CNS are mainly innate immune cells (e.g., microglia and other tissue-specific macrophages). However, peripheral adaptive and innate immune cells enter the CNS when the blood-brain barrier (BBB) is impaired (10).

Progenitors of microglia migrate to the CNS during perinatal development before the creation of the BBB (11). In the CNS, microglia function as the brain's constant gardeners. They survey the CNS for damage and danger signals, remove redundant and dead neurons, axons and synapses and eliminate pathogens and other targets that may endanger the CNS (11). In line with this, a growing body of evidence suggests that microglia play an important role in neurodevelopment, neurogenesis, synaptic plasticity, maintenance of neuronal networks and injury repair (11). Microglia are also central mediators of neuroinflammation (11).

Recent findings indicate a bilateral communication between the peripheral immune system and the peripheral nervous system. Immune cells release substances with neurotransmitter or neuromodulator functions and neurons express cytokine receptors and PRRs, enabling pathogens and active immune cells to trigger or alter afferent neural signaling. In turn, efferent neural activity influences the immune response. For example, vagus nerve stimulation suppresses circulating tumor necrosis factor (TNF) levels (12).

The immune system, the brain and the mind– partners in crime in psychiatric disease?

An increasing body of evidence indicates a link between the immune system, especially chronic inflammation and autoimmunity, and major psychiatric disorders, including major depressive disorder (MDD), schizophrenia and obsessive-compulsive disorder (OCD) (13, 14).

It has long been acknowledged that psychiatric manifestations can accompany infections (15). These observations are supported by contemporary epidemiological studies showing an increased risk of psychiatric disorders after infections (16). Further linking the immune system with psychiatric disease, comorbid autoimmune disorders are overrepresented in patients with psychiatric disorders (17-19). Elevated levels of pro-inflammatory cytokines and acute phase reactants are also observed in patients with various psychiatric disorders, including acute psychosis, depression and OCD (13, 14, 20). Schizophrenia is also associated with genes involved in the adaptive immune system and the major histocompatibility complex (MHC) (13).

Autoimmune encephalitis, a neuroinflammatory condition secondary to autoantibodies targeting antigens in the CNS, can also present with cognitive and psychiatric symptoms in addition to the more classical neurological symptoms (21). Several case studies suggest that milder forms of autoimmune encephalitis may present with mainly or exclusively psychiatric symptoms (22, 23). These observations have led to concern that patients with autoimmune encephalitis with mainly psychiatric manifestations may sometimes be misdiagnosed with a primary psychiatric disease (24), affecting prognosis due to delayed initiation of immunotherapy (25-27). To better identify patients with autoimmune encephalitis with mainly psychiatric features, different authors have proposed a variety of clinical red flags that should raise suspicion of CNS autoimmunity and lead to further investigation (28-30). However, these clinical red flags are yet to be validated.

Despite a growing interest in the potential role of autoimmunity and neuroinflammation in psychiatric disease, knowledge is still lacking regarding anti-neuronal antibodies and abnormal immunological findings in cerebrospinal fluid (CSF) in psychiatric patients. However, contrary to the fear of missing patients with primarily psychiatric features, established anti-neuronal antibodies in serum and CSF are only rarely found in patients with psychiatric disorders (31, 32). Still, it can be speculated that autoimmune psychiatric disease may be associated with other autoantibodies than the ones found in patients with classical (mainly neurological symptoms) autoimmune encephalitis. Supporting this idea, a few studies using tissue-based assays suggest that some seronegative psychiatric patients with suspected CNS autoimmunity may have autoantibodies targeting novel unknown targets in the CNS (23, 31).

In summary, new data are emerging from the growing research field of Immunopsychiatry that could help identify subgroups of psychiatric patients who could potentially benefit from immunomodulatory treatment.

CNS damage biomarkers

When neurons, axons and glial cells are damaged in the CNS, various proteins are released from the damaged area into the CSF and blood (33). Elevated levels of these proteins can often be detected in the CSF before clinical symptoms manifest or brain imaging shows signs of structural damage, making them potentially useful for identifying diffuse CNS damage and early CNS disease states (33).

Neurofilament light (NfL) and tau proteins are examples of cytoskeletal constituents of neuronal cells and axons that reflect ongoing neuronal and axonal damage when measured in CSF or blood (33). This makes them useful as biomarkers of disease and disease progression of inflammatory and non-inflammatory disorders associated with CNS damage. For example, NfL and tau proteins are used as biomarkers of traumatic brain injury, neurodegenerative disorders (e.g., Alzheimer's disease) and neuroinflammatory disorders (e.g., multiple sclerosis) (33, 34). NfL especially reflects damage to large-caliber myelinated axons, whereas total Tau (t-Tau) is a biomarker of damage to thin non-myelinated axons (34).

Neuronal autoantibodies may be related to CNS damage. Elevated t-Tau and NfL levels have for example been reported in patients with autoimmune encephalitis and may have implications for the clinical outcome (35). In the light of this, CNS damage biomarkers may be of potential interest for identifying psychiatric patients for whom autoimmune or neurodegenerative processes contribute to the disease state.

Blood or CSF biomarkers can also be used to assess other forms of CNS pathology than neuronal and axonal loss. For instance, elevated Glial fibrillary acidic protein (GFAp) levels indicate astrocyte pathology (activation, astrogliosis or astrocyte damage). GFAp is the main intermediate filament protein in mature astrocytes. It plays a vital role in supporting the astrocyte's cytoskeleton structure and its coordination of neuronal activity, promotion of synaptic plasticity and synaptic homeostasis of neurotransmitters. GFAp is also a critical factor in astrocytes' ability to maintain an intact BBB (36). When faced with basically any CNS pathology (including neuronal damage), astrocytes increase their expression of GFAp (61, 62), which subsequently results in elevated levels of GFAp in the CSF (36).

Despite brain imaging studies indicating signs of brain atrophy and neurodegeneration in major psychiatric disorders such as schizophrenia and MDD (37, 38), studies investigating biomarkers of CNS damage in a psychiatric population are rare (35, 39-43). Still, the number is growing. For

example, two recent studies observed a positive association between unipolar depression and GFAp levels in serum and CSF (43, 44).

Considering that elevated CNS damage biomarkers generally reflect an ongoing damage process, the timing of the measurement may be of importance. Therefore, it can be speculated that biomarker levels of CNS damage may sometimes be elevated only in the acute or preclinical state of a psychiatric disorder and not later in the disease progression. That is, the damage may already be done when the patient is investigated in psychiatric care and therefore not reflected in the blood or CSF.

Depression and inflammation

MDD is a common psychiatric disorder with a large disease burden (45-47). Core symptoms of depression are dysphoria, apathy and anhedonia. Other depressive symptoms include affected cognition, psychomotor activity, sleep and appetite (48). Traditional theories of the pathomechanisms of depression include a disruption of the monoamine neurotransmitter signaling, the hypothalamic-pituitary-adrenal (HPA)-axis, neurogenesis or neurotrophic factor regulation (49). Still, the mechanisms behind the etiology and pathophysiology of depression remain incompletely understood and a substantial proportion of patients with depression have a suboptimal response to standard treatment (49).

In the past decade, increasingly compelling evidence has been suggesting that immune dysregulation, especially chronic low-grade inflammation, may play a role in the pathophysiology of depression, at least for a subgroup of patients (13, 50). In support of this theory, MDD is often comorbid with disease conditions associated with chronic inflammation, such as rheumatoid arthritis and cardiovascular disease (13, 51). Furthermore, several systematic reviews and meta-analyses of cross-sectional studies corroborate that depressed patients have altered levels of pro-inflammatory cytokines, acute-phase reactants, chemokines and soluble adhesion molecules in peripheral blood and CSF compared to healthy controls (13, 50, 52-54). Particularly interleukin-6 (IL-6), IL-1β, TNF-α and CRP are repeatedly reported to be elevated in patients with MDD (13, 50, 53, 54). Imaging studies also observe associations between inflammation and activity alterations in brain regions important for motivation, reward, sensitivity to aversive stimuli and anxiety (50).

Although it remains undetermined whether chronic inflammation is a cause or consequence of depression, increasing evidence suggests that inflammation can cause depressive symptoms. For example, some longitudinal studies show that elevated circulating levels of IL-6 and CRP in childhood increase the risk for developing depressive symptoms in adulthood in a dose-respondent manner (13). Sickness behavior induced by pro-inflammatory cytokines also

resembles depression and interferon-alpha (INF-α) treatment induces MDD in 25% of cases, suggesting causal mechanisms (55-57). Administration of inducers of pro-inflammatory cytokines, such as endotoxin, to non-depressed individuals also causes temporary depressive symptoms (50, 57). Of note, several studies indicate that antidepressants have immunomodulating effects and that inflammation might undermine treatment response to antidepressants (50, 53, 58-62).

While much evidence suggests inflammation is involved in the pathophysiology of depression, elevated inflammatory markers might not be specifically related to the diagnosis itself. Inflammation might instead be associated with a depression subtype or symptom dimensions that are important for depression but exist across diagnoses, such as altered motivation and motor activity (anhedonia, fatigue, psychomotor impairment) and increased threat sensitivity (anxiety, arousal, alarm).

Inflammation might also be a shared underlying mechanism for various chronic disease states, not just psychiatric disorders, which are often comorbid with each other: For example, depression, schizophrenia, cardiovascular disease, obesity and T2DM. In support of this transdiagnostic dimensional theory, studies observe elevated inflammatory markers also in patients with other psychiatric disorders (50, 63, 64).

Potential mechanisms linking inflammation and depression

Little is known about the mechanisms linking depression to inflammation. A number of suggested mechanisms based on preclinical studies are, however, worth mentioning. First, an inflammatory response in peripheral tissues may affect the CNS in several ways, such as modulation of peripheral nerve signals, transport of cytokines across the BBB or trafficking of activated immune cells to the CNS (50).

Second, inflammation affects neurotransmitters important for mood regulation, such as serotonin. For example, activation of the enzyme indoleamine 2,3-dioxygenase (IDO) by pro-inflammatory cytokines increases the metabolism of the serotonin precursor tryptophan into kynurenine. Kynurenine can in turn be transformed into a neurotoxic metabolite called quinolinic acid by activated macrophages and monocytes in the brain. Quinolinic acid promotes glutamate release, which contributes to excitotoxicity and decreased production of brain-derived neurotrophic factor (BDNF), which is important for neurogenesis (50).

The inflammatory response can also disrupt the function of the glucocorticoid receptor, which can cause a subsequent hyperactivation of the HPA-axis. Hyperactivation of the HPA-axis is a common finding in patients with depression. If sustained over time, it may lead to neuronal damage in brain regions relevant for mood regulation and cognition due to long-term exposure to cortisol (65).

Furthermore, the NLRP3 inflammasome might be involved in the inflammation-depression link. In support of this, preclinical studies describe an upregulation of the expression of NLRP3 and caspase-1 in peripheral blood mononuclear cells of patients with depression (50). The NLRP3 inflammasome may contribute to the pathophysiology of depression through increased production of pro-inflammatory cytokines, increased insulin resistance and subsequently altered cerebral metabolism or chronic activation of the HPA-axis through cleavage of the glucocorticoid receptor (65).

Depression at the interface of immunometabolic dysregulation

In addition to chronic low-grade inflammation, depression is also associated with dysregulation of metabolic homeostasis (e.g., insulin resistance), supporting a role for immunometabolic dysregulation in depression (65, 66). Strong epidemiological evidence shows a bilateral link between obesity and depression, with each increasing the risk of the other, which is not fully explained by life-style factors or antidepressant medication (65). Recent studies further suggest that depression and obesity-related traits have a partially overlapping genetic base (65).

Possible shared biological mechanisms for these conditions include hyperactivation of the HPA-axis, chronic low-grade inflammation, dysregulation of adipokines (e.g., leptin), and other factors regulating energy homeostasis (65, 66). All these potential biological mechanisms can cause damage to cerebral regions relevant for mood and behavior, such as the hippocampus and the amygdala. They are also interconnected, which could contribute to a vicious cycle of adverse physiological adaptations (65). Moreover, it is important to consider that many behavioural and psychosocial factors that increase the risk for immunometabolic dysregulation and obesity are also common in patients with a depressed state (66). These factors include but are not limited to smoking, alcohol use, poor nutrition, poor sleep, low physical activity and socioeconomic status (66).

Several studies suggest that obesity and immunometabolic dysregulation may be specifically linked to atypical depressive symptoms, particularly increased appetite and weight gain (65, 66).

Leptin

Leptin, general aspects

The discovery of the hormone leptin (derived from the Greek word leptos for “thin”) in 1994 by Friedman and colleagues was a breakthrough for the understanding of energy homeostasis (67) and confirmed the theory that the adipose tissue is an endocrine organ (67).

Leptin is mainly synthesized in WAT, encoded by the LEP gene (68). In humans, leptin expression is greater in subcutaneous adipose tissue, whereas in rodents it is greater in visceral fat (69). Leptin is also synthesized in the placenta, ovaries, bone marrow and mammary epithelial cells in humans (70).

Leptin expression is correlated to adipocyte size, with larger adipocytes expressing more leptin (70). Levels of circulating leptin are in turn proportional to adipose tissue size and body mass index (BMI) (68, 70). Women have higher leptin concentrations than men. Whether sex hormones lead to the higher leptin concentrations in women is still controversial, although a study on murine adipocytes indicates a direct effect of sex steroid hormones on leptin transcription accumulation and secretion (70, 71). Other factors increasing human circulating leptin levels are overfeeding, impaired renal function, insulin, glucocorticoids, pro-inflammatory cytokines and alcohol (70).

Animal models show that the sympathetic nervous system tightly regulates the activity of adipocytes, including the synthesis and secretion of leptin (69). In response to fasting or cold exposure, the sympathetic tone to WAT increases, causing a decrease in circulating leptin levels (69). Fasting reduces circulating leptin levels by about 60-70% in obese and normal-weight humans (69). Other factors decreasing circulating leptin levels in humans are long-term exercise, lack of sleep and smoking (70, 72). Human leptin secretion has a circadian rhythm, peaking between 2:00 and 3:00 am (72).

Although leptin signaling typically occurs through the downstream targets signal transducer and activator of transcription (STAT)-3, STAT-5 and mitogen-activated protein kinase (MAPK), it has also been suggested to act through the phosphoinositide 3-kinase (PI3K) and AMP-activated protein kinase (AMPK) pathways (68, 69, 72). The leptin receptor is expressed widely in the CNS in humans, including the hypothalamus, the cerebellum, neocortex, amygdala and cranial nerve nuclei (73). Leptin is transported across the BBB by a regulated saturable transport system (68, 74).

Higher circulating leptin levels are common in individuals with obesity and can be regarded as a marker for leptin resistance. Different mechanisms of leptin resistance have been suggested. Some examples include genetic mutations causing secretion of leptin with ineffective signaling, self-regulation through leptin-induced receptor downregulation, limited tissue access through saturation of the transport across the BBB or cellular and circulating molecules that suppress leptin signaling or prevent leptin from binding to its receptor (75).

Consequences of leptin signaling

The key function of leptin is to regulate energy homeostasis, but there is increasing evidence that leptin is a hormone with multiple functions in various tissues, both in the periphery and the CNS (69, 70, 72). For example, studies

suggest that leptin influences reproductive functions, bone metabolism, cognitive function, normal brain development, innate and adaptive immunity and the HPA axis (68, 70, 72, 76, 77). Higher leptin levels are associated with increased risk of insulin resistance and cardiovascular disease (75).

In the immune system, leptin signaling has a primarily pro-inflammatory effect. For example, leptin promotes phagocytosis in monocytes, up-regulates expression of adhesion molecules and pro-inflammatory cytokine secretion and modulates the activation and proliferation of T cells with a switch towards Th1/Th17 cell immune responses. Leptin levels increase during acute infection and sepsis and some studies also show increased levels of leptin in autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematosus (SLE) (77).

Leptin and depression

Central or systemic administration of leptin in rodents has anti-depressant effects in animal models of depression-like behavior, such as the tail suspension test or forced swim test (47). Several mechanisms have been suggested for how leptin could affect mood, including HPA axis regulation, immunomodulatory effects, increased neurogenesis and neuroplasticity in the hippocampus and the direct targeting of leptin receptors in the CNS (47). In support of a direct impact by leptin receptor signaling, deletion of the leptin receptor in the hippocampus or the prefrontal cortex in mice causes depression-like behavior (47).

However, the results from clinical studies concerning the role of leptin in depression are conflicting. Several studies have observed lower circulating leptin levels in patients with MDD compared to healthy controls (78-81). A few also describe a negative correlation between circulating leptin levels and depressive symptom severity (78, 82). In contrast, other studies show higher leptin levels in individuals with MDD or a lifetime history of depression (83-88). Several studies have also observed a positive correlation between leptin levels and depressive symptom severity (85, 87, 89-91), whereas some studies found no association between leptin levels and depression or depressive symptoms (92-97). A recent meta-analysis observed no difference in leptin levels between groups with and without MDD but described higher leptin levels in a sample of older patients with BMI $\geq$25 and MDD (98).

One explanation for the conflicting results may be the clinical heterogeneity of depression, where separate biological underpinnings could explain different symptom profiles. In line with this view, recent studies report a specific positive association between leptin and atypical depressive features of MDD, especially increased appetite and weight gain (65, 66, 82, 99). Other potential explanations for the conflicting results include between-studies differences in age, sex, recruitment proceedings, choice of assay and depression severity. It is also possible that the relationship between depression

and circulating leptin is nonlinear. In support of this theory, high leptin levels in the periphery may not necessarily reflect high leptin signaling in the CNS. Instead, high levels of leptin in the periphery can be a consequence of leptin resistance (100).

A potential explanation for the discrepancy between preclinical and clinical studies is that all but one clinical study measured leptin in plasma or serum. Although leptin is generally highly correlated between CSF and plasma (101), it can be speculated that leptin resistance may affect the results when leptin is measured only in the periphery (100). In line with the suggested anti-depressive effect of leptin in preclinical studies, a study from Sweden reported lower CSF leptin levels in MDD inpatients with a recent suicide attempt compared to non-MDD inpatients with a recent suicide attempt. The study further reported a negative correlation between CSF leptin and depression severity in women (102).

Another possibility is that the preclinical studies measured other aspects of depression than the clinical studies. Although animal models have proven useful in psychiatric research, they are limited in that they can only assess the behavioral aspects of psychiatric symptoms (103). For example, an animal model can measure depressive behaviors (e.g., social withdrawal) but not assess subjective feelings of sadness, thoughts of worthlessness/guilt or suicidal ideation (103). Animal models can therefore only partially reproduce the state of depression observed in humans. Furthermore, few animal models have been developed to assess atypical depressive features (103).

Adiponectin

Adiponectin, general aspects

Adiponectin is another adipose-derived hormone discovered in the middle of the 1990s. It has received growing attention as a potential therapeutic target in recent years due to its many beneficial health effects. Adiponectin is present in high concentrations in the circulation in three major forms including low molecular weight (LMW) trimers, middle molecular weight (MMW) hexamers and high molecular weight (HMW) multimers (104-108). A globular fraction of full-length adiponectin can also be created with proteolytic cleaving in the circulation (105, 109).

The different forms of adiponectin have distinct biological properties and do not interconvert once they are in the circulation (107, 108). They also have a varying affinity to the two major adiponectin receptors: AdipoR1 and AdipoR2 (105). AdipoR1 has a higher affinity for globular adiponectin and AdipoR2 has a preference for HMW adiponectin (110). Downstream signaling of AdipoR1 and AdipoR2 is mediated mainly by activation of the AMPK, MAPK and peroxisome proliferator-activated receptor (PPAR)-α

signaling pathways (105). T-cadherin is considered a third receptor for adiponectin, but less is known about its effects (110). Expression of adiponectin receptors is described in various tissues, including adipose tissue, skeletal muscle, the liver, the myocardium, endothelial cells, macrophages, lymphocytes and the brain (111).

Adiponectin is constitutively produced and reported concentrations in plasma or serum vary between 0.5-30 μg/ml (104, 106, 109). However, there is presently no precise determination of what constitutes physiological levels of adiponectin in serum or plasma. Even though the degree of degradation of adiponectin is minimal in the circulation, adiponectin has a short plasma half-life of approximately 45-75 minutes (109). The primary site of adiponectin clearance is the liver (109).

Women have higher peripheral adiponectin concentration than men (105, 106), which might be caused by an inhibitory effect of testosterone on the secretion of HMW from adipocytes (106). Serum levels are also negatively correlated with obesity (105). Other factors important to consider when measuring adiponectin in blood is body fat distribution, renal and cardiac function, smoking, dietary factors and physical exercise (112). Several medications (e.g., statins and several blood pressure medications) and weight loss increase adiponectin levels (105-107, 113). Oxidative stress, endoplasmic reticulum stress, B-adrenergic agonists and sympathetic nervous system stimulation, pro-inflammatory cytokines (IL-6, TNF-α) and testosterone decrease adiponectin levels (105, 106, 108, 113).

Adiponectin is present in CSF and its receptors are expressed in the human pituitary, hypothalamus and hippocampus (108, 114-119). Adiponectin is known to pass the BBB in rodents (120) and adiponectin may also cross the BBB in humans (119). However, CSF concentrations of adiponectin are approximately 1000-fold lower in CSF than in serum (121).

Consequences of adiponectin signaling

Like most hormones, adiponectin has various and sometimes tissue-selective functions. In the periphery, adiponectin signaling leads to increased insulin sensitivity, increased glucose consumption and decreased gluconeogenesis and glycogenolysis. Together, these effects reduce blood sugar levels and protect the body against the development of T2DM. Adiponectin signaling also increases fatty acid oxidation and promotes the accumulation of lipids in adipocytes instead of hepatocytes, decreasing circulating lipid levels and ectopic lipid storage (105-108). Adiponectin is also described to have anti-atherogenic, antioxidant and mainly anti-inflammatory properties (104, 106, 109).

For example, adiponectin decreases the secretion of pro-inflammatory cytokines TNF-α and IL-6 by innate immune cells and promotes their

production of anti-inflammatory cytokines like IL-10 (9). Adiponectin also promotes the activation of dendritic cells, increases the number of regulatory T cells and limits macrophage proliferation and phagocytic activity (9). Surprisingly, some studies observe a more dual role for adiponectin in the immune system, with pro-inflammatory effects in autoimmune disease (9).

Lower peripheral adiponectin levels are associated with insulin resistance, atherosclerotic cardiovascular disease, essential hypertension, metabolic syndrome, obesity, non-alcoholic fatty liver disease, T2DM and dyslipidemia (104, 105, 107, 112). Higher adiponectin levels are associated with chronic renal failure and congestive heart failure (104, 105, 112). Finally, many studies further show a protective role by adiponectin against cancer (110).

Although much remains unknown regarding the role of adiponectin in the CNS, cumulative evidence suggests that adiponectin signaling has central effects. In rodents, adiponectin seems to regulate food intake and energy through AMPK signaling in the hypothalamus (121, 122). Preclinical studies also suggest that adiponectin has neuroprotective effects and promote neurogenesis (120, 121).

Adiponectin and depression

Similarly to leptin, systemic or intracerebroventricular administration of adiponectin in rodents has anti-depressant effects in animal models of depression-like behavior (47). Intracerebroventricular injection of an adiponectin neutralizing antibody also advances stress-induced depressive-like behavior (120, 123). A study in mice further suggests that physical exercise decreases depressive-like behavior and induces hippocampal neurogenesis mediated by adiponectin through AdipoR1-mediated activation of the AMPK pathway (120).

Most clinical studies observed lower circulating adiponectin in patients with MDD (83, 124-128), with some describing an inverse correlation between adiponectin levels and depressive symptom severity (83, 125, 127, 129). On the other hand, some studies reported no association between adiponectin and depression (86, 93, 128, 130-134) and a few studies observed higher adiponectin levels in patients with depression (128). A meta-analysis by Carvalho et al found lower adiponectin levels in patients with MDD than controls when measured with radioimmunoassay (RIA), but not enzyme-linked immunosorbent assay (ELISA) (135). A more recent meta-analysis by Cao et al also observed a negative association between MDD and adiponectin levels, although with a small effect size (98).

Although the accumulating preclinical and clinical findings suggest that adiponectin signaling may protect against depression, little is known about the underlying mechanisms. Based on the known effects of AdipoR1 and AdipoR2 signaling, potential mechanisms could however include neuroprotective effects through decreased neuroinflammation and oxidative

stress, increased hippocampal neurogenesis and direct effects on serotonin transmission (120, 136, 137). In support of the latter, the results of a recent study in mice indicate that adiponectin may directly affect 5-HT neurons through AdipoR1 receptors that influence depression-like behavior in a sex-dependent manner (136).

The role of leptin and adiponectin in eating behavior

One of leptin's main functions is to regulate energy balance by creating a sensation of satiety, as a negative feedback mechanism on energy storage (68). Overfeeding increases peripheral leptin levels in healthy humans and treatment with leptin causes weight loss and reduces food intake in patients with leptin deficiency (76). Similarly, in animal models, leptin signaling causes weight loss and decreases food intake as well as food-related reward (68, 69).

Overfeeding induces leptin expression, which indirectly activates proopiomelanocortin (POMC)/cocaine- and amphetamine- regulated transcript (CART) neurons. Leptin signaling also promotes the expression of anorexigenic neuropeptides POMC and CART (68, 69) in the hypothalamus. Simultaneously, leptin decreases the expression of orexigenic neuropeptides neuropeptide Y (NPY) and agouti-related protein (AgRP) and inhibits NPY/AgRP neurons (68, 69). Leptin signaling also promotes anorexigenic effects independent of hypothalamic signals, i.e. in the nucleus tractus solitarius (68). Moreover, preclinical studies indicate that leptin signaling suppresses food-related reward by influencing the activity of the mesolimbic dopamine system (138). In contrast, starvation decreases leptin signaling (68, 69).

While leptin's role in food intake and energy homeostasis is well studied in animals, less is known about adiponectin. A study by Kubota et al observed a decrease in serum and CSF adiponectin levels in mice after refeeding and an increase during fasting (122). The same study showed that adiponectin increases food intake and reduces energy expenditure in mice through stimulation of the AMPK pathway, enhancement of orexigenic signals in the hypothalamus and inhibition of leptin's suppressing actions on AMPK (122). In contrast, another study observed a decrease in food intake in rats after intracerebroventricular injection of adiponectin (139). A third study reported no effect of adiponectin on food intake in mice (140).

In support of a potential role for adiponectin in human eating behavior, a recent clinical study reported an association between an adiponectin gene variant (ADIPOQ rs1501299) and emotional eating behavior (i.e., a tendency to overeat in response to negative emotions) (141). In line with the observations in mice by Kubota et al, another clinical study indicated that

adiponectin contributes to disinhibited eating behavior but not to restrained eating behavior or hunger (142).

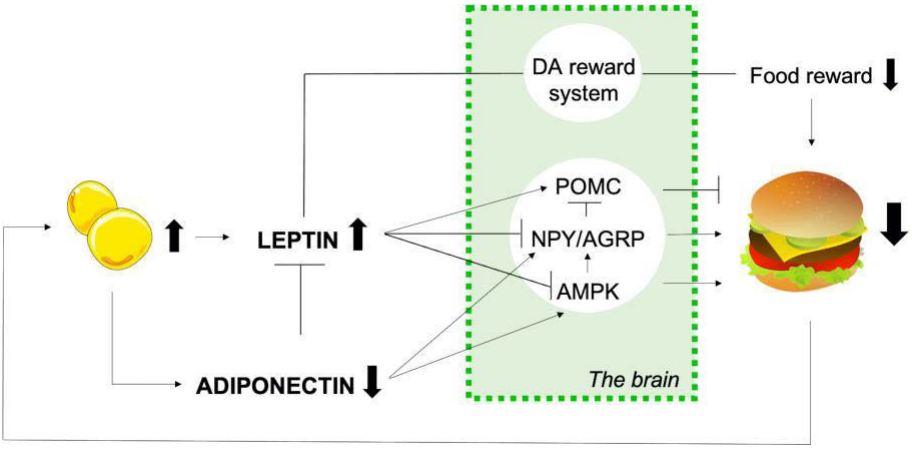

Figure 1. Illustration of the role of leptin and adiponectin in food intake. The thin arrows indicate stimulation/increased signaling and the fat arrows describe the effects of overfeeding. DA = Dopamine.

Leptin, adiponectin and bulimia nervosa

Because of their actions related to energy homeostasis, food-related reward and eating behavior, adipokines have been hypothesized to be involved in the development or maintenance of disordered eating behavior in patients with bulimia nervosa. Bulimia nervosa is an eating disorder characterized by recurrent episodes of binge eating, inappropriate compensatory behavior to prevent weight gain and self-evaluation unduly influenced by body weight or shape (48). The pathophysiology of bulimia nervosa is still mostly unknown. However, emerging evidence suggests that individuals with bulimia nervosa have dysregulation in central and peripheral modulators of appetite and energy homeostasis (143). Still, it remains unclear whether this is a state or trait.

Studies concerning leptin levels in individuals with bulimia nervosa show diverse results, but most observe reduced circulating leptin levels (143-149). Studies investigating circulating adiponectin levels in patients with bulimia nervosa are few, use different methods and have inconsistent and contradictory results (150-152). One study described elevated plasma levels of adiponectin in patients with bulimia nervosa that correlated to the severity of bingeing/purging behavior (150). Another observed reduced serum levels (152) and a third noted no significant difference in serum levels compared to controls (151).

Aims

The overall aim of this thesis was to investigate the role of immune dysregulation in the pathophysiology of psychiatric disease, with a primary focus on adipokines and other molecules involved in the crosstalk between the immune and metabolic response systems.

The specific aims of the thesis listed in number points was to:

I Investigate to what extent plasma levels of leptin and adiponectin are associated with dimensional measures of depressive symptoms in young adults with and without psychiatric disorders.

II Study the association between bulimia nervosa and adipokine levels and their longitudinal variation in patients with bulimia nervosa compared to age-matched patients without psychiatric disorders and controls.

III Examine whether neuroticism is associated with early immunometabolic biomarkers for cardiovascular and metabolic disease in young adults from a psychiatry cohort.

IV i) Describe the prevalence of demonstrable biological CNS pathology in a psychiatric patient cohort enriched for clinical red flags of suspected autoimmune psychiatric disease and ii) Explore associations between CNS damage biomarkers in CSF and clinical red flags and psychiatric symptoms.

Materials and methods

Design

The four studies in this thesis were cross-sectional observational studies. Paper II also included longitudinal data from patients with bulimia nervosa.

Setting

Uppsala Psychiatric Patient samples

The data used in paper I-IV were collected as part of the Uppsala Psychiatric Patient (UPP) samples, a research infrastructure designed to collect biological materials and psychiatric assessments from patients seeking psychiatric care at the Department of Psychiatry, Uppsala University Hospital. Controls without current or previous contact with psychiatry are recruited to UPP from university personnel and students.

Paper I-III

For paper I-III, patient data were collected between 2012 and 2014 from psychiatric patients aged 18-25 years. Most of these patients were diagnosed with mood or anxiety disorders. Control data were collected between 2013 and 2015. For study II, the patients with bulimia nervosa were contacted again to collect follow-up data in 2015.

Paper IV

For paper IV, patient data were collected from 2012 to 2020 from the Uppsala Immunopsychiatry (UIP) cohort. The UIP cohort consists of patients with moderate-severe psychiatric symptoms and clinical signs of suspected neuroinflammation or autoimmune disease in the CNS. Most UIP patients are recruited from the Uppsala Immunopsychiatry Clinic, which investigates and treats patients with established or suspected autoimmunity or other immunological involvement that may cause psychiatric symptoms.

Study populations

Paper I

623 consecutive patients were invited to participate in the UPP between 2012 and 2014. 230 patients (37%) agreed to participate. Patients with established cancer, systemic inflammatory disease, diabetes mellitus, celiac disease, pregnancy or ongoing testosterone treatment were excluded. Patients were also excluded if they had incomplete data, insufficient diagnostic assessments, or more than 4 months between the BMI measurement and the blood sample collection. In total, 194 (84%) patients were included in study I.

60 controls, 18-30 years old, agreed to participate in the UPP between 2013 and 2015. 57 (95%) were included in study I. Controls were excluded for the same reasons as patients, with two exceptions. First, controls were excluded if they had a current depressive episode, and second, an insufficient diagnostic assessment was not an exclusion criterion for the controls.

Paper II

The 230 patients and 60 controls from the UPP in study I were also considered for inclusion in study II: however, only the female patients (n=179) and controls (n=45) were included. Only women were included because too few men were diagnosed with bulimia nervosa in the UPP.

Patients were excluded from study II for the same reasons as in study I, with a few exceptions. First, patients treated with antibiotics within a one-month range of blood sample collection were also excluded. Second, patients with eating disorders were excluded if the time between blood sample collection and measurement of BMI diverted more than one month. Third, patients with celiac disease were included in the study. There were no exclusion criteria for the controls in study II.

In total, 148 female patients and 45 female controls were included in the statistical analyses. Fifteen of the patients were diagnosed with bulimia nervosa and 10 of these returned for follow-up data collection.

Paper III

Patients from the UPP in study I-II were also considered for inclusion in study III. These patients were excluded for the same reasons as in study I, with one exception. In study III, patients were also excluded if they had bulimia nervosa or anorexia nervosa. Controls were excluded for the same reasons as patients or if they screened positive for a current psychiatric disorder in diagnostic interviews or had current psychotropic medication.

In total, 218 participants (172 patients and 46 controls) were included in the study population in study III. However, one patient without known

diabetes was later excluded when discovered that she had an HbA1c value of 67.

Paper IV

In September 2020, 167 patients had been considered for participation in the UIP cohort. Of these, 156 (93%) consented to participate in the study. No patient declined to participate, but nine were unable to give informed consent and two withdrew their consent. Patients were excluded from the study if they lacked important clinical data or CSF or were included in other ongoing studies (Covid-19 or mastocytosis). Totally, 127 patients were included in the study population in study IV.

Psychiatric and other clinical assessments

Psychiatric diagnostic assessment – Paper I, II and III

Psychiatric diagnoses were assessed using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM- IV) criteria. Patients were interviewed with the Mini International Neuropsychiatric Interview (M.I.N.I.) or the Structural Clinical Interview for DSM IV axis I disorders (SCID-I) by trained physicians or psychologists at the psychiatric outpatient clinic for young adults. Controls were interviewed with M.I.N.I. by trained personnel in the research group.

Psychiatric self-assessment – Paper I, II and III

Montgomery-Åsberg Depression Rating Scale – Paper I

Depressive symptoms and severity were assessed with the self-rating version of the Montgomery-Åsberg Depression Rating Scale (MADRS-S). It is a self-rating scale assessing nine items: mood, feelings of unease, sleep, appetite, ability to concentrate, initiative, emotional involvement, pessimism and zest for life. The items are rated on a Likert scale from 0 to 6 points, with higher scores indicating greater severity. The total score ranges from 0 to 54 points. For the items sleep and appetite, 0 points indicate “normal or elevated” sleep or appetite. For the other items 0 points indicate “normal/not present”.

Eating Disorder Examination Questionnaire – Paper II

The Eating Disorder Examination Questionnaire (EDE-Q) was used to assess eating disorder symptoms. The EDE-Q is a self-report questionnaire that assesses a wide range of eating disorder symptoms and their severity. The EDE-Q produces two types of data: frequency of key behaviors featured in eating disorders (e.g., binge eating, fasting) and a global score and 4 subscale

scores (Restraint, Eating Concern, Shape Concern and Weight Concern) reflecting the severity of the eating disorder. A higher score indicates higher severity. The EDE-Q was administered retrospectively by telephone to patients with bulimia nervosa who returned for follow-up data collection.

Swedish universities Scales of Personality – Paper III

Personality traits were assessed with the Swedish universities Scales of Personality (SSP). It is a self-rating questionnaire designed to determine personality traits linked to vulnerability to psychopathology. The SSP is rated on a four-point Likert scale (1 "does not apply at all" to 4 "applies completely") with 91 items grouped into 13 scales where each scale is composed of seven items. It has previously demonstrated good psychometric properties in a Swedish normative sample. A neuroticism factor was constructed from the ratings on the following SSP subscales: Somatic trait anxiety, Psychic trait anxiety, Stress susceptibility, Lack of assertiveness, Embitterment and Mistrust.

Psychiatric clinician assessment – Paper IV

Busch Francis Catatonia Rating Scale

Catatonia symptoms and severity were assessed with the clinician-rated 23-item Bush Francis Catatonia Rating Scale (BFCRS). For assessment of catatonia severity, items 1-23 are rated using a scale of 0 to 3, with a higher score indicating increased symptom severity. The total BFCRS score is the sum of the scores on all 23 items, with a possible total score of 0 to 69. In addition to the total score, a four-factor model was used for BFCRS with the following factors: F1: Negative/withdrawal, F2: Automatic, F3: Repetitive/echo and F4: Agitated/resistive (153).

Brief Psychiatric Rating Scale-Expanded

Psychiatric symptoms and their severity were assessed with the extended version of the Brief Psychiatric Rating Scale (BPRS-E). The BRPRS-E is a 24-item semi-structured interview assessing a wide range of psychiatric symptoms. The BPRS-E items are rated on a seven-point Likert scale (1, not present; 7 extremely severe). The possible BPRS-E total score ranges from 24 to 168. In addition to the total score, a four-factor categorization termed "added value set model" (154) was used that included the factors: F1: Depressed/Anxiety, F2: Psychosis, F3: Negative Symptoms and F4: Activation.

Clinical Global Impression scale

Overall psychiatric disease severity was estimated with the Clinical Global Impression (CGI) rating scale (155). The GCI is a clinician-rated seven-point

scale, used to assess the severity of a patient's disease state at the time of assessment, relative to the clinician's experience. The score ranges from 1 to 7, with a higher score indicating higher severity. A score of 1 point indicates that the patient is "normal, not at all ill" and 7 points indicate that the patient is "among the most extremely ill of subjects".

Neurological examination – Paper IV

When feasible, a neurological examination was performed by an experienced neurologist or psychiatrist at the Uppsala Immunopsychiatry clinic. However, some patients were instead examined by the treating physician in conjunction with emergency care. The findings from the neurological examination documented in the medical records were evaluated and categorized for the study by an experienced neurologist.

Physical health examination

Participants in UPP have their weight, height and blood pressure measured at the time of inclusion. BMI was calculated as weight in kgs divided by height in squared meters.

Biological assessments

Blood and CSF sample collection

Whole blood and CSF were collected from non-fasting participants during office hours. Plasma and CSF were stored at –80° C in the Uppsala Biobank. Routine serum tests were performed at the Department of Clinical Chemistry and Clinical Immunology at Uppsala University Hospital.

Hormone analysis in plasma – Paper I, II and II

Total leptin and adiponectin were analyzed with a solid-phase sandwich ELISA (Mercodia AB, Uppsala, Sweden). To create a leptin/adiponectin (L/A) ratio, the plasma leptin concentration (ng/mL) was divided by the plasma adiponectin concentration (ug/mL).

Analysis of inflammatory biomarkers in plasma– Paper III

CRP, IL-6 and TNF-α were analyzed with an electrochemiluminescence sandwich immunoassay using the Meso Scale Discovery multiplex platform (K15049D and K15198D, Rockville, MD, USA).

Basic analysis in CSF and CNS damage biomarkers – Paper IV

Basic analysis in CSF was performed at an accredited medical laboratory. It included the measurement and assessment of IgG indices, age-related CSF/serum albumin quotient (AQ), oligoclonal bands (OCBs) in serum/and or CSF and white blood cell count (WBC). Neurofilament light (NfL) and glial fibrillary acidic protein (GFAp) concentrations were measured with ELISAs in CSF at Sahlgrenska University Hospital. T-Tau was analyzed with Lumipulse technology (Fujirebio, Ghent, Belgium).

Analysis of anti-neuronal antibodies in serum and CSF – Paper IV

The presence of anti-neuronal autoantibodies was investigated in serum and CSF using a fixed cell assay. Immunofluorescence was used to test for antibodies against established cell surface antigens NMDAR, voltage-gated potassium channel (VGKC)-associated antigen (including LGI1), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and gamma-aminobutyric acid (GABA) receptors on transfected cells (Euroimmune, Lübeck, Germany). If the Immunofluorescence screening suggested antibodies against intracellular neuronal antigens, an immunoblot was performed to test for specific antibodies against the established intracellular antigens Hu, Ri, Yo, Ma2, amphiphysin and CV.2. If the Immunofluorescence screening suggested the presence of antibodies targeting GAD, an ELISA was performed to specifically test for anti-GAD.

Neuroimaging and EEG – Paper IV

The study collected and re-evaluated all available results from magnetic resonance imaging (MRI) and electroencephalogram (EEG).

Magnetic resonance imaging

Patients' MRI images were systematically re-evaluated by a specialist in neuroradiology using a data extraction form. White matter changes were graded using the Fazekas scale and reported according to their localization (156). Atrophy was graded with the Scheltens' scale for medial temporal atrophy (157) and global cortical atrophy scale.

Electroencephalogram

The saved portions of standard EEG recordings between 2012 and 2020 were systematically re-evaluated by two specialists in neurophysiology. Three broad categories of EEG abnormalities were noted: (1) background abnormalities (e.g., diffuse slowing) (2) periodic and rhythmic patterns and

(3) seizures/status epilepticus or other epileptiform changes. The use of medication (e.g., antipsychotics) in conjunction with the EEG was also noted.

Statistics

Paper I

Statistical analyses were performed on men and women separately. Associations between total MADRS-S score and plasma levels of leptin and adiponectin were assessed by Spearman's correlation coefficients.

To better visualize the skewed leptin and adiponectin levels, they were divided into quartiles. The relationships between the total MADRS-S score and quartiles of leptin and adiponectin were then assessed with generalized linear models (GlzMs). The GlzMs were first carried out without and then with the inclusion of potential confounding factors (BMI and antidepressants).

In a post-hoc analysis, the Mann-Whitney test was performed to compare leptin and adiponectin levels between controls and patients with current MDD, followed by the Kruskal-Wallis test for comparisons between more than two groups (controls with total MADRS-S score <10, patients with no current depressive episode, patients with current MDD and patients with bipolar depression). Significant results of the post-hoc analyses were adjusted for potential confounders in a GlzM with gamma distribution. The Mann-Whitney test was further used to investigate how leptin levels relate to the use of mood stabilizers or antipsychotics.

Paper II

The Mann-Whitney test was performed to compare plasma adiponectin, leptin and L/A ratio levels between patients with and without bulimia nervosa and between patients with bulimia nervosa and controls.

Stepwise multiple linear regression analyses were performed to adjust for the effects of predetermined potential confounders. Transformed data with natural logarithms were used for leptin and L/A ratio in these analyses.

The Wilcoxon Signed Ranks Test was used to test if plasma adiponectin or leptin levels had changed between baseline and follow-up in patients with bulimia nervosa. Associations between plasma adiponectin and the EDE-Q global score and subscale scores were assessed with Spearman's correlation coefficients.

Paper III

Associations between the neuroticism score and immunometabolic biomarkers were assessed with Spearman’s correlation coefficients. The

Mann-Whitney test was used to compare the plasma biomarkers associated with neuroticism between participants with a high neuroticism score (1 SD or more above the norm) and a low-normative neuroticism score (below the norm). Effect size was estimated with Rosenthal's effect size algorithm ((r = z/(SQRT(n)))). The statistical analyses were repeated in men and women separately. GlzMs with gamma log link distribution were constructed for the variables associated with neuroticism in the Spearman's test. The GLzMs were repeated in the patient population and the female study population as a sensitivity analysis. The male study population was too small to perform GLzMs.

In an exploratory post-hoc analysis, Spearman's bivariate correlation coefficients were used to explore the associations between the SSP subscales constituting the neuroticism score and the immunometabolic biomarkers measured in plasma.

Paper IV

In study IV, descriptive statistics were used for the primary analyses. Chi-square tests were then used to compare clinical parameters (e.g., clinical red flags) and biological variables (e.g., elevated CNS damage biomarkers). The Mann-Whitney test was also used to compare psychiatric symptom ratings (BPRS-E and BFCRS scores) between subgroups of patients. Because of the exploratory approach of the non-descriptive statistical analyses, no correction for multiple testing was performed. To assess the predictive performance of clinical variables, random forest models (158) were fitted with binary variables indicating presence or non-presence of elevated levels of NfL, t-Tau and GFAp as response variables.

Summary of results

Leptin, adiponectin and depressive symptoms (Paper I)

Plasma leptin levels were weakly correlated with total MADRS-S scores in women ($r=0.18$, $p=0.01$) but not in men. The women with plasma leptin levels in the highest quartile (28.87 ng/mL), reported an approximately six-point higher MADRS-S total score than the women in the lowest quartile ($\leq$ 9.99 ng/mL) in the generalized linear model. However, this association did not withstand adjustment for the effects of BMI and the use of antidepressants. However, in a subgroup analysis of the women without antidepressants, the plasma leptin levels remained positively associated with the total MADRS-S score, independently of BMI.

Despite the link between leptin levels and depressive symptom severity, leptin levels were not associated with current MDD.

Plasma adiponectin levels were not associated with the total MADRS-S score or current MDD.

Leptin, adiponectin and bulimia nervosa (Paper II)

Patients with bulimia nervosa (n=15) had elevated plasma adiponectin levels compared to psychiatric patients without bulimia nervosa ($p<0.004$) and controls ($p<0.008$). Bulimia nervosa also remained a significant predictor of plasma adiponectin levels in a stepwise multiple linear regression analysis adjusting for the effects of BMI, substance addiction, smoking and the use of antipsychotics or mood stabilizers ($p<0.002$).

There was no significant difference in plasma leptin levels between patients with bulimia nervosa and other patients or controls in the Mann-Whitney test. However, bulimia nervosa was a significant predictor of plasma leptin levels in the stepwise multiple linear regression analysis adjusting for the effects of BMI, substance addiction, smoking, use of antipsychotics or mood stabilizers, hormonal contraceptives and thyroid disorder ($p<0.01$). Here, there was a negative association between leptin and bulimia nervosa.

The L/A ratio was reduced in patients with bulimia nervosa compared to patients without ($p<0.04$), but not to controls ($p<0.41$). Similar to adiponectin and leptin, bulimia nervosa was a significant predictor of the L/A ratio in the stepwise multiple regression analysis adjusting for the effects of BMI and

other confounders. Overall, bulimia nervosa and BMI were the best predictors of plasma adiponectin, leptin and the L/A ratio.

Plasma adiponectin levels did not change significantly between baseline and follow-up in patients with bulimia nervosa who returned for follow-up 1-2 years after baseline (n=10).

EDE-Q scores were not associated with plasma adiponectin levels at follow-up in patients with bulimia nervosa. However, after a patient with extreme outlying values and BMI >40 was excluded, the plasma adiponectin levels were positively correlated with the EDE-Q global score ($r=0.72$, $p<0.04$) and subscales Restraint ($r=0.68$, $p<0.05$) and Eating concern ($r=0.79$, $p<0.02$).

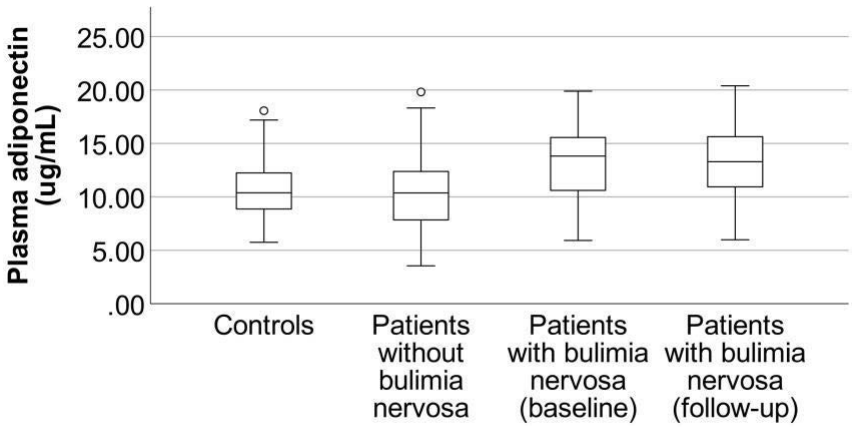

Figure 2. Boxplots of plasma adiponectin levels (ug/mL) in controls at baseline, patients without bulimia nervosa at baseline and patients with bulimia nervosa at baseline and follow-up.

Immunometabolic biomarkers and neuroticism (Paper III)

The neuroticism score was positively associated with the L/A ratio and plasma leptin and IL-6 levels when controlling for sex, MDD, anxiety disorder, antidepressants and substance addiction in the generalized linear models. However, adiponectin, CRP and TNF-α were not associated with the neuroticism score. In a subgroup analysis, the associations remained significant in the patient and the female study populations but not in the male study population.

The group with a high (≥60) neuroticism score had a higher L/A ratio (median=1.59) than the group with a low-normative (<50) neuroticism score

(median=0.89, p=0.002). Leptin levels were also higher in the high neuroticism group (median=17.01 ng/mL) than in the low-normative neuroticism score group (median=11.03 ng/mL, p=0.002). Similarly, the women reporting high neuroticism scores had more than twice as high L/A ratio and plasma leptin levels as those in the low-normative neuroticism score group.

In the exploratory post-hoc analyses, the L/A ratio and plasma leptin levels were positively correlated with several SSP subscales constituting the neuroticism score. The SSP subscale Stress susceptibility was also positively correlated with IL-6 and negatively correlated with adiponectin levels. Less consistent associations were found between IL-6, CRP and other SSP subscales.

CNS damage biomarkers in a patient cohort enriched for suspected autoimmune psychiatric disease (Paper IV)

Psychiatric and neurological symptomatology

The most common psychiatric symptoms in the cohort were psychosis, cognitive dysfunction, observable affective dysregulation symptoms and obsessions-compulsions. Twenty-three percent had a documented history of catatonia features. The median CGI at the time of assessment was 5 (markedly ill).

Eighty-four percent of patients were evaluated with a neurological examination and 46% of these had abnormal neurological findings. Seventeen percent had motor symptoms (e.g., dyskinesia, tremor), 14% had balance/coordination abnormalities, 12% had sensory symptoms (e.g., paresthesia, hypo/hyperalgesia), 11% had reflex abnormalities, 9% had eye movement abnormalities and 6% had weakness/paralysis.

Pathological findings suggesting CNS damage

127 patients were included in the study. Eighty-eight patients (69%) had available MRI images and 70 (55%) had available EEG recordings.

Thirty-three patients (27%) had elevated CNS damage biomarkers (NfL, GFAp or t-Tau) in CSF, suggesting neuronal-axonal damage or astroglial activation/damage. Fourteen patients had elevated NfL (11%), 14 patients had elevated GFAp (11%) and 16 patients had elevated t-Tau (13%).

Twenty-six patients had basic CSF alterations (21% of the tested), suggesting neuroinflammation or BBB dysfunction. These CSF alterations included detection of CSF-specific OCBs (8%), elevated IgG indices (5%), pleocytosis (3%) and elevated AQ (12%).

Established anti-neuronal antibodies were detected in serum or CSF in eight patients (6%). Three patients had antibodies targeting the NMDAR and five had antibodies targeting intracellular antigens (Ma2/Ta, Zic4, GAD65).

In the MRI images, 41% had white matter changes and 50% had some form of atrophy. Interestingly, white matter changes and atrophy were not exclusively found in older patients. Instead, 33% had white matter changes and 42% had at least grade 1 atrophy in patients ≤40 years old (n=73).

Twenty-seven percent (of 70 tested) had pathological EEG findings. Background abnormalities were observed in 19 patients, periodic and rhythmic patterns in 3 and seizures/status epilepticus or other epileptiform changes in 2.

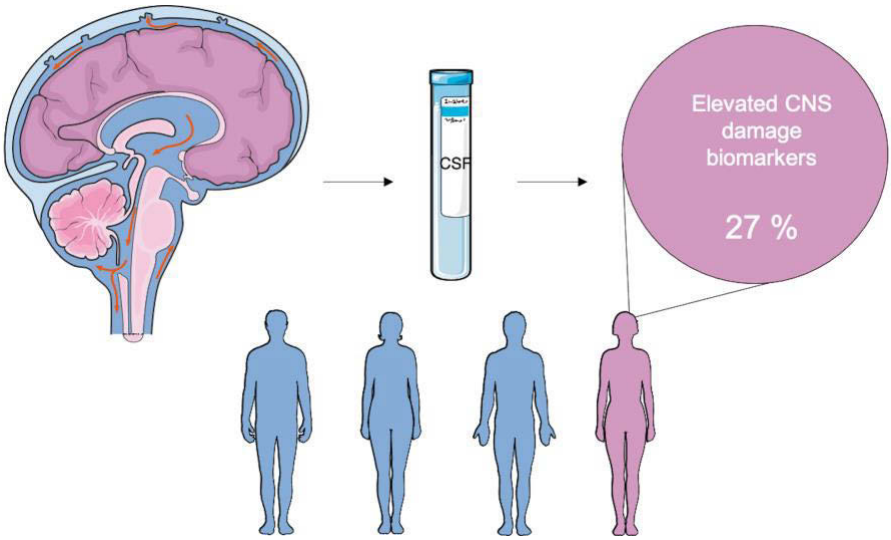

Figure 3. A fourth of the tested psychiatric patients with suspected autoimmune psychiatric disease had elevated CNS damage biomarkers (NfL, GFAp or t-Tau) in CSF.

CNS damage biomarkers and clinical red flags

Elevated levels of NfL were more common in CSF in patients with a comorbid autoimmune disorder (21%) than in patients without (6%, p=0.018) and less common in patients with a prodromal infection (4% vs. 16%, p=0.046).

Elevated GFAp levels were more common in patients with an atypical disease presentation (15% vs. 0%, p=0.021). Elevated GFAp levels were also more prevalent in patients with a rapid onset (17% vs 5%, p=0.044) and in patients with a prodromal infection (21% vs. 5%, p=0.008).

Elevated t-Tau levels were more common in patients with catatonia symptoms (27% vs. 9%, p=0.026).

Other suggested clinical red flags (comorbid tumors, suspected malignant neuroleptic syndrome, any abnormal finding in the neurological examination, accompanying motor symptoms and novel seizures) were not associated with elevated NfL, GFAp or t-Tau levels in CSF.

CNS damage biomarkers and psychiatric symptoms

Patients with elevated GFAp levels had a higher total BPRS-E score and a higher score on the BPRS-E factor F1: Depressed/Anxiety (p=0.021). Elevated GFAp levels were also positively associated with tics (p=0.006).

Patients with elevated t-Tau had higher ratings on the BPRS-E factor F3: Activation (p=0.033) and the BFCRS factor F4: Agitated/resistive (p=0.041).

Elevated NfL was not associated with BPRS-E or BFCRS scores. However, observable affective dysregulation symptoms were more common in patients with elevated NfL (86% vs. 48%, p=0.008).

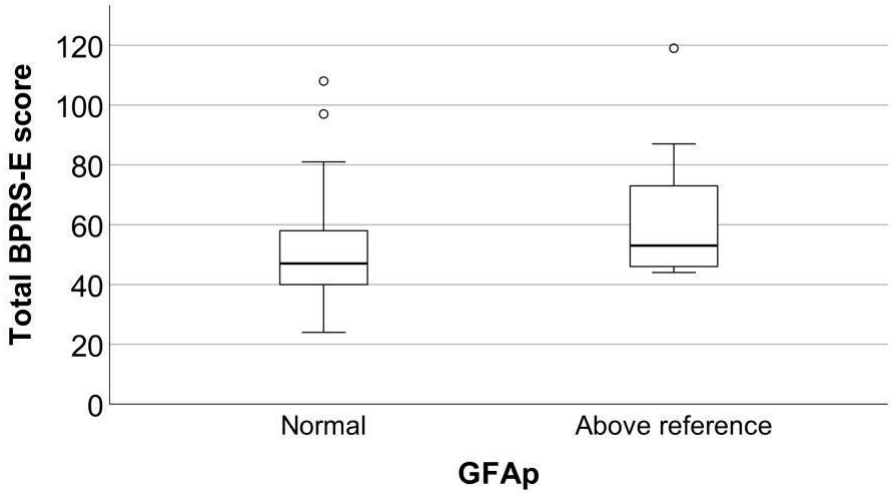

Figure 4. Boxplots of the total score on the Brief Psychiatric Rating Scale-Expanded (BPRS-E) in patients with GFAp levels above reference value and patients with normal GFAp in cerebrospinal fluid.

Discussion

The studies of this thesis have expanded the current knowledge of immunometabolic patterns in psychiatric disease. They demonstrated that those with higher plasma leptin levels among young adults with psychiatric morbidity, reported more severe depressive symptoms and a higher degree of neuroticism. Neuroticism was also linked to other signs of immunometabolic dysregulation. Moreover, we confirmed our hypothesis from paper II that bulimia nervosa is linked to elevated adiponectin levels in plasma. In women with bulimia nervosa, long-term stability in elevated plasma adiponectin levels was also observed. Finally, we showed that in a patient cohort enriched for suspected autoimmune psychiatric disease, a fourth had signs of neuronal/axonal damage or astroglial activation/damage and a fifth had CSF signs of neuroinflammation or BBB dysfunction. We also reported novel links between CNS damage biomarkers and clinical red flags for autoimmune psychiatric disease, as well as a positive association with overall psychiatric symptom burden and specific psychiatric features.

Immunometabolic biomarkers in depression and neuroticism

In paper I and III, immunometabolic alterations were observed in relation to high neuroticism and more severe depressive symptoms in a cohort of young adults with psychiatric morbidity. Unfortunately, it is not possible to determine the direction of causality for the correlations based on the data from paper I and III. However, inflammation and metabolic dysregulation could theoretically cause depressive symptoms, as described in-depth in the introduction. On the other hand, depressive behavior and chronic stress related to neuroticism could also contribute to the development of immunometabolic dysregulation.

Leptin has pro-inflammatory effects (77) and modulatory effects on the reward system (138, 149), which could theoretically contribute to anhedonia and fatigue. High leptin levels are also associated with insulin resistance (75), which has been linked to depression in previous studies (65, 159). However, in opposition to these hypotheses, leptin treatment in animals has anxiolytic and anti-depressive effects (47). Therefore, the elevated leptin levels we

observed in the periphery may actually be a sign of decreased leptin signaling in the CNS. This possibility needs further assessment in future work through simultaneous leptin measurements in plasma/serum and CSF.

Correlation heatmap

After completing study III, I had the nagging feeling that we might have measured the same phenomenon in paper I and III, given that the associations to leptin were so similar and a depressive state might make a person view themselves and the world through a depressive filter. Thus, writing the framework for this thesis, I created a correlation heatmap to overview how the subtraits of neuroticism (SSP subscales) and the different depressive symptoms (MADRS-S items) correlate with the immunometabolic biomarkers from paper III. The female study population from paper III was selected for these exploratory analyses for two reasons: 1) MADRS-S and SSP data were readily available in this population and 2) we only had negative findings in the male study population.

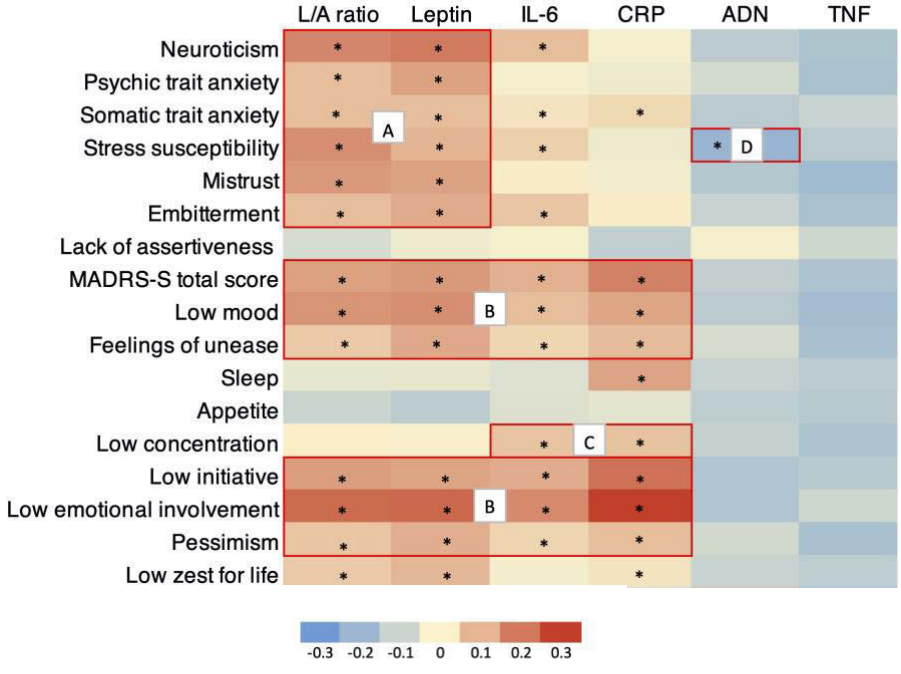

Figure 5. Correlation heatmap illustrating Spearman's coefficients between immunometabolic biomarkers and SSP and MADRS-S subscales in the female study population from paper III. ADN = Adiponectin; * = Significant correlation ($p<0.05$).

As can be seen in the correlation heatmap, it turned out that the immunometabolic patterns related to neuroticism and depressive symptoms had similarities and differences (see Figure 5). This finding suggests that although neuroticism and depressive symptoms overlap, we did not measure the same phenomenon in paper I and III.

Both depressive symptom severity and degree of neuroticism were positively correlated with leptin and L/A ratio, with moderate effect sizes (see group B in Figure 5). A reduced ability to feel (low emotional involvement) was the depressive symptom having the strongest correlation with immunometabolic dysregulation (higher CRP, leptin, L/A ratio and IL-6). A reduced ability to feel and lassitude (low initiative) were also the depressive symptoms most strongly associated with CRP levels.

The largest difference between neuroticism and depressive symptoms was the associations with CRP. While higher CRP levels were clearly associated with more severe depressive symptoms, they were not linked to neuroticism or most of its subtraits. Higher CRP and IL-6 levels, but not leptin or the L/A ratio, were also correlated with a decreased concentration ability (see group C, Figure 5). Insomnia was also correlated with CRP levels, but no other immunometabolic parameters.

Adiponectin was negatively associated with stress susceptibility but not with other neuroticism or depression features (see group D, Figure 5). As is discussed in paper III, this is in line with previous reports that adiponectin is protective against stress-induced negative effects (160, 161). Adiponectin levels also decrease in stress-susceptible mice in response to chronic stress (160).

The lack of an association between TNF-α and depressive symptoms is perplexing, as it has consistently been associated with depression in previous studies (54). Surprisingly, TNF-α levels were also correlated with IL-6 levels ($r=0.44$, $p<0.001$) but not with CRP ($r=0.104$, $p=0.19$). Because TNF-α is the only immunometabolic biomarker in plasma that was not correlated with the L/A ratio, BMI or waist-hip ratio, one interpretation of the results could be that depressive symptom severity and neuroticism were more related to immunometabolic dysregulation in the WAT than acute inflammation in our patient cohort of young adults with psychiatric morbidity.

Considering that it is relatively well-established that neuroticism is a risk factor for depression, it could be speculated that the immunometabolic variations observed in relation to high neuroticism might be a milder version or a pre-stage of what happens in depression (see Figure 6). This theory could explain why depressive symptoms are correlated with a wider range of immunometabolic dysregulation than neuroticism. However, it is also possible that this difference is explained by a pathomechanism specific for a depressed state, independent of neuroticism.

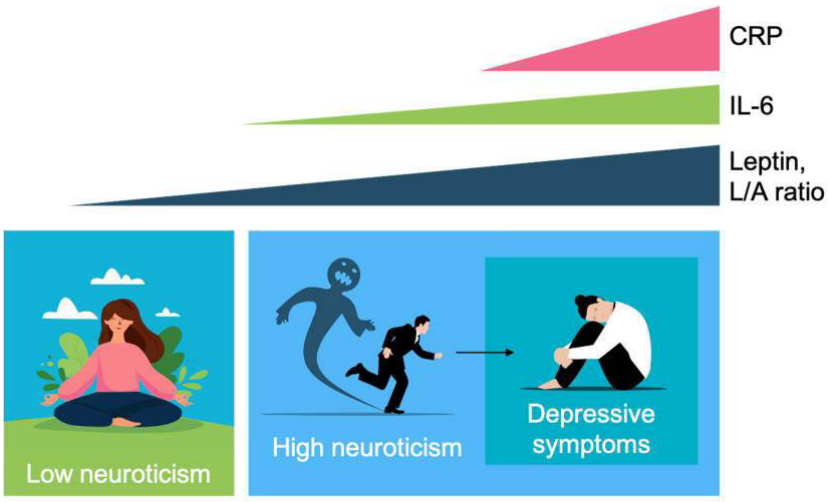

Figure 6. An illustration of a hypothesis for how immunometabolic dysregulation may relate to neuroticism and depressive symptoms.

Altered adipokine levels in bulimia nervosa

Our hypothesis in paper II that patients with bulimia nervosa have elevated plasma adiponectin and decreased plasma leptin and L/A ratio was confirmed. The results on leptin were in line with most previous studies (143-148). As for adiponectin, the results support an investigation by Monteleone et al. (150), that also reported elevated adiponectin levels in bulimia nervosa. Monteleone et al. also measured plasma adiponectin with ELISA-based methods (150), whereas the two studies with negative findings or contrasting results used RIA (151, 152).

The observed adipokine alterations may contribute to the maintenance of a vicious cycle of bulimic behavior. It is not unusual that the triggering factor for bulimia is a period of dieting. Fasting will decrease leptin and increase adiponectin levels in plasma (70, 122), increasing appetite, food reward and disinhibited and emotional eating behavior, thereby possibly triggering binge eating.

Fasting and other compensatory behavior are, however, not enough to explain our novel finding that patients with bulimia continued to have elevated adiponectin levels over time, despite reduced eating disordered behavior. The elevation in plasma adiponectin over time may instead be a protective mechanism to counteract insulin resistance and development of T2DM induced by binge eating, as suggested by Monteleone et al. (150). Consistent with this contention, patients with bulimia nervosa seem to have an increased lifetime risk for T2DM, likely linked to binge eating (162).

It is also possible that patients with bulimia nervosa have genetic or epigenetic variations that tilt the metabolic system towards higher adiponectin and lower leptin levels in plasma. This possibility could become a risk factor for overweight in childhood, which is a risk factor for eating disorders (163). It could also increase the risk for emotional or disinhibited eating behavior, thereby becoming a risk trait for the development of bulimia nervosa. Adiponectin gene (ADIPOQ*)* variations have previously been associated with eating behavior (141, 142, 164), but it is unknown if this is the case in patients with bulimia.

Screening for anti-neuronal antibodies in a psychiatric cohort

The high proportion of patients who consented to investigation with a lumbar puncture (88%) suggests that lumbar puncture examination is often feasible even in patients with severe psychiatric symptoms.

In paper IV, established anti-neuronal antibodies were detected in serum in 6% and CSF in 2%. This result supports previous findings that only a minority of psychiatric disease cases is explained by known anti-neuronal antibodies (31, 32, 165-167), also in a population enriched for clinical red flags.

Clinical red flags may still be helpful for the clinician trying to determine which psychiatric patients to investigate with a lumbar puncture. However, because there was no control group in paper IV, this hypothesis needs to be tested in future studies by comparisons between psychiatric patient groups with and without clinical red flags.

Previous studies have shown considerable variation in the prevalence of anti-neuronal antibodies in primary psychiatric populations, which is likely due to differences in population selection and methodology (167). For example, using fixed cell rather than live cell assays in this study may have underestimated the prevalence of anti-neuronal antibodies (167, 168). Seronegative findings also do not exclude the existence of an autoimmune process explaining the patient's psychiatric symptoms. For example, an increasing number of cases of young patients with suspected autoimmunity and psychiatric manifestations that are responsive to immunotherapy despite completely or almost normal CSF findings have been described (13,17–19).

CNS damage biomarkers, clinical red flags and psychiatric symptoms

Paper IV revealed that the CNS damage biomarkers (NfL, t-Tau, GFAp) appear related to different, specific clinical profiles.

Elevated NfL levels were related to comorbid autoimmune disease, especially SLE. This finding agrees with two previous studies describing NfL as a biomarker of brain involvement in SLE and primary Sjögren's syndrome (169, 170). Neuro-SLE or other autoimmune disorders with brain involvement should therefore be considered in patients with elevated NfL levels and neuropsychiatric symptoms. The usefulness of NfL as a potential biomarker for systemic autoimmune disorders with brain involvement in psychiatric patients should also be addressed in future work.

For the first time, we showed that elevated t-Tau levels might be linked to catatonia symptoms and psychomotor activation/agitation, suggesting a possible involvement of damage to thin non-myelinated axons in the pathophysiology of catatonia and excited catatonia features. However, the direction of causality is uncertain and needs to be further investigated with longitudinal studies.

Elevated GFAp levels were related to several clinical red flags (atypical disease presentation, rapid onset, prodromal infection) for psychiatric autoimmune disease. These clinical red flags are all included in the proposed guidelines for identifying cases of suspected autoimmune OCD (171). Astrocyte pathology could contribute to CNS autoimmunity or neuroinflammation in several ways. For example, astrocyte damage or dysfunction could disrupt the BBB, thereby permitting the entry of cytokines and autoantibodies into the brain (172). However, the causal direction may be the opposite, with neuroinflammation or neurodegenerative processes in the brain causing astroglial activation or damage (172).

Elevated GFAp levels were also associated with tics, which is a symptom of Pediatric Acute-onset Neuropsychiatric Syndrome. Elevated GFAp levels were further linked to more severe anxiety/depressive symptoms and overall psychiatric symptom burden. This observation concurs with two recent studies showing a link between major depression and elevated GFAp in CSF and serum (43, 44). Loss of astrocytes has also been connected to depression in animal and post-mortem tissue studies (173). Animal models further suggest that stress, a risk factor for depression, may cause a reduction of GFAp-positive astrocytes in the CNS (174).

Based on the data in paper IV, it is not possible to determine whether the elevated GFAp levels are a sign of astroglial damage or astroglia activation (e.g., as a response to neuronal damage). Still, the results of paper IV support a potential role for astroglial pathology in psychiatric disease, at least for a subgroup of patients.

Methodological considerations and limitations

The work included in this thesis needs to be considered in light of several limitations. First, the cross-sectional study design of papers I-IV prevents

conclusions on causality. Second, the focus on young adults in paper I-III limits the generalizability of the results to other age groups. Furthermore, a larger male sample size would have increased the informative value of study I and III. These studies need to be repeated in a more extensive male study population to determine whether the lack of associations observed in the men is caused by genuine sex-specific associations in women or a lack of power in the male study population of paper I and III.

Another limitation in paper I is that we could not assess "atypical" depressive symptoms, which might be specifically associated with leptin and immunometabolic dysregulation (82, 99). In this context, the MADRS-S is also sub-optimally designed for the rating of neurovegetative depressive symptoms. The answering option "0" on the MADRS-S items Sleep and Appetite is a conflated value, reflecting both absence of symptoms and increased sleep/appetite. This flaw makes the items difficult to interpret and might introduce information bias in how the total score reflects the depressive severity of patients with atypical depression. In accordance with this reasoning, the effect sizes for the plasma leptin vs. MADRS-S total score correlations increase slightly if the Sleep and Appetite items are removed from the MADRS-S total score. The design of the MADRS-S Appetite item may also explain why no association was found between plasma leptin and appetite in our cohort (see Figure 5), a finding in contrast with previous studies.

In paper II, the EDE-Q is used out of context by a retrospective telephone interview, which introduces the possibility of recall bias.

Because of the effects of food intake and circadian rhythms on plasma adipokine levels, another significant limitation of paper I-III was the choice to use non-fasting blood samples collected during office hours. However, a recent study reported high correlations between fasting and non-fasting blood samples for leptin, adiponectin and the L/A ratio (175). This finding suggests that the possible bias introduced by non-fasting blood samples may not be as significant as was previously feared.

Another limitation of paper I and III was that data on several potentially important confounders/mediators (e.g., sleep, physical activity, childhood trauma, diet) were unavailable. Most of the men also had missing data on smoking status. The missing data might be explained by the construction of the basic information questionnaire, as the question of smoking status was in close conjunction with questions concerning menstrual health.

BMI was chosen as the primary adiposity index in paper I-III because of its higher availability than waist-hip ratio. The missing data for waist and hip circumferences suggests that these measurements might be less tolerable for young psychiatric outpatients than weight measurement. However, the waist-hip ratio might provide more information on abdominal obesity, which has been linked to depression. Therefore, the waist-hip ratio may be more relevant than BMI for the research questions imposed in paper I and III.

Similar to most previous studies concerning depression, we analyzed only peripheral biomarkers in paper I-III. However, it is possible that peripheral alterations of these biomarkers do not reflect pathophysiological processes in the CNS. This reasoning would explain the discrepancies between our results in paper I and previous results in animal models. This assertation needs to be addressed in future work, with concurrent measurements of leptin and adiponectin in both plasma and CSF. Measurement of HMW and LMW adiponectin should also be considered in addition to total adiponectin, as the different isoforms of adiponectin may have varying physiological and pathophysiological effects. For instance, some studies suggest that the LMW isoforms may be the most important for adiponectin's central effects, whereas HMW is the major bioactive form in the periphery (176). The choice of assay to measure adiponectin should also be considered with caution in that different antibody-dependent assays (e.g., ELISA or RIA) may have different preferences for the isoforms of adiponectin (177). In this regard, a previous study described an inaccurate quantification of total adiponectin levels by RIA in individuals carrying an ADIPOQ mutation influencing isoform proportions (177).

Important limitations for paper IV include a selected study population without a control group, that patients were investigated at different stages in their disease progress (e.g., acute or chronic) and that some variables had missing data. For example, only half of the patients were investigated with EEG. This selection was most likely not random but based on a higher degree of suspicion of organic cause. The EEG results may therefore be influenced by selection bias. The selected study population limits the generalizability of the observed links between psychiatric symptomatology and CNS damage biomarkers to a general psychiatric population. Furthermore, the clinical red flag "atypical presentation" was difficult to define because it is mostly based on the clinician's experience of what constitutes a typical pattern for a psychiatric disorder. Such a broad definition will affect the reproducibility of the results. Another limitation in paper IV was that we could not reliably assess some of the clinical red flags suggested in previous studies (e.g., treatment resistance).

One methodological question that repeatedly re-surfaced was how we should adjust our observations for potential confounders. As can be seen in paper I-III, there is a progression in how we have managed this question that reflects an advancement in the literature. Because confounding bias can threaten the validity of the results, adjusting for the effects of confounders is vital in observational studies. However, adjustment for variables that are not confounders (e.g., mediators or colliders) may also reduce the validity of the results through over adjustment bias or reduced precision of the effect estimates (178). Thus, it is essential to carefully consider which variables may be confounders and which may be mediators or colliders, and then only adjust for the confounders. However, this ability to differentiate is sometimes easier

said than done, especially when it is unknown which variables precede the others or have a bilateral relationship.

Future considerations and clinical implications

The research field of Immunopsychiatry is rapidly growing and brings hope of new tools for patient stratification and treatment options for a group of patients with severe psychiatric symptoms. Still, interactions between the immune system, the metabolic system and the nervous system are complex and challenging to study. One way to find innovative approaches to address this complexity is through collaborations that bridge classical medical fields and involve researchers of both preclinical and clinical backgrounds.

It is now clear that there are links between immune regulation and psychiatric disease. Nevertheless, it remains to be explored how specific these immune alterations are for different psychiatric conditions, whether they are important only for subgroups of patients and how they relate to prognosis and treatment response. The question of causality also needs to be further investigated with longitudinal studies with repeated measurements, case studies and randomized controlled trials (RCTs).

Several RCTs for immunomodulatory treatments are now ongoing or planned for patients with depression and those with autoimmune psychiatric disorders. This research is a necessary step to determine causality and the clinical relevance of immune dysregulation in psychiatric disease. It is also the next step towards translating theoretical knowledge from the field of Immunopsychiatry into something that is directly useful for the patients. Some observational studies show promising results from immunotherapy in reducing psychiatric symptoms and improving functionality in psychiatric patients with positive findings of anti-neuronal antibodies (179). Moreover, observational studies and a few RCTs have shown beneficial effects of anti-inflammatory and anti-cytokine drugs for some patients with depression (13). Selection based on signs of inflammation (e.g., elevated IL-6) may help find appropriate candidates for immunotherapy within psychiatry, but this remains to be determined.

Clinical red flags may be a valuable tool for identifying patients who should be investigated for objective findings of autoimmune psychiatric disease and may be potential candidates for treatment with immunotherapy in clinical trials. Clinical red flags may also help detect psychiatric patients with signs of suspected autoimmune psychiatric disease, with seronegative findings for established anti-neuronal antibodies. For some of these patients, their psychiatric symptoms will not be explained by anti-neuronal antibodies. For others, the symptoms may be explained by novel and unknown anti-neuronal antibodies that are yet to be specified. If these patients can be better identified through clinical screening and with the help of biomarkers in blood and CSF,

their CSF can be tested on rodent brain tissue ("tissue tests") to determine whether they have antibodies in the CSF that bind to brain tissue.

In addition to immunomodulatory treatment, metabolic targets have been considered potential therapeutic targets for treating depression. For example, leptin-based treatments have been suggested for depression because of their antidepressant-like effects in animal models. These suggestions are not supported by the data of this thesis, as we observed a positive correlation between depressive symptoms and leptin and the L/A ratio. Still, much remains unknown regarding how leptin and adiponectin act in the CNS in relation to depression in humans. Future studies where leptin and adiponectin levels are measured simultaneously in blood and CSF are needed to better address this issue.

The results of paper I and III collaborate the position that immunometabolic alterations appear to be connected to a depressive state and depressive/anxiety traits. These alterations were observed already in young adults, suggesting that early preventive measures for metabolic health in teenagers and young adults should be of higher importance in society and health care, especially for individuals with psychiatric morbidity or ill-health. Preventive non-pharmaceutical interventions, such as exercise, have previously been shown to increase adiponectin and decrease leptin and inflammatory markers in both children and adults (180-183). Some studies in rodents and humans also suggest that exercise improves leptin resistance (184). Yet, it is unknown what the optimal plasma leptin and adiponectin levels are in young adults. Consequently, the paper I and III results cannot determine whether young patients with psychiatric morbidity have pathological values. This issue and the long-term effects of these alterations need to be further investigated in future studies.

Substantially less is known about biological alterations and their long-term effects on health in bulimia nervosa than in anorexia nervosa. Future work should address the metabolic dysregulations observed in paper III, preferably by investigating long-term metabolic regulation concerning eating disorder symptoms and genetic and epigenetic variations. The genes of neuropeptides involved in energy balance and food reward (e.g., adiponectin) are of particular interest. It also needs to be investigated if elevated plasma adiponectin may be a risk factor for the development or maintenance of bulimia nervosa, or if it is a consequence of the disorder. Neuropeptides involved in energy balance and food reward may also be potential therapeutic targets.

Paper IV found noteworthy links between psychiatric features and CNS damage biomarkers that need confirmation in other populations. Future work should also address whether CNS damage biomarker levels are related to disease progression or treatment response: For example, this could be executed by including repeated CNS damage biomarker measurements in RCTs.

Paper IV only used biomarkers and other readily available investigations in the psychiatric or neurological clinic. Investigations with more experimental biomarkers could be of interest in the future (such as biomarkers more specific for neuroinflammation).

Conclusions

Higher plasma levels of immunometabolic biomarkers, such as leptin, L/A ratio and IL-6, are related to more severe depressive symptoms and a higher degree of neuroticism in young women with psychiatric morbidity. Higher CRP is also linked to depressive symptom severity in young women but not to neuroticism.

In contrast, women with bulimia nervosa have higher adiponectin levels and lower leptin and L/A ratios in plasma. The plasma adiponectin levels also remain elevated over time despite improvement in eating disordered behavior, suggesting long-term metabolic dysregulation in patients with bulimia nervosa.

The thesis results demonstrate preliminary links between astrocyte and tau pathology and psychiatric features that need to be confirmed and explored in future work. The final study also shows that CSF analysis is feasible within psychiatry even in patients with severe psychiatric symptoms. The study further demonstrates that CNS pathology is found in CSF in patients with a broader range of psychiatric manifestations, not only psychosis, when other clinical red flags are present.

Taken together, the results of the thesis confirm a link between immunometabolic regulation and mental states and traits in patients with psychiatric morbidity.

Sammanfattning på Svenska

Bakgrund

Psykiatriska sjukdomar är komplexa tillstånd som drabbar vår tankeförmåga, vårt känsloliv, våra beteenden och hur vi uppfattar oss själva och omvärlden – med ofta allvarliga konsekvenser och ett stort lidande som följd. Trots att vi hela tiden lär oss mer vet vi fortfarande väldigt lite om deras bakomliggande orsaker och sjukdomsmekanismer, vilket bidrar till en bristfällighet i både diagnostik och behandling.

Det har länge funnits en misstanke om att psykisk sjukdom kan vara kopplat till förändringar i immunsystemet, åtminstone för en del patienter. De senaste decennierna har ett växande antal studier visat på just sådana kopplingar. Till exempel har låggradig, kronisk inflammation kopplats till flera psykiatriska diagnoser, som depression, schizofreni och tvångssyndrom. Det har också tillkommit fallbeskrivningar av patienter med terapiresistent psykisk sjukdom som förbättrats i sitt psykiska tillstånd av läkemedel som påverkar immunsystemet.

Immunförsvaret och kroppens energiregleringssystem är tätt sammankopplade och påverkan på det ena innebär ofta en påverkan också på det andra. Förändringar av immunförsvaret eller kroppens energibalans (t.ex. regleringen av blodsockernivåer) kan gemensamt kallas för immunometabola förändringar. Hormoner som produceras av fettvävnaden, t.ex. leptin och adiponektin, är ofta involverade i regleringen av både immunförsvaret och kroppens energibalans. Nivåerna av leptin och adiponektin i blodet har i tidigare studier visats vara kopplade till depression.

Leptinnivåerna ökar och adiponektinnivåerna minskar när fettvävnadens storlek ökar. Leptin hämmar aptiten och minskar matintaget. Leptin är också pro-inflammatoriskt och påverkar hjärnans stressregleringssystem (HPA-axeln) och normala utveckling. Adiponektin ökar insulinkänsligheten och minskar risken att utveckla diabetes, hjärtkärlsjukdom och cancer. Till skillnad från leptin verkar adiponektin vara i huvudsak anti-inflammatoriskt och ökar eventuellt matintaget.

Autoimmuna mekanismer i hjärnan, dvs. när immunförsvaret attackerar nervsystemets egen vävnad, har också kopplats till allvarliga psykiska symtom som psykos, svårt tvång och påverkad förmåga att minnas, fatta beslut och tolka information. Här är det fortfarande mycket som är oklart avseende diagnostiken, men typiskt för tillstånden är att symtombilden ofta är

förknippad med vissa varningsflaggor (s.k. röda flaggor), som ett snabbt sjukdomsförlopp och symtomdebut efter en period med infektionssymtom. Röda flaggor har föreslagits som ett möjligt screeningverktyg för att hitta de patienter med psykiska symtom som bör utredas mer utförligt för misstänkta förändringar i immunsystemet som kan tänkas bidra till sjukdomsbilden.

Motsvarande tillstånd med framträdande neurologiska symtom har behandlats framgångsrikt med immunoterapi. Förhoppningen inom forskningsfältet är därför att immunoterapi också skulle kunna vara till nytta för patienter med tecken på autoimmunitet och övervägande psykiska symtom. Olika metoder har föreslagits för att hitta de patienter som skulle kunna ha nytta av immunoterapi. Dessa metoder inkluderar utredning med hjärnavbildningstekniker och biomarkörer i blod och ryggmärgsvätska, som kan påvisa tecken på skada, inflammation eller autoimmunitet i hjärnan. Exempel på hjärnskademarkörer som kan användas för att påvisa olika typer av skada i hjärnan är t.ex. GFAp, totalt Tau (t-Tau) och NfL. GFAp är en biomarkör för skada på astrocyter, medan Tau och NfL är biomarkörer för skada på nervceller och deras axon.

Fortfarande kvarstår mycket att klargöra avseende hur immunometabola mekanismer kan påverka och påverkas av psykiska tillstånd och hur detta relaterar till diagnostik, prognos och behandlingsmöjligheter för psykiatriska patienter. Förhoppningen med den här avhandlingen har varit att bidra med ytterligare en pusselbit som kan leda till nya insikter om hur immunometabola förändringar är kopplade till olika aspekter av psykisk sjukdom och hur olika biomarkörer i blod och ryggmärgsvätska kan användas för att biologiskt stratifiera patienter med psykiska symtom.

Syfte

Det övergripande syftet med avhandlingen har varit att undersöka sambandet mellan psykisk sjukdom och en felriktad reglering av immunförsvaret. Syftet med de olika delarbetena i avhandlingen har varit följande:

I. Att undersöka kopplingen mellan svårighetsgraden av depressiva symtom och nivåer av hormonerna leptin och adiponektin i blod.

II. Att undersöka kopplingen mellan bulimi och nivåerna av leptin och adiponektin i blod och hur de varierar över tid hos personer med bulimi.

III. Att undersöka sambandet mellan neuroticism och leptin, adiponektin och andra inflammatoriska biomarkörer som kan tyda på ökad risk för hjärtkärlsjukdom/diabetes hos unga vuxna med psykiatriska tillstånd.

IV. Att undersöka förekomsten av objektiva tecken på hjärnskada/hjärninflammation hos en patientgrupp med kliniska tecken på misstänkt autoimmun psykiatrisk sjukdom. Delarbetet hade vidare som syfte att undersöka kopplingen mellan olika hjärnskademarkörer, psykiatrisk symtombild och kliniska tecken på misstänkt autoimmun psykiatrisk sjukdom (röda flaggor).

Metod

Studie I-III

I studie I, II och III undersöktes unga vuxna psykiatriska patienter (18-25 år) och kontroller (18-30 år). I alla tre studierna mättes nivåerna av hormonerna leptin och adiponektin i blod med en teknik som kallas för ELISA. I studie II och III skapades också en kvot av leptin och adiponektin nivåerna som kallades för L/A kvot. I studie III mättes utöver leptin och adiponektin också nivåerna av CRP, IL-6 och TNF-α i blod med en teknik som kallas för electrochemiluminescence immunoassay.

I studie I uppskattades svårighetsgraden av depressiva symtom med självskattningsformuläret MADRS-S.

I studie II fick patienterna med bulimi lämna blodprov vid två tillfällen med ca 1-2 års mellanrum. I samband med att de lämnade det andra blodprovet intervjuades de över telefon om förekomsten och svårighetsgraden av olika ätstörningssymtom.

I studie III mättes graden av neurotiska personlighetsdrag (t.ex. ångestbenägenhet och stresskänslighet) med ett självskattningsformulär.

Studie IV

I studie IV undersöktes patienter med svår psykisk sjukdom som misstänktes ha förändringar i immunförsvaret, t.ex. autoimmunitet, som bidrog till psykiska symtom. Patienterna genomgick en noggrann klinisk bedömning med psykiatrisk intervju, neurologisk undersökning och olika skattningsformulär av psykiska symtom. Patienterna undersöktes även med blodprov och lumbalpunktion för att mäta hjärnskademarkörer (NfL, GFAp, t-Tau), antikroppar riktade mot den egna hjärnvävnaden och andra tecken på inflammation/autoimmunitet i blod eller ryggmärgsvätska. I de fall patienterna hade undersökts med hjärnavbildningstekniker (magnetkameraundersökning eller EEG) samlades resultaten in och eftergranskades för tecken på hjärnskada eller hjärninflammation.

Resultat och slutsats

I. Högre nivåer av leptin i blodet var kopplade till svårare depressiva symtom hos kvinnorna, men inte hos männen. Kopplingen var beroende av BMI och användning av antidepressiva läkemedel.

II. Kvinnorna med bulimi hade högre nivåer av adiponektin i blodet. Nivåerna av adiponektin i blodet förblev förhöjda över tid, trots minskat ätstörningsbeteende.

III. Högre grad av neurotiska personlighetsdrag var kopplat till högre nivåer av leptin, L/A kvot och IL-6 i blodet. Associationen kvarstod även efter korrigering för depression och ångestsyndrom. Lägre nivåer av adiponektin var kopplade till en ökad stresskänslighet.

IV. En fjärdedel av patienterna med kliniska tecken på misstänkt autoimmun psykiatrisk sjukdom hade förhöjda nivåer av hjärnskademarkörerna NfL, GFAp eller t-Tau. Förhöjt NfL var vanligare hos patienter med SLE eller annan autoimmun sjukdom och kopplat till observerbara affektiva symtom. Förhöjt GFAp var kopplat till tics, större psykiatrisk symtombörda och depression/ångest. Förhöjt GFAp var också kopplat till följande röda flaggor: atypisk psykiatrisk sjukdomsbild, hastig sjukdomsdebut och infektion i anslutning till insjuknandet. Förhöjt t-Tau var kopplat katatoni och till symtom tydande på hyperaktivering och agitation. 21 % av patienterna som undersöktes med lumbalpunktion hade tecken på inflammation i nervsystemet eller störd blod-hjärnbarriär. Antikroppar mot egen hjärnvävnad påvisades i blodet hos 6 % av patienterna och i ryggmärgsvätskan hos 2 %. 58 % av patienterna hade psykotiska symptom, 42 % hade tvångssymtom och 24 % hade katatoni. Flera andra psykiska symtom förekom också, t.ex. sömnpåverkan, kognitiv påverkan och affektiva symtom som nedstämdhet.

Sammantaget visar dessa studier att högre nivåer av immunometabola biomarkörer i blodet är kopplade till svårare depressiva symtom och en högre grad av neuroticism hos unga kvinnor. Detta stärker vikten av förebyggande åtgärder för förbättrad kroppslig hälsa hos unga vuxna med benägenhet för ångest eller depressivitet. Studierna visar även på en koppling mellan bulimi och långvarigt förändrade nivåer i blodet av hormoner som kontrollerar kroppens energibalans och påverkar ätbeteenden, vilket skulle kunna både orsaka och vara orsakat av symtombilden vid bulimi.

Psykiatriska patienter med en atypisk sjukdomsbild, hastig sjukdomsdebut eller infektion i anslutning till insjuknandet verkar ha en högre förekomst av förhöjda GFAp nivåer, vilket kan tyda på ökad astrocyt-aktivering eller skada. Patienter med förhöjda GFAp nivåer verkar också i högre utsträckning besväras av tics och depression/ångest. För första gången visar vi också en koppling mellan katatoni och förhöjda t-Tau nivåer i ryggmärgsvätska, vilket

tyder på en pågående skada i nervcellerna eller deras axon. Förhöjda t-Tau nivåer var också kopplat till ökad agitation/hyperaktivering. Vi påvisar också en koppling mellan förhöjt NfL och autoimmun sjukdom (särskilt SLE), vilket stärker bilden av en autoimmun påverkan i nervsystemet hos dessa patienter med autoimmun sjukdom och psykiska symtom.

Resultaten i studie IV stödjer användandet av röda flaggor för att hitta patienter med avvikelser i blod och ryggmärgsvätska som tyder på inflammation, autoimmunitet eller skada i hjärnan som kan bidra till psykiska symtom. Samtidigt visar resultaten att inte bara patienter med psykos bör övervägas för utredning av autoimmun psykiatrisk sjukdom, utan också patienter med andra psykiska symtom som katatoni, tvång, affektiva symtom och kognitiv påverkan.

Sammanfattningsvis bekräftar avhandlingen att det finns olika typer av kopplingar mellan psykiska besvär/sjukdomar och tecken på hjärnskada och immunometabola förändringar i blod och ryggmärgsvätska, som potentiellt skulle kunna vara användbara för att biologiskt stratifiera patienter med psykiska symtom. Tydligare biologisk stratifiering skulle i sin tur kunna vara ett stöd i valet av behandling. Framöver behövs fortsatta studier för att vidareutveckla hur kunskapen om dessa kopplingar kan användas för att förbättra behandlingen av patienter med psykisk sjukdom, t.ex. genom att behandla de patienter som har psykisk sjukdom och tecken på autoimmunitet i nervsystemet med läkemedel riktade mot immunförsvaret.

Acknowledgements

This work was carried out at the Department of Neuroscience, Psychiatry, Uppsala University. I want to express my deepest gratitude to everyone involved in this thesis project and those who supported me throughout the process. Special thanks to:

I owe special gratitude to Janet Cunningham, my inspiring and imaginative principal supervisor, for all you have done for me throughout this process. Thanks to your guidance and example, I have dared to face challenges I never imagined myself capable of meeting. Thank you for having confidence in me and introducing me to the wondrous world of science. By supporting and challenging me, you have helped me grow not just as a scientist, but also as a clinician and person.

Special gratitude to Annica Rasmusson, my co-supervisor, for always making sure I am okay and for giving me a deeper understanding of research and scientific methods. You have the most wonderfully inquisitive mind. I am constantly inspired by how your curiosity drives you to always find new perspectives and reach out to people to create novel and exciting collaborations. Both your support and your scientific advice have been essential for me throughout this process.

Lisa Ekselius, my co-supervisor, for supporting, teaching and inspiring me throughout this whole process. Thank you for making all this possible and for everything you have taught me.

Robert Fredriksson, my co-supervisor, for support, guidance and invaluable knowledge of the molecular mechanisms of energy balance and food intake in the brain.

Fanny Söderquist, for your wisdom, guidance and for showing me how graphical illustrations can make a complicated concept easier to understand.

Emma Malmström, for your brilliance, thoroughness and ability to explain complex things in a way that makes them easy to understand. It has been a true pleasure to be your collaborative partner this last year.

Mia Ramklint, for excellent collaboration, astute scientific advice and understanding of psychometrics and affective disorders.

Johan Isaksson, for all your help in re-thinking the study design of paper III, sound scientific advice and understanding of psychological constructs.

Joachim Burman, for in-depth knowledge and expertise of the CNS and neuroinflammatory and other neurological conditions, brilliant scientific advice and a healthy dose of sound scepticism.

David Fällmar, Åsa Amundsson, Holger Rothkegel and Torsten Danfors for generously sharing your understanding of neuroimaging techniques and EEG and helping us view our data from new perspectives. I find the collaboration between our specialties very exciting. I hope it will bear fruit in future research results and a better understanding and communication between our specialties in our everyday clinical work.

My fellow co-authors, included the researchers mentioned above, for intriguing scientific discussions and outstanding collaboration.

A-C Fält, for being my administrative anchor in this PhD process! No matter the problem, big or small, you always know what to do or who to talk to. Without you, I would easily have been lost at sea many times over.

Hans Arinell, for patiently guiding me through the jungle of statistics and for your wise advice and overall invaluable support throughout these years.

Leslie Shaps, for excellent and rigorous proofreading of this thesis and overall helpful language advice.

To all my amazing fellow PhD students from Uppsala University and ”Forskarskolan i klinisk psykiatri” thank you for the many in-depth scientific discussions, brilliant advice, support and great company.

To all my colleagues in psychiatry, thank you for being such competent, compassionate and caring professionals and colleagues. The work you do is exceptional and a true inspiration!

Anne Fredriksson, Sofia Christopoulou and Karin Stolare, for supporting me in my residency in psychiatry and helping me combine my clinical work with research. Your commitment to us psychiatry residents is invaluable!

Special thanks to Ulla Nordén, Psykiatrimottagningen för Unga Vuxna and all the other colleagues and students who have contributed to the data collection

in UPP throughout the years. Together you have helped create a magnificent research infrastructure that will continue to contribute to exciting psychiatric research.

I would especially like to express my sincerest gratitude to all the patients who have chosen to participate in these studies. Your generous contribution is invaluable for the advancement of clinical psychiatric research and will hopefully end up helping a significant number of people in the future. Without you, this thesis would not have been possible.

My friends and family, you mean so much to me in so many ways. Thank you for being in my life!

To my mother Christina, my father Mikael and my sister Ella, thank you for your never-ending love and support. You are my biggest inspiration and my haven in a storm. I am so grateful to have you in my life!

Most of all, thank you Rasmus, my wonderful husband, for being my anchor so that I dare to fly. Without you I would not have had the confidence to begin this journey. Thank you for your unconditional love and support, for cheering me on, for inspiring me with your passion and curiosity, for continuously challenging me to think in new ways and for always believing in me. Thank you also for using your creative skills to help me convey my research with beautiful graphical illustrations, including the cover of this thesis.

The scientific illustrations in the thesis include adapted images from Pixabay (www.pixabay.com) and Servier Medical Art (www.smart.servier.com).

References

1. Glannon W. Mind-brain dualism in psychiatry: Ethical implications. Frontiers in psychiatry. 2020;11:85.
2. Pandya SK. Understanding brain, mind and soul: Contributions from neurology and neurosurgery. Mens sana monographs. 2011;9(1):129.
3. Hyman SE. Psychiatric disorders: Grounded in human biology but not natural kinds. Perspectives in Biology and Medicine. 2021;64(1):6-28.
4. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature. 2017;542(7640):177-85.
5. Brestoff JR, Artis D. Immune regulation of metabolic homeostasis in health and disease. Cell. 2015;161(1):146-60.
6. Barra NG, Henriksbo BD, Anhê FF, Schertzer JD. The NLRP3 inflammasome regulates adipose tissue metabolism. Biochemical Journal. 2020;477(6):1089-107.
7. Tsigalou C, Vallianou N, Dalamaga M. Autoantibody production in obesity: is there evidence for a link between obesity and autoimmunity? Current Obesity Reports. 2020:1-10.
8. Jernbom Falk A, Galletly C, Just D, Toben C, Baune BT, Clark SR, et al. Autoantibody profiles associated with clinical features in psychotic disorders. Translational Psychiatry. 2021;11(1):1-9.
9. Versini M, Jeandel P-Y, Rosenthal E, Shoenfeld Y. Obesity in autoimmune diseases: not a passive bystander. Autoimmunity reviews. 2014;13(9):981-1000.
10. Prinz M, Priller J. The role of peripheral immune cells in the CNS in steady state and disease. Nat Neurosci. 2017;20(2):136-44.
11. Salter MW, Stevens B. Microglia emerge as central players in brain disease. Nat Med. 2017;23(9):1018-27.
12. Chavan SS, Pavlov VA, Tracey KJ. Mechanisms and Therapeutic Relevance of Neuro-immune Communication. Immunity. 2017;46(6):927-42.
13. Khandaker G, Dantzer R, Jones P. Immunopsychiatry: important facts. Psychological medicine. 2017;47(13):2229-37.
14. Gerentes M, Pelissolo A, Rajagopal K, Tamouza R, Hamdani N. Obsessive-Compulsive Disorder: Autoimmunity and Neuroinflammation. Curr Psychiatry Rep. 2019;21(8):78.
15. Dale RC, Church AJ, Surtees RA, Lees AJ, Adcock JE, Harding B, et al. Encephalitis lethargica syndrome: 20 new cases and evidence of basal ganglia autoimmunity. Brain. 2004;127(1):21-33.
16. Köhler-Forsberg O, Petersen L, Gasse C, Mortensen PB, Dalsgaard S, Yolken RH, et al. A nationwide study in Denmark of the association between treated infections and the subsequent risk of treated mental disorders in children and adolescents. JAMA psychiatry. 2019;76(3):271-9.
17. Tiosano S, Farhi A, Watad A, Grysman N, Stryjer R, Amital H, et al. Schizophrenia among patients with systemic lupus erythematosus: population-based cross-sectional study. Epidemiol Psychiatr Sci. 2017;26(4):424-9.

18. Wang L-Y, Chen S-F, Chiang J-H, Hsu C-Y, Shen Y-C. Systemic autoimmune diseases are associated with an increased risk of obsessive–compulsive disorder: a nationwide population-based cohort study. Social psychiatry and psychiatric epidemiology. 2019;54(4):507-16.
19. McDonough E, Ayearst R, Eder L, Chandran V, Rosen CF, Thavaneswaran A, et al. Depression and anxiety in psoriatic disease: prevalence and associated factors. The Journal of rheumatology. 2014;41(5):887-96.
20. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry. 2011;70(7):663-71.
21. Herken J, Prüss H. Red flags: clinical signs for identifying autoimmune encephalitis in psychiatric patients. Frontiers in psychiatry. 2017;8:25.
22. Endres D, Maier V, Leypoldt F, Wandinger KP, Lennox B, Pollak TA, et al. Autoantibody-associated psychiatric syndromes: a systematic literature review resulting in 145 cases. Psychol Med. 2020:1-12.
23. Endres D, Rauer S, Pschibul A, Suss P, Venhoff N, Runge K, et al. Novel Antineuronal Autoantibodies With Somatodendritic Staining Pattern in a Patient With Autoimmune Psychosis. Front Psychiatry. 2020;11:627.
24. Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and characteristics of isolated psychiatric episodes in anti-N-methyl-d-aspartate receptor encephalitis. JAMA Neurol. 2013;70(9):1133-9.
25. Titulaer MJ, McCracken L, Gabilondo I, Armangue T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12(2):157-65.
26. Byrne S, Walsh C, Hacohen Y, Muscal E, Jankovic J, Stocco A, et al. Earlier treatment of NMDAR antibody encephalitis in children results in a better outcome. Neurol Neuroimmunol Neuroinflamm. 2015;2(4):e130.
27. Finke C, Kopp UA, Pajkert A, Behrens JR, Leypoldt F, Wuerfel JT, et al. Structural Hippocampal Damage Following Anti-N-Methyl-D-Aspartate Receptor Encephalitis. Biol Psychiatry. 2016;79(9):727-34.
28. Endres D, Leypoldt F, Bechter K, Hasan A, Steiner J, Domschke K, et al. Autoimmune encephalitis as a differential diagnosis of schizophreniform psychosis: clinical symptomatology, pathophysiology, diagnostic approach, and therapeutic considerations. Eur Arch Psychiatry Clin Neurosci. 2020;270(7):803-18.
29. Herken J, Pruss H. Red Flags: Clinical Signs for Identifying Autoimmune Encephalitis in Psychiatric Patients. Front Psychiatry. 2017;8:25.
30. Pollak TA, Lennox BR, Muller S, Benros ME, Pruss H, Tebartz van Elst L, et al. Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin. Lancet Psychiatry. 2020;7(1):93-108.
31. Endres D, Meixensberger S, Dersch R, Feige B, Stich O, Venhoff N, et al. Cerebrospinal fluid, antineuronal autoantibody, EEG, and MRI findings from 992 patients with schizophreniform and affective psychosis. Transl Psychiatry. 2020;10(1):279.
32. Guasp M, Giné-Servén E, Maudes E, Rosa-Justicia M, Martínez-Hernández E, Boix-Quintana E, et al. Clinical, Neuroimmunologic, and CSF Investigations in First Episode Psychosis. Neurology. 2021.
33. Gaetani L, Paoletti FP, Bellomo G, Mancini A, Simoni S, Di Filippo M, et al. CSF and blood biomarkers in neuroinflammatory and neurodegenerative diseases: Implications for treatment. Trends in Pharmacological Sciences. 2020.

34. Zetterberg H, Smith DH, Blennow K. Biomarkers of mild traumatic brain injury in cerebrospinal fluid and blood. Nature Reviews Neurology. 2013;9(4):201-10.
35. Kortvelyessy P, Pruss H, Thurner L, Maetzler W, Vittore-Welliong D, Schultze-Amberger J, et al. Biomarkers of Neurodegeneration in Autoimmune-Mediated Encephalitis. Front Neurol. 2018;9:668.
36. Middeldorp J, Hol EM. GFAP in health and disease. Prog Neurobiol. 2011;93(3):421-43.
37. Jamieson A, Goodwill AM, Termine M, Campbell S, Szoeke C. Depression related cerebral pathology and its relationship with cognitive functioning: A systematic review. Journal of affective disorders. 2019;250:410-8.
38. Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. Schizophrenia research. 2001;49(1-2):1-52.
39. Constantinescu R, Krysl D, Andren K, Asztely F, Bergquist F, Zetterberg H, et al. Cerebrospinal fluid markers of neuronal and glial cell damage in patients with autoimmune neurologic syndromes with and without underlying malignancies. J Neuroimmunol. 2017;306:25-30.
40. Katisko K, Cajanus A, Jääskeläinen O, Kontkanen A, Hartikainen P, Korhonen VE, et al. Serum neurofilament light chain is a discriminative biomarker between frontotemporal lobar degeneration and primary psychiatric disorders. Journal of neurology. 2020;267(1):162-7.
41. Nilsson IA, Millischer V, Karrenbauer VD, Juréus A, Salehi AM, Norring C, et al. Plasma neurofilament light chain concentration is increased in anorexia nervosa. Translational psychiatry. 2019;9(1):1-6.
42. Rodrigues-Amorim D, Rivera-Baltanás T, del Carmen Vallejo-Curto M, Rodriguez-Jamardo C, de Las Heras E, Barreiro-Villar C, et al. Plasma β-III tubulin, neurofilament light chain and glial fibrillary acidic protein are associated with neurodegeneration and progression in schizophrenia. Scientific reports. 2020;10(1):1-10.
43. Michel M, Fiebich BL, Kuzior H, Meixensberger S, Berger B, Maier S, et al. Increased GFAP concentrations in the cerebrospinal fluid of patients with unipolar depression. Translational Psychiatry. 2021;11(1):1-9.
44. Steinacker P, Al Shweiki MR, Oeckl P, Graf H, Ludolph AC, Schönfeldt-Lecuona C, et al. Glial fibrillary acidic protein as blood biomarker for differential diagnosis and severity of major depressive disorder. Journal of Psychiatric Research. 2021;144:54-8.
45. Lepine JP, Briley M. The increasing burden of depression. Neuropsychiatr Dis Treat. 2011;7(Suppl 1):3-7.
46. Gold PW. The organization of the stress system and its dysregulation in depressive illness. Mol Psychiatry. 2015;20(1):32-47.
47. Hryhorczuk C, Sharma S, Fulton SE. Metabolic disturbances connecting obesity and depression. Front Neurosci. 2013;7:177.
48. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4. ed ed. Washington, DC: American Psychiatric Association; 2000. 943 p.
49. Malhi GS, Mann JJ. Depression. Lancet. 2018;392(10161):2299-312.
50. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol. 2016;16(1):22-34.
51. Penninx BW. Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. Neurosci Biobehav Rev. 2017;74(Pt B):277-86.
52. Leighton SP, Nerurkar L, Krishnadas R, Johnman C, Graham GJ, Cavanagh J. Chemokines in depression in health and in inflammatory illness: a systematic review and meta-analysis. Mol Psychiatry. 2018;23(1):48-58.

53. Kohler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr Scand. 2017;135(5):373-87.
54. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010;67(5):446-57.
55. Dantzer R. Cytokine-induced sickness behavior: mechanisms and implications. Annals of the New York Academy of Sciences. 2001;933:222-34.
56. Udina M, Castellvi P, Moreno-Espana J, Navines R, Valdes M, Forns X, et al. Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. J Clin Psychiatry. 2012;73(8):1128-38.
57. Lasselin J, Schedlowski M, Karshikoff B, Engler H, Lekander M, Konsman JP. Comparison of bacterial lipopolysaccharide-induced sickness behavior in rodents and humans: relevance for symptoms of anxiety and depression. Neuroscience & Biobehavioral Reviews. 2020;115:15-24.
58. Strawbridge R, Arnone D, Danese A, Papadopoulos A, Herane Vives A, Cleare AJ. Inflammation and clinical response to treatment in depression: A meta-analysis. Eur Neuropsychopharmacol. 2015;25(10):1532-43.
59. Kohler CA, Freitas TH, Stubbs B, Maes M, Solmi M, Veronese N, et al. Peripheral Alterations in Cytokine and Chemokine Levels After Antidepressant Drug Treatment for Major Depressive Disorder: Systematic Review and Meta-Analysis. Mol Neurobiol. 2017.
60. Benedetti F, Poletti S, Hoogenboezem TA, Locatelli C, de Wit H, Wijkhuijs AJM, et al. Higher Baseline Proinflammatory Cytokines Mark Poor Antidepressant Response in Bipolar Disorder. J Clin Psychiatry. 2017;78(8):e986-e93.
61. Uher R, Tansey KE, Dew T, Maier W, Mors O, Hauser J, et al. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. Am J Psychiatry. 2014;171(12):1278-86.
62. Cattaneo A, Gennarelli M, Uher R, Breen G, Farmer A, Aitchison KJ, et al. Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. Neuropsychopharmacology. 2013;38(3):377-85.
63. Miller BJ, Goldsmith DR. Towards an Immunophenotype of Schizophrenia: Progress, Potential Mechanisms, and Future Directions. Neuropsychopharmacology. 2017;42(1):299-317.
64. Michopoulos V, Powers A, Gillespie CF, Ressler KJ, Jovanovic T. Inflammation in Fear- and Anxiety-Based Disorders: PTSD, GAD, and Beyond. Neuropsychopharmacology. 2017;42(1):254-70.
65. Milaneschi Y, Simmons WK, van Rossum EF, Penninx BW. Depression and obesity: evidence of shared biological mechanisms. Molecular psychiatry. 2019;24(1):18-33.
66. Milaneschi Y, Lamers F, Berk M, Penninx B. Depression Heterogeneity and Its Biological Underpinnings: Toward Immunometabolic Depression. Biol Psychiatry. 2020;88(5):369-80.
67. Fève B, Bastard J-P. From the conceptual basis to the discovery of leptin. Biochimie. 2012;94(10):2065-8.
68. Munzberg H, Morrison CD. Structure, production and signaling of leptin. Metabolism. 2015;64(1):13-23.
69. Caron A, Lee S, Elmquist JK, Gautron L. Leptin and brain-adipose crosstalks. Nat Rev Neurosci. 2018;19(3):153-65.
70. Margetic S, Gazzola C, Pegg GG, Hill RA. Leptin: a review of its peripheral actions and interactions. Int J Obes Relat Metab Disord. 2002;26(11):1407-33.

71. Jenks MZ, Fairfield HE, Johnson EC, Morrison RF, Muday GK. Sex Steroid Hormones Regulate Leptin Transcript Accumulation and Protein Secretion in 3T3-L1 Cells. Sci Rep. 2017;7(1):8232.
72. Farr OM, Tsoukas MA, Mantzoros CS. Leptin and the brain: influences on brain development, cognitive functioning and psychiatric disorders. Metabolism. 2015;64(1):114-30.
73. Burguera B, Couce ME, Long J, Lamsam J, Laakso K, Jensen MD, et al. The long form of the leptin receptor (OB-Rb) is widely expressed in the human brain. Neuroendocrinology. 2000;71(3):187-95.
74. Banks WA, Kastin AJ, Huang W, Jaspan JB, Maness LM. Leptin enters the brain by a saturable system independent of insulin. Peptides. 1996;17(2):305-11.
75. Martin SS, Qasim A, Reilly MP. Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease. J Am Coll Cardiol. 2008;52(15):1201-10.
76. Farooqi IS, O'Rahilly S. 20 years of leptin: human disorders of leptin action. J Endocrinol. 2014;223(1):T63-70.
77. Perez-Perez A, Vilarino-Garcia T, Fernandez-Riejos P, Martin-Gonzalez J, Segura-Egea JJ, Sanchez-Margalet V. Role of leptin as a link between metabolism and the immune system. Cytokine Growth Factor Rev. 2017;35:71-84.
78. Jow GM, Yang TT, Chen CL. Leptin and cholesterol levels are low in major depressive disorder, but high in schizophrenia. J Affect Disord. 2006;90(1):21-7.
79. Kraus T, Haack M, Schuld A, Hinze-Selch D, Pollmacher T. Low leptin levels but normal body mass indices in patients with depression or schizophrenia. Neuroendocrinology. 2001;73(4):243-7.
80. Yang K, Xie G, Zhang Z, Wang C, Li W, Zhou W, et al. Levels of serum interleukin (IL)-6, IL-1beta, tumour necrosis factor-alpha and leptin and their correlation in depression. Aust N Z J Psychiatry. 2007;41(3):266-73.
81. Cordas G, Gazal M, Schuch EM, Spessato BC, Branco J, Jansen K, et al. Leptin in depressive episodes: is there a difference between unipolar and bipolar depression? Neuroendocrinology. 2015;101(1):82-6.
82. Gecici O, Kuloglu M, Atmaca M, Tezcan AE, Tunckol H, Emul HM, et al. High serum leptin levels in depressive disorders with atypical features. Psychiatry Clin Neurosci. 2005;59(6):736-8.
83. Cizza G, Nguyen VT, Eskandari F, Duan Z, Wright EC, Reynolds JC, et al. Low 24-hour adiponectin and high nocturnal leptin concentrations in a case-control study of community-dwelling premenopausal women with major depressive disorder: the Premenopausal, Osteopenia/Osteoporosis, Women, Alendronate, Depression (POWER) study. J Clin Psychiatry. 2010;71(8):1079-87.
84. Pasco JA, Jacka FN, Williams LJ, Henry MJ, Nicholson GC, Kotowicz MA, et al. Leptin in depressed women: cross-sectional and longitudinal data from an epidemiologic study. J Affect Disord. 2008;107(1-3):221-5.
85. Rubin RT, Rhodes ME, Czambel RK. Sexual diergism of baseline plasma leptin and leptin suppression by arginine vasopressin in major depressives and matched controls. Psychiatry Res. 2002;113(3):255-68.
86. Zeman M, Jirak R, Jachymova M, Vecka M, Tvrzicka E, Zak A. Leptin, adiponectin, leptin to adiponectin ratio and insulin resistance in depressive women. Neuro Endocrinol Lett. 2009;30(3):387-95.
87. Esel E, Ozsoy S, Tutus A, Sofuoglu S, Kartalci S, Bayram F, et al. Effects of antidepressant treatment and of gender on serum leptin levels in patients with major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29(4):565-70.

88. Antonijevic IA, Murck H, Frieboes RM, Horn R, Brabant G, Steiger A. Elevated nocturnal profiles of serum leptin in patients with depression. J Psychiatr Res. 1998;32(6):403-10.
89. Morris AA, Ahmed Y, Stoyanova N, Hooper WC, De Staerke C, Gibbons G, et al. The association between depression and leptin is mediated by adiposity. Psychosom Med. 2012;74(5):483-8.
90. Labad J, Price JF, Strachan MW, Fowkes FG, Deary IJ, Seckl JR, et al. Leptin levels and depressive symptoms in people with type 2 diabetes: the edinburgh type 2 diabetes study. Psychosom Med. 2012;74(1):39-45.
91. Hood KK, Lawrence JM, Anderson A, Bell R, Dabelea D, Daniels S, et al. Metabolic and inflammatory links to depression in youth with diabetes. Diabetes Care. 2012;35(12):2443-6.
92. Kotan Z, Sarandol E, Kirhan E, Ozkaya G, Kirli S. Serum brain-derived neurotrophic factor, vascular endothelial growth factor and leptin levels in patients with a diagnosis of severe major depressive disorder with melancholic features. Ther Adv Psychopharmacol. 2012;2(2):65-74.
93. Tunçel ÖK, Akbaş S, Bilgici B. Increased Ghrelin Levels and Unchanged Adipocytokine Levels in Major Depressive Disorder. Journal of Child and Adolescent Psychopharmacology. 2016;26(8).
94. Strauss M, Mergl R, Kratzsch J, Brugel M, Strauss E, Hegerl U, et al. Differentiation between free and bound leptin in depressed patients. Psychiatry Res. 2014;219(2):397-9.
95. Miller GE, Freedland KE, Carney RM, Stetler CA, Banks WA. Pathways linking depression, adiposity, and inflammatory markers in healthy young adults. Brain Behav Immun. 2003;17(4):276-85.
96. Webb M, Davies M, Ashra N, Bodicoat D, Brady E, Webb D, et al. The association between depressive symptoms and insulin resistance, inflammation and adiposity in men and women. PLoS One. 2017;12(11):e0187448.
97. Akter S, Pham NM, Nanri A, Kurotani K, Kuwahara K, Jacka FN, et al. Association of serum leptin and ghrelin with depressive symptoms in a Japanese working population: a cross-sectional study. BMC Psychiatry. 2014;14:203.
98. Cao B, Chen Y, Brietzke E, Cha D, Shaukat A, Pan Z, et al. Leptin and adiponectin levels in major depressive disorder: A systematic review and meta-analysis. J Affect Disord. 2018;238:101-10.
99. Milaneschi Y, Lamers F, Bot M, Drent ML, Penninx BW. Leptin Dysregulation Is Specifically Associated With Major Depression With Atypical Features: Evidence for a Mechanism Connecting Obesity and Depression. Biol Psychiatry. 2017;81(9):807-14.
100. Caro JF, Kolaczynski JW, Nyce MR, Ohannesian JP, Opentanova I, Goldman WH, et al. Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. Lancet. 1996;348(9021):159-61.
101. Schwartz MW, Peskind E, Raskind M, Boyko EJ, Porte D, Jr. Cerebrospinal fluid leptin levels: relationship to plasma levels and to adiposity in humans. Nat Med. 1996;2(5):589-93.
102. Westling S, Ahren B, Traskman-Bendz L, Westrin A. Low CSF leptin in female suicide attempters with major depression. J Affect Disord. 2004;81(1):41-8.
103. Planchez B, Surget A, Belzung C. Animal models of major depression: drawbacks and challenges. Journal of Neural Transmission. 2019;126(11):1383-408.
104. Funahashi T, Matsuzawa Y. Adiponectin and the cardiometabolic syndrome: an epidemiological perspective. Best Pract Res Clin Endocrinol Metab. 2014;28(1):93-106.

105. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest. 2006;116(7):1784-92.
106. Liu M, Liu F. Transcriptional and post-translational regulation of adiponectin. Biochem J. 2009;425(1):41-52.
107. Tsao TS. Assembly of adiponectin oligomers. Rev Endocr Metab Disord. 2014;15(2):125-36.
108. Liu M, Liu F. Regulation of adiponectin multimerization, signaling and function. Best Pract Res Clin Endocrinol Metab. 2014;28(1):25-31.
109. Turer AT, Scherer PE. Adiponectin: mechanistic insights and clinical implications. Diabetologia. 2012;55(9):2319-26.
110. Nguyen TMD. Adiponectin: Role in physiology and pathophysiology. International Journal of Preventive Medicine. 2020;11.
111. Bondolfi G, Jermann F, Rouget BW, Gex-Fabry M, McQuillan A, Dupont-Willemin A, et al. Self- and clinician-rated Montgomery-Asberg Depression Rating Scale: evaluation in clinical practice. J Affect Disord. 2010;121(3):268-72.
112. Kishida K, Funahashi T, Shimomura I. Adiponectin as a routine clinical biomarker. Best Pract Res Clin Endocrinol Metab. 2014;28(1):119-30.
113. Phillips SA, Kung JT. Mechanisms of adiponectin regulation and use as a pharmacological target. Curr Opin Pharmacol. 2010;10(6):676-83.
114. Neumeier M, Weigert J, Buettner R, Wanninger J, Schaffler A, Muller AM, et al. Detection of adiponectin in cerebrospinal fluid in humans. Am J Physiol Endocrinol Metab. 2007;293(4):E965-9.
115. Ebinuma H, Miida T, Yamauchi T, Hada Y, Hara K, Kubota N, et al. Improved ELISA for selective measurement of adiponectin multimers and identification of adiponectin in human cerebrospinal fluid. Clin Chem. 2007;53(8):1541-4.
116. Kusminski CM, McTernan PG, Schraw T, Kos K, O'Hare JP, Ahima R, et al. Adiponectin complexes in human cerebrospinal fluid: distinct complex distribution from serum. Diabetologia. 2007;50(3):634-42.
117. Psilopanagioti A, Papadaki H, Kranioti EF, Alexandrides TK, Varakis JN. Expression of adiponectin and adiponectin receptors in human pituitary gland and brain. Neuroendocrinology. 2009;89(1):38-47.
118. Zhang D, Guo M, Zhang W, Lu XY. Adiponectin stimulates proliferation of adult hippocampal neural stem/progenitor cells through activation of p38 mitogen-activated protein kinase (p38MAPK)/glycogen synthase kinase 3beta (GSK-3beta)/beta-catenin signaling cascade. J Biol Chem. 2011;286(52):44913-20.
119. Kos K, Harte AL, da Silva NF, Tonchev A, Chaldakov G, James S, et al. Adiponectin and resistin in human cerebrospinal fluid and expression of adiponectin receptors in the human hypothalamus. J Clin Endocrinol Metab. 2007;92(3):1129-36.
120. Yau SY, Li A, Hoo RL, Ching YP, Christie BR, Lee TM, et al. Physical exercise-induced hippocampal neurogenesis and antidepressant effects are mediated by the adipocyte hormone adiponectin. Proc Natl Acad Sci U S A. 2014;111(44):15810-5.
121. Bloemer J, Pinky PD, Govindarajulu M, Hong H, Judd R, Amin RH, et al. Role of Adiponectin in Central Nervous System Disorders. Neural Plast. 2018;2018:4593530.
122. Kubota N, Yano W, Kubota T, Yamauchi T, Itoh S, Kumagai H, et al. Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. Cell Metab. 2007;6(1):55-68.
123. Liu J, Guo M, Zhang D, Cheng SY, Liu M, Ding J, et al. Adiponectin is critical in determining susceptibility to depressive behaviors and has antidepressant-like activity. Proc Natl Acad Sci U S A. 2012;109(30):12248-53.

124. Adam T, Schamarek I, Springer EA, Havel PJ, Epel EE. Adiponectin and negative mood in healthy premenopausal and postmenopausal women. Horm Behav. 2010;58(5):699-704.
125. Diniz BS, Teixeira AL, Campos AC, Miranda AS, Rocha NP, Talib LL, et al. Reduced serum levels of adiponectin in elderly patients with major depression. J Psychiatr Res. 2012;46(8):1081-5.
126. Lehto SM, Huotari A, Niskanen L, Tolmunen T, Koivumaa-Honkanen H, Honkalampi K, et al. Serum adiponectin and resistin levels in major depressive disorder. Acta Psychiatr Scand. 2010;121(3):209-15.
127. Leo R, Di Lorenzo G, Tesauro M, Cola C, Fortuna E, Zanasi M, et al. Decreased plasma adiponectin concentration in major depression. Neurosci Lett. 2006;407(3):211-3.
128. Vuong E, Nothling J, Lombard C, Jewkes R, Peer N, Abrahams N, et al. Peripheral adiponectin levels in anxiety, mood, trauma-and stressor-related disorders: A systematic review and meta-analysis. Journal of affective disorders. 2020;260:372-409.
129. Narita K, Murata T, Hamada T, Takahashi T, Kosaka H, Sudo S, et al. Adiponectin multimer distribution, not absolute amount of plasma, correlates with depression severity in healthy elderly subjects. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(1):124-7.
130. Mamalakis G, Kiriakakis M, Tsibinos G, Hatzis C, Flouri S, Mantzoros C, et al. Depression and serum adiponectin and adipose omega-3 and omega-6 fatty acids in adolescents. Pharmacol Biochem Behav. 2006;85(2):474-9.
131. Hung YJ, Hsieh CH, Chen YJ, Pei D, Kuo SW, Shen DC, et al. Insulin sensitivity, proinflammatory markers and adiponectin in young males with different subtypes of depressive disorder. Clin Endocrinol (Oxf). 2007;67(5):784-9.
132. Su SC, Sun MT, Wen MJ, Lin CJ, Chen YC, Hung YJ. Brain-derived neurotrophic factor, adiponectin, and proinflammatory markers in various subtypes of depression in young men. Int J Psychiatry Med. 2011;42(3):211-26.
133. Zeugmann S, Buehrsch N, Bajbouj M, Heuser I, Anghelescu I, Quante A. Childhood maltreatment and adult proinflammatory status in patients with major depression. Psychiatr Danub. 2013;25(3):227-35.
134. Wilhelm CJ, Choi D, Huckans M, Manthe L, Loftis JM. Adipocytokine signaling is altered in Flinders sensitive line rats, and adiponectin correlates in humans with some symptoms of depression. Pharmacol Biochem Behav. 2013;103(3):643-51.
135. Carvalho AF, Rocha DQ, McIntyre RS, Mesquita LM, Kohler CA, Hyphantis TN, et al. Adipokines as emerging depression biomarkers: a systematic review and meta-analysis. J Psychiatr Res. 2014;59:28-37.
136. Li C, Meng F, Garza JC, Liu J, Lei Y, Kirov SA, et al. Modulation of depression-related behaviors by adiponectin AdipoR1 receptors in 5-HT neurons. Molecular psychiatry. 2020:1-16.
137. Rizzo MR, Fasano R, Paolisso G. Adiponectin and cognitive decline. International journal of molecular sciences. 2020;21(6):2010.
138. Omrani A, de Vrind VA, Lodder B, Stoltenborg I, Kooij K, Wolterink-Donselaar IG, et al. Identification of Novel Neurocircuitry Through Which Leptin Targets Multiple Inputs to the Dopamine System to Reduce Food Reward Seeking. Biological psychiatry. 2021.
139. Coope A, Milanski M, Araujo EP, Tambascia M, Saad MJ, Geloneze B, et al. AdipoR1 mediates the anorexigenic and insulin/leptin-like actions of adiponectin in the hypothalamus. FEBS Lett. 2008;582(10):1471-6.
140. Qi Y, Takahashi N, Hileman SM, Patel HR, Berg AH, Pajvani UB, et al. Adiponectin acts in the brain to decrease body weight. Nat Med. 2004;10(5):524-9.

141. Awofala AA, Ogundele OE, Adekoya KO. ADIPOQ gene is linked to emotional eating behaviour in young Nigerian adults independent of psychological traits. Bulletin of the National Research Centre. 2020;44(1):1-7.
142. Awofala AA, Ogundele OE, Adekoya KO, Osundina SA. Adiponectin and human eating behaviour: a Mendelian randomization study. Egyptian Journal of Medical Human Genetics. 2019;20(1):1-7.
143. Tortorella A, Brambilla F, Fabrazzo M, Volpe U, Monteleone AM, Mastromo D, et al. Central and peripheral peptides regulating eating behaviour and energy homeostasis in anorexia nervosa and bulimia nervosa: a literature review. Eur Eat Disord Rev. 2014;22(5):307-20.
144. Brewerton TD, Lesem MD, Kennedy A, Garvey WT. Reduced plasma leptin concentrations in bulimia nervosa. Psychoneuroendocrinology. 2000;25(7):649-58.
145. Monteleone P, Di Lieto A, Tortorella A, Longobardi N, Maj M. Circulating leptin in patients with anorexia nervosa, bulimia nervosa or binge-eating disorder: relationship to body weight, eating patterns, psychopathology and endocrine changes. Psychiatry Res. 2000;94(2):121-9.
146. Jimerson DC, Mantzoros C, Wolfe BE, Metzger ED. Decreased serum leptin in bulimia nervosa. J Clin Endocrinol Metab. 2000;85(12):4511-4.
147. Monteleone P, Fabrazzo M, Tortorella A, Fuschino A, Maj M. Opposite modifications in circulating leptin and soluble leptin receptor across the eating disorder spectrum. Mol Psychiatry. 2002;7(6):641-6.
148. Monteleone P, Castaldo E, Maj M. Neuroendocrine dysregulation of food intake in eating disorders. Regul Pept. 2008;149(1-3):39-50.
149. Cassioli E, Rossi E, Squecco R, Baccari MC, Maggi M, Vignozzi L, et al. Reward and psychopathological correlates of eating disorders: The explanatory role of leptin. Psychiatry Research. 2020;290:113071.
150. Monteleone P, Fabrazzo M, Martiadis V, Fuschino A, Serritella C, Milici N, et al. Opposite changes in circulating adiponectin in women with bulimia nervosa or binge eating disorder. J Clin Endocrinol Metab. 2003;88(11):5387-91.
151. Housova J, Anderlova K, Krizova J, Haluzikova D, Kremen J, Kumstyrova T, et al. Serum adiponectin and resistin concentrations in patients with restrictive and binge/purge form of anorexia nervosa and bulimia nervosa. J Clin Endocrinol Metab. 2005;90(3):1366-70.
152. Tagami T, Satoh N, Usui T, Yamada K, Shimatsu A, Kuzuya H. Adiponectin in anorexia nervosa and bulimia nervosa. J Clin Endocrinol Metab. 2004;89(4):1833-7.
153. Ungvari GS, Goggins W, Leung S-K, Gerevich J. Schizophrenia with prominent catatonic features (‘catatonic schizophrenia’). II. Factor analysis of the catatonic syndrome. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2007;31(2):462-8.
154. Velligan D, Prihoda T, Dennehy E, Biggs M, Shores-Wilson K, Crismon ML, et al. Brief psychiatric rating scale expanded version: how do new items affect factor structure? Psychiatry research. 2005;135(3):217-28.
155. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont). 2007;4(7):28.
156. Fazekas F, Barkhof F, Wahlund LO, Pantoni L, Erkinjuntti T, Scheltens P, et al. CT and MRI rating of white matter lesions. Cerebrovasc Dis. 2002;13 Suppl 2:31-6.
157. Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry. 1992;55(10):967-72.
158. Breiman L. Random forests. Machine learning. 2001;45(1):5-32.

159. Watson KT, Simard JF, Henderson VW, Nutkiewicz L, Lamers F, Nasca C, et al. Incident major depressive disorder predicted by three measures of insulin resistance: a Dutch cohort study. American Journal of Psychiatry. 2021;178(10):914-20.
160. Guo M, Li C, Lei Y, Xu S, Zhao D, Lu XY. Role of the adipose PPARgamma-adiponectin axis in susceptibility to stress and depression/anxiety-related behaviors. Mol Psychiatry. 2017;22(7):1056-68.
161. Sun F, Lei Y, You J, Li C, Sun L, Garza J, et al. Adiponectin modulates ventral tegmental area dopamine neuron activity and anxiety-related behavior through AdipoR1. Mol Psychiatry. 2019;24(1):126-44.
162. Raevuori A, Suokas J, Haukka J, Gissler M, Linna M, Grainger M, et al. Highly increased risk of type 2 diabetes in patients with binge eating disorder and bulimia nervosa. International Journal of Eating Disorders. 2015;48(6):555-62.
163. Rankin J, Matthews L, Cobley S, Han A, Sanders R, Wiltshire HD, et al. Psychological consequences of childhood obesity: psychiatric comorbidity and prevention. Adolescent health, medicine and therapeutics. 2016;7:125.
164. Rohde K, Keller M, Horstmann A, Liu X, Eichelmann F, Stumvoll M, et al. Role of genetic variants in ADIPOQ in human eating behavior. Genes Nutr. 2015;10(1):449.
165. Rattay TW, Martin P, Vittore D, Hengel H, Cebi I, Tünnerhoff J, et al. Cerebrospinal fluid findings in patients with psychotic symptoms—a retrospective analysis. Scientific reports. 2021;11(1):1-12.
166. Bien CG, Rohleder C, Mueller JK, Bien CI, Koethe D, Leweke FM. Neural autoantibodies in cerebrospinal fluid and serum in clinical high risk for psychosis, first-episode psychosis, and healthy volunteers. Frontiers in psychiatry. 2021;12:382.
167. Theorell J, Ramberger M, Harrison R, Mgbachi V, Jacobson L, Waters P, et al. Screening for pathogenic neuronal autoantibodies in serum and CSF of patients with first-episode psychosis. Translational Psychiatry. 2021;11(1):1-7.
168. Cullen AE, Palmer-Cooper EC, Hardwick M, Vaggers S, Crowley H, Pollak TA, et al. Influence of methodological and patient factors on serum NMDAR IgG antibody detection in psychotic disorders: a meta-analysis of cross-sectional and case-control studies. The Lancet Psychiatry. 2021;8(2):109-20.
169. Tjensvoll AB, Lauvsnes MB, Zetterberg H, Kvaløy JT, Kvivik I, Maroni SS, et al. Neurofilament light is a biomarker of brain involvement in lupus and primary Sjögren's syndrome. Journal of neurology. 2021;268(4):1385-94.
170. Trysberg E, Nylen K, Rosengren LE, Tarkowski A. Neuronal and astrocytic damage in systemic lupus erythematosus patients with central nervous system involvement. Arthritis & Rheumatism. 2003;48(10):2881-7.
171. Endres D, Pollak TA, Bechter K, Denzel D, Pitsch K, Nickel K, et al. Immunological causes of obsessive-compulsive disorder: Is it time for the concept of an "autoimmune OCD" subtype? Transl Psychiatry. 2021(In press).
172. Sofroniew MV. Astrocyte barriers to neurotoxic inflammation. Nature Reviews Neuroscience. 2015;16(5):249-63.
173. O'Leary LA, Mechawar N. Implication of cerebral astrocytes in major depression: A review of fine neuroanatomical evidence in humans. Glia. 2021.
174. Bender CL, Calfa GD, Molina VA. Astrocyte plasticity induced by emotional stress: A new partner in psychiatric physiopathology? Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2016;65:68-77.
175. Hancox RJ, Landhuis CE. Correlation between measures of insulin resistance in fasting and non-fasting blood. Diabetol Metab Syndr. 2011;3(1):23.
176. Thundyil J, Pavlovski D, Sobey CG, Arumugam TV. Adiponectin receptor signalling in the brain. British journal of pharmacology. 2012;165(2):313-27.

177. Tabb KL, Gao C, Hicks PJ, Hawkins GA, Rotter JI, Chen YDI, et al. Adiponectin Isoform Patterns in Ethnic-Specific ADIPOQ Mutation Carriers: The IRAS Family Study. Obesity. 2017;25(8):1384-90.
178. Etminan M, Brophy JM, Collins G, Nazemipour M, Mansournia MA. Curriculum in Cardiology To Adjust or Not to Adjust: The Role of Different Covariates in Cardiovascular Observational Studies. American Heart Journal. 2021.
179. Hansen N, Timäus C. Immunotherapy in autoantibody-associated psychiatric syndromes in adults. Frontiers in Psychiatry. 2021;12:33.
180. Beavers KM, Brinkley TE, Nicklas BJ. Effect of exercise training on chronic inflammation. Clinica chimica acta. 2010;411(11-12):785-93.
181. Sirico F, Bianco A, D'Alicandro G, Castaldo C, Montagnani S, Spera R, et al. Effects of physical exercise on adiponectin, leptin, and inflammatory markers in childhood obesity: systematic review and meta-analysis. Childhood obesity. 2018;14(4):207-17.
182. Fedewa MV, Hathaway ED, Ward-Ritacco CL, Williams TD, Dobbs WC. The effect of chronic exercise training on leptin: a systematic review and meta-analysis of randomized controlled trials. Sports medicine. 2018;48(6):1437-50.
183. Becic T, Studenik C, Hoffmann G. Exercise increases adiponectin and reduces leptin levels in prediabetic and diabetic individuals: systematic review and meta-analysis of randomized controlled trials. Medical sciences. 2018;6(4):97.
184. Peng J, Yin L, Wang X. Central and peripheral leptin resistance in obesity and improvements of exercise. Hormones and Behavior. 2021;133:105006.

Errata

Paper II

In the Abstract in paper II the statement “P-leptin-adiponectin-ratio was significantly lower in patients with BN compared to controls ($p<0.04$)” should be “P-leptin-adiponectin-ratio was significantly lower in patients with BN compared to patients without BN ($p<0.04$)”.

Acta Universitatis Upsaliensis

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1793

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title "Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine".)

Distribution: publications.uu.se
urn:nbn:se:uu:diva-459466

ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2021